

Current Clinical Psychiatry
Series Editor: Jerrold F. Rosenbaum

Oliver Freudenreich

Psychotic Disorders

A Practical Guide

Second Edition



Humana Press

Current Clinical Psychiatry

Series Editor

Jerrold F. Rosenbaum
Department of Psychiatry
Massachusetts General Hospital
Boston, MA, USA

Current Clinical Psychiatry offers concise, practical resources for clinical psychiatrists and other practitioners interested in mental health. Covering the full range of psychiatric disorders commonly presented in the clinical setting, the Current Clinical Psychiatry series encompasses such topics as cognitive behavioral therapy, anxiety disorders, psychotherapy, ratings and assessment scales, mental health in special populations, psychiatric uses of nonpsychiatric drugs, and others. Series editor Jerrold F. Rosenbaum, MD, is Chief of Psychiatry, Massachusetts General Hospital, and Stanley Cobb Professor of Psychiatry, Harvard Medical School.

More information about this series at <http://www.springer.com/series/7634>

Oliver Freudenreich

Psychotic Disorders

A Practical Guide

Second Edition

 Humana Press

Oliver Freudenreich
Department of Psychiatry
Massachusetts General Hospital
Boston, MA
USA

ISSN 2626-241X
Current Clinical Psychiatry
ISBN 978-3-030-29449-6
<https://doi.org/10.1007/978-3-030-29450-2>

ISSN 2626-2398 (electronic)
ISBN 978-3-030-29450-2 (eBook)

© Springer Nature Switzerland AG 2020

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

The publisher, the authors, and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, expressed or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

This Humana imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Foreword for the First Edition Published in 2008

This book is a rarity among books about schizophrenia. It is written by somebody who spend the majority of his working life providing care to patients with schizophrenia. The authors of most books about schizophrenia spend their working lives writing grants and papers, and opining with their ilk at meeting on the basis of materials several steps distant from patient contact. Dr. Freudenreich is, at his core, a clinician, an astoundingly learned clinician who considers mitigating the effects of this disease on his patients' lives his most important purpose.

This book is about what is known *and* important. There is an immense literature on schizophrenia; thousands of new papers are published every year. History will show that more than 99% of what is published contributes nothing to the day-to-day care of patients with schizophrenia. Dr. Freudenreich is a voracious reader and careful curator of the schizophrenia literature. He provides for you in this book the quintessence (fifth distillate) of his scholarship. The material he has included has withstood repeated tests and challenges and has strong support. He tells you what you have to know and what you have to do to provide the best possible care for patients with schizophrenia.

If asked, almost all patients with schizophrenia deny that they are ill or need treatment. Yet, most come for the appointments and take their prescribed medications. When asked why they take their medications, having just denied a need for medications, they look surprised at the questioner's lack of sophistication and explain that "the doctor prescribed it." There is some common ground identified, if never reduced to words. There is some value applied in each patient's economy. Dr. Freudenreich's patients come to their appointments because he is interested in them. He understands their experiences that we, but not they, call psychopathology. He knows that they do not want to suffer side effects from their medications. He knows that they want the same things we want, "... something to do, and good people to do it with" (Hemingway). Dr. Freudenreich tries to hand them along on their ways toward these goals. He tells you in this book what you need to know to be able to do the same thing.

Joseph P. McEvoy, MD
John Umstead Hospital
Butner, NC, USA

Foreword for the Second Edition

Etymologically, a psychiatrist is the “physician of the soul” and nowhere does that meaning have more urgency and poignancy than in the understanding, diagnosis, care, and treatment of those with psychotic disorders. My respect for colleagues who have committed their careers to these conditions as clinicians, researchers, and teachers is enormous. From the prodromal phase to the first episode and positive symptoms to chronic course and negative symptoms, schizophrenia particularly challenges us to do more, study more, learn more, and innovate more. It is the North Star for psychiatric neuroscience, and as I read the scientific tea leaves, there is a potential for breakthroughs in defining the path from risk to pathology and in identifying methods to divert, blunt, and alter risk and to mitigate pathology. For now, however, and for the near future, there is considerable expertise to be taught, practiced, and sustained to do our job in diagnosing and treating psychotic disorders. And there is no practitioner of this art who has inspired me more than Oliver Freudenreich as a comprehensively knowledgeable, technically skilled, and spiritually compassionate clinician, teacher, and scholar in this field.

This volume will be the guide to feel and be competent in ministering to those with psychosis, to know both basics and advanced practice, so at the end of the day, as a practitioner, you can reassure yourself you have done the best that can be done now for your patients: delivering care, avoiding harm, and eliciting recovery or enhanced quality of life. Since the first edition, the book has extended the content to include more of the well-received tips and key points. Clarity and depth are brought to the important descriptions of phenomenology of psychopathology, the medical issues and challenges associated with the disorders and their treatments, guidance as to the state of the art of practice of psychopharmacology of psychosis, and finally the principles of patient centered-care and disease self-management. Our patients do better when we, the system of care, and their community are true partners in caring about them as fellow humans and their quality of life and well-being.

Jerrold F. Rosenbaum, MD
Massachusetts General Hospital
Harvard Medical School
Boston, MA, USA

Preface for the First Edition

“Well, doctor, tell me, exactly how many patients with this disease have you seen?,” my psychiatric consultation fellowship director, George B. Murray, would invariably ask after I once again self-assuredly presented to him in rounds a patient with a rare disease. Of course, I usually had to mumble, “one, if you count this one.” And George would invariably add, “So, in other words, you have not seen a lot of them?” His valid point, of course, was this: you can only know clinical medicine and psychiatry from seeing patients, many patients that is, so you appreciate a disease in all its forms and shades, and phases and stages.

To learn about psychotic disorders, then, see as many patients with psychosis as you can and ask your teachers to help you understand what you see. In addition, read articles and books about psychosis to add understanding to your clinical experience. I hope this book is your starting point for your journey into the fascinating world of psychotic disorders.

This book is about clinical aspects of psychosis: how to recognize that somebody is psychotic, how to arrive at a clinical diagnosis that explains the psychosis, and how to treat it. Schizophrenia constitutes the bulk of patients with psychosis, and the bulk of this book is therefore dedicated to diagnosing and treating schizophrenia and related conditions. A perhaps unique bent for a psychiatric text is the emphasis on medical comorbidity, a partly iatrogenic scourge for many patients with schizophrenia, adding medical insult to psychiatric injury.

I think of this book as a *vade mecum* (Latin for “go with me”): a little manual to carry around in your pocket because it is useful, probably mainly for medical students, psychiatric residents, and other health care professionals who need to evaluate and treat a psychotic patient. This is not a textbook of psychosis, and you will find little discussion of neurobiology and pathophysiology.

To make the material come alive, clinical vignettes are dispersed throughout the text. All vignettes are based on real patients that I am currently treating but, to paraphrase Thomas Mann, consider the vignettes “descriptions of the way things never were but always are.” Tips and key points are the clinical teaching pearls I use in my seminars or at the bedside, and should be taken with a grain of salt and not as absolutes. I included annotated recommendations for articles, books, and web sites for

further study at the end of each chapter, as well as pocket cards for use in the clinic (covering emergencies, rating scales, and wellness) in the appendices.¹

The chapters are a condensation of my teaching of residents from the Harvard MGH-McLean program and the Boston University program; my research in the Massachusetts General Hospital Schizophrenia Program; and my clinical experience as an attending physician in an emergency department and a forensic inpatient unit, as a psychiatric consultant, and as an outpatient psychiatrist. I have even worked as an alienist in a state hospital (see History of Schizophrenia Care in the United States in the last chapter, if you are confused about what alienists do). So, I hope, my thoughts and recommendations are a blend of clinical wisdom and pragmatic advice that is informed by the literature.

If you have the time for feedback, simply email me (ofreudenreich@partners.org). I welcome your comments about this *vade mecum*.

Boston, MA, USA

Oliver Freudenreich, MD

¹Those have been incorporated into the text in the 2nd edition.

Preface for the Second Edition

I did not realize how much psychiatry had changed in the decade since I wrote the first edition of this book until I started working on the revision – progress is too incremental to be perceived in your day-to-day work. Apart from concrete advances like new medications, psychiatry has become better integrated with medicine and, most critically, more attentive to the patient’s voice. Inevitably, my views about what it means to be a good psychiatrist have evolved as well. As a result, I substantially revised the book. All chapters have updated language, expanded content, new figures, and current references. I added several new chapters so that topics that I consider clinically important are in one place: first-episode psychosis, clozapine, and long-acting antipsychotics. I also added a chapter on the history of schizophrenia care because the view back informs us as we are designing a more effective, safer, and fairer mental healthcare system that reaches all who need psychiatric treatment.

This edition retains its character of a vade mecum for clinical psychosis care, with only scant attention paid to basic research or pathophysiology. The book’s conversational style with tips and key points reflects its emphasis on usefulness and readability, without being simplistic. I welcome your feedback; simply email me, Freudreich.Oliver@mgh.harvard.edu.

Oliver Freudreich, MD, FACLP
Massachusetts General Hospital,
Harvard Medical School
Boston, MA, USA

Acknowledgements for the First Edition

Nassir Ghaemi encouraged me to write this book and suggested my name to Charley Mitchell at Lippincott Williams & Wilkins, who trusted that I would produce a manuscript. Nancy Hoffmann, Sirkka Bertling, and Jennifer Harper turned the manuscript into a book. I am grateful to them, and to the editor of Practical Guides in Psychiatry, Daniel Carlat, who gave me the opportunity to contribute my favorite topic to his series.

What I wrote I could not have written without the mentorship of three individuals, in order of appearance in my professional life journey: Joseph McEvoy taught me most of what I know about the syndrome of schizophrenia. I will never forget my first few years in the country when I rounded with Joe at John Umstead Hospital in Butner, NC. Thank you, Joe, for those good years as your clinical research fellow. George Murray taught me general hospital psychiatry when I came to MGH to be one of his fellows on the psychiatric consultation service. George, your dictums and metaphors helped me appreciate the human condition and also see my own humanity. And Donald Goff, my current boss, taught me how to be an academic public-sector psychiatrist, if there is such a thing. Don, I am grateful that you continue to guide me through the thicket of clinical care, clinical research, and publishing.

My former co-fellows, now colleagues and friends, John “Jack” Querques and Nick “Stavros” Kontos, helped me substantially with the book. Some teaching points are theirs, not mine. Without their friendship, and our private think tank, Boston would be a much colder New England town.

My colleagues in the MGH Schizophrenia Program all dedicated their time and talents to critique individual chapter: Cori Cather, Eden Evins, Dave Henderson, Daphne Holt, Jen Park, and Tony Weiss. Our fellows, Constantin Tranulis and Ruth Barr, also edited chapters, as did Larry Park of MGH. I was lucky to have Raj Gandhi from the MGH HIV clinic always willing to help me with the “medical stuff.” Nassir Ghaemi was available to guide me through the process of writing a book whenever I needed him.

Stuart Schwartz at UMDNJ, as well as Janet Osterman and Dominic Ciraulo of Boston University, launched my teaching career. Unwittingly, the psychiatry residents at MGH-McLean and Boston University have helped create and fine-tune

much of what is in this book. I thank them for their enthusiasm and keeping the special teacher-student relationship alive for me.

I am grateful to all the patients who trusted my judgment over the last decade or so, even if it was not their idea to see a psychiatrist. Through them, I have remained a student, and collectively they have given me more than I could ever have imagined.

Last, I thank my family for putting up with me “at the computer” instead of going to the ballet, throwing the football, or pushing the swing. Thank you, Catherine, Sheldon, and Sophie, respectively.

Acknowledgements for the Second Edition

This book reflects my academic career at Massachusetts General Hospital where I have spent the past 20 years. Without the backing of my incredible department, I would have had no academic career and never written a book. All this time, Jerry Rosenbaum was my chief. Jerry, you have taught me about humanism and leadership in any interaction. I will miss you in your little corner office as you move on.

I remain deeply indebted to Joe McEvoy, my mentor, colleague, and friend. Joe, each encounter with you remains precious; you are the wisest person I know. Nick “Stavros” Kontos and John “Jack” Querques have remained a source of support for 20 years, since our CL fellowship year. Bravo, Jack, va bene; danke, Stavros; there is a lot in this book that is yours. Derri Shtasel has dedicated countless hours to teach me administrative psychiatry. Thank you, Derri for your patience with me. Sarah MacLaurin has been my nurse practitioner for many years. Sarah, you always remind me why our work matters. Nassir Ghaemi has continued to be a friend and mentor for my writing career.

Other bosses, mentors, and colleagues who have shaped my views about psychiatric care reflected in this book are Maurizio Fava, David Henderson, Daphne Holt, Janet Wozniak, Ted Stern, Travis Baggett, Felicia Smith, and Scott Beach; Don Goff, now in New York, continues to be as accessible as ever, when our offices were in the same hallway; Dost Ongur and Joe Stoklosa of McLean; and Kathy Sanders of DMH. I am grateful to the staff at the MGH Psychiatry Academy and to Prakash Masand from Global Medical Education for affording me the opportunity to teach my peers; there is no better way of learning. My colleagues in the MGH Schizophrenia Clinical and Research Program and the clinical trials team are important people in my professional life who have shaped my views about schizophrenia.

Many people have reviewed individual chapters or provided ideas and feedback, not always without fully appreciating it, in alphabetical order: David Beckmann, Cori Cather, Drew Coman, Shana Coshal, Abbie Donovan, Jose Hidalgo, Nick Kontos, Sarah MacLaurin, Michel Mennesson, John Querques, and Kristina Schnitzer. Fellows, chief residents, and residents of the MGH/McLean Adult Psychiatry Residency Program through their curiosity have kept me honest and current; unwittingly, they have contributed much content to this book.

Regina Schmitt has reconnected me to European psychiatry and keeps me appraised about developments at my alma mater; Matthias Kaltenmaier will always be my most trusted friend and colleague.

This book would not exist without my patients and the staff at the Freedom Trail Clinic. The leadership team at North Suffolk Mental Health Association has supported me for 20 years. I thank Jackie Moore and Judi Lemoine and, more recently, Manjola Ujkaj.

Several families have supported my academic work. I am grateful for their willingness to do so: Jim and Donna Stearns, Ashoke and Vinita Rampuria, and the Laura and Lorenz Reibling Foundation. Lorenz, it is because of you that I included a small section on physician responsibility in times of national catastrophe.

My own family deserves mentioning for tolerating my academic misadventures. Thank you, Catherine, Sheldon, and Sophie.

Last, I would like to thank the team at Springer for turning a manuscript into something real: Nadina Persaud (clinical medicine editor) and Gina Kahn (development editor).

Arlington, MA, USA

June 4, 2019

Contents

1	Psychotic Signs and Symptoms	1
2	Psychosis Interview.....	17
3	Delirium	27
4	Drug-Induced Psychosis.....	37
5	Secondary Schizophrenia.....	49
6	Psychiatric Differential Diagnosis of Psychosis	69
7	Natural History of Schizophrenia	87
8	Diagnostic Assessment of Schizophrenia.....	101
9	Prevention and Clinical Staging	115
10	Emergency Management of Acute Psychosis	127
11	First-Episode Psychosis	137
12	Treatment-Resistant Schizophrenia	157
13	Antipsychotics: Overview.....	171
14	Antipsychotics: Motor Side Effects.....	185
15	Antipsychotics: Nonmotor Side Effects	201
16	Antipsychotics: Clinical Effectiveness.....	215
17	Clozapine	231
18	Long-Acting Injectable Antipsychotics.....	249
19	Adjunctive Medications	263

20 Antipsychotic Drug Interactions	277
21 Polypharmacy	289
22 Psychological Treatments: The Patient	301
23 Psychological Treatments: The Family	313
24 Psychiatric Rehabilitation and Recovery	323
25 Medical Morbidity and Mortality	335
26 Dual Diagnosis	351
27 Tobacco Use Disorder	359
28 Negative Symptoms	375
29 Cognition in Schizophrenia	385
30 Depression and Suicide	399
31 Illness Insight and Antipsychotic Medication Adherence	411
32 Social Aspects of Schizophrenia Care	425
33 Forensic Aspects of Schizophrenia Care	435
34 History of Schizophrenia Care	451
Index	465

Contributor

Oliver Freudenreich, MD, FACP Co-Director, MGH Schizophrenia Clinical and Research Program, Massachusetts General Hospital, Associate Professor of Psychiatry, Harvard Medical School, Boston, MA, USA

Chapter 1

Psychotic Signs and Symptoms



Essential Concepts

- Descriptive psychopathology provides the building blocks for psychiatric diagnosis. It provides the language for observed behaviors and inner experiences.
- In a narrow sense, psychosis is operationally defined as the presence of certain symptoms: delusions or hallucinations, sometimes also including disorganized thinking. Use it only in this technical sense.
- Disorders of thought are based on content (delusions) or form (formal thought disorders).
- Delusions are beliefs characterized by falsity, certainty, and incorrigibility. However, none of those features while characteristic is essential.
- Delusions, hallucinations, formal thought disorder, grossly disorganized behavior, and catatonia are considered positive symptoms.
- Overvalued ideas straddle the world of normal beliefs and psychosis. They are often shared by groups of people who fanatically pursue their ideas, regardless of personal cost.
- Knowing Schneiderian first-rank symptoms (FRS) is useful to screen for psychosis, not to make a specific diagnosis. Somebody who reports FRS is clearly actively psychotic.
- Catatonic symptoms comprise a variety of quite varied motor symptoms that occur in patients with schizophrenia (among other conditions) and may therefore be seen in patients who are psychotic.

Man sieht nur, was man weiß. [1]

(You only see what you know.)

- Johann Wolfgang von Goethe, 1749–1832

Descriptive psychopathology is that branch of psychiatry that concerns itself with the precise definition of terms for clinical phenomena you might encounter when examining the mental state of a patient such as psychosis, the topic of this book. Descriptive psychopathology includes (a) observing behavior and (b) inquiring into the subjective experience of patients, with the goal not to explain but to correctly label their reported experiences as “symptoms in the mind.” The attempt to accurately describe inner pathological experiences is a branch of descriptive psychopathology known as phenomenology. Karl Jaspers, who wrote the classic text on psychopathology over a century ago [2], put it best: “Subjective symptoms cannot be perceived by the sense-organs, but have to be grasped by transferring oneself, so to say, into the other individual’s psyche; that is, by empathy” [3]. Today we might say that you have to put yourself in the patient’s shoes. Phenomenology in contrast to disease-focused symptomatology is person-centered in that it keeps the person’s subjective experience at the forefront of our clinical thinking [4]. Psychopathology may be a tool to rehumanize psychiatry in cases where the patient was lost in the quest for diagnostic reliability using symptom checklists [5].

“Psychosis” as a term has evolved rather significantly. Originally introduced to separate all disorders that fall into the realm of psychiatry from those of neurology, it has since seen a significant narrowing in meaning [6]. First, it was restricted to serious disorders like schizophrenia spectrum disorders but also including manic-depressive illness (patients typically seen in state hospitals who were “insane” and cared for by the alienists as these hospital-based psychiatrists were known as), in contrast to the neurotic disorders (patients seen in outpatient practices, building on the insights of Freud). In older textbooks, you still see this fundamental distinction. Today, psychosis is operationally defined (delusions, hallucinations, disorganized thinking) at the level of symptoms.

In this chapter, I describe the signs and symptoms to look for when you are trying to decide if somebody is experiencing psychosis or not. Reflecting the importance of French and German psychiatry at the time when psychiatry established itself as a specialty over a century ago [7] and the fight over patients between neurology and psychiatry, you will encounter many foreign language terms, different terms for similar phenomena and obscure concepts. Unfortunately, we are still waiting for a twenty-first-century descriptive psychopathology that harmonizes terminologies and brings clinical observation in line with neuroscience [8]. In the interim, read the descriptions, and then find teachers who will show you what the phenomena look like in real patients, to “feel the Mississippi mud between your toes,” in the words of one of my mentors, the late George Murray. In addition, read the next chapter to learn more about how to interview a patient to get at his psychotic experiences.

Psychotic Signs and Symptoms

Key Point

In its most narrow conceptualization, psychosis is operationally defined as the presence of delusions or clear-cut hallucinations, punctum. In broader definitions, formal thought disorder, behavioral disorganization, and catatonia are included in its definition [9]. Psychotic symptoms are neither specific for any disorder nor even necessarily pathologic.

Conceptually, psychosis is “impaired reality testing,” the famous “break from reality.” Clinically, this is not terribly useful: How do you know when it is present? Attempts have been made to identify clinical signs and symptoms suggestive of this “impaired reality testing,” giving rise to the above operationalized definition of (narrowly defined) psychosis as delusions or hallucinations, sometimes including disorganized thinking. A narrow conceptualization is critical to avoid mislabeling anyone “weird” as psychotic. Also do not label patients generically as “psychotic” merely because they appear seriously ill or worse because you do not know what they have but only use psychosis in today’s narrow technical sense (i.e., psychotic symptoms are present).

Delusions

Key Point

For pragmatic, clinical purposes, delusions are fixed, false beliefs: beliefs that are held with great conviction even in the face of overwhelming evidence to the contrary and are not shared by the members of the patient’s own culture or subculture. Delusions are disorders of thought content: what people believe. However, this definition is also epistemologically incorrect: delusions are not necessarily fixed, they are not necessarily false, and they might not be beliefs at all. Delusions force us to reflect on the nature of truth and how we come to know it, including who decides.

You might think a core concept of psychiatry, the “basic characteristic of madness,” as Karl Jaspers called delusions, is well understood. As it turns out, delusions defy easy understanding. Karl Jaspers identified three key characteristics of delusions: impossible content (falsity), held with conviction (certainty), and not susceptible to correction (incorrigibility) [10]. All three characteristics do not withstand closer scrutiny. Certainty in a delusional belief is frequently not absolute but subject

to doubt; and many patients can challenge and correct their delusional assumptions (the basis for cognitive-behavioral treatment for psychosis). They are able to shift their point of view, like Copernicus. In contrast, we all hold certain beliefs dear to our heart with conviction and defend them against modification (e.g., scientific beliefs). Probably most problematic from a philosophical point of view is the assumption that “false” (impossible) ideas are somehow different from “unusual” or normal ideas. Often, delusions seem mere grotesque exacerbations of surrounding beliefs rather than “false.” Even far-fetched delusions frequently contain a kernel of truth. To complicate matters further: normal ideas and delusions *feel* the same to patients. The impossible content problem leads to the inclusion of a reference group to determine the veracity of an idea by majority vote: if enough people (e.g., your church community) share your world view, the idea is not considered delusional. This solution worked reasonably well when our world was not connected. Now, people with fringe views including delusion-like ideas can get together virtually and form potentially quite large groups of believers. I should say that despite great theoretical problems, delusions are usually easy to spot in the clinic. The problem is reminiscent of defining pornography (“I know it when I see it,” in the famous words of Supreme Court Justice Potter Stewart [11]). That said, the distinction toward overvalued ideas (see below) and confabulation [12] may not always be easy.

Once you have encountered a delusion, assess the following aspects:

- What is the delusion about? Delusions as a disorder of thought content are conveniently classified according to the dominant theme, e.g., delusions of grandeur, love, persecution, reference, control, or religious delusions. Table 1.1 lists eponyms of psychotic presentations.
- Is the delusion bizarre? Already Kraepelin noted the delusions in dementia praecox “often show … an extraordinary, sometimes whole *nonsensical* stamp.” While the distinction between bizarre and nonbizarre delusions used to play a big role in psychiatric nosology (e.g., you could not have delusional disorder if your delusions were bizarre), this has been de-emphasized in current nosology, in part because of the difficulties to operationalize “bizarreness.” Still, the presence of a bizarre belief will make you more confident that the belief is delusional. Not even this is an easy task, however, and psychiatrists disagree when a delusion becomes bizarre [13]. I would consider if a belief is (currently) physically possible or not to settle the question of bizarreness in my mind.
- Is the delusion mood-congruent? Typically but not necessarily, delusions of depression are morbid, those of mania grandiose.
- How pervasive is the delusions? Is it encapsulated within an otherwise intact personality or are you dealing with a well-formed, systematized delusional system in which everything and everybody is connected to the delusions?
- How firmly entrenched is the delusions? Is doubt a possibility? Ask, “Is it possible that you are wrong, that you are overinterpreting events and people’s intentions?” “Could *chance* explain your observation?”
- Are you sure you are not dealing with memories of delusions? Patients are not actively psychotic anymore, but they are unable to challenge the accuracy of

Table 1.1 Eponyms of psychotic and related presentations^a

Bell's mania. Delirious mania: A severe form of excited mania in which the patient appears delirious (disoriented and with fever) [14]. Death from exhaustion can occur [15]. Some consider it a form of excited catatonia [16].

Capgras syndrome. Delusions of doubles: A friend or relative has been replaced by an imposter (an exact double). Suspect organicity, it is often seen at some point in Alzheimer's disease. The patient needs to be sent for neurocognitive testing and magnetic resonance imaging (MRI). Capgras syndrome is only one of several delusional misidentification syndromes [17]. In the illusions of 'Fregoli' a persecutor is seen in many people, as the persecutor is disguised and changes in appearance.

Charles Bonnet syndrome. Vivid and complex visual (pseudo-)hallucinations that are the result of eye disease [18]. The hallucinations are friendly, for example, little people sitting on the coach in the living room. The patient needs to see an ophthalmologist, not a psychiatrist!

De Clérambault syndrome. Erotomania: Delusional conviction that somebody (usually a man of higher station) is in love with you (usually a female), despite virtually no contact. Can occur in its "pure," primary form or embedded in other psychiatric illnesses. Three stages: hope, resentment, overt hostility – the loved person is in danger in the third stage.

Ekbom's syndrome. Dermatozoenwahn. Chronic tactile hallucinosis or delusional parasitosis: Patients imagining infestations with bugs, worms, and insects. The patient often presents to dermatology ("positive matchbox sign" with "trapped" evidence) but should see you (they never do)! Make sure there is not amphetamine misuse. A modern variant is Morgellons disease.

Cotard's syndrome. Characterized by nihilistic delusions that can be quite bizarre: Patients believe they are literally dead; they believe they do not exist or that the world does not exist; that they have no heart for example, "I am being prepared for execution." It occurs in psychotic, depressive state.

Ganser syndrome. Characterized by *vorbeireden* – talking past the point; giving approximate answers to simple questions; all answers are absurdly wrong but barely: 3 plus 3 is 7. A camel has five legs. The color green is called orange. Possibly malingering, maybe a twilight state.

Jerusalem syndrome. Not an eponym but a collection of psychiatric presentations at the interface of religion and psychosis that afflicts travelers to Jerusalem [19].

Korsakoff's psychosis. A misnomer today, as no psychosis in the modern sense is present. It is the possible residual state following acute Wernicke's encephalopathy. Patients cannot form new memories (anterograde amnesia) and confabulate. Try thiamine for treatment.

Kraepelin-Morel disease. Rarely used eponym for schizophrenia.

Lhermitte's (peduncular) hallucinosis. Vivid, colorful visual (pseudo-)hallucinations caused by a midbrain lesion.

Münchhausen syndrome. One of the factitious disorders. Patients seek admission to hospital, often with incredible stories (also known as "pseudologia fantastica"). When patients are found wandering from hospital to hospital in search of admission, they are known as "hospital hobos."

Othello syndrome. Characterized by delusions of infidelity. Occurs as morbid (pathological to the point of delusional) jealousy in alcoholics and in neurodegenerative disorders. In Shakespeare's play, Othello was manipulated into believing that his wife Desdemona was unfaithful (a case of "gas-lighting"), and he murdered her. The play gets it right in that patients can pose a danger to their partner.

Wernicke's encephalopathy. An acute confusional state due to severe thiamine (vitamin B1) deficiency. Other symptoms include ataxia and ophthalmoplegia to form the classic triad. Alcoholism is an important risk factor for reduced thiamine intake (but not the only one!).

^aHistorically, no distinctions were made between "organic" presentations, mania, and psychosis in the modern sense. Some terms are wrong based on modern definitions, and for many conditions, different names are used

their past psychotic experiences (“I know a chip was implanted 20 years ago so I cannot have an MRI.”). This matters since antipsychotics cannot change memories of delusions (as opposed to delusional memories which are the result of active psychosis).

Although today often understood to mean persecuted, “paranoia” was the term Kraepelin originally used for conditions in which delusions were the only psychopathological feature. The term is still used in that sense in “paranoid schizophrenia,” an unofficial clinical subtype of schizophrenia in which *any type* of delusion dominates the clinical presentation.

Overvalued Ideas

The German neuropsychiatrist Carl Wernicke (of Wernicke’s encephalopathy and Wernicke’s aphasia [20]) used the term “overvalued idea” for people with a passionate attitude, also known as “fanatics” in lay terms. One important aspect of overvalued ideas is that they are shared with other people, making them potentially destructive. Remember that delusions, by contrast, are generally uniquely false ideas held by individuals and identified by others as erroneous. While most people would not jeopardize their careers or lives for overvalued ideas, some will (and are secretly regarded as heroes by those less inclined to fight for an idea). This is to say that it is not the idea itself but the reckless (toward oneself or others) pursuit that causes isolation and suffering. In forensic settings, extreme nonpsychotic, overvalued ideas might be a more helpful characterization than psychosis if one wants to understand a person’s motivations for action, including violence against society [21]. However, we need to be careful to not overreach and label all persons with differing opinions as holding overvalued ideas as evidence for a clinical condition in need of treatment.

Tip

The best way of getting patients to talk about delusions and delusion-like ideas is by taking a stance of curiosity and confusion, best exemplified by Peter Falk’s LAPD Detective Columbo: “I am confused. On the one hand, you work for the CIA but then you are not getting a paycheck.” With the Columbo technique of approaching your topic of interest obliquely, you challenge inconsistencies without appearing to doubt the patient’s account of events.

Hallucinations

The French psychiatrist Jean-Étienne Dominique Esquirol defined hallucinations as a “percept without an object.” Think of hallucinations as *false* perceptions (there is a perception without an external object) in contrast to *altered* perceptions (e.g., illusions or sensory distortions where a real object is experienced as distorted).

Table 1.2 Visual hallucinations in nonpsychiatric conditions

Delirium (often frightening)
Dementia
Toxic states and drug withdrawals
Organic lesions in visual pathways
Ocular pathology (e.g., Charles Bonnet syndrome)
Migraine
Epilepsy
Peduncular hallucinations from midbrain pathology

Auditory hallucinations (AH) are frequent in schizophrenia but not obligatory. In schizophrenia, AH can be noises but typically are “voices,” more often unpleasant than pleasant. Three types of voices are so typical that they are used to diagnosis schizophrenia (see below under Schneiderian first-rank symptoms). This does not mean that AH do not occur in other disorders or that hallucinations other than AH do not occur in schizophrenia. As a rule of thumb, visual hallucinations (VH) should make you suspicious of a delirium or dementia (Table 1.2). Descriptively, VH are either unformed (simple) or formed (complex). Olfactory hallucinations are typical for epileptic auras but can occur in schizophrenia, unfortunately for the patient usually as a fetid smell or as evidence that poison gas is pumped into the apartment. Tactile hallucinations might suggest amphetamine use (formication: the feeling of ants crawling on or just under ones skin) but also overlap with strange, bodily sensations, often of a sexual nature in schizophrenia (some use the mouthful “cenesthesia” for difficult to describe bodily sensations [22]). Musical hallucinations would be very unusual for schizophrenia. Some hallucinations occur only in certain situations: as hypnagogic or hypnopompic hallucinations during sleep-wake cycle transitions (consider narcolepsy) or as functional hallucinations (e.g., only when the shower is on or the air conditioner is humming).

It needs to be emphasized that experiencing auditory hallucinations does not equate suffering from schizophrenia. A famous person who heard voices, Jeanne d’Arc, probably suffered from epilepsy [23]. Population-based studies have found that auditory hallucinations are not uncommon in the general population, particularly during adolescence, and not necessarily the sign of a serious mental disorder (although they could be a harbinger of a beginning psychotic disorder) [24]. Worldwide, people who hear voices have banded together with their peers in Hearing Voices Networks (HVN) in order to normalize the experience of hearing voices and challenge the particularly Western view that hearing voices is a sign of psychopathology and need for medical treatment [25].

Tip

To evaluate auditory hallucinations, ask directly: “Do you sometimes hear somebody talk, but to your surprise, nobody is around?” Then get specifics: “Where are the voices coming from? What are they saying? Are they insulting?” Do not miss potentially dangerous command hallucinations: “Are they instructing you what to do?” Check for hallucinations typical for schizophrenia (see Schneiderian first-rank symptoms, below).

Pseudohallucinations

Some patients recognize that their hallucinations are “not real” or that they are “in my mind” that they could be their own thoughts. They seem to arise in some inner space (like a memory) and are not perceived as a coming from the external world. Some authors use “pseudohallucinations” to indicate the presence of insight into the pathology of the experience [26]. A good example of such self-recognized (pseudo-) hallucinations is the visual hallucinations of the Charles Bonnet syndrome. Hearing the voice of the deceased or seeing the loved one during bereavement might fall into this category as well [27]. Hypnagogic and hypnopompic hallucinations are also often considered pseudohallucinations. However, the term pseudohallucinations is ontologically imprecise and not uniformly applied; for many practitioners it might simply mean “not real” which is of course not the patient’s experience at all. It might be best to avoid the term in clinical discussions [28]. I still list it for completeness and to illustrate that a complaint of “hearing voices” requires a thoughtful assessment.

Tip

With effective antipsychotic treatment, hallucinations take on the character of pseudohallucinations. Ask: “Point where you hear the voice” and “Is it possible that it is your own thoughts you are hearing?”

Hallucinosis

Hallucinosis describes a mental state characterized by hallucinations in a clear sensorium. Alcoholic hallucinosis and Lhermitte’s (peduncular) hallucinosis are well-recognized entities. Delusional interpretation of hallucinations is possible, albeit not prominent.

Schneiderian First-Rank Symptoms

Kurt Schneider, former chair of the Department of Psychiatry at Heidelberg University (my alma mater), lives on in his concept of “Schneiderian first-rank symptoms (FRS).” This is a list of originally 11 (depending how you count and what you count) straightforward psychotic phenomena (Table 1.3) that are often encountered in schizophrenia and that can be reliably identified [29]. (I admit that there is some circular reasoning involved: several FRS, because they are thought prototypical for schizophrenia, became part of the definition of schizophrenia itself). They all capture the positive, paranoid-hallucinatory symptoms of psychosis.

Table 1.3 List of Schneiderian first-rank symptoms

Primary delusion (delusion is a sudden apophany or revelation)
Delusional perception (an observation is misinterpreted)
Auditory hallucinations
Voices arguing
Voices commenting (running commentary)
Audible thoughts (thought echo, <i>Gedankenlautwerden</i>)
Delusions of thought interference
Thought insertion
Thought withdrawal
Thought broadcasting
Delusions of control (“passivity experiences, made experiences”)
Passivity of feelings (made feelings)
Passivity of action (made volitional acts)
Passivity of impulse (made impulses)
Somatic passivity (made sensations)

Related and overlapping (but not identical) with FRS are self-disturbances (Ich-Störungen in German). They represent what earlier clinicians considered fundamental disturbances of how patients with schizophrenia experience the self [30]. As opposed to normal self-awareness (I exist; I am one person; I am separate from the outside world), patients with self-disturbances struggle with a loss of ego boundaries: where does the self end, and where does the world begin? Such unity and interconnectedness experiences are well described in psychedelic states. Nihilistic Cotard’s delusions are an extreme example where existence itself is no longer experienced. Milder forms of self-disturbances include depersonalization. There has been a renewed interest in these self-disturbances as they occur early, in the prodromal phase of schizophrenia.

Key Point

None of the FRS is pathognomonic of schizophrenia; they lack specificity. You will hear about them, for example, from patients with delirium or a mood disorder. As a result, FRS have been de-emphasized in modern psychiatric nosology [31]. They are, however, very prevalent in schizophrenia and other nonschizophrenia psychotic disorders [32], as they are basically evidence of psychosis. I use this fact to screen for psychosis by asking about FRS, not necessarily to make specific diagnosis of schizophrenia [33]. A good clinical assessment includes a careful search for FRSs [34].

It is my impression that patients with schizophrenia who have one of the FRS have others as well (perhaps because all FRS are the expression of some basic fail-

ure to recognize thoughts, feelings, or behaviors as internally generated, patients instead attribute them to something coming or forced on them from outside; or, in Schneider's words, FRS are "a lowering of the barrier between the self and the surrounding world;" see above discussion of self-disturbances). The absence of any Schneiderian FRS should make you question that diagnosis of schizophrenia [34]. Note that the list of FRS includes delusions of thought and control that will strike you immediately as quite bizarre and inconsistent with normal. Often misunderstood is this: It is the experience that is delusional; there does not have to be a delusional explanatory system.

Asking About Voices

Get an exact description of the voices, which are usually insulting, talking to the person in the third person ("He is such a loser"); second-person voices are typical for the self-accusatory talk of the depressed person ("You are such a loser"). Are they talking among themselves about you (arguing voices)? Are they commenting on everything you do as you do it (running commentary)? Do people repeat aloud what you think (thought echo)?

Asking About Alien Influence on Thought, Feeling, and Behavior

- Do you feel that your thoughts are not private? That people can read your thoughts?
- Do you feel controlled by some force? That you are being hypnotized?
- Do you feel as if your feelings or your actions or your thoughts are not your own?
- Do you experience sensations such as being radiated? Being experimented on?

Formal Thought Disorder ("Thought Disorder")

Thinking can be disordered in two ways: by what patients say (problem with content, such as delusions as discussed in the previous section) and how they say it (problem with form). If patients do not seem to make sense, not because of what they say but how they say it, a formal thought disorder (or disorder of thought process) might be present. Disorganized thought is a severe variant of a formal thought disorder. Because we can only judge how somebody thinks by what the person says, this is also known as disorganized speech. In severe cases of disorganized speech, speech has lost its communicative function. In subtle cases, you might be initially impressed but come to conclude that many things the patient said were "pseudophilosophical." Some patients produce little speech that is shallow and empty in what is said (see chapter on negative symptoms). Look out for perseveration which is closer to neurology and thought blocking.

Tip

You need a speech sample to judge if a formal thought disorder is present: Let the patient talk and simply listen (not easy for physician who tend to interrupt patients quickly)! Ask an “essay” questions (“What do you think of European soccer?”), and then sit back and listen, asking yourself how your patient is developing his or her ideas. If you cannot reconstruct your questions or if it is unclear what is said (despite many words), a formal thought disorder might be present.

Nota Bene

Before you diagnosis a formal thought disorder, make sure you are not dealing with confusion (check orientation and attention) or aphasia (check if the patient can name, comprehend, and repeat). A patient with a fluent aphasia or a patient with a delirium can appear thought disordered. If you do not have a baseline, the determination on clinical exam alone can be difficult.

In a formal thought disorder, thoughts are not properly associated, hence the overarching term looseness of associations (LOAs). Derailment and “knights move thinking” are other terms that describe the same phenomenon. Loose associations can be at the level of sentences of even within a sentence. In tangential speech each thought is connected to the next, but the overall goal is lost and never reached. If combined with an acceleration of speech, you have the flight of ideas of manic patients. In extreme cases of loose associations, there is no connection between words, and the patient becomes incoherent to the point of producing word salad. You can encounter many other speech pathologies (“non-neurogenic language disorders”) in psychotic patients, for example, clang associations, neologisms, the “lalias” (e.g., echolalia), or the frequent misuse of words and use of stock phrases [35]. Foreign language syndrome is an interesting experience if you have ever encountered a patient who displays it. Dysarthria, stuttering, or dysphonia should steer you toward neurology.

Not all peculiarities of speech are necessarily pathological. Don’t be fooled by street slang which may contain neologisms [36]! In circumstantial speech, the goal of answering your question is not lost; the patient is merely adding unnecessary (and for a time-pressured physician) maddening detail. If you interrupt a long-winded, overinclusive patient, the patient will say “I know, I am getting to it,” suggesting he or she has not lost track of the goal. Circumstantial speech can be a personality quirk; good storytellers effectively use circumstantiality as a device.

Tip

In the mental status examination (MSE), I try to make a note if LOAs are mild, moderate, or severe. I will also note neologisms (new words with meaning to the patient, e.g., to transchieve) – make sure you consult your dictionary before your patients expose your ignorance – and non sequiturs (abrupt and unexpected statements that do not follow what was said). A patient might ask out of the blue: “Do you like pizza?”). I use the earthy term “rambling” to indicate LOAs that have a hard-to-interrupt, disinhibited quality that does not represent dialogue with you. Figure 1.1 depicts schematically various formal thought disorders.

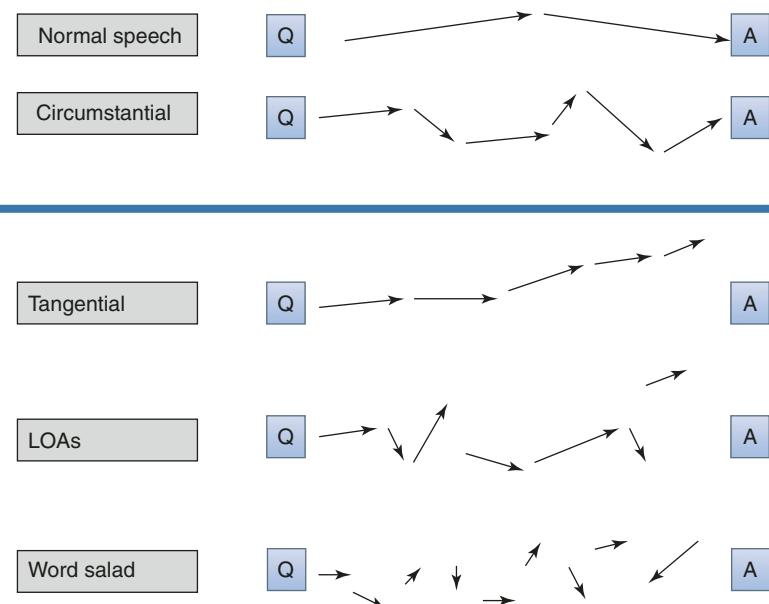


Fig. 1.1 Formal thought disorder. LOAs looseness of associations, Q question, A answer; note that in normal conversation, the goal of speech is toward answering a question. In abnormal speech, this goal is missed. Circumstantial speech is a variant of normal

The state of affairs with the precise description of language using only the tool of a clinical exam is unsatisfactory and will benefit from more objective assessment tools. In the not so distant future, artificial intelligence (automated speech analysis and machine learning) will quite likely meaningfully inform not just diagnosis but also disease prediction by providing objective data about speech changes in early disease phases (e.g., speech alterations like reduced semantic fluency in beginning Alzheimer's disease and reduced semantic coherence in people at high-risk for developing schizophrenia [37]).

Behavioral Disorganization and Catatonia

Peculiar motor behaviors can be clearly seen in old pictures and clinical descriptions of schizophrenia from the pre-neuroleptic era. Movements are not always easy to classify, and often convention replaces understanding. Common problems seen even in the absence of treatment with antipsychotics are mannerisms, stereotypies, grimacing, and spontaneous dyskinesias. Behavioral disorganization is a term used to indicate odd and bizarre behaviors like the ones just mentioned but also other behaviors that are even harder to put your fingers on. These behaviors make your patient stand out, as social norms (or rules of common sense) are violated without obvious reason (i.e., patients are not trying to make a statement). Multilayered clothing in the summer, wearing a hard hat in the library, urinating or masturbating in public, and random shouting or laughter are examples of behavioral disorganization. Affect can be childlike, silly, or inappropriate to what you are discussing and prone to sudden shifts (you might wonder if you are being belittled).

Tip

Consider behavioral disorganization if your patient fails the subway test (i.e., the crowd moves away from the patient because he or she is identified as having psychological difficulties). There are of course other reasons for failing the subway test such as frank psychosis.

Catatonia comprises a quite varied list of psychomotor abnormalities that you can encounter in psychiatric but also neurological or medical conditions [38]. The abnormalities exist on a continuum ranging from too little movement (or no movement at all in its most extreme form, catatonic stupor) to too much movement (see Table 1.4).

Table 1.4 Catatonia – signs and symptoms

<i>Hypokinetic phenomena</i>	
Catatonic stupor	Patient is immobile and unresponsive to environment
Catatonic mutism	Patient talks little or not at all
Catalepsy-posturing	Patient maintains a posture even if uncomfortable or imposed; if you try to move the patient, there can be some initial resistance, and the muscle tone feels like bending a wax candle (<i>flexibilitas cerea</i> or waxy flexibility). Grimacing is seen if the face is affected, <i>Schnauzkrampf</i> if the “snout”
Staring	Patient stares straight ahead instead of looking around; blinks less
<i>Hyperkinetic phenomena</i>	
Catatonic motor excitement	Motor activity without provocation and without purpose or goal
Stereotypies	Repetitive movements without goals; can be repetition of senseless movements (e.g., clapping, rocking) or of words (e.g., verbigeration or palilalia – repeating of phrases)

Table 1.4 (continued)

Mannerisms	Goal-directed, purposeful movements that appear odd, out of place, or exaggerated; e.g., saluting, unbuttoning; shaking hands in a stilted, awkward way; speaking with a fake accent
Echolalia and echopraxia	Two examples of echophenomena; patients repeat what they hear or what they observe (which gets in the way if they repeat the examiner's questions!)
<i>Signs that need to be elicited</i>	
Negativism	Without clear motive, patients resist your examination. <i>Gegenhalten</i> (paratonia) is seen: the harder you try to move the patient, the harder the patient resists
Automatic obedience ^a	Patient is unable to resist instruction even if told to do something painful (e.g., "Stick out your tongue so I can pinch it with a needle"). <i>Mitgehen</i> is seen: patient raises arm in response to light pressure even if instructed to resist (anglepoise lamp sign)
Ambitendency	Patient hesitates and is stuck and indecisive to your conflicting instructions (e.g., stretching out greeting hand while telling patient "Don't shake my hand")

Based on [39]

^aExaggerated cooperation

Catatonic features are often missed because they are regarded as rare and hence not considered or examined for. In a series of more than 100 consecutively admitted psychiatric inpatients, 10% of patients displayed catatonic features [40]. Pay attention to any motor abnormality even if subtle (e.g., the patient appeared slowed down or seemed to have difficulties with motor sequences; the patient has difficulties initiating speaking). If you see one catatonic symptom, look for another; if you see two, you are probably dealing with catatonics.

References

1. Goethe. Available from: <https://gutezitate.com/zitat/183167>. Accessed Jan 7 2019.
2. Fusar-Poli P. One century of Allgemeine Psychopathologie (1913 to 2013) by Karl Jaspers. Schizophr Bull. 2013;39:268–9.
3. Broome MR, Harland M, Owen GS, Stringaris A. Jaspers' approach 1: static understanding – 'phenomenology'. In: Broome MR, Harland M, Owen GS, Stringaris A, editors. The Maudsley reader in phenomenological psychiatry. New York: Cambridge University Press; 2012. p. 91–100.
4. Stanghellini G, Broome MR. Psychopathology as the basic science of psychiatry. Br J Psychiatry. 2014;205:169–70.
5. Stanghellini G. Psychopathology: re-humanizing psychiatry. Acta Psychiatr Scand. 2013;127:436–7.
6. Ban TA. Evolution of diagnostic criteria in psychoses. Dialogues Clin Neurosci. 2001;3:257–63.
7. Crocq MA. French perspectives on psychiatric classification. Dialogues Clin Neurosci. 2015;17:51–7.
8. de Leon J. Is it time to awaken sleeping beauty? European psychiatry has been sleeping since 1980. Rev Psiquiatr Salud Ment. 2014;7:186–94.

9. Gaebel W, Zielasek J. Focus on psychosis. *Dialogues Clin Neurosci.* 2015;17:9–18.
10. Jaspers K. General psychopathology. Baltimore: The Johns Hopkins University Press; 1997.
11. Latzman P. The origins of Justice Stewart's "I know it when I see it". *The Wall Street Journal.* 2007 September 27, 2007.
12. Glowinski R, Payman V, Frencham K. Confabulation: a spontaneous and fantastic review. *Aust N Z J Psychiatry.* 2008;42:932–40.
13. Spitzer RL, First MB, Kendler KS, Stein DJ. The reliability of three definitions of bizarre delusions. *Am J Psychiatry.* 1993;150:880–4.
14. Karmacharya R, England ML, Ongur D. Delirious mania: clinical features and treatment response. *J Affect Disord.* 2008;109:312–6.
15. Mash DC. Excited delirium and sudden death: a syndromal disorder at the extreme end of the neuropsychiatric continuum. *Front Physiol.* 2016;7:435.
16. Fink M. Delirious mania. *Bipolar Disord.* 1999;1:54–60.
17. Baruelle A, Luaute JP. Capgras syndrome and other delusional misidentification syndromes. *Front Neurol Neurosci.* 2018;42:35–43.
18. Pang L. Hallucinations experienced by visually impaired: Charles Bonnet syndrome. *Optom Vis Sci.* 2016;93:1466–78.
19. Bar-el Y, Durst R, Katz G, Zislin J, Strauss Z, Knobler HY. Jerusalem syndrome. *Br J Psychiatry.* 2000;176:86–90.
20. Pillmann F. Carl Wernicke (1848–1905). *J Neurol.* 2003;250:1390–1.
21. Rahman T, Resnick PJ, Harry B. Anders Breivik: extreme beliefs mistaken for psychosis. *J Am Acad Psychiatry Law.* 2016;44:28–35.
22. Jenkins G, Rohricht F. From cenesthesia to cenesthopathic schizophrenia: a historical and phenomenological review. *Psychopathology.* 2007;40:361–8.
23. Schildkrout B. Joan of Arc-hearing voices. *Am J Psychiatry.* 2017;174:1153–4.
24. Hielscher E, Connell M, Lawrence D, Zubrick SR, Hafekost J, Scott JG. Prevalence and correlates of psychotic experiences in a nationally representative sample of Australian adolescents. *Aust N Z J Psychiatry.* 2018;52:768–81.
25. Hearing Voices Network. Available from: <https://www.hearing-voices.org/>. Accessed Jan 7 2019.
26. Taylor FK. On pseudo-hallucinations. *Psychol Med.* 1981;11:265–71.
27. Kamp KS, Due H. How many bereaved people hallucinate about their loved one? A systematic review and meta-analysis of bereavement hallucinations. *J Affect Disord.* 2019;243:463–76.
28. Denning TR, Berrios GE. The enigma of pseudohallucinations: current meanings and usage. *Psychopathology.* 1996;29:27–34.
29. Schneider K. Klinische Psychopathologie. 15. Auflage. Stuttgart: Georg Thieme Verlag; 2007.
30. Mishara AL, Lysaker PH, Schwartz MA. Self-disturbances in schizophrenia: history, phenomenology, and relevant findings from research on metacognition. *Schizophr Bull.* 2014;40:5–12.
31. Tandon R, Gaebel W, Barch DM, Bustillo J, Gur RE, Heckers S, et al. Definition and description of schizophrenia in the DSM-5. *Schizophr Res.* 2013;150:3–10.
32. Peralta V, Cuesta MJ. Diagnostic significance of Schneider's first-rank symptoms in schizophrenia. Comparative study between schizophrenic and non-schizophrenic psychotic disorders. *Br J Psychiatry.* 1999;174:243–8.
33. Soares-Weiser K, Maayan N, Bergman H, Davenport C, Kirkham AJ, Grabowski S, et al. First rank symptoms for schizophrenia. *Cochrane Database Syst Rev.* 2015;1:CD010653.
34. Heinz A, Voss M, Lawrie SM, Mishara A, Bauer M, Gallinat J, et al. Shall we really say goodbye to first rank symptoms? *Eur Psychiatry.* 2016;37:8–13.
35. Mendez MF. Non-neurogenic language disorders: a preliminary classification. *Psychosomatics.* 2018;59:28–35.
36. Howes OD, Weinstein S, Tabraham P, Valmaggia L, Broome M, McGuire P. Street slang and schizophrenia. *BMJ.* 2007;335:1294.
37. Bedi G, Carrillo F, Cecchi GA, Slezak DF, Sigman M, Mota NB, et al. Automated analysis of free speech predicts psychosis onset in high-risk youths. *NPJ Schizophr.* 2015;1:15030.

38. Denysenko L, Sica N, Penders TM, Philbrick KL, Walker A, Shaffer S, et al. Catatonia in the medically ill: etiology, diagnosis, and treatment. The academy of consultation-liaison psychiatry evidence-based medicine subcommittee monograph. Ann Clin Psychiatry. 2018;30:140–55.
39. Freudreich O, Francis A, Fricchione GL. Psychosis, mania, and catatonia. In: Levenson JL, editor. The American Psychiatric Association Publishing textbook of psychosomatic medicine and consultation-liaison psychiatry. 3rd ed. Washington, D.C.: American Psychiatric Association Publishing; 2019. p. 249–79.
40. Chalasani P, Healy D, Morriss R. Presentation and frequency of catatonia in new admissions to two acute psychiatric admission units in India and Wales. Psychol Med. 2005;35:1667–75.

Additional Resources

Websites

<https://www.hearing-voices.org/>. Hearing Voices Network (HVN) is an alliance of support groups that operates worldwide and provides an alternative, non-medicalized view of hallucinations. It represents an effort by the peer movement to destigmatize hearing voices and avoid aggressive, unhelpful psychiatric treatment. I consider them an important, alternative voice, hopefully collaborative and not in opposition to mainstream care, even if I do not agree with all their assumptions.

Books

- Oyebode F. Sims' symptoms in the mind: textbook of descriptive psychopathology. 6th ed: Elsevier; 2018. The standard (English) text since its first edition in 1988 about everything you ever wanted to know about descriptive psychopathology, written in clear language.
- Enoch MD, Ball HN. Uncommon psychiatric syndromes. 4th ed. London: Arnold; 2001. Detailed account of 11 more unusual, mostly eponymous psychiatric syndromes like Capgras. A book that used to be in the psychiatric canon.
- Sacks O. Hallucinations. New York: Vintage Books; 2013. A brilliant book by the late neurologist and medical writer about the varied facets of hallucinations.

Article

- Berrios GE, Dening TR. Pseudohallucinations: a conceptual history. Psychol Med. 1996;26:753–63.
An excellent discussion about the conceptual history of pseudohallucinations and its problems.

Chapter 2

Psychosis Interview



Essential Concepts

- In acute settings, you are most concerned if active psychosis is present (on cross-sectional symptom review); in other settings, a history of psychosis becomes as important (on longitudinal symptom review).
- Think of the entire patient interview as the mental status examination (MSE); you get data from observing and listening, supplemented by direct questioning about inner experiences and cognition.
- Approach psychotic experiences obliquely and with sensitivity. For many patients, those experiences are confusing and frightening.
- To establish a history of psychosis, rely on collateral information, not on patient recollection and interpretation alone.
- As you are collecting information, keep in mind that you may need to present your findings to somebody else. The most effective way to present a case is by telling a coherent story, with a beginning, a middle, and an end, perhaps with the help of a timeline drawn on a whiteboard.
- Uncharacteristic personality changes (e.g., social withdrawal, neglect of hygiene, easy irascibility) can indicate covert psychosis.
- Consider malingering when supposed psychopathology is unconvincing.

You can observe a lot by watching.

-Yogi Berra, baseball Hall of Famer, 1972 [1]

The great divide in psychiatric nosology between psychotic and nonpsychotic disorders makes identification of psychosis crucial for accurate differential diagnosis and treatment selection. Any psychiatric interview must, therefore, accomplish one thing: ascertain with a reasonable degree of certainty that psychosis is either present or absent, both now or in the past. This chapter is not a comprehensive guide to the psychiatric interview but focuses solely on this critical interview goal,

including how to cohesively present the information you obtained to a supervisor. Other goals of the interview (e.g., judging dangerousness) are covered in separate chapters.

The First Few Minutes

Prepare for the patient encounter, and review records that accompany the patient before you see him or her. Otherwise, you might never touch on the main reason for the patient's presentation and completely miss the boat.

Clearly introduce yourself and describe your role. I always show patients my hospital ID tag (also for the obvious problems with spelling and pronunciation of my last name). With an outpatient, engage in some small talk on the way to your office ("Did you have trouble finding my office, finding parking?") to put patients at ease. After you sit down, an open-ended question that puts the ball in the patient's court is often the best way of starting: "What is the purpose of the visit with me?" or "How can I help you today?" To patients whose arms were twisted to come in, pose the question "Whose idea was it to come here today?" followed by "Does your family, the police have a point?" and "What is your side of the story?"

Looking for Current Psychosis: History and the Mental Status Exam

The MSE (Table 2.1) can be considered the equivalent of the physical examination in medicine, with the organ under examination being the mind/brain. Just like the physical examination, the MSE is a cross-sectional record of signs and symptoms of mind/brain malfunction *at the time of the examination* (this is often done incorrectly, e.g., hallucinations heard earlier, before the time of the MSE are recorded in the current MSE – they should be noted in the history). In contrast to the physical examination, the MSE begins with the patient encounter and is interwoven with the history taking [2]. In interpreting your exam, always take into account native language, culture, and education [3].

Table 2.1 Key components of the mental status examination

Appearance, attitude, and behavior (including eye contact and psychomotor abnormalities)
Affect and mood
Speech and thought process
Perception and thought content (delusions, overvalued ideas, obsessions; SI, HI)
Sensorium and cognition (awareness and orientation; attention and memory; intelligence)
Insight and judgment

SI suicidal ideation, HI homicidal ideation

Data You Get from Observation

Observe your patient unobtrusively; I usually get patients from the waiting area myself so I can walk with them to my office. Is the patient laughing to himself or herself while waiting? Preoccupied and nervous? Paying attention to the surrounding or apathetic?

Tip

Note what a patient is wearing. If a patient wears a T-shirt that says “Swabia Rules,” ask about it! Also note tattoos. Tattoos are the “bumper stickers of the soul,” ask about the story behind the tattoos.

A patient’s wallet, pockets, and purse can be windows to his or her functioning. Where does he or she put the prescriptions you wrote? How long does it take the patient to write down the new appointment date on a piece of paper or type into the smart phone?

Do not interrupt a patient who talks spontaneously, but simply listen. You need a good speech sample to judge speech and thought process. However, interrupt politely yet firmly the rambling and disorganized or the overinclusive patient who needs structure, once you have a first impression: “I have to interrupt you here and switch topics, if that is OK with you. We have not talked at all about your family.” Do not call a patient a “poor historian,” but try to understand his life story. It is not the patient’s but your job to structure the interview and (re-)interpret the story as told from the patient’s perspective so it makes sense psychiatrically.

Data You Need to Inquire About

Although you can sometimes deduce your patient’s inner experiences from behavior (e.g., patient is yelling back at voices), you usually have to inquire about them specifically.

Tip

To screen for psychosis, I ask every patient two questions: “Have you ever had the sense that your thoughts were not private?” and “Have you noticed any coincidences lately?” The first question gets at audible thoughts and thought broadcasting or related experiences, the second at ideas or delusions of reference.

With patients in whom I suspect a psychotic illness, I always go through a complete list of psychotic symptoms and tell patients that I will ask them about experiences they might or might not have had. “If this has never been your experience, simply say no.” Table 2.2 provides a list of questions that are helpful in “sniffing out” psychosis. The two most unhelpful questions that you might as well skip are, “Do you hear voices?” and “Are you paranoid?” You need to approach the symptoms of psychosis more obliquely. Referring to hallucinations as “thoughts” is less threatening than referring to “voices.” Similarly, using vague langue (“they” or “it”) initially helps to get patients comfortable.

A full review of systems (ROS) is important as psychotic patients can have a wide variety of somatic experiences, both as part of psychosis but also as signs of a

Table 2.2 Sniffing out psychotic symptoms

<i>Paranoia</i>
Do you trust people, or do you think that it is better not to? Do you have reasons for not trusting easily?
Do people have tried on purpose to hurt you? Does it feel at times like everyone or somebody is against you or is trying to get you in trouble? Are people obstructing you?
Do you sometimes feel that people/parents/family spend too much time watching you or monitoring you? Do they ever put microphones or cameras in your room for instance?
<i>Hallucinations</i>
Does it ever happen to you to see something from the corner of your eyes and when you turn around, it is not there? Like a shadow or a shape or more elaborate images?
Does your mind or your ears play tricks on you? Does your mind come up with weird ideas? Like what?
Do you ever worry that your mind is going crazy? What makes you think so? Is it scary?
Do you ever have thoughts that pop into your head out of nowhere, at times telling you what to do or making comments about you or people around you?
Does it ever happen to you that you seem to hear a noise, footsteps, or even your name being called and when you look around, there is no one there? Do you hear sometimes someone muttering something that you cannot quite understand? Does this tell you what to do or is making comments about people around you, that sometimes make you want to laugh? Are those thoughts pleasant or helpful like warning you about danger or about not trusting some people? Or do they keep you company or seem comforting to you?
Do they tell you what to do? Is it hard to resist?
Do you sometimes feel like there is an argument in your mind with one side saying one thing and the other the opposite? Does it consume a lot of your time?
<i>Schneiderian first-rank symptoms^a</i>
Do you ever have a sense that people can read your mind like a book or hear your thoughts?
Do you ever sense that your actions are not yours?
<i>Delusions</i>
Do sometimes people make fun of your beliefs or of your view on politics or on the way the world works? Give me an example.
Do you find difficult to share your thoughts and understanding about the way the system works with others because people would not understand?

Courtesy of Dr. Michel Mennesson

^aSee Table 1.3 for a longer list of useful questions to elicit Schneiderian first-rank symptoms

medical illness. Always ask specifically about strange bodily experiences that patients cannot explain, as coenesthetic (somatic) hallucinations are often not reported spontaneously. Whereas bizarre delusions should become obvious to you during the interview, nonbizarre delusions can be missed, not because they are not mentioned but because they are not recognized as delusions. In the MSE, record “no delusions” (or “no obvious delusions,” since you can never be absolutely sure), but do not write “patients denies delusions,” which makes no sense.

You also need to ask about emotional experiences: “How would you describe your mood?” Psychotic patients can experience a range of emotions, from anxiety and depression to dysphoria, anger, or fear.

Do not wait too long before you examine cognition. Early in the interview, you should ask patients their birth date and the current date; this can be accomplished unobtrusively when obtaining some basic demographic information. For a more detailed cognitive exam, see Chap. 29.

Looking for Past Psychosis: Past Psychiatric History

Collateral information is often crucial, as the patient might simply recall a “nervous breakdown,” yet deny any history of psychotic symptoms. Some detective work and deductive reasoning are often required, judging by medications prescribed and the types of hospitals a patient had been to. I have encountered many patients with schizophrenia whose positive symptoms had remitted who flatly denied a history of psychosis: “I never heard voices.”

Tip

For past information, collateral information will often be more useful than patient recollection. Tracking down an old discharge summary that reveals a clear-cut manic episode as the true meaning behind the “nervous breakdown” is time well spent.

Presenting Your Findings

Sometimes your information gathering is informed by keeping the end in mind: to present your findings in a logical and cohesive way to a supervisor (or to yourself, when you write your clinic note). Most importantly, think of your case presentation as a story about the patient, with a beginning, middle, and an end [4]. Organizing information obtained through the interview and mental status exam into such a story is your responsibility. It does not fall on the patient to be the proverbial “good historian” [5]. For outpatients with a long treatment history, going back to the beginning of their illness, before they developed schizophrenia, is often a more productive

starting point than the most recent hospitalization. Use synthesis and judgment: the best way to bore an audience is to tell them everything [4]. Your case presentation should set you up to propose a treatment plan that flows from your findings but also make explicit gaps that you were unable to fill during the initial encounter [6].

Tip

The psychiatric diagnosis is going to be found in the illness course, not the cross-sectional findings. To facilitate thinking longitudinal, literally draw a line on a whiteboard (blackboard), and add major goal posts in a patient's life (e.g., normal life events, like graduations, marriage, immigration, or other moves but also markers of illness, like hospitalizations, detoxification stays, or suicide attempts). Doing this timeline (a better German term is "Lebenslinie" or "life-line") exercise with a patient that emphasizes "big things" (the goal posts) can focus most patients enough to obtain good information and not get lost in minute details about past mental states. Many patients are able to locate a first hospitalization for example vis-à-vis their school history, even if they are unsure about exact dates (e.g., if a first hospitalization happened during high school or after finishing college). You may recognize my timeline-on-a-whiteboard approach as the poor man's version of Adolf Meyer's life chart method, a pedagogical tool to make explicit how personal biography consists of intertwined strands of normal life events, unfortunate illness-related problems, and the larger societal context, reflecting the complex causation of psychiatric illness.

Common Mistakes in the Assessment of Psychosis

- Accepting patients' description of their internal state as the correct *terminus technicus*. Somebody might say, "I get paranoid." Clarify what the patient means, summarize what you think you heard, and invite the patient to correct you. Always make sure you truly understand the patient and the patient understands you – the true task of phenomenology.
- Disregarding or overvaluing collateral information. It is a mistake to rely only on patients to rule out or rule in psychosis. On the other hand, make sure your patients are not gaslighted (made to believe they cannot trust their senses and are going crazy – after the 1938 play Gaslight, by Patrick Hamilton) [7]. Families might exaggerate or misconstrue observations in order to have somebody hospitalized, for example. Often, there is in fact misunderstanding of what a patient said or did. In the days of cutting and pasting in the electronic medical record, incorrect information can easily become the truth about a patient that can be hard for you to sort out.
- Disregarding limbic clues. If you feel threatened in any way, trust your limbic read of the situation and get out! Simply state, "Let me step out for a minute. I will be right back."

- Missing psychosis because of more prominent affective symptoms, particularly depression or irritability.
- Favoring irrelevant cultural explanations or missing relevant cultural factors as explanation for psychosis. While culture always matters for aligning with the patient for treatment, very rarely represents psychosis, particularly sustained psychosis, a cultural expression of distress.
- Dismissing your patient's account as unreliable. Our patients face “epistemic injustice”: their “testimonial” (giving knowledge to others) accounts of events or their inner experiences are often doubted simply because they have schizophrenia and consequently are not afforded credibility [8].

Sometimes you will come away from the interview unsure whether the patient is psychotic. Psychosis can be intermittent or attenuated, or your patient may be unable (or unwilling) to explain his or her experiences in sufficient detail to help you diagnostically. Assuring longitudinal follow-up in such cases will be the key intervention. At other times, if you think psychosis is likely based on observable yet nonspecific personality changes characteristic for people who have developed psychosis (Table 2.3), a medication trial can be offered. In any case, keep the diagnosis open. It is acceptable to put “undiagnosed” or “schizophrenia (working diagnosis)” in the chart. Anyone who tells you differently has never examined a real patient. It is as important to recognize what you know as it is to know what you were unable to assess.

Table 2.3 Nonspecific signs and symptoms suggestive of underlying psychosis

Marked reduction of interest and initiative
Social withdrawal
Loss of social competence and role failure
Unconcern about social etiquette
Uncharacteristic self-neglect
Aggression seemingly without purpose
Change in personality (easy irascibility, labile affect, and impatience)
Short fuse with poor stress tolerance (emotional overreactivity)
Suspiciousness about people's motives in routine, day-to-day encounters
Becoming self-absorbed, with no regard of other people (lack of empathy)
Inability to reason with other people without getting argumentative
Inability to sequence routine tasks
Uncharacteristic poor judgment

Note: Many of those symptoms can be traced to networks involving the frontal lobes and the social brain which are often impaired in patients with psychosis

Patients Unwilling or Unable to Cooperate

Patient refuses to talk with you *Do not take it personally, but try to figure out why. Is the patient afraid of something, is the patient paranoid, or is the patient angry? Tell the patient that it is in fact his or her choice to not talk with you. I sometimes summarize what I know, asking for input if this is correct. Point out that you are trying to help sort out the situation but that you will need some cooperation. Portray yourself as somebody sent in to help solve “the problem,” merely a “cog in the machine” yourself.*

Patient is very confused and makes little sense *Thought-disordered patients usually can contribute only limited information. This is the time to seriously consider a broad differential diagnosis, including dementia and a delirium. The main focus should be on the MSE and the physical examination, not on obtaining a longitudinal history. A neurologist might have to help determine if an aphasia is present (i.e., when the onset of “thought disorder” was acute).*

Patient is too psychiatrically ill to cooperate *A good example would be a volatile, manic patient or an irritable, paranoia patient. Once you have established the presence of syndrome (e.g., mania), start the treatment. Do not waste time; often you accomplish the opposite of what you want, and the patient becomes more over-stimulated the more you ask. You can get more information later.*

Patient is hostile or outright threatening *Abort the interview if you are uncomfortable; trust your limbic system, which is trying to warn you! You might have to treat in the face of insufficient information.*

In all cases, collateral information is critical. Sources are family and friends, work, the school, or the police, depending on the circumstances.

Patients Who Malingering Psychosis

Some patients claim to be psychotic to avoid responsibility, get disability payments, or gain hospital admission. In any forensic context, the simulation of symptoms (or their exaggeration), technically known as malingering, is a real possibility. Thinking “dirty” about your patient’s hidden motivations or deceptions and being able to tolerate the affect surrounding such encounters is a necessary clinical skill [9].

Clinical Vignette

A young homeless man presents to the emergency department on a snowy Boston night with a chief complaint of “the voices are telling me to walk into traffic.” There is no formal thought disorder, no negative symptoms, and no further elaboration of his complaint. He enjoys a sandwich and the company of other waiting patients while expecting admission.

One of the most common bogus complaints in psychiatric emergency rooms must be the isolated and lonely symptom of an auditory hallucination of the command type. In this setting and with no supporting evidence beyond a single, stereotyped, and impoverished complaint, you should suspect malingering. Patients with schizophrenia can use their knowledge of psychopathology to gain hospital admission simply by exaggerating residual symptoms.

Here are some red flags that should raise your index of suspicion for malingered psychosis, particularly in the aforementioned scenarios:

- If very rare symptoms are reported
- If there are no supporting signs of schizophrenia except “voices.” (This was used in the famous Rosenhan study where researchers gained admission to psychiatric hospitals based on feigned, isolated hallucinations [10].)
- If the story keeps shifting during the evaluation process
- If the patient cannot identify anyone to give collateral information
- If there are many “I don’t know” responses
- If patients give absurd answers to straightforward questions (because they falsely assume that psychotic patients are globally impaired)
- If you succeed in getting affirmative answers to absurd questions asked with a straight face (courtesy of Dr. Joseph P. McEvoy): “Do your bowel movements glow in the dark, do your teeth itch, or do you have pain behind your eyes when urinating?”
- If patients look sick with you but well on a smoke break
- If patients are eager to point out their “delusions” to you to make sure you don’t overlook them

Tip

Clearly document your assessment and your reasoned choice of disposition [11]. Be aware that you could be wrong *either way*. Even if you are convinced that a patient malingers, always acknowledge uncertainty by saying “strong possibility of malingering due to the following factors;” don’t just put *malingering, punctum*. Appreciate that you are passing judgment on a patient who might challenge your assessment legally [12].

References

1. Wikiquote: Yogi Berra. Available from: https://en.wikiquote.org/wiki/Yogi_Berra. Accessed Jan 7 2019.
2. Carlat DJ. The psychiatric interview. 4th ed. Philadelphia: Wolters Kluwer; 2017.
3. Norris D, Clark MS, Shipley S. The mental status examination. Am Fam Physician. 2016;94:635–41.
4. Querques J, Freudenberg O, Kontos K. Rediscovering the lost art of the oral case presentation [pearls series]. Curr Psychiatry. 2010;9:56.
5. Tiemstra J. The poor historian. Acad Med. 2009;84:723.
6. Mellsoop GW, Banzato CE. A concise conceptualization of formulation. Acad Psychiatry. 2006;30:424–5.
7. Thomas L. Gaslight and gaslighting. Lancet Psychiatry. 2018;5:117–8.
8. Crichton P, Carel H, Kidd IJ. Epistemic injustice in psychiatry. BJPsych Bull. 2017;41:65–70.
9. Beach SR, Taylor JB, Kontos N. Teaching psychiatric trainees to “think dirty”: uncovering hidden motivations and deception. Psychosomatics. 2017;58:474–82.
10. Rosenhan DL. On being sane in insane places. Science. 1973;179:250–8.
11. Kontos N, Taylor JB, Beach SR. The therapeutic discharge II: an approach to documentation in the setting of feigned suicidal ideation. Gen Hosp Psychiatry. 2018;51:30–5.
12. Weiss KJ, Van Dell L. Liability for diagnosing malingering. J Am Acad Psychiatry Law. 2017;45:339–47.

Additional Resources

Book

Carlat DJ. The psychiatric interview. 4th ed. Philadelphia: Wolters Kluwer; 2017. A very practical guide to all aspects of the psychiatric interview, already in its 4th edition. From the same “Practical Guides in Psychiatry Series” that the 1st edition of this book you are reading is based on.

Chapter 3

Delirium



Essential Concepts

- Delirium is the clinical expression of an acutely failing brain, leading to disturbances of alertness and attention (also known as confusion). Delirium is often accompanied by agitation and psychosis.
- There is always at least one, sometimes several, medical causes for a delirium that need to be identified and treated.
- The end stage of very severe psychiatric states can be a delirium (e.g., delirious mania).
- The treatment of choice for managing the symptoms of delirium is antipsychotics, including for delirium tremens.
- Non-pharmacological maneuvers (avoiding immobility, avoiding sleep deprivation, avoiding sensory deprivation) should be instituted routinely to prevent and help manage delirium in hospitalized patients. The prevention of a postoperative delirium on the other hand with prophylactic antipsychotics is not well established.

“If you can’t convince them, confuse them.” [1]

—Harry S. Truman, 33rd US President, 1884–1972

Clinical Presentation

When the brain as an organ fails acutely from a wide variety of insults, a fairly stereotyped clinical syndrome, delirium, is the result. Different terms for the same thing are used in other specialties (neurology uses the term toxic metabolic encephalopathy) or other countries (acute organic psychosyndrome). The onset of delirium

Table 3.1 Differential diagnosis of delirium

Dementia	Chronic onset, symptoms stable. Usually alert and able to attend. Immediate memory OK. Establish premorbid function with help of family members. Dementia is a risk factor for delirium
Psychosis	Patients are alert and oriented with intact memory and attention. However, this can be difficult to assess in acute psychosis when patients are disorganized and uncooperative. Onset of psychotic illness is very rarely days but usually weeks (or an even longer prodromal period). Psychosis can be part of delirium
Depression	Can be confused with hypoactive delirium. Depressed patients can often participate in cognitive testing once you overcome their lack of motivation (persist when patient bemoans: “I can’t do that.”)
Mania	Delirious mania (Bell’s mania) is a subtype of mania characterized by severe lack of sleep and constant moving about, among other manic symptoms that can lead to a state of dangerous physical exhaustion [3] and death [4]. Catatonic symptoms are common

is rather sudden, although an unspecific prodrome with anxiety and restlessness can predate the full-blown picture. One diagnostically useful hallmark of delirium is its fluctuation in severity over the course of the day.

Delirium is fundamentally a disturbance of consciousness, with both arousal and attention being affected. Patients are unable to pay attention, to shift attention, or to sustain attention. As attention is one of the basic brain functions that supports higher functions, other cognitive deficits are usually present. Patients are often unable to learn new information and appear puzzled, perplexed, and confused (hence the synonymous term “acute confusional state” for delirium). Patients are usually, *but not obligatory*, disoriented to time (often), place (sometimes), and person (only in severe cases); the key is the inability to attend. The level of consciousness can be altered in both directions, from hypervigilant to lethargic or stuporous. Some patients are anxious, labile, and agitated (hyperactive delirium); others are withdrawn (hypoactive delirium); most show a mixed pattern. Other patients might be rambling or be grossly incoherent. You should not expect to get a good history from a delirious patient. In addition, the sleep-wake cycle is disturbed, and patients are awake at night and sleepy during the day.

Psychoses (delusions and hallucinations) are seen in 40% of deliria [2]. The psychosis of delirium is characterized by fleeting, poorly formed delusions, often more a misinterpretation of the situation. Hallucinations are often visual; you may see patients picking at things. It is not always clear if you are dealing with misperceptions (illusions) and misinterpretations or hallucinations and delusions. Table 3.1 presents a differential diagnosis of delirium. Psychosis can be a prominent feature of a delirium and overshadow attentional difficulties, leading the treatment team to miss this critical diagnosis.

Diagnosis

Have a low threshold for suspecting a delirium in the right clinical setting. An elderly hospitalized patient with new-onset psychosis has a delirium until proven otherwise, not late-onset schizophrenia. Even seemingly benign medications (e.g., zolpidem

added for insomnia) can cause a delirium when other delirium risk factors are present [5]. Any sudden change in mental status is a red flag for the presence of a delirium. However, patients with known psychiatric disorders can have a superimposed delirium: A delirium can develop in a manic patient who has not eaten or had anything to drink on his quest for the Holy Grail; a psychotic patient who is inadvertently overdosing on his benztropine because of disorganization can become delirious. “Bad behavior” can stem from subtly confused patients. While very severe psychiatric states might cause a “non-medical” delirium (e.g., Bell’s mania [3]), I suspect any delirium in these states is ultimately the result of some medical derangement.

Key Point

A delirium always has a medical cause. Therefore, treatment begins with a search for medical etiologies. In many cases, not a single cause alone is responsible. (Table 3.2 presents etiologies of delirium.) I like the term “acute brain failure” for delirium because it impresses a sense of urgency, as a delirium increases mortality.

Once you have suspected the presence of a delirium, identify its four cardinal features to make the diagnosis (these are taken from a widely used screening instrument, the Confusion Assessment Method or CAM [7]):

1. Acute onset with fluctuating course (collateral history from family and nursing staff)
2. Inattention (the patient was unable to focus on your questions or was easily distracted)
3. Disorganized thinking (the patient was rambling or hard to follow)
4. Altered level of consciousness (anything but alert counts!)

Table 3.2 Etiologies of delirium

Withdrawal (alcohol, sedatives)

Intoxication (illicit drugs, medications, toxins)

Medical conditions

Hypoxemia (from any cause, e.g., hypotension, anemia)

Hypoglycemia

Hypertensive encephalopathy

Intracranial pathology (stroke, encephalitis, tumor, trauma, bleeding, seizures)

Infections (UTI, pneumonia, cellulitis, SBE)

Metabolic (Wernicke’s encephalopathy, hepatic encephalopathy, uremia, electrolyte abnormalities)

Endocrine (thyroid, parathyroid, adrenal disease)

Psychiatric conditions (leading to medical conditions associated with a delirium)

Severe states of excitation or agitation (e.g., Bell’s mania)

Severe disorganization

Severe psychomotor withdrawal states (depression, catatonia)

Severe eating disorders

Severe drug use disorders

Adapted from [6]

UTI urinary tract infection, SBE subacute bacterial endocarditis

Casual observation of patients is insufficient to detect a delirium in all but the most obvious cases; you need to pursue a diagnosis with a good clinical mental status exam [8]. The digit span is a good and quick test of attention. The Mini-Mental State Examination (MMSE) in particular is not helpful in delirium due to its lack of specificity.

Tip

To briefly assess and follow the course of a delirium longitudinally, a minimum bedside examination must establish two things: the level of consciousness and the degree to which attention is impaired. To gauge the latter, ask patients to repeat random strings of numbers (in adults up to 7, in geriatric patients up to 5) using a test called forward digit span. If somebody can recite the months of the year backward (use days of the week if your patient has trouble doing the months), he is probably not delirious.

A basic work-up to identify the cause(s) of delirium is the next step (Table 3.3). The exact tests to order will depend on the clinical circumstances (i.e., which ser-

Table 3.3 Initial work-up of delirious patients

History and chart review
Medication review
Vital signs
Physical and neurological examination
Mental status examination with emphasis on cognition
<i>Basic laboratory work-up</i>
CBC with differential
Glucose
Chemistry profile, including calcium, magnesium, and phosphate
Test of renal function
Liver function tests (including ammonia level)
TSH
Serum drug levels (if applicable, e.g., digoxin, cyclosporine)
Serum alcohol level
Urine drug screen
Urinalysis with C + S
Electrocardiogram
Chest X-ray
<i>Ancillary tests</i>
CT/MRI of brain if suspected intracranial process (MRI preferred unless intracranial hemorrhage suspected)
LP if suspected brain infection
EEG if suspected seizure activity (i.e., nonconvulsive status epilepticus or protracted postictal state)
<i>Specific blood tests based on clinical situation (e.g., HIV test; autoimmune markers)</i>
Based on [6]
<i>CBC</i> complete blood count, <i>TSH</i> thyroid-stimulating hormone, <i>CT</i> computed tomography, <i>MRI</i> magnetic resonance imaging, <i>LP</i> lumbar puncture, <i>EEG</i> electroencephalogram, <i>HIV</i> human immunodeficiency virus, <i>C + S</i> culture and sensitivity

vice consults you to help manage the delirium, as this will help determine the initial differential diagnosis of most likely offenders). As you are searching for an etiology, optimize the overall medical management.

Avoid these diagnostic mistakes:

- A delirium is not considered because the patient looked well during morning rounds. Serial examinations (and a chart review) are important as delirium fluctuates: Dr. Jekyll may look well at breakfast but still be Mr. Hyde at night. Sundowning is not a normal phenomenon of aging.
- The search for causes of a delirium is prematurely terminated once something is found. A risk factor model suggests that often several factors need to interact to produce a delirium [9]; find and address *all of them*.
- A delirium is not considered because the patient has a history of schizophrenia and seems merely paranoid and thought-disordered. The patient might not be paranoid at all but does not talk with you because of perplexity and confusion. A confused patient can be indistinguishable from a thought-disordered patient.
- An “underlying” psychiatric condition is made in the presence of a delirium (usually “depression”). You cannot make any psychiatric diagnosis until the delirium has cleared.
- Make sure you do not miss a delirium because you think the patient is catatonic: catatonic symptoms can occur in a delirium [10]! Your treatment of catatonia with benzodiazepines can also induce a delirium.

Tip

A standard electroencephalogram (EEG) can be a helpful tool to diagnose a delirium in unclear cases [11]. The EEG of a delirious patient shows *diffuse slowing*. In delirium tremens, you also see superimposed low-voltage beta activity. An abnormal EEG will also assist you in implementing your treatment plan if the medical team suspects the patient’s behavior is willful (“psychiatric”). You cannot will an abnormal EEG!

Treatment

Antipsychotics are the mainstay of pharmacologic treatment, including in delirium tremens [12]. Antipsychotics treat the agitation and psychosis that can accompany any delirium but not the pathophysiology of delirium itself. A recent meta-analysis favored second-generation antipsychotics over first-generation antipsychotics with regard to both efficacy and safety [13]. Still for an acutely agitated patient after cardiac surgery, I tend to be rather conservative and use strategies with a proven track record and well-known toxicities (i.e., intravenous haloperidol, see Table 3.4).

One advantage of haloperidol is that it can be given orally and IV. The oral haloperidol is twice the IV dose. Curiously enough, when given IV at large doses, immediate motor side effects are much less than what one would expect [15]. In less acute situations, low-dose, second-generation antipsychotics (e.g., risperidone 0.25–1 mg bid, olanzapine 2.5–5 mg bid, or quetiapine 25–50 mg bid) have largely supplanted

Table 3.4 Intravenous haloperidol

Treatment principles	
	Goal is a calm, but awake patient (not a mildly agitated patient)
	Stay with the patient until your goal is achieved
	Start by ensuring an adequate medical work-up and optimize medical management
1.	Check ECG, if QTc >450 msec, consider alternatives
	Always check the QT interval manually and calculate the QTc, as the machine-calculated QTc is prone to error. The Hodges formula is QTc = QT + 0.00175 ([60/RR] – 60)
2.	Check Mg++ (replete to Mg++ ≥ 2)
	Check K+ (replete to K+ ≥ 4)
3.	Haldol 5 mg ^a IV × 1, wait 20–30 min ^b
4.	If still agitated in 20–30 min, recheck ECG. If QTc > 500 msec or increased by 25%, consider alternatives or consult cardiology and use telemetry
5.	Double (or repeat) haloperidol dosage (not higher than 10 mg), and go back to step 4 ^c
6.	Once no longer agitated, give the final dosage as a divided dose over the next 24 hours
7.	If patient remains calm, reduce dose by 50% every 24 hours and discontinue haloperidol as soon as possible

Based on [14]

^aFor mild agitation 0.5–2 mg, for moderate agitation 2–5 mg, for severe agitation 5–10 mg; if patients are frail or antipsychotic-naïve, start with 0.5–2 mg regardless of level of agitation

^bWaiting is important as there is a lag time of about 30 minutes for the full effect

^cCould consider adding or alternating with lorazepam 1–2 mg IV

Example: Haloperidol 5 → still agitated after 30 min → haloperidol 10 mg → still agitated after 30 min → haloperidol 20 → calm, awake after 30 min. Then give haloperidol 5 mg IV q6 hrs × 24 hours (for a total of 20 mg/d)

the use of haloperidol. Since the efficacy of other pharmacological approaches (e.g., anticholinesterase inhibitors) remains to be established [16], they cannot substitute for antipsychotics if the clinical situation calls for them.

Avoid these common mistakes when you are treating a delirium:

- Treatment is not instituted immediately and/or not followed up. Be prepared to help implement and monitor your clinical plan *closely*.
- Pharmacotherapy becomes confusing if you use several agents to treat agitation. I would pick one agent and stick with it. In particular, avoid benzodiazepines if you can, so as not to worsen confusion with iatrogenic benzodiazepine toxicity (except in alcohol or sedative withdrawal).
- Be careful when you use have to use benzodiazepines. You can reach a point where a patient becomes delirious from benzodiazepine toxicity.

Tip

I try to discontinue antipsychotics used to treat a delirium before a patient goes to rehabilitation or home to minimize the risk of tardive dyskinesia (TD) or antipsychotic-induced Parkinsonism, although with short hospital stays this might not always be possible. In geriatric patients, the TD risk even from short-term antipsychotic exposure (e.g., a few weeks) is very high [17].

Prevention

Non-pharmacological measures to prevent a delirium constitute a best practice and should be implemented during a hospital stay [18]. Avoid excessive stimulation and provide a structured and safe environment (e.g., large clock, pictures of family members, remove dangerous items) for the patient at risk for delirium. Get patients their eye glasses and hearing aid, so they are not sensory-deprived. Mobilize them early and encourage normal sleep-wake cycles. However, these measures are ancillary and no substitute for the proper pharmacologic treatment once a delirium has developed. Optimal and timely pharmacotherapy will decrease the need for physical restraints, which may even increase agitation as a confused patient tries to remove them. In contrast to the established efficacy of antipsychotics to treat a delirium, the prophylactic use of antipsychotics to prevent a delirium is probably ineffective in most cases [19].

References

1. Quote Investigator. Available from: <https://quoteinvestigator.com/2013/12/02/confuse-them/>. Accessed on 7/1/2019.
2. Webster R, Holroyd S. Prevalence of psychotic symptoms in delirium. Psychosomatics. 2000;41:519–22.
3. Karmacharya R, England ML, Ongur D. Delirious mania: clinical features and treatment response. J Affect Disord. 2008;109:312–6.
4. Mash DC. Excited delirium and sudden death: a syndromal disorder at the extreme end of the neuropsychiatric continuum. Front Physiol. 2016;7:435.
5. Freudenreich O, Menza M. Zolpidem-related delirium: a case report. J Clin Psychiatry. 2000;61:449–50.
6. Stern TA, Celano CM, Gross AF, Huffman JC, Freudenreich O, Kontos N, et al. The assessment and management of agitation and delirium in the general hospital. Prim Care Companion J Clin Psychiatry. 2010;12:PCC 09r00938.
7. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990;113:941–8.
8. Oldham MA, Flanagan NM, Khan A, Boukrina O, Marcantonio ER. Responding to ten common delirium misconceptions with best evidence: an educational review for clinicians. J Neuropsychiatry Clin Neurosci. 2018;30:51–7.
9. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet. 2014;383:911–22.
10. Wilson JE, Carlson R, Duggan MC, Pandharipande P, Girard TD, Wang L, et al. Delirium and catatonia in critically ill patients: the delirium and catatonia prospective cohort investigation. Crit Care Med. 2017;45:1837–44.
11. Sidhu KS, Balon R, Ajluni V, Boutros NN. Standard EEG and the difficult-to-assess mental status. Ann Clin Psychiatry. 2009;21:103–8.
12. Leentjens AF, Rundell J, Rummans T, Shim JJ, Oldham R, Peterson L, et al. Delirium: an evidence-based medicine (EBM) monograph for psychosomatic medicine practice, commissioned by the Academy of Psychosomatic Medicine (APM) and the European Association

- of Consultation Liaison Psychiatry and Psychosomatics (EACLPP). *J Psychosom Res.* 2012;73:149–52.
13. Kishi T, Hirota T, Matsunaga S, Iwata N. Antipsychotic medications for the treatment of delirium: a systematic review and meta-analysis of randomised controlled trials. *J Neurol Neurosurg Psychiatry.* 2016;87:767–74.
 14. Cassem NH, Murray GB. Delirious patients. In: Cassem NH, Stern TA, Rosenbaum JF, Jellinek MS, editors. *Massachusetts General Hospital handbook of general hospital psychiatry.* 4th ed. St. Louis: Mosby – Year Book, Inc.; 1997. p. 101–22.
 15. Menza MA, Murray GB, Holmes VF, Rafuls WA. Decreased extrapyramidal symptoms with intravenous haloperidol. *J Clin Psychiatry.* 1987;48:278–80.
 16. Yu A, Wu S, Zhang Z, Dening T, Zhao S, Pinner G, et al. Cholinesterase inhibitors for the treatment of delirium in non-ICU settings. *Cochrane Database Syst Rev.* 2018;6:CD012494.
 17. Jeste DV, Caligiuri MP, Paulsen JS, Heaton RK, Lacro JP, Harris MJ, et al. Risk of tardive dyskinesia in older patients. A prospective longitudinal study of 266 outpatients. *Arch Gen Psychiatry.* 1995;52:756–65.
 18. Oh ES, Fong TG, Hsieh TT, Inouye SK. Delirium in older persons: advances in diagnosis and treatment. *JAMA.* 2017;318:1161–74.
 19. Neufeld KJ, Yue J, Robinson TN, Inouye SK, Needham DM. Antipsychotic medication for prevention and treatment of delirium in hospitalized adults: a systematic review and meta-analysis. *J Am Geriatr Soc.* 2016;64:705–14.

Additional Resources

Book Chapter

Caplan JP. Delirious patients. In: Stern TA, Freudenberg O, Smith FA, Fricchione GL, Rosenbaum JF, editors. *Massachusetts General Hospital handbook of general hospital psychiatry.* 7th ed. Edinburgh: Elsevier; 2018. p. 83–93. – From my department's book on General Hospital Psychiatry. The CL service at MGH has extensive experience with the management of delirium, and this chapter contains detailed instructions about how to optimally treat a delirium, including IV haloperidol.

Articles

- Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet.* 2014;383:911–22. – Excellent conceptual overview of delirium by one of the pioneers in delirium research.
- Oldham MA, Flanagan NM, Khan A, Boukrina O, Marcantonio ER. Responding to ten common delirium misconceptions with best evidence: an educational review for clinicians. *J Neuropsychiatry Clin Neurosci.* 2018;30:51–7. – Readable and practical guide for clinicians that corrects commonly held misconceptions about delirium.
- Hall W, Zador D, et al. *Lancet.* 1997;349:1897–900. – Remains one of the best articles on the basic principles of alcohol withdrawal, which I did not cover in this chapter.
- Stern TA, Celano CM, Gross AF, Huffman JC, Freudenberg O, Kontos N, et al. The assessment and management of agitation and delirium in the general hospital. *Prim Care Companion J Clin Psychiatry.* 2010;12:PCC 09r00938. – A clinical article about the diagnosis and treatment of agitation and delirium in the general medical hospital.

Wu YC, Tseng PT, Tu YK, Hsu CY, Liang CS, Yeh TC, et al. Association of delirium response and safety of pharmacological interventions for the management and prevention of delirium: a network meta-analysis. *JAMA Psychiatr.* 2019;76:526–35. – If you like network meta-analyses, here are the results from one: haloperidol plus lorazepam worked best for the treatment of delirium, ramelteon for its prevention.

Chapter 4

Drug-Induced Psychosis



Essential Concepts

- Some drugs of abuse cause psychosis during intoxication (or during withdrawal in the case of alcohol or sedative-hypnotics). Prolonged psychosis is typical for phenylcyclohexyl piperidine (PCP) and methphetamines.
- History of drug ingestion supported by urine drug testing and resolution of symptoms in a manner characteristic for the drug suggests a drug-induced psychosis.
- A diagnosis of drug-induced psychosis is prognostically ominous. In up to 50% of cases of cannabis-induced psychosis, patients are later diagnosed with a serious mental disorder like schizophrenia.
- Chronic alcoholism can cause chronic psychosis in the form of alcoholic hallucinosis and delusional jealousy (Othello syndrome).
- Synthetic cannabinoids and high-potency cannabis have increased the risk for psychosis during intoxication and also for triggering schizophrenia. Cannabis is considered a component cause for schizophrenia in vulnerable people.
- Stimulants and hallucinogens predictably cause a usually short-lived, drug-induced psychosis (methamphetamine psychosis can last weeks).
- PCP can cause a severe, agitated psychosis lasting many days.
- Therapeutic benefits from hallucinogens (e.g., reducing existential anxiety in cancer) and ketamine (e.g., rapid reversal of acute suicidality) are actively studied.
- Many medical medications are associated with psychosis as a rare side effect. Glucocorticoids are the most common culprit.

“Drugs are a bet with your mind.” [1]

—Jim Morrison, The Doors, 1943–1971

Many drugs can cause psychosis (delusions and/or hallucinations) in a clear sensorium (i.e., in the absence of a delirium). This is true not only for legal drugs (e.g., alcohol, cannabis) or illegal drugs but also for prescribed medications (e.g., steroids, digoxin), herbal medications, and over-the-counter medications. In this chapter, I discuss patients who present to the emergency department (ED) with drug-induced psychosis (or substance-induced psychotic disorder, in DSM-5 and ICD-11 terminology), including psychosis from medical medications. Drug-induced psychosis is diagnosed in cases where the psychosis is believed to be the direct (physiological) result of the substance, either during intoxication or withdrawal. The assumption for a case of drug-induced psychosis is that psychosis resolves once the responsible drug is removed. For a discussion of comorbid drug use in schizophrenia, see the chapter on Dual Diagnosis (Chap. 26). Several psychoactive drugs are being re-examined for therapeutic use (e.g., 3,4-methylenedioxymethamphetamine (MDMA) [2] or ketamine [3]) which may result in an increase in cases of psychosis from those drugs.

Diagnosis of Drug-Induced Psychosis

Some drugs predictably induce psychosis in most individuals after single use: PCP and lysergic acid diethylamide (LSD) are examples. Some drugs do so only in a small minority of patients (cannabis unless high-potency) or after prolonged use (cocaine). The rate of cannabis-related psychosis has increased with the increasing concentration of THC (the psychomimetic property in cannabis) and the introduction of high-potency synthetic cannabinoids. The major drugs that cause psychosis during withdrawal are alcohol and the sedative-hypnotics (barbiturates and benzodiazepines), as well as the club drug gamma-hydroxybutyrate (GHB, one of the so-called date rape drug) [4] (Table 4.1). Opiates as a rule of thumb are not associated with psychosis, although the exception proves the rule. Dextromethorphan (DXM), a morphine-derivative in cough syrup, is a hallucinogen at high doses and a cause of psychosis [5]. Inhalant use has also been associated with psychosis although it may be triggering psychosis in susceptible individuals (like cannabis, see below) [6].

Table 4.1 Drug-induced psychosis

	During intoxication	During withdrawal	Prolonged
Alcohol	Yes	Yes	Yes
Sedatives	Yes	Yes	Yes
Cannabis	Yes	No	With high-potency products
Stimulants	Yes	No	Yes (methamphetamine)
Hallucinogens	Yes	No	Not usually
PCP	Yes	No	Yes
Opiates	Not usually	Not usually	Not usually

The diagnosis of drug-induced psychosis is complex and often not straightforward. Clinicians must synthesize a history of drugs use, symptoms, and results of urine drug testing. Knowledge of local drug use patterns are an important clue to a drug intoxication. Chewing the herbal stimulant khat, for example, common in East Africa and associated with psychosis [7], would be an unusual cause of psychosis in a local New England college student where you would rather expect the use of prescription stimulants. Designer drugs, readily available over the internet, have made it difficult to always pinpoint the cause of a drug-induced psychosis [8].

Tip

All drug use is local. Knowing the patterns of use in your community helps with the correct diagnosis and which tests to order. Is your patient from an immigrant community? What drugs are currently common in your high school? Is your patient from a subpopulation (e.g., patient with HIV)?

Ideally, a 4-week period of abstinence is necessary to judge if psychosis resolves in a time consistent with the drug. Unfortunately, the necessary abstinence period is frequently not achieved, and you are left wondering how much psychosis is fueled by intermittent, low-grade drug use.

Patients who receive a diagnosis of substance-induced psychosis have an ominous prognosis with regard to eventually developing a serious mental disorder. In one population-based study, one third of patients given a diagnosis of substance-induced psychosis were eventually diagnosed with bipolar disorder or schizophrenia [9]. The highest conversion rate (about 50%) was seen in patient initially diagnosed with cannabis-induced psychosis. I hesitate to diagnose schizophrenia in an antisocial patient with indiscriminate and heavy drug use (“polysubstance use”), particularly if there are no negative symptoms. Experiencing visual hallucinations may tip the scales toward a drug-induced psychosis, particularly if there is drug addiction and substance use in parents [10]. Patients with good premorbid adjustment, a shorter duration of untreated psychosis, better insight into their psychosis, and less severe psychosis have a good prognosis for recovery from a substance-induced psychosis [11]. Note that these predictors of recovery are identical to good prognosis factors in schizophrenia.

Psychopathology

Unfortunately, the cross-sectional psychiatric symptom picture will not help you determine if a mental state is caused by “functional” psychosis like schizophrenia or if it is drug-induced. In fact, many drugs (e.g., amphetamines) can cause a model psychosis that has helped the field understand the pathophysiology of schizophrenia. Do not rely on Schneiderian symptoms or symptoms thought to be typical for

“organicity” (e.g., visual hallucinations) alone to determine if a functional or an organic presentation, respectively, is more likely. Harris and Batki [12] carefully characterized 19 patients with stimulant-induced psychosis; for example 95% had bizarre delusions, 64% had Schneiderian first-rank symptoms, and 26% had substantial negative symptoms.

Key Point

There is no one psychiatric symptom or symptom constellation that is pathognomonic for a drug-induced psychosis.

History of Drug Use

A history of drug use might be unavailable or incomplete. Patients themselves might not know what they ingested or whether they were taken adulterated drugs (e.g., cannabis with PCP). Therefore, urine drug testing is mandatory even in cases in which a specific drug or no drug use is reported.

Tip

The drug subculture has its own lingo. Do not play it cool; ask if you do not know. I always ask what patients mean if they use a drug name, as those are not tightly regulated and patients might use the names differently from you. Names for illicit drugs that you grew up with might also no longer be in use.

Urine Drug Testing

Urine for drug testing should be obtained routinely in psychotic patients who present to the ED. This rule applies to new-onset psychosis but also to patients with established schizophrenia, as comorbid drug use is so common (but not recognized). However, there are limitations to what drug testing can accomplish: you can only detect what you test for. Most urine drug screens (UDS) contain the standard “National Institute on Drug Abuse (NIDA) 5,” cocaine, amphetamines, cannabis, opiates, and PCP, supplemented by benzodiazepines and barbiturates. Note that drugs that interest us in the context of psychosis but are not tested for include LSD, hallucinogens, and the so-called club drugs and synthetic designer drugs. The interpretation of drug testing results is also not straightforward. If a drug test is negative, the timing between ingestion and testing might simply have been too long, and urine

drug level fell below the detection limit of the assay. Even if a drug test is positive (and the patient took the detected substance), this does not establish that the drug is in fact responsible for the mental state. Lastly, false-positive drug tests can lead clinicians down the wrong diagnostic path; review the medication list with regard to the possibility of a false-positive drug test. Unfortunately, for immunoassay-based urine drug tests commonly used in the ED setting, any official list of medications known to show cross-reactivity with drugs of misuse is going to be incomplete [13]. Indiscriminate urine drug screening without clinical suspicion (i.e., a situation of low prior probability) is unhelpful and only increases the chances for false-positive test results. A false-positive drug test will unfairly put a patient in the basically impossible position to prove his or her innocence.

Except for serum alcohol level, serum drug testing is rarely useful in the ED unless results are immediately available. Serum cocaine levels can be useful because positive results indicate recent (within a few hours) use. Other tests, such as benzodiazepine levels, might still be useful for diagnostic purposes later on, and you might consider saving a tube of blood.

Treatment of Drug-Induced Psychosis

Deciding how to best treat a self-limited drug-induced psychosis is difficult, as anti-psychotic poses some risk (e.g., causing acute dystonic reactions if patients have used cocaine [14]). Consider using benzodiazepines alone as your initial treatment if you think psychosis is drug-induced and mild, and you expect quick improvement (e.g., uncomplicated cocaine intoxication); but do not hesitate to use antipsychotics if benzodiazepine alone prove insufficient. Obviously, you recommend substance use treatment and cessation of substance use.

Specific Substances of Misuse

Alcohol and Sedatives

Several psychotic disorders can occur in patients with alcohol use disorders. Alcohol (and sedatives including hypnotics and anxiolytics) can cause psychosis during intoxication (rare outside a delirium), during withdrawal, or during delirium tremens. In patients with chronic alcoholism, chronic hallucinosis [15] and paranoia to the point of delusional jealousy [16] can develop. Patients with severe alcohol use disorder are at risk for other medical complications which could cause psychosis (e.g., thiamine deficiency [17]).

Clinical Vignette

Maurice, now in his forties, who had been a heavy drinking for two decades, was admitted to a psychiatric inpatient unit after detoxification because of persecutory delusions and persistent auditory hallucinations. He had brought with him tapes he had made to capture the very prominent derogatory voices. No antipsychotics were administered, and his hallucinations resolved completely within a week. Two weeks after admission, we listened to the tapes together. He agreed that there was nothing recorded but maintained: “I know that the voices are on there because I heard them and recorded them.”

This case of a typical alcoholic hallucinosis illustrates that severe alcoholism can result in psychosis. Antipsychotics should be withheld to see if hallucinations resolve during a period of sobriety. It is important to not confuse ongoing psychosis with memories of the deluded state; in this case, the patient was unable to recognize his past experiences as the results of psychosis but he was not actively psychotic. The patient received thiamine to prevent Wernicke-Korsakoff syndrome.

Cannabis and Cannabinoids

Cannabis (“weed,” “reefer”) use is widespread and, due to liberalization efforts, legal in an increasing number of states. With increasing legalization, cannabis has moved from the back porches and home gardens to industrial production and diversification of cannabis-containing products. One consequence of this industrialization has been an increasing number of cannabis-containing product (edibles) and more potent cannabis strains (higher content of the psychomimetic tetrahydrocannabinol (THC), reduced concentration of the protective cannabidiol (CBD)). Edible cannabis products can easily lead to inadvertent intoxications by inexperienced users. Synthetic cannabinoids, originally developed to study the human endocannabinoid receptor system and some 100-fold more potent than THC, are now widely available through the internet [18]. They are sold as legal highs with names like K2 or spice. Their use can lead to a wide variety of medical and psychological complication, including death [19]. Compared to the mellow pot smoker on the back porch, synthetic cannabinoid users are often aggressive and violent. Their easy availability further complicates the management of already difficult to care for populations (e.g., K2 use in homeless patients). Synthetic cannabinoids are not detected by the standard urine drug test panel.

Many users consider cannabis fairly innocuous. Apart from the obvious potential for legal problems and acute intoxications, however, there has been the vexing possibility that cannabis constitutes a component cause in the development of schizophrenia for that group of patients who are biologically predisposed. The epidemiologic and experimental link between heavy cannabis use and psychosis is quite strong [20]. In one classic study, the frequent use of cannabis (more than 50

times) assessed at the time of conscription into military service with the Israeli Defense Forces increased the risk for developing schizophrenia in 15-year follow-up by sixfold [21]. A recent study has shown a dose effect for the risk of new cases of psychosis (incidence) which is consistent with a causal role [22]. The authors estimated that 12% of cases would be avoided if high-potency cannabis were not available in their particular population (using a statistic called the population attributable risk). Experimentally, cannabis exacerbates psychosis in vulnerable people like patients with schizophrenia [23]. Together, the evidence makes a strong case for cannabis being a real environmental cause of schizophrenia, down to explaining the variance in schizophrenia incidence in different populations. Put differently, cannabis is one of the strongest risk factors known for schizophrenia! If true, the public health implications are significant [24].

Tip

Not that psychiatrists should encourage cannabis use, but anyone with a family history of psychosis or personal history of unusual experiences from experimentation with cannabis should abstain. Identifying such patients in the ED and counseling them would be an important prevention task.

Stimulants: Cocaine and Amphetamines, Prescription Stimulants

Amphetamines are sold legally as prescription stimulants and produced illegally as methamphetamine (speed, crystal meth) and the designer club drug methylene-dioxymethamphetamine (MDMA [ecstacy or “Adam”]; for more information, see [section LSD and Hallucinogens](#)).

Stimulants can lead to psychosis in normal people if taken at a high enough dose to cause an intoxication. People who are dependent on methamphetamine and who are using it frequently are at high-risk for developing drug-induced psychosis [25]. In contrast, clinical doses of prescription stimulants to treat ADHD should not cause intoxication and psychosis (but see below for a caveat). As noted earlier, it is impossible to distinguish a drug-induced stimulant psychosis from primary schizophrenia based on psychopathology alone. The time course might help differentiate the two: cocaine has a short half-life, and psychosis should thus be short-lived [26]. In patients with a decade or so of heavy cocaine use, cocaine use can last longer (due to sensitization) and is accompanied by choreoathetoid motor abnormalities (“crack dancing”). This is important to know: If somebody presents to the ED with clear psychosis several hours after cocaine use, he or she is probably genetically vulnerable and/or severely addicted. Unfortunately, in some locales, this simple rule of thumb is not useful: if methamphetamine use is used, drug-induced psychosis can last days or even weeks. On college campuses, the misuse of prescription stimulants

is rampant, and psychosis from high-dose use is possible. In a college kid with “new-onset ADD” suspect prodromal schizophrenia and do not use a stimulant [27]. In this scenario, cognitive difficulties may be the harbinger of an incipient psychotic episode which may be triggered by a stimulant.

Should clinicians be concerned about the use of stimulants for ADHD in pediatric patients with regard to later causing schizophrenia (as a component cause in biologically vulnerable individuals like in the case of cannabis)? It is reassuring in this context that two large datasets suggest that new-onset psychosis attributable to prescription stimulants is a very rare event, occurring in 1 in 660 patients [28]. If stimulants are clinically indicated, it seems nevertheless prudent to use the lowest effective dose (in case there is a dose effect) and to perhaps prefer methylphenidate over amphetamine (as the latter had a twofold higher risk of causing psychosis in the aforementioned study). Careful monitoring for emerging psychosis may help avert full-blown psychosis. Since untreated ADHD is a risk for a host of adverse childhood outcomes, optimal treatment should be offered, including stimulants if needed.

In stimulant-induced psychosis, you might have to use antipsychotics if psychosis does not resolve in a few hours or if psychosis is severe enough to impair judgment (e.g., paranoia leading patients to feel they need to defend themselves).

Tip

The presence of formication (the tactile hallucination that insects are crawling on the body or under the skin) should alert you to the possibility of cocaine use (“cocaine bugs”) or methamphetamine use (“met mites”) [29]. Look for skin excoriations from picking in this drug-induced form of delusional parasitosis. Other possibilities include delirium tremens or benzodiazepine withdrawal.

LSD and Hallucinogens

Although many hallucinogens can be found naturally in plants (e.g., morning glory seeds or “magic” mushrooms containing psilocybin and psilocin, mescaline from the peyote cactus) and have been used in many cultures, hallucinogen use took off with the discovery of the prototypical hallucinogen, LSD (German for *Lysergsäurediethylamid*) by the Swiss chemist Albert Hofmann of Sandoz in 1943 (the year he took the drug himself to describe its mind-altering effects [30]). While LSD is safe medically (not psychiatrically), hallucinogens that are derived from amphetamines (and are sometimes classified with amphetamines), e.g., MDMA, can lead to renal failure, seizures, and death. Some plant-derived hallucinogens, e.g., Jimson weed, are very anticholinergic and can cause anticholinergic toxicity. Therapeutically, the mystical, openness-promoting effects of hallucinogens are (re)-discovered for their potential in augmenting psychotherapy [31], which may also lead to a resurgence of their misuse.

LSD is the most potent hallucinogen. A dose of only 20 microgram has a marked clinical effect. LSD trips last 12 hours, with another 12 hours recovering. A typical “acid trip” has prominent visual distortions: colors and shapes are altered; synesthesia (most often as “seeing sounds”); and our-of-body experiences. This state of altered perception is usually accompanied by euphoria, but “bad trips” with panic can occur.

Most intoxications with hallucinogens are short-lived, usually measured in hours or a few days at the most. One of the pioneers in LSD research, Henry David Abraham, has written that LSD trips can be good, bad, or permanent. Permanent damage in the form of flashbacks (the modern term is hallucinogen-persisting perception disorder or HPPD [32]) is reasonably well accepted. In susceptible individuals, even one-time use of LSD is feared to trigger schizophrenia. The clinical picture of psychosis in “acid heads” is not distinguishable from schizophrenia, although auditory hallucinations are rare. Expect to discuss themes of cosmic peace and altered reality with your patient.

PCP and Ketamine

PCP (“angel dust”) and its analogue, ketamine (“Special K”), deserve a special entry, as they produce a model psychosis that is indistinguishable from schizophrenia. Originally developed as dissociative anesthetics, these agents were found to induce psychosis in patients who received them for anesthesia. There is interest in ketamine as a rapid-acting treatment for suicidal ideation and depression [33]. Esketamine which is administered intranasally is FDA-approved for the adjunctive treatment of treatment-resistant depression [34].

PCP is often smoked and mixed with cannabis, frequently sold as something else or used to adulterate other drugs. PCP can cause severe psychosis and severe violence [35]. Medical complications are possible as PCP is catecholaminergic (hyperthyria and seizures). A neurological sign, nystagmus, is fairly specific. Because PCP is lipophilic, it is released over days, leading to prolonged psychosis lasting many days. Ketamine has a much shorter duration of action and is one of the club drugs. It is usually eaten, smoked, snorted, or injected. Note that while PCP is often included in urine drug tests and can be detected for many days after use, ketamine is not revealed by the PCP assay.

Medication- and Toxin-Induced Psychosis

A wide variety of medications and toxins can cause psychosis [36]. The most common reason is treatment with glucocorticoids [37], but examine a patient’s medication list for other possibilities (e.g., INH, mefloquine, digoxin, levodopa). The detection of toxin-induced psychosis requires a high index of suspicion. Potential

exposure at a patient's work place may a clue. The main culprits are carbon monoxide, heavy metals (arsenic, manganese, mercury, thallium), and organophosphates.

References

1. [The-Philosophy.com](https://www.the-philosophy.com/jim-morrison-quotes). Jim Morrison Available from: <https://www.the-philosophy.com/jim-morrison-quotes>. Accessed on 7/1/2019.
2. Feduccia AA, Holland J, Mithoefer MC. Progress and promise for the MDMA drug development program. *Psychopharmacology*. 2018;235:561–71.
3. Grunebaum MF, Galfalvy HC, Choo TH, Keilp JG, Moitra VK, Parris MS, et al. Ketamine for rapid reduction of suicidal thoughts in major depression: a midazolam-controlled randomized clinical trial. *Am J Psychiatry*. 2018;175:327–35.
4. Tarabar AF, Nelson LS. The gamma-hydroxybutyrate withdrawal syndrome. *Toxicol Rev*. 2004;23:45–9.
5. Martinak B, Bolis RA, Black JR, Fargason RE, Birur B. Dextromethorphan in cough syrup: the poor man's psychosis. *Psychopharmacol Bull*. 2017;47:59–63.
6. Mustonen A, Niemela S, McGrath JJ, Murray GK, Nordstrom T, Maki P, et al. Adolescent inhalant use and psychosis risk – a prospective longitudinal study. *Schizophr Res*. 2018;201:360–6.
7. Adorjan K, Odenwald M, Widmann M, Tesfaye M, Tessema F, Toennes S, et al. Khat use and occurrence of psychotic symptoms in the general male population in Southwestern Ethiopia: evidence for sensitization by traumatic experiences. *World Psychiatry*. 2017;16:323.
8. Huestis MA, Tyndale RF. Designer drugs 2.0. *Clin Pharmacol Ther*. 2017;101:152–7.
9. Starzer MSK, Nordentoft M, Hjorthoj C. Rates and predictors of conversion to schizophrenia or bipolar disorder following substance-induced psychosis. *Am J Psychiatry*. 2018;175:343–50.
10. Caton CL, Drake RE, Hasin DS, Dominguez B, Shrout PE, Samet S, et al. Differences between early-phase primary psychotic disorders with concurrent substance use and substance-induced psychoses. *Arch Gen Psychiatry*. 2005;62:137–45.
11. Caton CL, Hasin DS, Shrout PE, Drake RE, Dominguez B, Samet S, et al. Predictors of psychosis remission in psychotic disorders that co-occur with substance use. *Schizophr Bull*. 2006;32:618–25.
12. Harris D, Batki SL. Stimulant psychosis: symptom profile and acute clinical course. *Am J Addict*. 2000;9:28–37.
13. McCain CF, Namey LB, Freudenreich O. Lamotrigine cross-reactivity with phencyclidine in rapid urine toxicology in a research study. *Prim Care Companion CNS Disord*. 2018;20(4) pii. 17l02192.
14. van Harten PN, van Trier JC, Horwitz EH, Matroos GE, Hoek HW. Cocaine as a risk factor for neuroleptic-induced acute dystonia. *J Clin Psychiatry*. 1998;59:128–30.
15. Tsuang JW, Irwin MR, Smith TL, Schuckit MA. Characteristics of men with alcoholic hallucinosis. *Addiction*. 1994;89:73–8.
16. Soyka M, Naber G, Volcker A. Prevalence of delusional jealousy in different psychiatric disorders. An analysis of 93 cases. *Br J Psychiatry*. 1991;158:549–53.
17. Isenberg-Grzeda E, Kutner HE, Nicolson SE. Wernicke-Korsakoff-syndrome: under-recognized and under-treated. *Psychosomatics*. 2012;53:507–16.
18. Freund SA, Banning AS. Synthetic cannabinoids: a review of the clinical implications of a new drug of choice. *JAAPA*. 2017;30:1–4.
19. Drummer OH, Gerostamoulos D, Woodford NW. Cannabis as a cause of death: a review. *Forensic Sci Int*. 2019;298:298–306.
20. Marconi A, Di Forti M, Lewis CM, Murray RM, Vassos E. Meta-analysis of the association between the level of cannabis use and risk of psychosis. *Schizophr Bull*. 2016;42:1262–9.

21. Andreasson S, Allebeck P, Engstrom A, Rydberg U. Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. *Lancet.* 1987;2:1483–6.
22. Di Forti M, Quattrone D, Freeman TP, Tripoli G, Gayer-Anderson C, Quigley H, et al. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. *Lancet Psychiatry.* 2019;6:427–36.
23. D'Souza DC, Abi-Saab WM, Madonick S, Forselius-Bielen K, Doersch A, Braley G, et al. Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. *Biol Psychiatry.* 2005;57:594–608.
24. Murray RM, Quigley H, Quattrone D, Englund A, Di Forti M. Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis. *World Psychiatry.* 2016;15:195–204.
25. Arunogiri S, Foulds JA, McKetin R, Lubman DI. A systematic review of risk factors for methamphetamine-associated psychosis. *Aust N Z J Psychiatry.* 2018;52:514–29.
26. Tang Y, Martin NL, Cotes RO. Cocaine-induced: psychotic disorders presentation, mechanism, and management. *J Dual Diagn.* 2014;10:98–105.
27. Freudreich O, Cather C, Holt D. Stimulant misuse in college for “pseudo-attention deficit disorder” during schizophrenia prodrome. *Am J Psychiatry.* 2006;163:2019.
28. Moran LV, Ongur D, Hsu J, Castro VM, Perlis RH, Schneeweiss S. Psychosis with methylphenidate or amphetamine in patients with ADHD. *N Engl J Med.* 2019;380:1128–38.
29. Brewer JD, Meves A, Bostwick JM, Hamacher KL, Pittelkow MR. Cocaine abuse: dermatologic manifestations and therapeutic approaches. *J Am Acad Dermatol.* 2008;59:483–7.
30. The Guardian. Basel in the spotlight: the city that learned to love LSD. 2018 Available from: <https://www.theguardian.com/cities/2018/apr/19/basel-in-the-spotlight-the-city-that-learned-to-love-lsd-albert-hofmann>. Accessed on 7/1/2019.
31. Barrett FS, Griffiths RR. Classic hallucinogens and mystical experiences: phenomenology and neural correlates. *Curr Top Behav Neurosci.* 2018;36:393–430.
32. Martinotti G, Santacroce R, Pettoruso M, Montemirto C, Spano MC, Lorusso M, et al. Hallucinogen persisting perception disorder: etiology, clinical features, and therapeutic perspectives. *Brain Sci.* 2018;8.
33. Sanacora G, Frye MA, McDonald W, Mathew SJ, Turner MS, Schatzberg AF, et al. A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry.* 2017;74:399–405.
34. Canuso CM, Singh JB, Fedgchin M, Alphs L, Lane R, Lim P, et al. Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: results of a double-blind, randomized, placebo-controlled study. *Am J Psychiatry.* 2018;175:620–30.
35. Baldridge EB, Bessen HA. Phencyclidine. *Emerg Med Clin North Am.* 1990;8:541–50.
36. Freudreich O, Brown HE, Holt DJ. Psychosis and schizophrenia. In: Stern TA, Fava M, Wilens TE, Rosenbaum JF, editors. Massachusetts General Hospital comprehensive clinical psychiatry. 2nd ed. Philadelphia: Elsevier; 2016. p. 307–23.
37. Dubovsky AN, Arvikar S, Stern TA, Axelrod L. The neuropsychiatric complications of glucocorticoid use: steroid psychosis revisited. *Psychosomatics.* 2012;53:103–15.

Additional Resources

Web Sites

<https://www.drugabuse.gov/> – The National Institute on Drug Abuse (NIDA) website. NIDA is the branch of the NIH that studies addictions.

<https://www.drugabuse.gov/drugs-abuse/club-drugs> – NIDA's section on club drugs.

Books

Huxley A. *The doors of perception*. New York: Harper & Brothers; 1954. – The English writer Huxley describes his psychedelic experiences under mescaline. His philosophical insights make this book worth reading today, particularly as psychiatry rediscovers the therapeutic values of mind-altering drugs. While you may never use psychedelic substances yourself, the book may open your mind (sorry about this pun which is intended) to the limits of day-to-day experiences.

Articles

Murray RM, Quigley H, Quattrone D, Englund A, Di Forti M. Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis. *World Psychiatry*. 2016;15:195–204. – A good overview over the changes in potency of cannabis products and the unresolved public health questions.

Nour MM, Carhart-Harris RL. Psychedelics and the science of self-experience. *Br J Psychiatry*. 2017;210:177–9. – A topic that I did not cover in detail: the therapeutic use of currently mostly illicit psychedelic substances. Psilocybin for example is being tested for use in cancer patients with depression and existential concerns.

Chapter 5

Secondary Schizophrenia



Essential Concepts

- Before diagnosing (primary) schizophrenia, you must rule out one of the secondary schizophrenias (i.e., schizophrenic symptoms are secondary to a nonpsychiatric medical disorder, either from a systemic disorder that affects the brain or from demonstrable neuropathology in the brain).
- Only a very small number of patients with first-episode schizophrenia (diagnosed with modern criteria), around 5%, will have an identifiable, medical etiology of their psychosis.
- Psychopathology is of no help to differentiate between primary and secondary causes of schizophrenia. The cross-sectional psychopathology is non-specific with regard to the etiology of psychosis. Do not give undue weight to one particular type of hallucination alone (e.g., visual hallucinations or Schneiderian voices) when making your diagnosis.
- Merely detecting a medical condition does not establish causality. Establishing causality between an identified medical condition and psychosis relies on atypical features for schizophrenia (age of onset, symptoms *in aggregate*, treatment response, course), temporality, and biological plausibility.
- Apart from some basic screening tests to exclude obvious medical organ disease and specific, highly treatable disorders, the further extent of the work-up is determined by your clinical suspicion for an underlying medical condition. Indiscriminate screening in psychotic but otherwise unremarkable patients is ill-advised as any positive result is likely false-positive.
- The value of neuroimaging in first-episode patients is disputed as the yield is low. Expect non-specific (and in almost all cases clinically irrelevant) MRI findings in about 1 in 5 patients.

- A wide variety of medical/neurologic disorders and some toxins are associated with psychosis, mimicking schizophrenia. Their diagnoses if there are no ancillary signs and symptoms require a combination of screening, a high index of suspicion, and clinical follow-up.
- Even if psychosis is the result of identifiable pathology, symptomatic treatment with an antipsychotic in addition to medically treating the underlying disease is often necessary. Antipsychotics may be less effective than in schizophrenia and poorly tolerated, particularly in neurological conditions.

“Crude exogenous organic damage of the most varying kind can produce acute psychotic clinical pictures of a basically uniform kind.” (cited in [1])

—Karl Bonhoeffer, 1868–1948

(The father of “organic” psychiatry [2], also the father of the theologian Dietrich Bonhoeffer [3])

Many medical disorders can potentially mimic schizophrenia. In this chapter, I outline a clinical approach for a patient with psychosis of unknown etiology in order to not miss a medical disease that could account for the psychosis. For those schizophrenia-like psychoses that are the result of medical illness, I follow the suggestion of Spitzer and colleagues [4] to abandon the old term, “organic mental disorder,” and use “secondary schizophrenia” or “secondary psychosis” instead, terminology consistent with ICD-11 that uses “secondary psychotic syndrome” [5]. For brevity’s sake, I still occasionally use the adjective “organic” to indicate non-psychiatric causes. In the older literature, you may encounter “idiopathic” schizophrenia to indicate primary schizophrenia. The distinction between primary and secondary disorders is familiar to physicians; it helpfully does not imply that schizophrenia is not brain-based (a wrong conclusion fostered by calling it a “functional” disorder). In this article, I focus on secondary schizophrenia due to a medical illness. Psychosis associated with substance use and psychosis in the context of a delirium are covered in the preceding Chaps. 3 and 4, respectively. It is important, however, to not forget that substance use disorders and delirium are both commonly associated with psychosis.

Differential Diagnosis

You could organize your approach to the differential diagnosis of psychosis by arranging etiologies in two large vats and six smaller bins: primary psychosis that is due to schizophrenia or another psychiatric disorder (with psychosis) or secondary

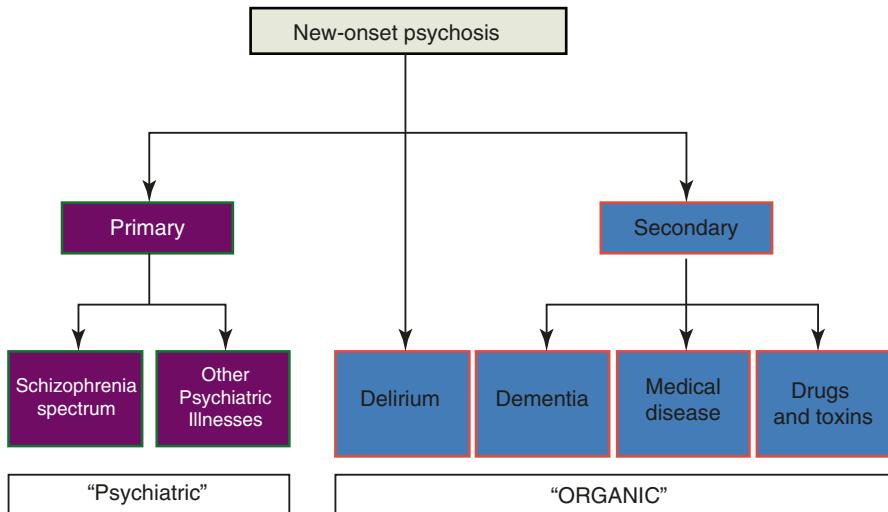


Fig. 5.1 Differential diagnosis of new-onset psychosis

psychosis that is due to secondary (“organic”) causes, the latter including delirium, dementia, drugs and toxins, or a medical disease (i.e., symptoms are secondary to a nonpsychiatric medical disease, either a systemic disease that affects the brain or demonstrable neuropathology in the brain) (see Fig. 5.1 [6] for the vats and bins). For pedagogical purposes and because of its importance in clinical care, dementia has its own bin; dementia could be put together with the medical disease. In a narrow sense, a secondary psychotic syndrome (secondary schizophrenia) refers only to psychosis due to a medical disease and not due to delirium or substance-induced psychosis. Some authors will even consider psychosis in the setting of mood disorders to be secondary; I will not follow this convention.

Psychosis could be attributable to a combination of factors (like a delirium which is often multifactorial), and all of them must be systematically examined. Determining causation is not always easy once you detect a medical condition (see the case in the Additional Resources). After its discovery, you need to determine if the condition is an incidental finding (fortuitous), relevant at some etiological level (“triggering” schizophrenia), or solely responsible for the psychopathology (if you remove it, the psychosis resolves). Criteria to use are atypicality (i.e., the presentation does not quite look like schizophrenia vis-à-vis age of onset; there is no prodrome; there are symptoms including other physical findings that are unusual; the symptoms in aggregate point toward organicity (visual hallucinations, olfactory hallucinations, lack of Schneiderian first-rank symptoms); the treatment response to standard treatment is poor), temporality (the time course of psychosis parallels time course of the medical condition), and biological plausibility (the medical condition is known to cause psychosis) [7].

Clinical Vignette

A young man developed a textbook case of paranoid psychosis. During the routine work-up for first-episode psychosis, a pituitary tumor was detected by magnetic resonance imaging (MRI) and partially resected. The patient now receives maintenance treatment for schizophrenia, as well as a dopamine agonist to reduce prolactin levels.

This case exemplifies the occasional scenario of an incidental discovery of a medical condition during the work-up for first-episode psychosis. You will need to judge if the discovered medical condition is etiologically related to the psychosis, etiologically unrelated yet important for management, or etiologically unrelated and not important for management. In this case, the finding is etiologically unrelated to schizophrenia but complicates the management of schizophrenia (treatment with a dopamine agonist).

Psychosis in otherwise healthy appearing first-episode patients diagnosed according to modern criteria is rarely due to an unrecognized medical condition. Johnstone and colleagues [8] found organic disease (judged to be relevant for the psychiatric presentation) in 15 out of 258 (less than 6%) patients with first-episode schizophrenia. Specific conditions identified were syphilis, lung cancer, autoimmune multisystem disease, cerebral cysticercosis, thyroid disease, and previous head injury. In a different sample, 22% of patients with first-episode psychosis who underwent clinical MRI scanning had an unsuspected finding [9]. Notably, first-episode patients and scans from healthy controls had similar rates of non-specific abnormal findings. However, only three patients (2%) of the first-episode group required an urgent referral (vascular lesion, arachnoid cyst, possible Huntington's disease). Given the sensitivity of MRI imaging, non-specific findings are going to be detected in a significant minority of patients (about 1 in 5 patients).

Tip

A nonhierarchical approach (i.e., simply listing schizophrenia and medical conditions (including drugs and toxins) without making causal assumptions about their relationship) is often most appropriate unless the psychosis is clearly the result of the medical disease. How do you make this judgment? If you think that controlling the medical disease will eventually resolve the psychosis and not require long-term treatment with an antipsychotic, you are probably dealing with a secondary psychosis.

Clinical Presentation

Unfortunately, there is no easy way to differentiate primary from secondary psychoses phenomenologically. As noted in the epigraph, the father of organic psychiatry, Karl Bonhoeffer recognized 100 years ago that the psychiatric clinical picture pro-

duced by a medical condition was rather uniform and unspecific, regardless of etiology [10]. Later authors have similarly failed to differentiate primary from secondary psychosis based on psychopathology alone [11, 12]. While certain symptoms suggest a medical or toxic etiology (e.g., visual hallucinations, olfactory hallucinations, dream-like quality of delusions (patient as observer), lack of Schneiderian first-rank symptoms) [1], there are no pathognomonic signs or symptoms that unequivocally point clinicians either way. Schneiderian first-rank symptoms are common in schizophrenia, quasi per definition (50%), and less common *but not unusual* in secondary psychoses, particularly if there is a clear sensorium (20%) [13]. We often attribute visual hallucinations to drug use and olfactory hallucinations, but we need to be cautious since visual hallucinations also occur in 25% of schizophrenia patients [14]. Olfactory hallucinations, while probably relatively uncommon in schizophrenia, are less carefully assessed; they are often unpleasant smells or stenches (feces) and co-occur with tactile experiences [15]. To complicate matters, some psychiatric presentations can include acute confusion and perplexity which usually indicates a more medical etiology [16].

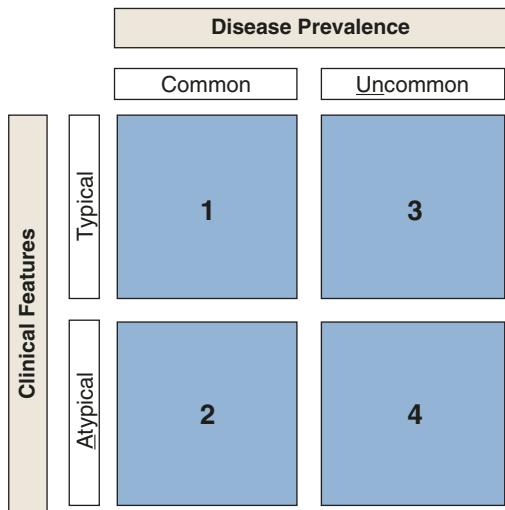
Key Point

You cannot determine from cross-sectional psychopathology if psychosis is due to schizophrenia or due to a medical condition. There are no pathognomonic symptoms that would steer you either way. Do not give undue weight to one particular type of hallucination alone (e.g., visual hallucinations or Schneiderian voices) when making your diagnosis [17].

Diagnosis

A primary psychotic disorder, such as schizophrenia, can only be made once secondary causes of psychosis have been excluded. Diagnostically, you are facing a problem that cannot be solved easily: there are simply many medical or toxic conditions that could *potentially* cause psychosis [7]. Some diseases are very rare (either *per se* or rare in your locale), and other conditions are common but only rarely cause psychosis. Clinicians may not be familiar typical presentations of uncommon diseases (uncommon in terms of prevalence *per se* but also uncommon where they practice). They may also not recognize atypical presentations of common diseases. Figure 5.2 depicts this dilemma graphically [18]. Schizophrenia would reside in quadrant 1 (typical presentation of a common disease: “That’s what we see.”); malaria which can cause psychosis but is rare where you practice, say in Boston, is in quadrant 3 (typical presentation of an uncommon disease: “I once saw a case.”); multiple sclerosis causes psychosis only rarely is an example for quadrant 2 (atypical presentation of a common disease: “We can see that in that syndrome.”); a rare metabolic disease presenting atypically with psychosis in adulthood would be a quadrant 4 example (atypical presentation of an uncommon disease: “I have never seen that.”).

Fig. 5.2 Diagnostic dilemma of psychosis in rare or atypical diseases



All patients with new-onset psychosis (and all chronic patients with a symptom exacerbation for that matter) therefore need a medical work-up. There is no generally agreed-upon work-up that every patient with psychosis must have. Some clinicians will be rather skeptical about expansive work-ups, others more enthusiastic. The neurologist Vladimir Hachinski noted that “without therapeutic enthusiasm there would be no innovation, and without skepticism there would be no proof” which captures the tension between those two poles nicely [19].

The overall clinical situation is very important in narrowing down the initial differential diagnosis to keep the work-up manageable and determine the degree of urgency. A chronic schizophrenia patient who had stopped his antipsychotic is probably psychotic because he stopped his medications (although patients may acquire a medical problem while psychotic). New-onset psychosis in a hospitalized, elderly patient following hip surgery is a delirium; and antisocial patient with polysubstance dependence who presents at the emergency department is likely suffering from a drug-induced psychosis [20]. Approximately 60% of older patients with new-onset psychosis in late-life will have a secondary psychosis [21]. Expand your search particularly for medical etiologies in atypical presentations (atypical with regard to age, symptoms include physical signs or psychiatric symptoms *in aggregate* are unusual or poor treatment response). A travel history may be a critical piece of information. As noted earlier, use the criteria of typicality, temporality, and biological plausibility to judge if any medical condition that you find is causally related to psychosis [7]. Table 5.1 describes the initial medical work-up for a patient presenting with a first-episode of schizophrenia. You will note that this work-up merges with a delirium work-up (ancillary tests, if clinically indicated) if clinical features make primary schizophrenia unlikely.

Table 5.1 Initial work-up for first-episode schizophrenia^a

Laboratory tests
<i>Screen broadly</i>
Complete blood count
Electrolytes including calcium
Renal function tests (BUN/creatinine)
Liver function tests
Erythrocyte sedimentation rate (ESR)
Antinuclear antibodies (ANA)
Glucose
Urinalysis
Urine drug screen
<i>Exclude specifically</i>
TSH
Vitamin B12 and folate
HIV screening ^b
FTA-Abs for syphilis (RPR not sufficient)
Ceruloplasmin ^c
Neuroimaging
MRI to rule out demyelinating disease, brain tumor, or stroke ^d
Ancillary tests, as clinically indicated
EEG
CXR, lumbar puncture, blood cultures, arterial blood gases (in infections)
Autoantibodies (CSF!)
Karyotype (early onset schizophrenia)
Serum cortisol
Medication drug levels
Toxin search

Adapted from [22, 23]

BUN blood urea nitrogen, EEG electroencephalogram, CXR chest X-ray, CSF cerebrospinal fluid

^aThis list of tests is not exhaustive but represents merely one possible initial work-up. Other tests should be considered if the clinical history and the clinical picture suggest they might be useful diagnostically, taking into account epidemiology and immune status

^bRecommended as part of routine care for any patients [24]

^cExtremely low yield, many false positive results

^dControversial as low yield

Follow these principles for selecting the tests to exclude secondary schizophrenia:

- Put together a screening test battery to exclude common and a few selected yet very treatable diseases.
- Epidemiology counts, both literally and figuratively: The extent of your work-up is determined by an emphasis on treatable condition *from your neighborhood or brought back to your neighborhood* (i.e., travel).
- More tests are not necessarily better: Indiscriminate screening for rare diseases without clinical suspicion for the disease is inadvisable because of false-positive (and false-negative) test results [25]. Order specific tests to rule in or rule out a disease you suspect clinically.

- An MRI will provide reassurance that a silent brain tumor (e.g., frontal lobe meningioma) is not missed, although the clinical yield of ordering an MRI in this context will be low [9]. Expect to detect mostly innocuous, incidental MRI abnormalities seen in 20% of the normal population [26].
- Electroencephalograms (EEGs) can be difficult to interpret since almost half of patients with first-episode schizophrenia will have EEG abnormalities of unclear significance [27]. Moreover, a normal (surface) EEG does not exclude epilepsy. You need to pursue a diagnosis by *repeat* (serial) testing under optimal conditions (special lead placement, sleep-deprived) [28]. As my late mentor, George Murray would point out, “If you don’t catch a fish in the ocean, that does not mean there are no fish.”
- Order the correct test: For example, to exclude neurosyphilis, your patient needs to have a highly sensitive and specific serum treponemal-specific test (fluorescent treponemal antibody absorption test (FTA-Abs)) and, if positive, a lumbar puncture, not the commonly (and incorrectly) ordered rapid plasma reagin (RPR) blood test [29].
- In poorly responsive psychosis, expand your search to exclude paraneoplastic syndromes or similar autoimmune inflammatory brain diseases, epilepsy, and sarcoidosis.

Tip

Longitudinal follow-up by the same person is probably the best safeguard against missing secondary schizophrenia, assuming that the medical disease “declares itself” with new and nonpsychiatric findings. Thus, any change in symptoms or new symptoms should lead you to revisit your initial impression.

Secondary Schizophrenias

Genetic Disorders

Several genetic syndromes have an increased risk for schizophrenia, particularly Klinefelter’s syndrome, fragile X syndrome, and velo-cardio-facial syndrome (VCFS). VCFS, which stems from a deletion on the long arm of chromosome 22 (22q11), is one of the strongest genetic risk factors for schizophrenia-like presentations, possibly in up to 25% of VCFS cases [30]. Consider VCFS testing in children with mild cognitive impairments [31].

Tip

Currently, genetic testing is not routinely recommended for patients with psychosis unless there is the clinical suspicion that a genetic syndrome is present (e.g., family history of Huntington’s disease). Even if there is no treatment,

making a syndromal diagnosis of a genetic disease is important for counseling and to look for other syndromal features that might be treatable (e.g., cardiac problems that are part of a syndrome). I suspect that psychiatrists will need to keep up with genetics when whole exome and whole genome sequencing becomes part of the work-up for neuropsychiatric disorders [32].

Endocrine Diseases

One of the easiest-to-correct endocrine conditions associated with psychosis is hypoglycemia. Screen for thyroid disease with a thyroid-stimulating hormone test (TSH), to exclude both hyperthyroidism [33] and hypothyroidism (myxedema madness) [34]. In addition, consider Addison's disease, Cushing's disease [35], and hyperparathyroidism, as well as hypoparathyroidism. A pheochromocytoma is a very rare cause of psychosis [36].

Metabolic Diseases

Many inborn errors of metabolism include psychosis in the list of possible symptoms. Almost all are diagnosed during childhood, but atypical, adult onset is possible (e.g., Niemann-Pick type C [37]). Only acute intermittent porphyria is sufficiently common that you should suspect it if abdominal pain and peripheral motor neuropathy are present in a patient with psychosis [38].

Tip

It is probably almost impossible to diagnosis a rare presentation (psychosis alone) of a rare disorder (metabolic diseases) that presents at an atypical age (adulthood). You need other clues and a high index of suspicion that would suggest a metabolic disease.

Autoimmune Diseases

The most important disorder to consider is systemic lupus erythematosus (SLE) [39]. In the case of SLE, treatment with steroids greatly complicates diagnostic issues [40]. A highly steroid-sensitive form of autoimmune thyroiditis is Hashimoto's encephalopathy [41]. Patients with schizophrenia have higher than expected titers of antibodies related to celiac disease [42]; however, their pathogenic role remains to be better understood before routine screening for celiac disease can be recommended. Rarely, classic paraneoplastic limbic syndromes can be a cause of psychosis [43].

The more recently discovered NMDA receptor encephalitis is described in more detail under Neurologic Conditions.

Narcolepsy

The hypnagogic hallucinations that are part of the narcolepsy tetrad (in addition to cataplexy, sleep paralysis, and excessive daytime sleepiness) can lead to a mistaken diagnosis of schizophrenia [44]. In one series of state hospital patients diagnosed with schizophrenia, 7% were found to suffer from narcolepsy [45]. In some, psychosis is probably related to the treatment of narcolepsy with stimulants.

Tip

Screen all patients with psychosis for the narcolepsy tetrad; however, only 10% of patients have the full tetrad. Consider a nocturnal sleep study, followed by a multiple sleep latency test (MSLT) to identify reduced daytime sleep latency and sleep onset rapid eye movement (SOREM) periods. Human leukocyte antigen (HLA)-typing and cerebrospinal fluid levels of hypocretin-1 can further assist in making the correct diagnosis if psychosis appears to be limited to the sleep-wake transitions, even in the absence of other symptoms of narcolepsy [46].

Neurologic Conditions

Stroke Poststroke psychosis is a rare but possible complication of stroke [47]. To complicate matters, in many cases, seizures obfuscate the picture and might be related to the emergence of psychosis. Peduncular hallucinosis is a syndrome of vivid, colorful formed visual hallucinations, often of animals (e.g., of a parrot in full plumage), with localizing value as a focal lesion of the midbrain cause them, hence “peduncular.”

Seizures Epilepsy and psychosis share a long history [48], and many psychiatrists have noted that there seems to be a higher prevalence of schizophrenia in patients with epilepsy (seizures leading to psychosis) but also an antagonism between the two conditions (seizures treating psychosis, leading to the development of electro-convulsive therapy, or ECT). Particularly in temporal lobe epilepsy, neurodevelopmental lesions are common. Psychosis following seizures (postictal psychosis) typically emerges within a day after the seizure and can last a few weeks or even months and can resolve or with time develop into a more chronic condition [49]. The interictal schizophrenia-like psychosis of epilepsy does not emerge until a decade or more after seizures first occur, suggesting that epilepsy is a risk factor for

this type of psychosis [50]. Many patients with epilepsy display other psychiatric symptoms, including significant negative symptoms [51].

Demyelinating diseases Demyelinating diseases are an interesting model for schizophrenia as they are a cause of disconnectivity between brain regions (leading to widespread network dysfunctions) which is believed to underlie schizophrenia [52]. It is interesting that the most common demyelinating disease, multiple sclerosis (MS), does not usually cause psychosis, probably since the disconnecting lesions in MS are discreet and random [53]. Other rare disorders affecting white matter globally are more likely to cause psychosis (i.e., the leukodystrophies: metachromatic leukodystrophy [54], X-linked adrenoleukodystrophy, and Marchiafava-Bignami disease).

Autoimmune inflammatory brain diseases Described only in 2007, N-methyl-D-aspartate (NMDA) receptor encephalitis is now a well-established clinical entity [55]. It is an autoimmune inflammatory disease of the brain caused by IgG autoantibodies directed against the NMDA receptor. Many but not all cases are associated with tumors, frequently ovarian teratomas. The clinical picture is one of rapid development of a severe neurological disease that can progress to death even with optimal treatment (i.e., immunotherapy). Seizures, aggression, catatonia, dyskinesias, and autonomic instability are typical symptoms in severe cases, leaving little doubt in the clinician's mind that a neurological disorder is present. Unfortunately, a small group of patients presents initially with only psychiatric symptoms such as psychosis which delays effective treatment [56]. A diagnostic lumbar puncture is required to confirm the presence of the pathogenic NMDA antibodies and inflammation in the brain; testing for serum antibodies alone is not helpful, and an MRI is often normal [57]. It remains to be seen if what we are seeing is merely the tip of the iceberg [58] and if there are lesser virulent forms (formes frustes). Autoantibodies against neural surface receptors other than NMDA have been described as well [59]. Do not confuse those antibodies with the classic paraneoplastic antibodies targeting intracellular antigens (e.g., anti-Hu) and causing classic limbic encephalitis. Those antibodies seem to play a very small if any role in patients with a pure psychiatric phenotype without neurological signs or symptoms [60].

Basal ganglia diseases In this category, Huntington's, Wilson's, and Parkinson's disease are thought to be associated with psychosis [61]. Psychosis can precede motor symptoms in Huntington's disease, but the diagnosis should become clear with the emergence of motor symptoms [62]. Although screening for Wilson's disease (because it is treatable) is usually suggested as part of a psychosis work-up, there remains some doubt in the literature if Wilson's disease can in fact present with schizophrenia-like psychosis alone [63]. Extrapyramidal sensitivity is quite pronounced [64]. The psychosis of Parkinson's disease is characterized by visual hallucinations [65], often attributed to antiparkinsonian medications but more recently linked to rapid eye movement (REM) sleep behavior disorder (RBD).

Increasingly, a wider spectrum of psychosis (nonvisual hallucinations) and similar phenomena (sense of presence) are appreciated in Parkinson's disease [66].

Tip

Any time you are dealing with extreme sensitivity to antipsychotics or the early development of a movement disorder (mistakenly attributed to antipsychotics as tardive dyskinesia), consider a neurology consult to exclude neurologic disease.

Traumatic brain injury Significant head injury, including the temporal lobes, is a risk factor for the eventual development of psychosis [67]. There is a substantial lag time of several years between the head injury and the emergence of psychosis.

Dementias Dementias are commonly accompanied by behavioral problems such as agitation, depression, and psychosis. Delusions and hallucinations are frequently seen in the most common form of dementia, Alzheimer's dementia [68], particularly in later disease stages [69]. Hallucinations in Alzheimer's dementia may be related to difficulties with the suppression of irrelevant memories that intrude into consciousness [70]. In Lewy body dementia (LBD), recurrent and well-formed visual hallucinations are a core diagnostic feature of the disease [71, 72]. Very poor tolerability of antipsychotics (prescribed for the hallucinations) is a clinical tip-off. In LBD, cholinesterase inhibitors prescribed for the cognitive problems may also treat the psychotic symptoms [73]. Neuropsychiatric symptoms greatly complicate dementia management and are often the proverbial straw that breaks the camel's back, leading to institutionalization.

Brain tumors The major concern is missing frontal lobe tumors that are "silent," i.e., the neurological examination is normal [74]. Meningiomas are treatable! Other space-occupying lesions have been implicated in psychosis (e.g., brain abscess, cysts, cerebrovascular malformations involving the temporal lobes, normal-pressure hydrocephalus).

Vitamin Deficiencies

Pernicious anemia must be ruled out in every patient (by checking a vitamin B12 level), as psychosis can predate anemia and neurologic (spinal) symptoms [75, 76]. Pellagra (niacin deficiency) is now very rare in the United States but used to be the prototype of a reversible organic psychosis from a nutritional deficiency [77]. Look for the four Ds – dementia, dermatitis, and diarrhea (death is the forth one) – and for stomatitis and glossitis. Very rarely, vitamin A, vitamin D, and zinc deficiencies have been associated with psychosis.

Infections

Infections are important, often treatable causes of psychosis. The exact pathogens will vary, depending on region and immune status; consider tuberculosis, cerebral malaria, toxoplasmosis, and neurocysticercosis, when appropriate. In the United States, the most important infections to rule out are herpes simplex encephalitis [78], followed by neurosyphilis [79] and human immunodeficiency virus (HIV). Diagnosing herpes simplex encephalitis is urgent as any delay in administering acyclovir worsens prognosis [80]. Neurosyphilis can only have neuropsychiatric symptoms, mostly in the form of slowly developing dementia with episodes of delirium; tabes dorsalis is uncommon in the antibiotic era. Screening has evolved and is now done with the highly sensitive (and specific) serum treponemal-specific test (it used to be a non-treponemal test); a negative treponemal-specific test makes neurosyphilis unlikely [29]. A lumbar puncture is needed to confirm neurosyphilis. HIV can present with psychosis, and HIV screening should be strongly considered during an admission for first-episode psychosis [81]. Neuroborreliosis (Lyme disease) is often listed as a cause of psychosis [82], although evidence for direct causation is disputed.

Toxins

Psychosis that is caused by environmental toxins requires a very high index of suspicion. Take into account that patients' living situations and occupations to make a judgment if they could be poisoned by any of the following toxins: carbon monoxide, heavy metals (specifically arsenic, manganese, mercury, or thallium), or organophosphates.

Treatment

The best treatment for secondary psychosis is the treatment of the underlying disease, if possible, and *concomitant treatment of psychosis*. Only in mild cases, when rapid correction of the medical problem and rapid resolution of psychosis are expected, should you delay antipsychotic treatment. Often, you will still have to treat the psychosis symptomatically with an antipsychotic, as resolution of psychosis might lag behind greatly (or the underlying disease is not treatable). The treatment of choice for LBD is cholinesterase inhibitors, not antipsychotics [73]; in this instance, a more specific treatment addressing the underlying pathophysiology can be given. Cholinesterase inhibitors may delay or reduce the need for antipsychotics in Alzheimer's dementia as well [83]. Steroid-induced psychosis may respond to dose reduction; in addition to antipsychotics, mood stabilizers are often used [84].

Note that the dosing guidelines for antipsychotics are based on treating schizophrenia, and patients with psychosis from medical causes are generally antipsychotic-naïve and very sensitive to extrapyramidal side effects. In some disorders that affect basal ganglia (e.g., Parkinson's disease or HIV infection), this can cause major difficulties with finding a tolerable regimen. To minimize the risk for tardive dyskinesia, limit the exposure to antipsychotics in medical patients.

Antipsychotics are quite problematic for older patients with dementia-related psychosis. First-generation antipsychotics carry a very high-risk of tardive dyskinesia for geriatric patients. Unfortunately, second-generation antipsychotics (SGAs) have been shown to be neither particularly effective for psychosis in dementia patients nor well tolerated. In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Alzheimer trial [85], which compared olanzapine, quetiapine, and risperidone for behavioral problems in patients with Alzheimer's disease, antipsychotics were ineffective or poorly tolerated, with two thirds discontinued after 12 weeks and more than 80% after 36 weeks. The silver lining in this trial was that those patients who were able to tolerate their antipsychotic seemed to derive some benefit from it. All antipsychotics carry a class black box warning about increased risk of death in geriatric patients who receive them for dementia-related psychosis. The mortality risk appears to be dose-related [86]. The risk for cerebrovascular events, such as a stroke, may also be increased if dementia patients are treated with antipsychotics although it is possible that this risk is specific to particular antipsychotics [87]. A risk-benefit assessment might still justify a time-limited antipsychotic trial if the behavior is clinically disruptive or dangerous and other treatments, including non-pharmacological interventions, have failed [88].

In 2016, the non-dopaminergic antipsychotic, pimavanserin was approved by the FDA for the treatment of psychosis in Parkinson's disease [89]. In one pivotal clinical trial, pimavanserin's effect size was moderate (Cohen's d 0.5) [90]. Longer clinical experience with this medication is needed to determine its full spectrum of benefit but also its mortality risk, particularly when compared to antipsychotics like quetiapine that is often used to treat the psychosis of Parkinson's disease [91].

Similar to psychotic experiences in primary psychiatric disorders, psychoeducation and teaching patients how to cope with symptoms are important ancillary measures to take. The pathophysiological basis of "organic" hallucinations or delusions may not be related to excessive dopamine release in limbic areas, and the response to antipsychotics would accordingly be quite poor.

References

1. Cutting J. The phenomenology of acute organic psychosis. Comparison with acute schizophrenia. *Br J Psychiatry*. 1987;151:324–32.
2. Strohle A, Wräse J, Malach H, Gestrich C, Heinz A. Karl Bonhoeffer (1868–1948). *Am J Psychiatry*. 2008;165:575–6.
3. Strohle A, Wräse J, Malach H, Gestrich C, Heinz A. Dietrich Bonhoeffer (1906–1945). *Am J Psychiatry*. 2008;165:577–8.

4. Spitzer RL, First MB, Williams JB, Kendler K, Pincus HA, Tucker G. Now is the time to retire the term “organic mental disorders”. *Am J Psychiatry*. 1992;149:240–4.
5. World Health Organization. International Classification of Diseases 11th revision (ICD-11). Available from: <https://icd.who.int/en/>. Accessed on 7/1/2019.
6. Freudenreich O. Differential diagnosis of psychotic symptoms: medical “mimics”: Psychiatric Times; 2012. Available from: <https://www.psychiatrictimes.com/forensic-psychiatry/differential-diagnosis-psychotic-symptoms-medical-mimics>. Accessed on 7/1/2019.
7. Keshavan MS, Kaneko Y. Secondary psychoses: an update. *World Psychiatry*. 2013;12:4–15.
8. Johnstone EC, Macmillan JF, Crow TJ. The occurrence of organic disease of possible or probable aetiological significance in a population of 268 cases of first episode schizophrenia. *Psychol Med*. 1987;17:371–9.
9. Lubman DI, Velakoulis D, McGorry PD, Smith DJ, Brewer W, Stuart G, et al. Incidental radiological findings on brain magnetic resonance imaging in first-episode psychosis and chronic schizophrenia. *Acta Psychiatr Scand*. 2002;106:331–6.
10. Neumarker KJ. Karl Bonhoeffer and the concept of symptomatic psychoses. *Hist Psychiatry*. 2001;12:213–26.
11. Johnstone EC, Cooling NJ, Frith CD, Crow TJ, Owens DG. Phenomenology of organic and functional psychoses and the overlap between them. *Br J Psychiatry*. 1988;153:770–6.
12. De Ronchi D, Bellini F, Cremante G, Ujkaj M, Tarricone I, Selleri R, et al. Psychopathology of first-episode psychosis in HIV-positive persons in comparison to first-episode schizophrenia: a neglected issue. *AIDS Care*. 2006;18:872–8.
13. Marneros A. Schizophrenic first-rank symptoms in organic mental disorders. *Br J Psychiatry*. 1988;152:625–8.
14. Chouinard VA, Shinn AK, Valeri L, Chouinard PA, Gardner ME, Asan AE, et al. Visual hallucinations associated with multimodal hallucinations, suicide attempts and morbidity of illness in psychotic disorders. *Schizophr Res*. 2019;208:196–201.
15. Stevenson RJ, Langdon R, McGuire J, Olfactory hallucinations in schizophrenia and schizoaffective disorder: a phenomenological survey. *Psychiatry Res*. 2011;185:321–7.
16. Legesse B, Freudenreich O, Murray E, Price B. A case report of confusional psychosis with abrupt onset and rapid resolution of symptoms. *Psychosomatics*. 2011;52:468–71.
17. Waters F, Fernyhough C. Hallucinations: a systematic review of points of similarity and difference across diagnostic classes. *Schizophr Bull*. 2017;43:32–43.
18. Freudenreich O, Schulz SC, Goff DC. Initial medical work-up of first-episode psychosis: a conceptual review. *Early Interv Psychiatry*. 2009;3:10–8.
19. Fogel BS, Duffy J, McNamara ME, Salloway S. Skeptics and enthusiasts in neuropsychiatry. *J Neuropsychiatry Clin Neurosci*. 1992;4:458–62.
20. Caton CL, Drake RE, Hasin DS, Dominguez B, Shrout PE, Samet S, et al. Differences between early-phase primary psychotic disorders with concurrent substance use and substance-induced psychoses. *Arch Gen Psychiatry*. 2005;62:137–45.
21. Reinhart MM, Cohen CI. Late-life psychosis: diagnosis and treatment. *Curr Psychiatry Rep*. 2015;17:1.
22. Freudenreich O, Holt DJ, Cather C, Goff DC. The evaluation and management of patients with first-episode schizophrenia: a selective, clinical review of diagnosis, treatment, and prognosis. *Harv Rev Psychiatry*. 2007;15:189–211.
23. Freudenreich O, Holt DJ, Goff DC. Psychotic patients. In: Stern TA, Freudenreich O, Smith FA, Fricchione GL, Rosenbaum JF, editors. *Massachusetts General Hospital handbook of general hospital psychiatry*. 7th ed. Edinburgh: Elsevier; 2018. p. 109–21.
24. Branson BM, Handsfield HH, Lampe MA, Janssen RS, Taylor AW, Lyss SB, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep*. 2006;55:1–17.
25. Baldessarini RJ, Finklestein S, Arana GW. The predictive power of diagnostic tests and the effect of prevalence of illness. *Arch Gen Psychiatry*. 1983;40:569–73.
26. Katzman GL, Dagher AP, Patronas NJ. Incidental findings on brain magnetic resonance imaging from 1000 asymptomatic volunteers. *JAMA*. 1999;282:36–9.

27. Manchanda R, Norman R, Malla A, Harricharan R, Takhar J, Northcott S. EEG abnormalities and two year outcome in first episode psychosis. *Acta Psychiatr Scand.* 2005;111:208–13.
28. Salinsky M, Kanter R, Dasheiff RM. Effectiveness of multiple EEGs in supporting the diagnosis of epilepsy: an operational curve. *Epilepsia.* 1987;28:331–4.
29. Henao-Martinez AF, Johnson SC. Diagnostic tests for syphilis: new tests and new algorithms. *Neurol Clin Pract.* 2014;4:114–22.
30. Murphy KC, Jones LA, Owen MJ. High rates of schizophrenia in adults with velo-cardio-facial syndrome. *Arch Gen Psychiatry.* 1999;56:940–5.
31. Murphy KC, Jones RG, Griffiths E, Thompson PW, Owen MJ. Chromosome 22q11 deletions. An under-recognised cause of idiopathic learning disability. *Br J Psychiatry.* 1998;172:180–3.
32. Besterman AD, Moreno-De-Luca D, Nurnberger JI Jr. 21st-century genetics in psychiatric residency training: how do we get there? *JAMA Psychiatry.* 2019;76(3):231–2.
33. Brownlie BE, Rae AM, Walshe JW, Wells JE. Psychoses associated with thyrotoxicosis – ‘thyrotoxic psychosis.’ A report of 18 cases, with statistical analysis of incidence. *Eur J Endocrinol.* 2000;142:438–44.
34. Heinrich TW, Graham G. Hypothyroidism presenting as psychosis: myxedema madness revisited. *Prim Care Companion J Clin Psychiatry.* 2003;5:260–6.
35. Saad MF, Adams F, Mackay B, Ordonez NG, Leavens ME, Samaan NA. Occult Cushing’s disease presenting with acute psychosis. *Am J Med.* 1984;76:759–66.
36. Benabarre A, Bosch X, Plana MT, Lecube A, Vieta E, Cirera E, et al. Relapsing paranoid psychosis as the first manifestation of pheochromocytoma. *J Clin Psychiatry.* 2005;66:949–50.
37. Walterfang M, Fietz M, Fahey M, Sullivan D, Leane P, Lubman DI, et al. The neuropsychiatry of Niemann-Pick type C disease in adulthood. *J Neuropsychiatry Clin Neurosci.* 2006;18:158–70.
38. Tishler PV, Woodward B, O’Connor J, Holbrook DA, Seidman LJ, Hallett M, et al. High prevalence of intermittent acute porphyria in a psychiatric patient population. *Am J Psychiatry.* 1985;142:1430–6.
39. Wright MT. Neuropsychiatric illness in systemic lupus erythematosus: insights from a patient with erotomania and Geschwind’s Syndrome. *Am J Psychiatry.* 2010;167:502–7.
40. Appenzeller S, Cendes F, Costallat LT. Acute psychosis in systemic lupus erythematosus. *Rheumatol Int.* 2008;28:237–43.
41. Wilcox RA, To T, Koukourou A, Frasca J. Hashimoto’s encephalopathy masquerading as acute psychosis. *J Clin Neurosci.* 2008;15:1301–4.
42. Cascella NG, Kryszak D, Bhatti B, Gregory P, Kelly DL, McEvoy JP, et al. Prevalence of celiac disease and gluten sensitivity in the United States clinical antipsychotic trials of intervention effectiveness study population. *Schizophr Bull.* 2011;37:94–100.
43. Foster AR, Caplan JP. Paraneoplastic limbic encephalitis. *Psychosomatics.* 2009;50:108–13.
44. Dauvilliers Y, Arnulf I, Mignot E. Narcolepsy with cataplexy. *Lancet.* 2007;369:499–511.
45. Douglass AB, Hays P, Pazderka F, Russell JM. Florid refractory schizophrenias that turn out to be treatable variants of HLA-associated narcolepsy. *J Nerv Ment Dis.* 1991;179:12–7.
46. Cao M. Advances in narcolepsy. *Med Clin North Am.* 2010;94:541–55.
47. Chemerinski E, Robinson RG. The neuropsychiatry of stroke. *Psychosomatics.* 2000;41:5–14.
48. Sachdev P. Schizophrenia-like psychosis and epilepsy: the status of the association. *Am J Psychiatry.* 1998;155:325–36.
49. Devinsky O. Postictal psychosis: common, dangerous, and treatable. *Epilepsy Curr.* 2008;8:31–4.
50. Blumer D, Wakhu S, Montouris G, Wyler AR. Treatment of the interictal psychoses. *J Clin Psychiatry.* 2000;61:110–22.
51. Getz K, Hermann B, Seidenberg M, Bell B, Dow C, Jones J, et al. Negative symptoms in temporal lobe epilepsy. *Am J Psychiatry.* 2002;159:644–51.
52. Friston KJ, Frith CD. Schizophrenia: a disconnection syndrome? *Clin Neurosci.* 1995;3:89–97.
53. Feinstein A. The neuropsychiatry of multiple sclerosis. *Can J Psychiatr.* 2004;49:157–63.

54. Hyde TM, Ziegler JC, Weinberger DR. Psychiatric disturbances in metachromatic leukodystrophy. Insights into the neurobiology of psychosis. *Arch Neurol.* 1992;49:401–6.
55. Dalmau J, Tuzun E, Wu HY, Masjuan J, Rossi JE, Voloschin A, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol.* 2007;61:25–36.
56. Kayser MS, Titulaer MJ, Gresa-Arribas N, Dalmau J. Frequency and characteristics of isolated psychiatric episodes in anti-N-methyl-d-aspartate receptor encephalitis. *JAMA Neurol.* 2013;70:1133–9.
57. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol.* 2016;15:391–404.
58. Jorgensen A, Hansen BS, Stanislaus S, During S, Jorgensen MB, Pinborg LH, et al. Anti-N-methyl-D-aspartate receptor encephalitis is an important differential diagnosis in acute psychiatric disease. *Acta Psychiatr Scand.* 2015;131:69–70.
59. Pollak TA, Rogers JP, Nagele RG, Peakman M, Stone JM, David AS, et al. Antibodies in the diagnosis, prognosis, and prediction of psychotic disorders. *Schizophr Bull.* 2019;45:233–46.
60. Saether SG, Schou M, Kondziella D. What is the significance of onconeural antibodies for psychiatric symptomatology? A systematic review. *BMC Psychiatry.* 2017;17:161.
61. Freudenberg O, Flaherty AW. Patients with abnormal movements. In: Stern TA, Freudenberg O, Smith FA, Fricchione GL, Rosenbaum JF, editors. Massachusetts general handbook of general hospital psychiatry. 7th ed. Edinburgh: Elsevier; 2018. p. 231–29.
62. Amann B, Sterr A, Thoma H, Messer T, Kapfhammer HP, Grunze H. Psychopathological changes preceding motor symptoms in Huntington's disease: a report on four cases. *World J Biol Psychiatry.* 2000;1:55–8.
63. Denning TR, Berrios GE. Wilson's disease. Psychiatric symptoms in 195 cases. *Arch Gen Psychiatry.* 1989;46:1126–34.
64. Zimbres PC, Schilsky ML. The spectrum of psychiatric symptoms in Wilson's disease: treatment and prognostic considerations. *Am J Psychiatry.* 2015;172:1068–72.
65. Holroyd S, Currie L, Wooten GF. Prospective study of hallucinations and delusions in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 2001;70:734–8.
66. Fenelon G, Soulard T, Zenasni F, Cleret de Langavant L, et al. Mov Disord. 2010;25:763–6.
67. Fujii D, Fujii DC. Psychotic disorder due to traumatic brain injury: analysis of case studies in the literature. *J Neuropsychiatry Clin Neurosci.* 2012;24:278–89.
68. Murray PS, Kumar S, Demichele-Sweet MA, Sweet RA. Psychosis in Alzheimer's disease. *Biol Psychiatry.* 2014;75:542–52.
69. Craig D, Mirakhur A, Hart DJ, McIlroy SP, Passmore AP. A cross-sectional study of neuropsychiatric symptoms in 435 patients with Alzheimer's disease. *Am J Geriatr Psychiatry.* 2005;13:460–8.
70. El Hajj M, Galloj K, Dehon H, Roche J, Laroi F. Hallucinations in Alzheimer's disease: failure to suppress irrelevant memories. *Cogn Neuropsychiatry.* 2018;23:142–53.
71. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology.* 2005;65:1863–72.
72. Nagahama Y, Okina T, Suzuki N, Matsuda M, Fukao K, Murai T. Classification of psychotic symptoms in dementia with Lewy bodies. *Am J Geriatr Psychiatry.* 2007;15:961–7.
73. Lin YW, Truong D. Diffuse Lewy body disease. *J Neurol Sci.* 2019;399:144–50.
74. Madhusoodanan S, Danan D, Moise D. Psychiatric manifestations of brain tumors: diagnostic implications. *Expert Rev Neurother.* 2007;7:343–9.
75. Evans DL, Edelsohn GA, Golden RN. Organic psychosis without anemia or spinal cord symptoms in patients with vitamin B12 deficiency. *Am J Psychiatry.* 1983;140:218–21.
76. Herr KD, Norris ER, Frankel BL. Acute psychosis in a patient with vitamin B(12) deficiency and coincident cervical stenosis. *Psychosomatics.* 2002;43:234–6.
77. Prakash R, Gandotra S, Singh LK, Das B, Lakra A. Rapid resolution of delusional parasitosis in pellagra with niacin augmentation therapy. *Gen Hosp Psychiatry.* 2008;30:581–4.

78. Steadman P. Herpes simplex mimicking functional psychosis. *Biol Psychiatry*. 1992;32:211–2.
79. Friedrich F, Geusau A, Greisenegger S, Ossege M, Aigner M. Manifest psychosis in neurosyphilis. *Gen Hosp Psychiatry*. 2009;31:379–81.
80. Poissy J, Wolff M, Dewilde A, Rozenberg F, Raschilas F, Blas M, et al. Factors associated with delay to acyclovir administration in 184 patients with herpes simplex virus encephalitis. *Clin Microbiol Infect*. 2009;15:560–4.
81. Alvarez-Segura M, Villero S, Portugal E, Mayoral M, Montilla P, Fraguas D. Psychosis induced by decreased CD4+ T cell and high viral load in human immunodeficiency virus infection: a case report. *Biol Psychiatry*. 2008;64:e3–4.
82. Roelcke U, Barnett W, Wilder-Smith E, Sigmund D, Hacke W. Untreated neuroborreliosis: Bannwarth's syndrome evolving into acute schizophrenia-like psychosis. A case report. *J Neurol*. 1992;239:129–31.
83. Cummings J, Lai TJ, Hemrungrajn S, Mohandas E, Yun Kim S, Nair G, et al. Role of donepezil in the management of neuropsychiatric symptoms in Alzheimer's disease and dementia with Lewy bodies. *CNS Neurosci Ther*. 2016;22:159–66.
84. Dubovsky AN, Arvikar S, Stern TA, Axelrod L. The neuropsychiatric complications of glucocorticoid use: steroid psychosis revisited. *Psychosomatics*. 2012;53:103–15.
85. Schneider LS, Tarot PN, Dagerman KS, Davis SM, Hsiao JK, Ismail MS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med*. 2006;355:1525–38.
86. Maust DT, Kim HM, Seyfried LS, Chiang C, Kavanagh J, Schneider LS, et al. Antipsychotics, other psychotropics, and the risk of death in patients with dementia: number needed to harm. *JAMA Psychiatr*. 2015;72:438–45.
87. Hsu WT, Esmaily-Fard A, Lai CC, Zala D, Lee SH, Chang SS, et al. Antipsychotics and the risk of cerebrovascular accident: a systematic review and meta-analysis of observational studies. *J Am Med Dir Assoc*. 2017;18:692–9.
88. Stevens JR, Jarrahzadeh T, Brendel RW, Stern TA. Strategies for the prescription of psychotropic drugs with black box warnings. *Psychosomatics*. 2014;55:123–33.
89. Sahli ZT, Tarazi FI. Pimavanserin: novel pharmacotherapy for Parkinson's disease psychosis. *Expert Opin Drug Discov*. 2018;13:103–10.
90. Cummings J, Isaacson S, Mills R, Williams H, Chi-Burris K, Corbett A, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. *Lancet*. 2014;383:533–40.
91. Moreno GM, Gandhi R, Lessig SL, Wright B, Litvan I, Nahab FB. Mortality in patients with Parkinson disease psychosis receiving pimavanserin and quetiapine. *Neurology*. 2018;91:797–9.

Additional Resources

Books

- Cahalan S. *Brain on fire: my month of madness*. New York: Free Press; 2012. – The personal journey of a young woman who developed a serious neuropsychiatric disorder that ultimately ends well: after the correct diagnosis of an “organic” condition, anti-NMDR encephalitis is made.
- Lipska BK. *The neuroscientist who lost her mind: my tale of madness and recovery*. Boston: Houghton Mifflin Harcourt Publishing Company; 2018. – Excellent description of the effects of brain metastases on affect, cognition and perception as well as insight by a neuroscientist who developed metastatic melanoma.

Articles

- Freudenreich O, Schulz SC, Goff DC. Initial medical work-up of first-episode psychosis: a conceptual review. *Early Interv Psychiatry*. 2009;3:10–8. – A conceptual article about the “organic” work-up of patients with psychosis.
- Pollak TA, Rogers JP, Nagele RG, Peakman M, Stone JM, David AS, et al. Antibodies in the diagnosis, prognosis, and prediction of psychotic disorders. *Schizophr Bull*. 2019;45:233–46. – An excellent review of antibodies and psychosis, including diagnostic antibodies for autoimmune encephalitis. This is an area of psychiatry where I have seen progress in my life-time, including the delineation of a new syndrome (NMDA receptor encephalitis) that psychiatrist must recognize in order to assure correct medical treatment.
- Hogan C, Little BP, Carlson JCT, Freudenreich O, Ivkovic A, Baron JM. Case 5–2019: a 48-year-old woman with delusional thinking and paresthesia of the right hand. *N Engl J Med*. 2019;380:665–74. – A case discussion from the MGH clinico-pathological conference, highlighting the difficulties in deciding if an identified medical disease (vitamin B12 deficiency) is solely responsible for what appears to be a chronic psychotic illness.

Chapter 6

Psychiatric Differential Diagnosis of Psychosis



Essential Concepts

- Schizophrenia spectrum disorders include schizophrenia, schizoaffective disorder, delusional disorder, and schizotypal disorder as well as atypical (non-affective) psychoses.
- While the classic, clinical subtypes of schizophrenia (paranoid, disorganized/hebephrenic, catatonic) have been abandoned, there is a great need to develop biomarker-based subtypes that guide treatment.
- Most patients who are given a diagnosis of schizoaffective disorder while acutely ill have schizophrenia when viewed from a longitudinal perspective.
- Atypical psychoses are non-affective, remitting illnesses with an acute onset of symptoms.
- Delusional disorder is a psychotic disorder with the hallmark of delusions in an otherwise unremarkable person.
- Mood disorders can be accompanied by psychosis, including Schneiderian first-rank symptoms. In textbook cases, mood disorders are episodic (i.e., have periods of illness clearly delineated from normal), and psychosis is only present during the mood episodes, not in the interepisode period.
- Catatonia is a syndrome with an extensive differential diagnosis that includes medical causes and mood disorders. Catatonic schizophrenia is but one diagnostic consideration.
- Schizotypal and schizoid personality disorders are disorders that share attenuated positive and negative symptoms with schizophrenia, respectively.

- A psychotic variant of obsessive-compulsive disorder has been described in which patients no longer have insight into the pathological nature of their intrusive symptoms.
- Autism and schizophrenia share clinical characteristics, particularly in the realm of social cognition and social connectedness.

“A paranoid man is a man who knows a little about what’s going on.” [1]

—William S. Burroughs, 1914–1997, of the Beat Generation

Psychosis can occur in a wide variety of psychiatric conditions. “Primary” psychotic disorders are distinguished from “secondary” psychotic disorder; in the first case, the psychosis occurs in the context of a psychiatric illness, and in the latter, psychosis is the result of a medical illness or drugs [2]. While schizophrenia is the prototypical *primary* psychotic illness, many other primary psychotic disorders need to be considered (see Table 6.1). The most important differential diagnosis is toward psychotic mood disorders as their treatment differs. See the next two chapters for a detailed description of schizophrenia (Chap. 7) and its clinical diagnosis (Chap. 8).

Table 6.1 Psychiatric differential diagnosis of psychosis

Schizophrenia ^a
Schizophreniform disorder, brief psychotic disorders, acute and transient psychotic disorders (ATPD) ^a
Schizoaffective disorder ^a
Delusional disorder ^a
Psychotic mania
Psychotic depression
Late paraphrenia (late-life psychosis)
Postpartum psychosis
Obsessive-compulsive disorder (if severe with no insight)
Pfropfschizophrenie (schizophrenia “grafted upon” mental retardation)
Folie à deux
Catatonia
Post-traumatic stress disorder (PTSD), dissociation, trance states
Personality disorders (paranoid personality disorder, schizoid and schizotypal personality ^a disorder; borderline and histrionic personality disorder)
Autism
Other pervasive developmental disorders (Asperger’s syndrome, Heller’s syndrome, Rett syndrome)
Nonpathological, attenuated psychotic symptoms in general population
Nonpsychotic, extreme beliefs (overvalued ideas)
Malingering

^aSometimes referred to as “schizophrenia spectrum disorders”

Schizophrenia Spectrum Disorders

Several primary psychotic disorders are grouped together as schizophrenia spectrum disorders as they share clinical features to the point that they are difficult to differentiate from each other. Which disorders to include differs, but a broad spectrum includes schizophrenia, schizoaffective disorder, delusional disorder, and schizotypal disorder as well as atypical (non-affective) psychoses [2]. Schizotypal disorder is sometimes grouped together with the personality disorders.

Schizophrenia

The clinical symptoms and course of prototypical schizophrenia are described in the next two chapters. In this section, I merely want to note that psychiatrists have long tried to delineate distinct subgroups of patients within the syndrome of schizophrenia. Eugen Bleuler basically recognized that schizophrenia was a heterogeneous syndrome when he called his influential textbook, *Dementia Praecox or the Group of Schizophrenias* [3]. Reducing presumed biological heterogeneity and introducing more homogeneous subgroups based on different etiologies and particularly pathophysiolgies are seen as a prerequisite for better treatments.

Traditionally, patients were assigned to clinical subtypes, based on the predominant clinical picture (paranoid, disorganized (hebephrenic), catatonic). Given overlap between subtypes (and resulting in an “undifferentiated subtype”), longitudinal instability, and lack of prognostic relevance clinical subtypes have been abandoned in recent revisions of the major classification systems. You could say that clinicians and researchers voted with their feet when they simply stopped using classic subtypes [4]. There is one exception: the catatonic subtype of schizophrenia. It is critical to identify catatonic symptoms in your patients with psychosis since this group of patients requires a different treatment approach (see below).

There is on the other hand great interest in delineating biological subgroups of schizophrenia using biomarkers as such subtypes may lead to different and targeted treatments. The work on gluten sensitivity in schizophrenia patients represents one such an effort as the gut may need to be target if this line of inquiry proves to be relevant [5]. Patients with insulin resistance are less responsive to antipsychotics and may require treatment of the inflammatory status for an optimal response [6]. Another example separates schizophrenia into two molecular subtypes based on the dorsolateral prefrontal cortex (DLPFC) transcriptome [7]. However, at this point none of those genetic-biological subtypes have found their way into the clinic to help clinicians with their day-to-day clinical management of schizophrenia.

Schizoaffective Disorder

Some patients experience the symptoms of schizophrenia and bipolar disorder simultaneously and equally prominently, leading to a diagnosis of schizoaffective disorder. The necessity for this residual diagnostic category is a challenge for nosology and has led to the idea of a “unitary psychosis,” in which any patient can be located on a continuum between schizophrenia-like illness and bipolar-like illness, with varying admixtures of mood and psychotic symptoms [8]. According to DSM-5, schizoaffective disorder can be diagnosed if a manic or depressive episode has been present concurrent with characteristic psychotic symptoms of schizophrenia and if psychotic symptoms have persisted for at least 2 weeks when there were no prominent mood symptoms. In addition, mood symptoms need to be present “for the majority of the total duration of the active and residual portions of the illness” [9]. It should be obvious that these complex rules are open to interpretation (and require knowledge of longitudinal symptoms that is often impossible to ascertain). Moreover, we rarely see patients completely untreated, the effect of treatment obscuring the true longitudinal symptom picture. Consequently, the inter-rated reliability of schizoaffective disorder is low [10]. Combined with its questionable validity, one may ask if we should use this term at all [11].

In clinical practice, a diagnosis of schizoaffective disorder is often given purely based on the cross-sectional symptom picture during an acute illness episode (which is also the approach that ICD-11 takes [2]) and not based on a lifetime symptom picture (the approach DSM-5 would like you to take [12]). When I am faced with a patient who shows symptoms of schizophrenia and of bipolar disorder, I try to decide between four clinical possibilities to guide treatment:

1. The patient has a severe form of bipolar disorder and not schizophrenia. Some patients with bipolar disorder have episodes of psychosis severe enough to overshadow the mood component. This is important to recognize since every effort, including use of electroconvulsive therapy, should be made to achieve remission from this episode before it becomes chronic and to prevent future episodes with mood stabilizers. Consider this possibility particularly if there is a strong family history of clear-cut bipolar disorder.
2. The patient has schizophrenia and comorbid dysthymia or recurrent depression. Patients with schizophrenia are vulnerable to demoralization or depressive episodes, particularly at times of stress. This conceptualization suggests the need for maintenance treatment with antipsychotics but also gives you very specific ideas about the treatment of the comorbid mood disorders, including non-pharmacological approaches.
3. The patient has schizophrenia and is chronically disinhibited, often disorganized. Neuropsychiatrically, the medial prefrontal brakes are not working well, and the patient appears maniform (mania-like). These patients do not have an episodic course to their mood symptoms and seem always “up” and never experience depression.

4. The patient has “true” schizoaffective disorder. I accept the limitations of making diagnoses based on symptoms alone and occasionally will use this category for those patients who are not better captured by the above categories and in whom psychosis and mood seem to be intertwined and equally prominent. This will often be the case in patients with substance use or in patients who are early in the course of schizophrenia. For treatment purposes, it is a variant of schizophrenia.

Key Point

Most patients who are given a diagnosis of schizoaffective disorder while acutely ill have schizophrenia when viewed from a longitudinal perspective; schizoaffective disorder should be a rare diagnosis, not the most common diagnosis in your patients with psychosis. Do not forget that depressive symptoms (dysphoria, demoralization) are consistent with schizophrenia. Maniform symptoms (disinhibition, disorganization) can be the result of neurocognitive impairment in prefrontal circuits (dorsolateral and medial) which is consistent with schizophrenia as well.

Atypical Psychoses

Some patients experience brief psychotic episodes with return to good baseline function between episodes and no significant residual impairment. Clinically, the onset tends to be rather acute, and confusion and bewilderment are prominent; patients are described as “perplexed” [13]. Those patients with such atypical psychoses present a diagnostic dilemma. Although it is certainly conceivable that they represent a forme fruste of schizophrenia, they might also be very different illnesses [14], a third group of psychoses other than schizophrenia and bipolar disorder. The clinical point here is that narrowly defined schizophrenia assumes a particular disease course, marked by some form of deterioration and often a typical prodrome. Those atypical (non-affective) psychoses in contrast are acute onset and remitting [15]. Until we better understand the pathophysiology of schizophrenia, we should be conservative in diagnosing it and consider somebody undiagnosed when face with atypical psychosis.

Older psychiatrists have spent much energy to better delineate these atypical psychoses. Cycloid psychoses or the Kleist-Leonhard classification [16] are examples of such nosologies [17]. These elaborate systems while interesting offer insights into the clinical richness of psychotic disorders but have limited practical value. In DSM-5 terminology, atypical patients are classified as having a brief psychotic disorder if symptoms of psychosis last for more than 1 day but for less than 30 days and schizopreniform disorder if symptoms last for less than 6 months. Schizopreniform disorder is a heterogeneous category. About 50% of patients diagnosed with

schizophreniform cases will in fact have schizophrenia [18] in which case a diagnosis of provisional schizophrenia would have been correct. It is only for technical reasons that a different diagnostic term is assigned for the first 6 months, until the DSM-5 duration criterion for schizophrenia is fulfilled. Some cases of schizophreniform disorder fully remit within a few weeks, and patient may never have again another episode or only many years later. Acute and transient psychotic disorders (ATPD) and *bouffée délirante* (in French-speaking countries like Haiti) are other terms applied to this good-prognosis patient group. Interestingly, atypical cases of psychosis are more common in non-Western cultures than in the United States or Europe, with many societies having their own term for these acute-onset, good-prognosis illnesses. “Psychogenic” psychosis is a form of psychosis induced by severe stress which has been proffered as a possible mechanism to explain this phenomenon although some cases may be “organic” and caused by infections [19].

Delusional Disorders (Paranoia)

Delusional disorder, the paranoia of late, is a disorder of midlife, with the hallmark of usually *non-bizarre* (i.e., possible) delusion(s) in the absence of other prominent psychotic symptoms; only minimal formal thought disorder or hallucinations are allowed. Patients’ personalities are intact: in casual conversation, you do not suspect a psychiatric disorder unless you happen to come upon the delusion. Even though the bizarreness criterion has been removed in DSM-5, the delusional themes tend to be credible beliefs that are neither absurd nor physically impossible. You are usually able to fit your patient, based on the content of the delusion, into one of these subtypes: persecutory, grandiose, jealous (Othello syndrome [20]), erotomanic (de Clérambault syndrome [21]), and somatic (e.g., Ekbom’s syndrome or delusional parasitosis [22]). Patients with the delusional olfactory syndrome are concerned that their body odor is offensive to other people; it may be better viewed as an anxiety disorder [23]. Munro has used the term monosymptomatic hypochondriacal psychoses to describe patients with delusional medical concerns [24]. Some patients with medically contested syndrome are likely to have delusional disorder. Morgellons, for example, is modern variant of the old delusional infestation or parasitosis [25].

Some degree of depressive overlay can be present in delusional disorder, leading to a mistaken diagnosis of psychotic depression. The degree of social impairment depends on the nature of delusion, the degree of encapsulation (i.e., the extent to which the ramifications of a delusional system are connected to a common theme). Grandiose and persecutory delusions are very impairing once these delusions spread and extend into all spheres of life.

A diagnosis of delusional disorder can be difficult as the theme of the delusions is understandable and often not patently wrong or absurd: what a patient reports is possible. In many cases, a kernel of truth is present as many delusional themes are exaggerations of real-life concerns or began with a real experience (see Kleist’s

novella in additional resources). As noted in Chap. 1, the line between overvalued ideas and delusions can be difficult to draw. While some patients with undue somatic concerns may have somatic delusions, the majority have health anxiety or other somatic symptom disorders. Somatic delusions in schizophrenia tend to be bizarre elaborations of unusual somatic experiences (e.g., “I felt my brain turning and twisting”).

Patients with delusional disorders are notoriously difficult to treat, to the point of being untreatable. This is not due to antipsychotic unresponsiveness (contrary to common perception, antipsychotics are an effective first-line treatment, if taken [26]) but because patients tend to categorically reject psychiatric treatments, as they do not feel ill. Patients with somatic delusions usually present to their primary care doctor and often categorically reject any psychiatric diagnosis or treatment. Despite great efforts on your part with engaging the patient, “insight” in the form of a medication trial is often not forthcoming, and patients follow up with you mainly to convince you that they are right and you are wrong. In less severe cases, cognitive-behavioral therapy might lead to some improvement without medications. Sometimes you can provide symptomatic relief with ancillary treatments, e.g., benzodiazepines or antidepressants that target areas of concern for a patient (“stress” or “depression”). There are ethical challenges in treating patients with delusional syndromes as you may be telling them the truth but not the whole truth (e.g., that you are offering antipsychotics to help with stress and sleep) [27]. Managing contested illnesses requires a collaborative stance, an acknowledgment that “the truth” may not be forthcoming, and a commitment to safe medical practice [28].

Clinical Vignette

An engineer in his 30s lost his job after repeatedly accusing his co-workers of spreading rumors about his sexual orientation. When he confronted an innocent bystander from a different department about a perceived insult, he was arrested. He never actually heard anyone talk about him or insult him but merely had the impression, deduced from gestures, that people were conspiring against him. He had an excellent response to antipsychotics, with complete resolution of persecutory delusions. However, he never acknowledged the possibility that his experience might have been the result of a psychiatric illness and only took antipsychotics under duress as part of court-imposed probation.

The management of patients with delusional disorder is further complicated by the real possibility of violence, particularly in patients who feel persecuted or harassed (which can lead to self-defense); wronged (which can lead to retaliation); or loved (which can lead to stalking) [29]. A good risk assessment and risk plan is an important part of treatment to prevent passion-driven violence. Seek consultation

and input from your institution and law enforcement if you are affected by a stalking patient as you may be a target [30].

Psychosis in Mood Disorders

Psychotic symptoms (i.e., delusions and hallucinations) can occur in primary mood disorders like unipolar depression or bipolar disorder (manic-depressive illness). Unfortunately, there are no pathognomonic psychotic symptoms that allow you to decide if psychosis is part of a mood disorder or schizophrenia. Be cognizant of the effect of race on your diagnostic assessment: depressive symptoms in an African American are often overlooked if psychosis is present, resulting in an overdiagnosis of schizophrenia at the expense of correctly diagnosing a psychotic mood disorder [31].

Tip

An episodic mood disorder (with psychotic mania and/or psychotic depression) is an important diagnostic consideration in any patient with psychotic symptoms. It is a critical diagnostic error to miss a mood disorder because psychosis overshadows the “underlying” condition. The presence of psychosis during times of euthymia is incompatible with a mood disorder but suggests a schizophrenia spectrum disorder.

Psychotic Depression

An episode of psychotic depression can represent unipolar or bipolar depression. Without a previous history of mania or a family history of bipolar disorder, the distinction can be impossible to make on clinical grounds alone, although psychomotor-retarded melancholic and atypical episode features (i.e., increased sleep and appetite and leaden paralysis) are more characteristic of bipolar depression [32]. However, bipolar depression is a disorder of late adolescence, unipolar depression one of middle adulthood: age of onset alone allows you to make an educated guess about the right diagnosis. Psychotic (unipolar) depression seems to be a distinct subtype of depression, not merely a particularly severe form of depression. A significant number of patients with depression, about 20%, are affected. Psychosis increases the suicide risk in depressed patients [33]. Table 6.2 presents a list of differential diagnoses of psychosis with depression.

The full syndrome of psychotic depression is unmistakable. Some patients show extreme psychomotor retardation; others are agitated, ruminating without reprieve about the mood-congruent delusional themes of guilt, worthlessness, and death. Some patients lament their fate and ask to be put out of their misery. They perceive themselves to be a burden to family and society, and suicide can be a constant

Table 6.2 Differential diagnoses of psychosis with depression

Psychotic unipolar depression
Bipolar depression
Schizoaffective disorder
Post-psychotic depression
Delusional disorder with depressive overlay
Dementia with psychosis
Organic syndromes with psychosis and depression

thought. Paranoid ideation and ideas or delusions of reference are common. Many family members are exasperated at accusations of stealing from the depressed person or the person's delusion of impoverishment. In the extreme of nihilistic delusions, patients deny any future or their own existence, to the point of claiming to be already dead: "Feel me, I am cold" (known as delusions of negation or Cotard's syndrome [34]; see Table 1.1). Somatic complaints are common. Patients often have the same delusions they previously held whenever a new episode develops [35]. Families often know when their family member becomes sick again when particular themes and topics of concern resurface even if they do not reach the level of delusions.

Tip

Consider psychotic depression in all depressed patients refractory to your usual treatment. Psychosis can be subtle, e.g., somatic preoccupation or self-reproach. In some patients, paranoia is so prominent that the depressive episode is missed.

If acute suicidality or florid psychosis is present, or if the patient becomes medically compromised (e.g., not eating), a hospitalization becomes necessary. An antidepressant combined with an antipsychotic is usually the treatment of choice for unipolar psychotic depression [36], followed by electroconvulsive therapy (ECT) if medications fail. Some patients respond to an antidepressant alone or an antipsychotic alone, but you are not going to know which patients, leading to the recommendation to use both, at least for the acute treatment [37]. Second-generation antipsychotics have mostly replaced first-generation antipsychotics in the treatment of psychotic mood disorders.

For bipolar depression, antidepressants are often added if first-line antidepressant mood stabilizers alone (lithium, lamotrigine, valproate) are not effective. This is controversial as antidepressants are at best ineffective for this indication [38], at worst potentially course destabilizing in the long run [39]. It is quite difficult to explain to depressed patients that "antidepressants" will not work. If you are therefore considering antidepressants, chose those with a lower risk of inducing a switching from depression to mania (SSRIs or bupropion) [40]. Bipolar depression is increasingly managed with second-generation antipsychotics, with several agents FDA-approved for this indication (e.g., quetiapine, lurasidone) [41].

Psychotic Mania

Mania is often, but not obligatory, accompanied by psychosis. In a large sample of 1000 acutely manic patients admitted to an inpatient unit in France (Azorin, 2007), only about 50% were psychotic [42]. The typical psychotic symptoms are mood-congruent: patients are elated and full of energy and plans, and they feel they can take on the world or solve the world's problems. This change can be easy to spot in a usually stoic plumber from Maine but harder to determine in a usually irascible, successful business executive with a hyperthymic temperament. However, Schneiderian first-rank symptoms are common as well, and do not argue against a diagnosis of bipolar disorder [43]. Although the mood in mania is classically euphoric, this can quickly change to irritability or frank hostility, particularly if the patient feels you are stymieing his or her plans. A patient whose mood episode is more dysphoric often shows significant paranoia or other psychotic symptoms, leading to a mistaken diagnosis of schizophrenia.

Mania is usually a severe enough illness to require hospitalization (see also Bell's mania in Table 1.1), if only to prevent impulsive and regrettable decisions. Agitation needs to be controlled, and treatment with a mood stabilizer, often together with an antipsychotic and/or benzodiazepine, initiated. Following resolution of mania, maintenance treatment with at least one first-line mood stabilizer is necessary to prevent further mood episodes [44]. One episode of mania suggests a very high-risk of having a second episode (90%).

Folie à Deux

Folie à deux (“infectious insanity,” induced delusional disorder, shared psychotic disorder in DSM-5) is a psychiatric curiosity that you might never see in your career: in a close relationship, usually in the same family, one person is psychiatrically ill with delusions, and another person adopts the delusional beliefs [45]. Treatment involves separation, with psychiatric treatment for the primarily delusional person (the “primary” or “inducer” or “dominant”) and spontaneous recovery of the person in whom delusions were induced (the “secondary” or “acceptor” or “submissive”). There are variants of this mechanism involving more than two people. Similar psychological mechanisms are at play in mass hysteria or cults.

Catatonia

Catatonic symptoms (see Table 1.4) cut across nosologic boundaries. I follow Taylor and Fink's [46] suggestion to view catatonia as a syndrome with different etiologies (Table 6.3). In their scheme, catatonic schizophrenia would be seen as (usually) nonmalignant catatonia secondary to a psychotic disorder (i.e., schizophrenia), neu-

Table 6.3 Classification of catatonia^a

Subtypes based on severity/lethality	
Nonmalignant catatonia	Responds to lorazepam (6–20 mg/d)
Delirious catatonia	Requires high-dose lorazepam or ECT
Malignant catatonia	Requires life support in addition
Specifiers to indicate etiology	
Secondary to a mood disorder	
Secondary to a general medical condition or toxic state	
Secondary to a neurologic disorder	
Secondary to a psychotic disorder	

Based on Ref. [46]

^aKahlbaum syndrome

roleptic malignant syndrome (NMS) as a drug-induced form of malignant catatonia. Their approach assigns appropriate importance to catatonic symptoms which have very effective specific treatment (in the form of benzodiazepines and ECT) and emphasize the need for a differential diagnosis that guides your treatment of the underlying etiology. It guards against the inappropriate and outdated assumption that catatonia indicated schizophrenia [47]. Do not ignore, however, that motor symptoms including catatonia are one of the symptom clusters in schizophrenia [48]. Suspect the catatonic syndrome if you see the cardinal signs of immobility, mutism, or stupor accompanied by catalepsy, automatic obedience, or posturing or (in the absence of cardinal signs) a combination of several catatonic symptoms.

A psychiatric syndrome with catatonia, periodic catatonia, is a rare familial disorder described in the European literature in which patients have repeated episodes of catatonic stupor or excitement [49]. Between episodes, patients often have residual affective symptoms or show signs of thought disorder or psychosis. Lithium should be considered to prevent episodes.

Personality Disorders

In some families, you find individuals with clinically diagnosed schizophrenia, as well as “normal” relatives who share some psychopathological characteristics with their ill relative, albeit at a lesser degree, suggesting some common genetic liability toward schizophrenia [50]. Patients with so-called schizotypal traits show what seems like attenuated positive symptoms: ideas of reference, odd and magical thinking, unusual perceptions, or speech oddities. Interpersonal deficits are usually present in addition to the muffled positive symptoms. When you encounter schizotypal features, consider four possibilities: they can be normal (fairly common as transient, stress-related phenomena during adolescence), they can indicate stable liability toward schizophrenia (schizotypal personality disorder), they can represent

prodromal signs of schizophrenia [51], or you may be dealing with a patient who has autism. Many patients with stable schizotypal features are on the sideline of society, with fringe ideas and lives (see case vignette).

Clinical Vignette

I once evaluated a patient who worked as a psychic in the downtown, family-owned business of several generations. He communicated with the dead, and he described himself as an “empathic medium,” able to “feel” people via their energy fields. He did not have the experience of thought control, thought insertion, or thought broadcasting. In the right setting, with a client but not usually spontaneously, he heard voices. He felt somewhat uncomfortable in social settings because he felt scrutinized and he worried about making a fool of himself. Nevertheless, in the interview, he was witty and delightful. He obviously was not impaired vocationally, with the family business going well. Himself a college graduate, he had a brother with schizophrenia.

Think of schizotypal traits (or schizotypal personality disorder, if severe) when you hear about psychic abilities, extrasensory perception (ESP), astrology, or Area 51 in Nevada where, as we all know, “the government” keeps aliens hidden away. This case illustrates the lack of societal impairment, despite attenuated psychotic symptoms, and the familial aspect of this condition.

By contrast, schizoid traits resemble negative symptoms of schizophrenia. Solitude is preferred to company; consequently, such people are (incorrectly) labeled “antisocial” by the lay public. Often, the only human contact they have is with other family members. They simply do not care about leaving an impression on you; accordingly, the interview is difficult.

Patients with paranoid personality disorder are pathologically suspicious, easily questioning your loyalty, fearing exploitation, and always looking for who is going to take advantage of them. Litigation is a real risk, and patients go to great extremes to seek what they think is justice (see Kleist’s Kohlhaas in the additional resources). The border to delusional disorder is not always easy to draw.

Sometimes patients with borderline personality disorder have episodes of “micro-psychosis,” like paranoid ideation or brief hallucinations. Rarely are those experiences sustained. The quality of these psychotic experiences is often different as well (and hence they are probably better regarded as nonpsychotic phenomena). For example, histrionic or borderline patient who endorses hallucinations typically locates voices inside the head, not in external space; they are generally able to acknowledge that the voices are the product of their own mind (not imposed from the outside).

In traumatized patients, consider dissociation (e.g., depersonalization) or trance states. I suspect that some cases of culture-bound, stress-induced psychotic states fall into this category of “psychogenic psychosis.”

Obsessive-Compulsive Disorder

Like mood disorders, obsessive-compulsive disorder (OCD) has a psychotic variant. Patients with nonpsychotic OCD display a panoply of characteristic intrusive, obsessive concerns (contamination, sexual, or religious taboo themes, symmetry) that are accompanied by compulsions. Patients with OCD retain insight into the pathological nature of their symptoms which are experienced as ego-dystonic. In some patients with otherwise typical OCD, this insight is lost, and they can appear rather psychotic. Recognizing such psychotic OCD is important as the underlying disorder needs to be treated with high-dose antidepressants; antipsychotics will be ineffective. Phenomenologically, both obsessive ideas and psychotic thought insertion are similar in that they are experienced as intrusive. They differ, however, in important ways otherwise. Obsessive thoughts are readily identified by the patient as unwanted product of his own mind, whereas thought insertion is felt as being imposed by some outside force [52]. Admittedly, this distinction based on insight is not always clear-cut.

Ten percent schizophrenia patients have an admixture of OCD-typical symptoms and schizophrenia-typical symptoms [53], in which case both OCD and schizophrenia should be diagnosed. While obsessive symptoms in schizophrenia patients are not uncommon, I believe they are also often misdiagnosed, merely reflecting cognitive inflexibility and need for reassurance because of poor memory and sharing more similarities with the rigidity of obsessive-compulsive *personality* disorder than OCD. Ritualistic behaviors not in response to obsessive thoughts are a feature of schizophrenia and should similarly not be confused with OCD symptoms. An obsessive variant of schizophrenia (schizo-obsessive disorder) portrays a poor prognosis [54], particularly if there is only obsessive slowness not accompanied by any compulsive behaviors. Of note, clozapine has been associated with the induction or worsening of obsessive symptoms [55].

Autism

After decades of strictly separating autism from schizophrenia, recent years have seen a rapprochement between autism spectrum and schizophrenia spectrum disorders [56], perhaps not surprisingly given that both are neurodevelopmental in origin. Many patients with schizophrenia show subtle signs of neurodevelopmental

difficulties like soft motor signs or developmental delays prior to the onset of psychosis [57]. Autistic symptoms are more common in schizophrenia than in normal control patients but less common than in autism (the latter should not be too surprising) [58]. The earlier the onset of psychosis, the more likely a diagnosable pervasive development disorder is going to be present in a child. In childhood-onset schizophrenia (COS), expect 30% of children to have a syndromal diagnosis of autism [59] and essentially all children to have some social impairment [57]. Thus, autism and schizophrenia co-occur more often than explained by chance. Taken together, there is clearly a link between autism and schizophrenia, likely representing common risks factors and overlapping problems in brain development. Recent studies have shown that genetic risk factors are shared across major psychiatric and neuro-developmental conditions, including schizophrenia and autism [60].

On the clinical side, there are obvious phenomenological similarities between patients with autism and with schizophrenia, leading Eugen Bleuler to identify and coin the term “autism” – used descriptively as a deficit in relatedness and partaking in the world, not in the syndromal sense – as a core symptom of schizophrenia (one of his “4 As”). I learned after September 11 what Bleuler meant when he described autistic features in his schizophrenia patients. While most of us were absorbed with the magnitude of the destruction and deaths on that day and the implications for our collective future, only one of my patients with schizophrenia made reference to the event in the weeks following the attack; for all other patients, it was business as usual, with petty complaints and preoccupations with their own lives.

Autism and schizophrenia share clinical characteristics particularly in the realm of social cognition. The core deficits in autism, social communication (both verbal and nonverbal), are also impaired in many patients with schizophrenia. Schizophrenia patients have difficulties interpreting social clues and decoding language, often only understand language concretely, consistent with theory of mind and empathic deficits characteristic of autism. Patients with prominent negative symptoms avoid eye contact and struggle with social closeness, just like patients with autism. Many patients with autism are odd in their social interaction, with peculiar language and unusual ideas. It is not difficult to see how those overlap with the positive symptoms of schizophrenia. Notably, these shared vulnerabilities in both conditions can not only lead to difficulties with social relationships but also education and vocational challenges as well as reduced quality of life. Additional psychiatric disorders (e.g., anxiety, depression, obsessive-compulsive disorder) are commonly experienced within both conditions as well [61]. Superficially overlapping social deficits in both conditions may represent rather distinct social skills profiles at the neurobiological level [62]. These distinctions are very difficult to make for the average adult psychiatrist not trained in pediatric neurology and psychiatry.

Even though autism per se is not characterized by psychosis, social incompetence and concreteness can lead to diagnostic confusion. Some adult patients with high-function autism (Asperger’s syndrome) are misdiagnosed as schizophrenia simply because oddness is taken as signifying psychosis.

Tip

In children who report psychotic symptoms, consider autism as a separate diagnosis. Verify that psychosis is actually present and not based on a misunderstanding due to difficulties communicating internal experiences. In older patients with schizophrenia, consider autistic traits if social difficulties are prominent and the patient communicates oddly.

References

1. Wikiquote. William S. Burroughs. Available from: https://en.wikiquote.org/wiki/William_S._Burroughs. Accessed on 7/1/2019.
2. Gaebel W. Status of psychotic disorders in ICD-11. *Schizophr Bull*. 2012;38:895–8.
3. Bleuler E. *Dementia praecox or the group of schizophrenias*. New York: International Universities Press; 1911/1950.
4. Braff DL, Ryan J, Rissling AJ, Carpenter WT. Lack of use in the literature from the last 20 years supports dropping traditional schizophrenia subtypes from DSM-5 and ICD-11. *Schizophr Bull*. 2013;39:751–3.
5. McLean RT, Wilson P, St Clair D, Mustard CJ, Wei J. Differential antibody responses to gliadin-derived indigestible peptides in patients with schizophrenia. *Transl Psychiatry*. 2017;7:e1121.
6. Tomasik J, Lago SG, Vazquez-Bourgon J, Papiol S, Suarez-Pinilla P, Crespo-Facorro B, et al. Association of insulin resistance with schizophrenia polygenic risk score and response to anti-psychotic treatment. *JAMA Psychiatry*. 2019; (in press).
7. Bowen EFW, Burgess JL, Granger R, Kleinman JE, Rhodes CH. DLPFC transcriptome defines two molecular subtypes of schizophrenia. *Transl Psychiatry*. 2019;9:147.
8. Peterson DL, Webb CA, Keeley JW, Gaebel W, Zielasek J, Rebello TJ, et al. The reliability and clinical utility of ICD-11 schizoaffective disorder: a field trial. *Schizophr Res*. 2019;208:235–41.
9. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-5*. 5th ed. Arlington: American Psychiatric Association; 2013.
10. Santelmann H, Franklin J, Busshoff J, Baethge C. Interrater reliability of schizoaffective disorder compared with schizophrenia, bipolar disorder, and unipolar depression – a systematic review and meta-analysis. *Schizophr Res*. 2016;176:357–63.
11. Heckers S. Is schizoaffective disorder a useful diagnosis? *Curr Psychiatry Rep*. 2009;11:332–7.
12. Malaspina D, Owen MJ, Heckers S, Tandon R, Bustillo J, Schultz S, et al. Schizoaffective disorder in the DSM-5. *Schizophr Res*. 2013;150:21–5.
13. Legesse B, Freudenreich O, Murray E, Price B. A case report of confusional psychosis with abrupt onset and rapid resolution of symptoms. *Psychosomatics*. 2011;52:468–71.
14. Marneros A. Beyond the Kraepelinian dichotomy: acute and transient psychotic disorders and the necessity for clinical differentiation. *Br J Psychiatry*. 2006;189:1–2.
15. Castagnini AC, Fusar-Poli P. Diagnostic validity of ICD-10 acute and transient psychotic disorders and DSM-5 brief psychotic disorder. *Eur Psychiatry*. 2017;45:104–13.
16. Teichmann G. The influence of Karl Kleist on the nosology of Karl Leonhard. *Psychopathology*. 1990;23:267–76.
17. Salvatore P, Bhuvaneswar C, Ebert D, Maggini C, Baldessarini RJ. Cycloid psychoses revisited: case reports, literature review, and commentary. *Harv Rev Psychiatry*. 2008;16:167–80.
18. Naz B, Bromet EJ, Mojtabai R. Distinguishing between first-admission schizopreniform disorder and schizophrenia. *Schizophr Res*. 2003;62:51–8.

19. Malhotra S, Varma VK, Misra AK, Das S, Wig NN, Santosh PJ. Onset of acute psychotic states in India: a study of sociodemographic, seasonal and biological factors. *Acta Psychiatr Scand.* 1998;97:125–31.
20. Gajwani AK, Abdi S, Adwani GB. The Othello syndrome. *Can J Psychiatr.* 1983;28:157–8.
21. Jordan HW, Lockert EW, Johnson-Warren M, Cabell C, Cooke T, Greer W, et al. Erotomania revisited: thirty-four years later. *J Natl Med Assoc.* 2006;98:787–93.
22. Campbell EH, Elston DM, Hawthorne JD, Beckert DR. Diagnosis and management of delusional parasitosis. *J Am Acad Dermatol.* 2019;80:1428–34.
23. Skimming KA, Miller CWT. Transdiagnostic approach to olfactory reference syndrome: neurobiological considerations. *Harv Rev Psychiatry.* 2019;27:193–200.
24. Munro A, Chmara J. Monosymptomatic hypochondriacal psychosis: a diagnostic checklist based on 50 cases of the disorder. *Can J Psychiatr.* 1982;27:374–6.
25. Freudenberg O, Kontos N, Tranulis C, Cather C. Morgellons disease, or antipsychotic-responsive delusional parasitosis, in an HIV patient: beliefs in the age of the internet. *Psychosomatics.* 2010;51:453–7.
26. Opler LA, Klahr DM, Ramirez PM. Pharmacologic treatment of delusions. *Psychiatr Clin North Am.* 1995;18:379–91.
27. Bartels J, Ryan CJ. How should physicians see their authority to name a stigmatizing diagnosis and respond to a patient's experience? *AMA J Ethics.* 2018;20:E1119–25.
28. Murphy M, Kontos N, Freudenberg O. Electronic support groups: an open line of communication in contested illness. *Psychosomatics.* 2016;57:547–55.
29. Delgado MG, Bogousslavsky J. De Clerambault syndrome, Othello syndrome, folie à deux and variants. *Front Neurol Neurosci.* 2018;42:44–50.
30. Logan TK, Walker R. Stalking: a multidimensional framework for assessment and safety planning. *Trauma Violence Abuse.* 2017;18:200–22.
31. Gara MA, Minsky S, Silverstein SM, Miskimen T, Strakowski SM. A naturalistic study of racial disparities in diagnoses at an outpatient behavioral health clinic. *Psychiatr Serv.* 2019;70:130–4.
32. Mitchell PB, Wilhelm K, Parker G, Austin MP, Rutgers P, Malhi GS. The clinical features of bipolar depression: a comparison with matched major depressive disorder patients. *J Clin Psychiatry.* 2001;62:212–6.
33. Gournellis R, Tournikioti K, Touloumi G, Thomadakis C, Michalopoulou PG, Christodoulou C, et al. Psychotic (delusional) depression and suicidal attempts: a systematic review and meta-analysis. *Acta Psychiatr Scand.* 2018;137:18–29.
34. Dieguez S. Cotard syndrome. *Front Neurol Neurosci.* 2018;42:23–34.
35. Lykouras E, Christodoulou GN, Malliaras D. Type and content of delusions in unipolar psychotic depression. *J Affect Disord.* 1985;9:249–52.
36. Nelson EB. Psychotic depression--beyond the antidepressant/antipsychotic combination. *Curr Psychiatry Rep.* 2012;14:619–23.
37. Farahani A, Correll CU. Are antipsychotics or antidepressants needed for psychotic depression? A systematic review and meta-analysis of trials comparing antidepressant or antipsychotic monotherapy with combination treatment. *J Clin Psychiatry.* 2012;73:486–96.
38. Ghaemi SN, Wingo AP, Filkowski MA, Baldessarini RJ. Long-term antidepressant treatment in bipolar disorder: meta-analyses of benefits and risks. *Acta Psychiatr Scand.* 2008;118:347–56.
39. McGirr A, Vohringer PA, Ghaemi SN, Lam RW, Yatham LN. Safety and efficacy of adjunctive second-generation antidepressant therapy with a mood stabiliser or an atypical antipsychotic in acute bipolar depression: a systematic review and meta-analysis of randomised placebo-controlled trials. *Lancet Psychiatry.* 2016;3:1138–46.
40. Pacchiarotti I, Bond DJ, Baldessarini RJ, Nolen WA, Grunze H, Licht RW, et al. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. *Am J Psychiatry.* 2013;170:1249–62.

41. Avery LM, Drayton SJ. Bipolar depression: managing patients with second generation anti-psychotics. *Int J Psychiatry Med.* 2016;51:145–59.
42. Azorin JM, Akiskal H, Akiskal K, Hantouche E, Chatenet-Duchene L, Gury C, et al. Is psychosis in DSM-IV mania due to severity? The relevance of selected demographic and comorbid social-phobic features. *Acta Psychiatr Scand.* 2007;115:29–34.
43. Peralta V, Cuesta MJ. Diagnostic significance of Schneider's first-rank symptoms in schizophrenia. Comparative study between schizophrenic and non-schizophrenic psychotic disorders. *Br J Psychiatry.* 1999;174:243–8.
44. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord.* 2018;20:97–170.
45. Shimizu M, Kubota Y, Toichi M, Baba H. Folie a deux and shared psychotic disorder. *Curr Psychiatry Rep.* 2007;9:200–5.
46. Taylor MA, Fink M. Catatonia in psychiatric classification: a home of its own. *Am J Psychiatry.* 2003;160:1233–41.
47. Tandon R, Heckers S, Bustillo J, Barch DM, Gaebel W, Gur RE, et al. Catatonia in DSM-5. *Schizophr Res.* 2013;150:26–30.
48. Ungvari GS, Caroff SN, Gerevich J. The catatonia conundrum: evidence of psychomotor phenomena as a symptom dimension in psychotic disorders. *Schizophr Bull.* 2010;36:231–8.
49. Madigand J, Lebain P, Callery G, Dollfus S. Catatonic syndrome: from detection to therapy. *Encéphale.* 2016;42:340–5.
50. Rosell DR, Futterman SE, McMaster A, Siever LJ. Schizotypal personality disorder: a current review. *Curr Psychiatry Rep.* 2014;16:452.
51. Bedwell JS, Donnelly RS. Schizotypal personality disorder or prodromal symptoms of schizophrenia? *Schizophr Res.* 2005;80:263–9.
52. Zink M. Comorbid obsessive-compulsive symptoms in schizophrenia: insight into pathomechanisms facilitates treatment. *Adv Med.* 2014;2014:317980.
53. Rodriguez CI, Corcoran C, Simpson HB. Diagnosis and treatment of a patient with both psychotic and obsessive-compulsive symptoms. *Am J Psychiatry.* 2010;167:754–61.
54. Scotti-Muzzi E, Saide OL. Schizo-obsessive spectrum disorders: an update. *CNS Spectr.* 2017;22:258–72.
55. Leung JG, Palmer BA. Psychosis or obsessions? Clozapine associated with worsening obsessive-compulsive symptoms. *Case Rep Psychiatry.* 2016;2016:2180748.
56. Canitano R, Pallagrosi M. Autism spectrum disorders and schizophrenia spectrum disorders: excitation/inhibition imbalance and developmental trajectories. *Front Psych.* 2017;8:69.
57. Rapoport J, Chavez A, Greenstein D, Addington A, Gogtay N. Autism spectrum disorders and childhood-onset schizophrenia: clinical and biological contributions to a relation revisited. *J Am Acad Child Adolesc Psychiatry.* 2009;48:10–8.
58. De Crescenzo F, Postorino V, Siracusano M, Riccioni A, Armando M, Curatolo P, et al. Autistic symptoms in schizophrenia spectrum disorders: a systematic review and meta-analysis. *Front Psych.* 2019;10:78.
59. Driver DI, Gogtay N, Rapoport JL. Childhood onset schizophrenia and early onset schizophrenia spectrum disorders. *Child Adolesc Psychiatr Clin N Am.* 2013;22:539–55.
60. Cross-Disorder Group of the Psychiatric Genomics C, Lee SH, Ripke S, Neale BM, Faraone SV, Purcell SM, et al. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet.* 2013;45:984–94.
61. Buckley PF, Miller BJ, Lehrer DS, Castle DJ. Psychiatric comorbidities and schizophrenia. *Schizophr Bull.* 2009;35:383–402.
62. Morrison KE, Pinkham AE, Penn DL, Kelsven S, Ludwig K, Sasson NJ. Distinct profiles of social skill in adults with autism spectrum disorder and schizophrenia. *Autism Res.* 2017;10:878–87.

Additional Resources

Books

McKenna P. Delusions: understanding the un-understandable. Cambridge: Cambridge University Press; 2017. – Our current understanding of the un-understandable (a criterion for delusions, “Unverstehbarkeit,” according to Karl Jaspers). This book includes a section on delusional disorder.

Article

Gerevich J, Ungvari GS. The description of the litigious querulant: Heinrich von Kleist’s Novella Michael Kohlhaas. *Psychopathology*. 2015;48:79–83. – If you find the time, get the short book by the German romantic writer (available in English) and read his classic case study about how an injustice becomes an all-consuming quest for justice, resulting in catastrophe. You may recognize in Kohlhaas patients in your treatment system whose life mission is litigation to rectify a wrong. While the term querulant paranoia is sometimes employed, some patients may be better described by having overvalued ideas.

Freudenberg O, Kontos N, Tranulis C, Cather C. Morgellons disease, or antipsychotic-responsive delusional parasitosis, in an HIV patient: beliefs in the age of the Internet. *Psychosomatics*. 2010;51:453–7. – A discussion of one of the contested diseases and the power struggle between patients and physicians about who has the authority to make diagnoses.

Chapter 7

Natural History of Schizophrenia



Essential Concepts

- Schizophrenia is a clinical diagnosis based on a combination of characteristic symptoms of sufficient duration and severity (in the absence of other factors that would account for them) that typically begin in late adolescence or early adulthood. Female patients have a later illness onset, including a second peak around menopause.
- In some patients, the onset of schizophrenia is already in childhood (childhood-onset schizophrenia) or later in life (late-onset schizophrenia and very late-onset schizophrenia-like psychosis).
- Patients who develop schizophrenia undergo a transition through several phases: from a premorbid phase (clinically silent) to a prodromal phase (unspecific symptoms) before they enter their first episode of psychosis (frank psychosis).
- An unspecific prodromal phase of several months or years precedes the onset of psychosis. Poor concentration, depression, social withdrawal, and role failure characterize the prodrome. Attenuated psychotic symptoms begin to appear at the end of the prodromal period, heralding the emergence of full psychosis.
- At the beginning of schizophrenia, patients may first experience delusional mood (“something is up”) that is followed by delusional perceptions and self-referential delusions.
- Once a first episode of schizophrenia is successfully treated, there is a high-risk of recurrence of psychotic symptoms. For most patients, schizophrenia is a relapsing-remitting illness, with periods of acute psychotic against a background of chronic negative and cognitive symptoms that are stable.
- Psychotic relapse in a chronic patient is usually preceded by a several-week period of nonpsychotic symptoms that follows a predictable course and symptom development unique to this patient.

- We are not very good at predicting the eventual outcome of schizophrenia-spectrum disorders, with outcomes ranging from full recovery to severe, unremitting illness requiring institutionalization. In most cohorts, about one quarter of patients does well, regardless of treatment received.
- The sociocultural context of care impacts prognosis greatly, particularly if treatment is available or not. The reported better clinical outcomes in developing countries may be overstated.

“It’s tough to make predictions, especially about the future.” [1]

Often (mis-)attributed to Yogi Berra, baseball Hall of Famer, 1972

The father of psychiatric nosology, Emil Kraepelin, divided severe psychiatric disorder into the episodic mood disorders (i.e., manic-depressive illness or bipolar disorder) and non-episodic psychotic disorders (i.e., dementia praecox or schizophrenia) [2]. Now, 100 years later, we still use this fundamental dichotomy. In his scheme, schizophrenia is the prototypical psychotic illness marked by prominent psychosis in the absence of psychiatric or medical disorders that would explain psychosis; patients who have this disease suffer from some degree of social impairment. In the real world of clinical cases, patients do not always fit the syndrome of schizophrenia: some patients experience short periods of illness without obvious impairment; others display rather significant admixtures of mood symptoms (see previous chapter). In this chapter, I provide a clinical description of the schizophrenia that focuses on its “natural history” or the progression through several illness phases (prodrome, acute psychosis, chronic phase) as the correct diagnosis of schizophrenia hinges on knowledge about the longitudinal history. How to make a clinical diagnosis of schizophrenia using current diagnostic criteria is discussed in the next chapter.

Natural History

Modern and narrowly defined schizophrenia follows a rather prototypical longitudinal illness course. The natural history of schizophrenia can be divided into four clinical phases [3]. A clinically asymptomatic premorbid phase gives way to a prodromal period with progressive yet unspecific symptoms until frank psychosis develops and a patient experiences his first psychotic episode of psychosis. Finally, patients enter a relatively stable chronic phase.

Schizophrenia is typically a disease of late adolescence or early adulthood. About 50% of patients will become ill between ages 15 and 25 and about 80% between ages 15 and 35. However, earlier illness onset during childhood and much later onset during late adulthood are possible (see below). Gender differences exist:

more males than females are affected, and females have a later onset (by about 3–4 years) and a less virulent disease, with fewer negative symptoms [4]. Females also have a second peak around menopause. The typical male patient experiences his first psychotic episode in college.

Schizophrenia is not a progressive brain disease in the sense used in neurology [5]. During the prodromal, first-episode, and immediate post-psychotic period that can last a few years, there is some deterioration in the brain function, giving rise to the term, “critical period.” Eventually, however, patients settle into a chronic period where the brain changes and function are stable [6]. There is a wide variability in the degree of impairment between individual patients. The chronic period is characterized by episodic acute illness episodes, particularly if there is nonadherence to treatment. A highly schematic prototypical course of schizophrenia is depicted in Fig. 7.1 [6]. While excessive synaptic pruning may be the molecular mechanism that underlies the decline around the early years of illness [7], the developmental neurobiology driving the development of schizophrenia remains to be elucidated.

You may rightly criticize the term “natural history” of schizophrenia as it assumes a disease process that relentlessly drives an outcome that is completely independent from any external factors. Paul Farmer has pointed out that there is no such thing as a “natural history” of disease as all disease takes place in a particular time and place [8]. The “natural” history of tuberculosis in the twenty-first century in Boston is going to be one of early identification through screening and treatment which is not the same natural history for an inmate in a Russian prison who will die from tuberculosis. Even if we stipulate that “natural” means no treatment, we recognize that the availability of clean water, for example, may make a difference in surviving a diarrheal infection – there is always a context, and isolating a disease from its context is only possible in the most abstract way. As an abstraction, however, the natural history of schizophrenia remains a useful idea as we can create a blueprint for a

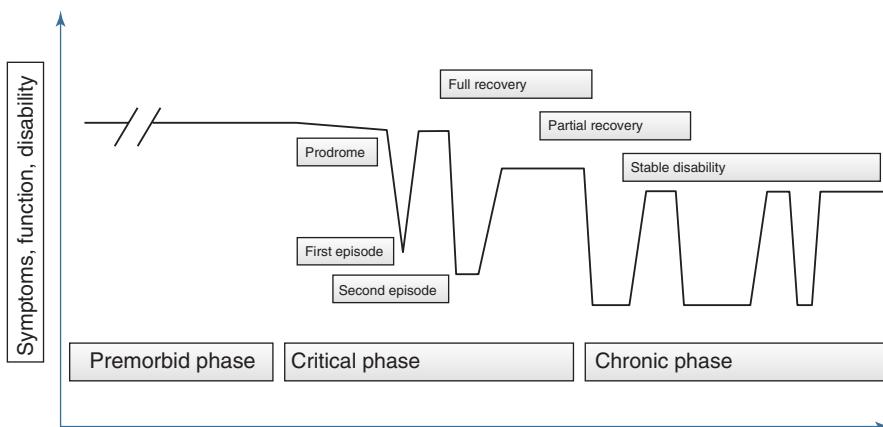


Fig. 7.1 Typical course of schizophrenia. Note the following features: excellent and quick recovery after first episode (V-shaped). Increasing difficulties to achieve prior level of function with each relapse. Eventual plateau at patient's own level of disability (no progressive decline)

prototypical illness course that allows us to diagnose schizophrenia and devise treatments to change disease trajectories.

Key Point

The longitudinal history is critical for a diagnosis of schizophrenia. Without understanding the course of the illness, you will not be able to differentiate schizophrenia from other disorders, particularly good-prognosis atypical psychotic disorders or episodic mood disorders.

Childhood-Onset Schizophrenia

Childhood-onset schizophrenia (COS), arbitrarily (and inconsistently) defined as onset by age 12, is very rare but not impossible [9]; it is extremely rare before age 10. Its prognosis is ominous. Many children have problems that are apparent long before the onset of psychosis: premorbid function is poor, and children are developmentally delayed in language, motor development, and social skills. The younger a child, the more difficult the diagnosis; normal development (e.g., imaginary friends) must be taken into account to avoid overdiagnosing schizophrenia in childhood.

The symptoms of COS are similar to the symptoms seen in adults, with the obvious adjustment for age-appropriate themes (e.g., “monsters”). Multiple domains of perception are usually affected (auditory hallucinations, visual hallucinations, tactile hallucination). The more persistent symptoms suggestive of psychosis are, the more one should worry about the possibility of a psychotic disorder; the more fleeting or unclear the psychotic symptoms, the more one should consider other diagnoses, e.g., dissociative disorders or autism-spectrum disorder (see Chap. 6). Family history can help, as genetic loading is more common in COS. One important developmental task of childhood is schooling; every effort should be made to successfully complete the afflicted child’s education.

Late-Onset Schizophrenia

Schizophrenia is generally not considered a disorder of middle or old age, but a significant minority of patients (around 10%) has late-onset schizophrenia (LOS) [10]. Dilip Jeste, a researcher specializing in LOS, has argued that age of onset between 40 and 60 years should be considered LOS [11]. What if psychosis develops after 60 or 65? For this age bracket, the term “very late-onset schizophrenia-like psychosis” has been proposed to indicate the somewhat different clinical features and probably risk factors vis-à-vis LOS [12].

Most patients with LOS are female, with better-preserved cognition, less prominent or no affective blunting, and no formal thought disorder. The positive symptom

presentation is often paranoid. To me, late-onset paranoid schizophrenia in females with no blunting or thought disorder starts to look very much like delusional disorder. British authors in particular use the term “late paraphrenia” for cases of late-life psychosis [13]: lonely, never-married, elderly “spinsters” with problems hearing who develop a paranoid psychosis with few other symptoms. For some patients with LOS, the onset of psychosis represent the prodrome of what will later turn out to be a dementing illness [14].

Tip

I would suggest that you look very hard for medical disorders in any elderly person presenting with psychosis, including early dementia, subclinical delirium, unrecognized alcohol use, or psychotic depression before diagnosing schizophrenia or delusional disorder. Make sure patients are not sensory deprived, and get them eye glasses and hearing aids [15].

Postpartum Psychosis

While postpartum depression is common, mild, and self-limited, the perinatal period also increases the risk for serious psychiatric disorders [16]. Postpartum psychosis (puerperal psychosis) which occurs within 1 month of childbirth is rare, occurring in 1 out of 1000 births [17]. In most cases, postpartum psychosis is the expression of bipolar illness (psychotic mania) and not of schizophrenia [18]. In future pregnancies, prophylactic treatment is necessary since the recurrence risk is high (around 30%) [19]. Postpartum psychosis is a psychiatric emergency, and a mother who develops postpartum psychosis needs to be hospitalized. There is a risk of maternal infanticide which, if it occurs, leads in the United States to draconian punishment of the mother [20].

Premorbid Phase

This phase is clinically silent, at least on the surface. If one looks more closely, one can find clues in some children that hint at a brewing neurodevelopmental disorder. In birth cohort studies, antecedents of schizophrenia include motor delays and language deficits [21]. Academic underachievement in schizophrenia compared to their peers and siblings is another well-established finding [22]. However, childhood precursors of schizophrenia are non-specific and also only present in a subgroup of children who will later be diagnosed with schizophrenia. Most clumsy children will not go on to develop schizophrenia, whereas, conversely, the star athlete in high school may. Nevertheless, the group-level finding of cognitive changes that translate into educational difficulties in middle school or even earlier is important if we want to develop effective interventions to prevent schizophrenia [23]. The

neurodevelopmental origin of schizophrenia challenges us to answer the question when schizophrenia begins.

Schizophrenia Prodrome

In medicine, many illnesses are preceded by an unspecific prodromal state during which no diagnosis can be made (e.g., erythema infectiosum or fifth disease) until certain characteristic symptoms (telltale rash in this case) appear. Similarly, the full syndrome of schizophrenia with frank psychosis is preceded in most cases by a prodrome that varies in length from several weeks to years. The ABC Schizophrenia Study was an influential cohort study conducted in the Heidelberg-Mannheim area, Germany, that retrospectively collected detailed information about the period before admission for a first episode of psychosis [24]. Lessons learned from this study gave rise to attempts to identify putatively prodromal patients *prospectively* in order to prevent schizophrenia (see Chap. 9 on prevention and clinical staging and Chap. 11 on first-episode psychosis).

Key Point

A prodromal period of 2–4 years with unspecific symptoms and social difficulties is often present before acute psychosis declares the presence of schizophrenia [24]. Given its non-specific nature *per definitionem*, a prodrome can only be determined retrospectively. About 20% of patients experience no prodrome but have a rather abrupt onset of psychosis.

The prodrome itself can be divided into two phases: a prepsychotic phase is marked by varied and unspecific symptoms that often result in a psychiatric evaluation and some treatment, usually for depression [25]. During a second phase, attenuated psychotic symptoms develop that begin to raise concerns about schizophrenia. Pay attention to suicidal thinking that can occur during the prodromal period [26]. Table 7.1 lists common symptoms observed during the prodrome.

Table 7.1 Prodromal symptoms of schizophrenia

Change in thinking and feeling

Unspecific (early): anxiety, depression, difficulties concentrating, difficulties sleeping

Attenuated psychotic symptoms (late): ideas of reference, paranoia, “odd,” unusual perceptions, difficulties communicating, preoccupation with new ideas

Impaired function

Role failure (drop in grades or job performance)

Decline in self-care

Social withdrawal

Based on [27]

Not only are prodromal symptoms unspecific, but they are also prevalent in normal populations. In one survey of 657 normal 16-year-old high school students, individual prodromal symptoms were endorsed at rates reaching 50% [28]. The prodromal phase of schizophrenia has received much attention, as there is hope that treatment during the prodrome might prevent schizophrenia or change its “natural” course if treated earlier (see Chap. 9 on prevention and clinical staging).

Tip

As you are reviewing a person’s longitudinal history, see if you can identify a “Knick in der Lebenslinie” (a “bend in the life line”) which is when the person began to deviate from a projected trajectory. In many patients, families are able in hindsight to pinpoint to a period when their son or daughter changed in very significant ways and started doing things out of character for them and inconsistent with their upbringing and interests. A well-adjusted college student, with friends and sports activities who had planned to go to medical school but instead takes off to go to India to study “the nature of being,” is an example where a psychotic process explains his behavior better than some adolescent rebellion. The more “normal” a person was prior to illness onset, the more obvious this “Knick” will be.

Up to this point, we have mostly looked from the outside as most prodromal symptoms are behavioral observations suggestive of a profound change in thinking. The work of the German psychiatrist Klaus Conrad is informative if we want to better understand the inner experience of people who are developing psychosis [29]. He had the opportunity to interview over 100 soldiers just around the time that they began to become psychotic. His stage model of beginning schizophrenia is summarized in Table 7.2. This model, particularly the early phases, fits nicely with biological theories about the role of random dopamine release that imbues neutral events with personal meaning in need of an explanation (aberrant salience) [30]. You can imagine how an initially just vague sense that “something is in the air, something is about to happen” (trema) begins to become more concrete as patients make delusional observations that need to be connected (apophany) and how everything seems to be about him, as chance can no longer explain the observations (anastrophe). You may remember that delusional perception is a Schneiderian first-

Table 7.2 Conrad’s stage model of beginning schizophrenia

Stage		Clinical experience
I	Trema	Delusional mood or atmosphere
II	Apophany	Delusional perceptions (Aha! experiences)
	Anastrophe	Delusions of reference
III	Apocalypse	Acute psychosis with strong affect

Based on [29]

rank symptom. Look for experiences of self-referential thinking (Conrad's second stage) if you are worried about your patient beginning to experience psychosis.

First Episode of Psychosis

Once a psychosis threshold, defined in terms of both psychotic symptom severity and duration, is crossed, patients are no longer in the prodromal phase of the illness. Rather, they are experiencing their first episode of psychosis. The dividing line between attenuated and frank psychosis is admittedly drawn arbitrarily and not always clear clinically [31], particularly in the case of a patient with brief, stuttering episodes of low-level psychotic symptoms.

Few patients receive treatment for psychosis immediately. The median duration of untreated psychosis (DUP), as the time from clear-cut psychotic to the initiation of treatment is called, ranges from 4 to 50 weeks, according to one meta-analysis [32]. In the recent RAISE study in the United States (see first-episode Chap. 11), the median DUP was at 74 weeks quite long [33]. A small group of patients with insidious illness onset receive treatment only after a delay of many years, during which they are quietly psychotic. Patients with a more acute onset of illness, particularly if they are violent, will be brought to care much earlier. Diagnostic uncertainty is common during this phase of the illness if mood symptoms and drug use obfuscate the picture.

Key Point

Depressive symptoms during a first episode of psychosis are the norm, not the exception in schizophrenia. Up to 75% of patients will have significant depressive symptoms, with 22% meeting severity criteria for full syndromal depression [34]. Depressive symptoms in a first-episode patient do not argue against a diagnosis of schizophrenia-spectrum disorder!

Chronic Phase

After recovery from the initial psychotic episode, almost all patients will experience more episodes over the course of their lives. The first few years can be rather "virulent," and frequent hospitalizations and poorly controlled symptoms often interfere with rehabilitation efforts and usually result in a lower "baseline" than where the patient was prior to the onset of schizophrenia [3]. As noted earlier, eventually patients settle at their own level of disability without further decline in function. Cognitive and negative symptoms are the greatest impediment to good function. These two symptom clusters seem to correspond more to a biological set point for a given patient than being a reflection of our current treatments (i.e., we currently have no disease-modifying medications).

As patients with schizophrenia grow older, the illness can lessen in its acuity, and patients may improve or even recover. However, I have also seen geriatric patients with schizophrenia worsen simply from decades of not taking care of their brains (e.g., alcoholism, smoking, no exercise).

Clinical Vignette

A young college student was hospitalized with florid psychosis following 6 months of depressive symptoms and difficulties concentrating. Because he had used stimulants to concentrate and taken a hallucinogen at a party, a drug-induced psychosis was diagnosed. As a result of the severity of psychosis, antipsychotics were given, and he recovered completely within 2 weeks. Then, 6 months later, the patient was rehospitalized with psychosis, this time without drug use, about 1 month after stopping his antipsychotic.

This is a typical history in that the first psychotic episode, while suggestive of schizophrenia (onset of psychosis was preceded by a characteristic prodromal period), left some diagnostic uncertainty (i.e., the role of drug use). The second episode of psychosis confirmed that he had schizophrenia. Usually, long-term follow-up clarifies the diagnosis.

Psychotic Relapse

Patients in the chronic phase of illness who are relapsing follow a pattern that is similar to a prodromal period of the first episode of schizophrenia in that they experience non-specific symptoms (early warning signs) indicative of their impending relapse [35]. Depression and withdrawal are common early warning signs, prior to the resurgence of psychosis. The time course of relapse is highly variable. However, relapse is usually measured in weeks or even months, not in days. It is not a “bolt from the blue” but the process takes several weeks to unfold [36]. You can observe this unfolding of neurobiology in your patient [37]. One of my patients struggled with explaining things during a visit 1 month after stopping treatment, but it was only a month later when he returned to clinic that he had a clear formal thought disorder. Many patients have a relapse signature (time course and symptoms) that is recognizable by clinicians or family members familiar with previous episodes [38]. Patients become, for example, preoccupied with a particular topic that they are not usually concerned about.

Long-Term Outcome

“It’s tough to make predictions,” Yogi Berra is supposed to have said, “especially about the future.” Clearly, schizophrenia is not the hopeless, progressive disease that the term usually conjures up, even among young doctors who may only be exposed

to serious forms of the illness in acute care settings, according to the adage, you know what you see. The pioneering work of the Swiss psychiatrist Eugen Bleuler of the famous Burghölzli Clinic in Zürich, Switzerland, who together with his son, Manfred Bleuler, studied the long-term course of schizophrenia, showed that there is not one course or outcome of schizophrenia [39]. Closer to home, Courtney Harding has been able to follow up patients discharged from a Vermont state hospital [40]. Her conclusion was rather positive: among her patients, three quarters required little or no help two decades after discharge. In many cohorts, a certain percentage of schizophrenia patients, about 20%, will do rather well and not need ongoing care and treatment [41]. A useful analogy is again with multiple sclerosis, which allows for patients with just one episode, episodic cases with no disability, episodic cases with accrued disability over time, and a progressive subtype [42].

In the United States, the outcome of schizophrenia can, for pedagogical purposes, be depicted in four quadrants (the exact percentages will differ between cohorts, summarized in [43]):

1. 25% have one or few psychotic episodes, usually of acute onset, from which they completely recover. These “good-prognosis cases” seem to be more common in the developing world. In the United States, this quadrant might be much smaller, more like 10%.
2. 25% have episodes with good symptomatic recovery but some degree of functional limitation; patients are able to live independently. They may have a private psychiatrist or receive care through their primary care doctor.
3. 25% have episodes with incomplete recovery and hence significant inter-episode residual symptoms. This group of patients needs substantial support from family or the state. They are often cared for in community mental health centers.
4. 25% have a very poor prognosis, with relentless, impairing symptoms requiring continued hospitalization or institutionalization (Kraepelinian subtype of schizophrenia). Patients with so-called simple schizophrenia have an insidious onset and a very poor prognosis; they display prominent negative symptoms, with little if any overt positive symptoms [44].

Unfortunately, we are unable to predict a person’s course. We do not know who belongs into the very good prognosis group in need of very little care, for example, an important question with regard to the need for maintenance treatment with anti-psychotics. Normal development, good premorbid adjustment, and later onset (which are usually females) as well as a sudden onset of illness (without a long prodromal period) are considered clinical factors that suggest a good prognosis.

Tip

Families will invariably ask you about prognosis: what to expect if their loved one was diagnosed with schizophrenia. Strike a balance between realism (schizophrenia is a neurodevelopmental disorder with neurocognitive deficits,

for example, not just a psychological affliction) but also counter the narrative of progressive worsening and inevitable chronic disability. I emphasize the wide variability in outcomes and that treatment can make a very real difference but improvement will take time. Always convey a sense of cautious hopefulness.

The Role of Culture for Outcome

It is often said that schizophrenia has a better course in developing countries, a finding that stems from a series of cross-sectional studies conducted by the World Health Organization many decades ago [45]. This almost mythical belief may not be true [46] and in my mind defies common clinical sense and observations by psychiatrists working in developing countries. Several more recent studies have described the outcomes of untreated patients in different countries. In one study of untreated patients in rural China, three quarter of patients remained psychotic and worsened with increasing duration of psychosis, whereas treated patients fared much better [47]. Colleagues in Ethiopia who followed a cohort of about 300 mostly treatment-naïve schizophrenia patients confirmed the heterogeneous course of schizophrenia. In their cohort, a good outcome (full, long-term remission) was very low (6%) [48]. In many cohort studies, untreated patients fare very poorly with regard to numerous outcome markers, including the all-important outcome of death [49]. Psychiatrists in developing countries will also tell you that stigma prevents many families from seeking help, if resources even exist. As a result, patients may need to be kept locked up at home. That said, some measures of outcome (e.g., function) may very well depend on the type of community that a person lives in (see above about the impossibility of separating schizophrenia from its context), also known as “culture” [50] (see also the book in Additional Resources). Patients with schizophrenia may indeed be better cared for in more collectivist societies where large family networks and communities can share the burden of care, including finding niche jobs for the afflicted person. In postmodern America, overstretched nuclear families are psychologically ill-equipped to handle a patient with schizophrenia given conflicting societal messages about their duties toward an ill family member, particularly if state support is limited [51].

As noted at the beginning of the chapter, schizophrenia is not a progressive brain disease. Observed outcomes instead represent a complex mixture of not only biology, drug use, medical comorbidities, and nonadherence but also of access to high-quality treatment and rehabilitation services [5], which gets me back to Paul Farmer’s point: there is no abstract “natural” outcome for real patients outside the realities of the society they actually live in.

References

1. Wikipedia. Yogi Berra. Available from: https://en.wikiquote.org/wiki/Yogi_Berra. Accessed on 7/1/2019.
2. Shorter E. The history of nosology and the rise of the diagnostic and statistical manual of mental disorders. *Dialogues Clin Neurosci*. 2015;17:59–67.
3. Lieberman JA. Neurobiology and the natural history of schizophrenia. *J Clin Psychiatry*. 2006;67:e14.
4. Aleman A, Kahn RS, Seltzer JP. Sex differences in the risk of schizophrenia: evidence from meta-analysis. *Arch Gen Psychiatry*. 2003;60:565–71.
5. Zipursky RB, Reilly TJ, Murray RM. The myth of schizophrenia as a progressive brain disease. *Schizophr Bull*. 2013;39:1363–72.
6. Lieberman JA, Perkins D, Belger A, Chakos M, Jarskog F, Boteva K, et al. The early stages of schizophrenia: speculations on pathogenesis, pathophysiology, and therapeutic approaches. *Biol Psychiatry*. 2001;50:884–97.
7. Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR, Kamitaki N, et al. Schizophrenia risk from complex variation of complement component 4. *Nature*. 2016;530:177–83.
8. Farmer PE, Nizeye B, Stulac S, Keshavjee S. Structural violence and clinical medicine. *PLoS Med*. 2006;3:e449.
9. Nicolson R, Rapoport JL. Childhood-onset schizophrenia: rare but worth studying. *Biol Psychiatry*. 1999;46:1418–28.
10. Girard C, Simard M. Clinical characterization of late- and very late-onset first psychotic episode in psychiatric inpatients. *Am J Geriatr Psychiatry*. 2008;16:478–87.
11. Maglione JE, Thomas SE, Jeste DV. Late-onset schizophrenia: do recent studies support categorizing LOS as a subtype of schizophrenia? *Curr Opin Psychiatry*. 2014;27:173–8.
12. Howard R, Rabins PV, Seeman MV, Jeste DV. Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: an international consensus. The International Late-Onset Schizophrenia Group. *Am J Psychiatry*. 2000;157:172–8.
13. Riecher-Rossler A, Rossler W, Forstl H, Meise U. Late-onset schizophrenia and late paraphrenia. *Schizophr Bull*. 1995;21:345–54.
14. Brodaty H, Sachdev P, Koschera A, Monk D, Cullen B. Long-term outcome of late-onset schizophrenia: 5-year follow-up study. *Br J Psychiatry*. 2003;183:213–9.
15. Almeida OP, Howard RJ, Levy R, David AS. Psychotic states arising in late life (late paraphrenia). The role of risk factors. *Br J Psychiatry*. 1995;166:215–28.
16. Jones I, Chandra PS, Dazzan P, Howard LM. Bipolar disorder, affective psychosis, and schizophrenia in pregnancy and the post-partum period. *Lancet*. 2014;384:1789–99.
17. Sit D, Rothschild AJ, Wisner KL. A review of postpartum psychosis. *J Women's Health*. 2006;15:352–68.
18. Chaudron LH, Pies RW. The relationship between postpartum psychosis and bipolar disorder: a review. *J Clin Psychiatry*. 2003;64:1284–92.
19. Bergink V, Rasgon N, Wisner KL. Postpartum psychosis: madness, mania, and melancholia in motherhood. *Am J Psychiatry*. 2016;173:1179–88.
20. Spinelli M. Infanticide and American criminal justice (1980–2018). *Arch Womens Ment Health*. 2019;22:173–7.
21. Welham J, Isohanni M, Jones P, McGrath J. The antecedents of schizophrenia: a review of birth cohort studies. *Schizophr Bull*. 2009;35:603–23.
22. Tempelaar WM, Termorshuizen F, MacCabe JH, Boks MP, Kahn RS. Educational achievement in psychiatric patients and their siblings: a register-based study in 30 000 individuals in the Netherlands. *Psychol Med*. 2017;47:776–84.
23. Reichenberg A, Harvey PD. Neuropsychological impairments in schizophrenia: integration of performance-based and brain imaging findings. *Psychol Bull*. 2007;133:833–58.

24. Hafner H, Loffler W, Maurer K, Hambrecht M, an der Heiden W. Depression, negative symptoms, social stagnation and social decline in the early course of schizophrenia. *Acta Psychiatr Scand.* 1999;100:105–18.
25. Hafner H, Maurer K, an der Heiden W. ABC schizophrenia study: an overview of results since 1996. *Soc Psychiatry Psychiatr Epidemiol.* 2013;48:1021–31.
26. Yung AR, McGorry PD. The initial prodrome in psychosis: descriptive and qualitative aspects. *Aust N Z J Psychiatry.* 1996;30:587–99.
27. Klosterkötter J. Indicated prevention of schizophrenia. *Dtsch Arztebl Int.* 2008;105:532–9.
28. McGorry PD, McFarlane C, Patton GC, Bell R, Hibbert ME, Jackson HJ, et al. The prevalence of prodromal features of schizophrenia in adolescence: a preliminary survey. *Acta Psychiatr Scand.* 1995;92:241–9.
29. Mishara AL. Klaus Conrad (1905–1961): delusional mood, psychosis, and beginning schizophrenia. *Schizophr Bull.* 2010;36:9–13.
30. Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry.* 2003;160:13–23.
31. Tranulis C, Park L, Delano L, Good B. Early intervention in psychosis: a case study on normal and pathological. *Cult Med Psychiatry.* 2009;33:608–22.
32. Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Arch Gen Psychiatry.* 2005;62:975–83.
33. Addington J, Heinssen RK, Robinson DG, Schooler NR, Marcy P, Brunette MF, et al. Duration of untreated psychosis in community treatment settings in the United States. *Psychiatr Serv.* 2015;66:753–6.
34. Koreen AR, Siris SG, Chakos M, Alvir J, Mayerhoff D, Lieberman J. Depression in first-episode schizophrenia. *Am J Psychiatry.* 1993;150:1643–8.
35. Gleeson JF, Rawlings D, Jackson HJ, McGorry PD. Early warning signs of relapse following a first episode of psychosis. *Schizophr Res.* 2005;80:107–11.
36. Spaniel F, Bakstein E, Anyz J, Hlinka J, Sieger T, Hrdlicka J, et al. Relapse in schizophrenia: definitively not a bolt from the blue. *Neurosci Lett.* 2018;669:68–74.
37. Remington G, Foussias G, Agid O, Fervaha G, Takeuchi H, Hahn M. The neurobiology of relapse in schizophrenia. *Schizophr Res.* 2014;152:381–90.
38. Wiedemann G, Hahlweg K, Hank G, Feinstein E, Muller U, Dose M. Detection of early warning signs in schizophrenic patients. Possible applications in prevention of recurrence. *Nervenarzt.* 1994;65:438–43.
39. Bleuler M, Huber G, Gross G, Schuttler R. Long-term course of schizophrenic psychoses. Joint results of two studies. *Nervenarzt.* 1976;47:477–81.
40. Harding CM, Zubin J, Strauss JS. Chronicity in schizophrenia: revisited. *Br J Psychiatry Suppl.* 1992;161:27–37.
41. Volavka J, Vevera J. Very long-term outcome of schizophrenia. *Int J Clin Pract.* 2018;72:e13094.
42. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) advisory committee on clinical trials of new agents in multiple sclerosis. *Neurology.* 1996;46:907–11.
43. Torrey EF. Onset, course, and prognosis. In: *Surviving schizophrenia : a family manual.* 7th ed. New York: Harper Perennial; 2019. p. 85–114.
44. Lally J, Maloudi S, Krivoy A, Murphy KC. Simple schizophrenia: a forgotten diagnosis in psychiatry. *J Nerv Ment Dis.* 2019;207(9):721–5.
45. Edgerton RB, Cohen A. Culture and schizophrenia: the DOSMD challenge. *Br J Psychiatry.* 1994;164:222–31.
46. Cohen A, Patel V, Thara R, Gureje O. Questioning an axiom: better prognosis for schizophrenia in the developing world? *Schizophr Bull.* 2008;34:229–44.
47. Ran M, Xiang M, Huang M, Shan Y. Natural course of schizophrenia: 2-year follow-up study in a rural Chinese community. *Br J Psychiatry.* 2001;178:154–8.

48. Alem A, Kebede D, Fekadu A, Shibre T, Fekadu D, Beyero T, et al. Clinical course and outcome of schizophrenia in a predominantly treatment-naïve cohort in rural Ethiopia. *Schizophr Bull.* 2009;35:646–54.
49. Taipale H, Mittendorfer-Rutz E, Alexanderson K, Majak M, Mehtala J, Hoti F, et al. Antipsychotics and mortality in a nationwide cohort of 29,823 patients with schizophrenia. *Schizophr Res.* 2018;197:274–80.
50. Hopfer K, Wanderling J. Revisiting the developed versus developing country distinction in course and outcome in schizophrenia: results from ISoS, the WHO collaborative follow-up project. *International Study of Schizophrenia. Schizophr Bull.* 2000;26:835–46.
51. Karp DA. *The burden of sympathy : how families cope with mental illness.* Oxford: Oxford University Press; 2001.

Additional Resources

Book

Watters E. *The shifting mask of schizophrenia in Zanzibar. Crazy like us: the globalization of the American psyche.* New York: Free Press; 2011. – Read this book! It makes you question the wisdom of imposing our Western ideas about psychiatric illnesses (what counts as disease, how to you best treat it) on other, non-Western societies. Some societies may offer a more hopeful conceptual framework that allows for inclusion and healing and prevents psychological damage to patients. The book contains a chapter on schizophrenia.

Articles

Farmer PE, Nizeye B, Stulac S, Keshavjee S. Structural violence and clinical medicine. *PLoS Med.* 2006;3:e449. – A manuscript worth reading if you are interested in a critique of the idea of a “natural history” of any disease. Paul Farmer is an ID doctor from Boston who has brought first-rate health care to Haiti, proving that the outcome of disease is fundamentally a function of the society you live in – that social interventions are at least as important as any molecular advance.

Mishara AL. Klaus Conrad (1905–1961): delusional mood, psychosis, and beginning schizophrenia. *Schizophr Bull.* 2010;36:9–13. – An excellent summary in English if you are interested in learning more about Conrad’s descriptions of beginning psychosis.

Chapter 8

Diagnostic Assessment of Schizophrenia



Essential Concepts

- Schizophrenia is a clinical diagnosis you can make if typical symptoms are present long enough and are severe enough in the absence of other causative factors (i.e., drug use, medical illness, or other psychiatric disorders).
- Schizophrenia can be reliably diagnosed using criteria-based diagnostic schemes (e.g., DSM-5 or ICD-11). Diagnostic criteria are a mere shadow of the richness of clinical phenomena encountered in patients with schizophrenia.
- Psychosis by *longitudinal symptom review* is key for a diagnosis of schizophrenia and not if the patient is psychotic in your office.
- Typical symptoms of schizophrenia are psychosis and negative symptoms, but other symptom domains need to be assessed as well. Organize your dimensional assessment around six symptom clusters (motor, disorganization, paranoid-hallucinatory, negative, cognition, affective).
- An outcomes-focused assessment includes three elements: symptoms, function, and quality of life.
- The judicious use of screening tools and rating scales can inform clinical care and strengthen your treatment alliance with patients.

“Madness is tonic and invigorating. It makes the sane more sane. The only ones who are unable to profit by it are the insane.” [1]

Henry Miller, American writer, 1891–1980

The syndrome of schizophrenia, as described in the previous chapter, can be reliably diagnosed using criteria such as those developed by the American Psychiatric Association or the World Health Organization [2]. These diagnostic criteria represent

a consensus among experts, identifying narrowly defined, core schizophrenia. They are not a comprehensive description of the full breadths of clinical symptoms that you will encounter in patients with schizophrenia (covered in more detail in the respective sections in this book). In this chapter, I provide guidance on (1) how to put together the information gathered in your interview and mental status exam to reach or reject a diagnosis of schizophrenia and (2) how to assess schizophrenia comprehensively, beyond a mere categorical “schizophrenia present or not.”

Diagnosing Schizophrenia for the First Time

All psychiatric disorders are diagnosed by typical symptoms and a typical course *only after “organic” factors have been ruled out*. Nevertheless, I do not like to call schizophrenia a “diagnosis of exclusion,” as this often implies “by default”; schizophrenia is still diagnosed *positively*, only if typical signs and symptoms and a typical course are present.

Key Point

Psychosis does not equal to schizophrenia: there are many etiologies of psychosis, with schizophrenia merely one diagnostic possibility. A differential diagnosis to exclude other reasons for psychosis is necessary.

To diagnose schizophrenia, answer the following questions, not necessarily in this order:

- How did psychiatric symptoms develop over time (see Chap. 7) and what symptoms are currently present (see Chaps. 1 and 2)?
- Is a delirium present (see Chap. 3)?
- Could this be a drug-induced psychosis (see Chap. 4)?
- Is one of the secondary schizophrenias responsible for the psychosis (see Chap. 5)?
- Are there clinical features more typical for another psychotic disorder, particularly bipolar disorder or psychotic depression (see Chap. 6)?

Your interview, review of collateral information, and mental status exam provide you with the information you need to diagnose schizophrenia. The next step is to formally confirm that your clinical diagnostic impression can be called schizophrenia using diagnostic criteria.

Diagnostic Criteria

While your diagnosis of the schizophrenia is made *clinically*, the name (or label) that you give your patient’s disease is based on criteria for classification (of which there are competing schemes) such as the American Psychiatric Association’s

Table 8.1 Key diagnostic features of schizophrenia (according to DSM-5)

<i>Active-phase symptoms^a</i>
Core psychotic symptoms
Delusions
Hallucinations
Disorganized speech
Grossly disorganized behavior or catatonia
Negative symptoms
<i>Duration of symptoms</i>
6 months of illness (<i>including prodrome</i>); 1 month of acute symptoms (<i>unless treated</i>)
<i>Functional decline</i>
Required

Note: This list is based on the fifth edition of the American Psychiatric Association's Diagnostic and Statistical Manual, DSM-5 [3]. Other diagnostic schemes differ in the criteria required for a diagnosis of schizophrenia. For example, the World Health Organization's 11th edition of the International Classification of Diseases, ICD-11, requires only 1 month of symptoms and no functional decline [2]

^aAt least two active-phase symptoms are needed. One must be a core psychotic symptom

Diagnostic and Statistical Manual (DSM) [3] or the World Health Organization's International Classification of Diseases (ICD) [2] (see Table 8.1).

As noted earlier, the clinical phenomena are much richer than the diagnostic criteria, so avoid resorting to "checklist psychiatry" in which all you know about schizophrenia is a limited list of symptoms that you check off your clipboard [4], thereby turning a handful of criteria into the real thing of schizophrenia (a problem called reification in epistemology [5]). Those criteria work well to increase the reliability of the terms (two psychiatrists will use the same name for a clinical condition) but do not automatically establish validity of the syndrome of schizophrenia. It will not solve the issue if bipolar disorder and schizophrenia are two separate disorders (dichotomy introduced by Kraepelin) or if they represent two poles of a unitary psychosis (continuum model of psychopathology) [6]. The continued existence of schizoaffective disorder hints at this vexing and unresolved validity problem in psychiatric nosology [7].

Last, as you are searching for diagnostic criteria, keep in mind that sometimes the clinical picture may not overlap well with diagnostic criteria even though the syndrome of schizophrenia would be the best clinical diagnosis for a patient [8]. Conversely, sometimes a patient seems to "meet criteria" (not a phrase I particularly like as it demeans your analytical-synthetic clinical skills) but does not fit clinically. Diagnostic criteria are not a substitute for your clinical judgment. A prototype approach (i.e., matching how close a patient in front of you resembles a prototypical clinical description of a syndrome) may be better suited to capture the complexity of patients [9]. I suspect many clinicians intuitively use a prototype approach together with diagnostic criteria in an iterative process.

Tip

Sometimes you may be trying too hard. Given the limitations of our current knowledge, a best clinical diagnosis and differential diagnoses (working diagnosis) may be all that is possible. Sometimes, the correct diagnosis will emerge over time but not always. Be pleased with diagnosing “schizophrenia spectrum disorder.” The major distinction is toward a truly episodic mood disorder where lithium should be offered.

Confirming Schizophrenia in the Established Patient

You will often take over the care of established patients who come to you on maintenance antipsychotics with a “history of chronic schizophrenia” (Your proverbial “inherited patient”). The basics of confirming a diagnosis of schizophrenia are not different from diagnosing new patients, except that you do not have to reinvent the wheel. Use data already collected for you. During your interview, go for milestones (high school graduation) and clear-cut life events (suicide attempts, psychiatric hospitalizations) to avoid getting bogged down in details that may not help you diagnostically.

Tip

Get collateral information that is both recent and distant. From patients with a long history of schizophrenia, get the first and last hospital discharge summaries to learn how it all started; and also to get a recent view and a chronological summary, if you are lucky. Look for consultation reports; a neurologist might have summarized the history helpfully. Be aware that diagnostic standards and treatments have changed. In the United States, 1980 is a watershed year because of the introduction of a narrow concept of (DSM-III) schizophrenia, also known as the neo-Kraepelinian approach [10].

In some patients you will be able to make a diagnosis of schizophrenia simply because of the patient’s presentation with typical symptoms despite treatment (if you assume that the patient’s symptoms are stable and that an “organic” disease would have declared itself by now). However, some treated patients are fairly asymptomatic (the antipsychotic is working). This can leave you with the dilemma of not having seen florid psychopathology yourself (no substitute for having seen it yourself!) and having to make diagnostic and treatment decisions based on second-hand information, including imprecise language (“I had a break-down”) and sloppy discharge summaries that mostly contain checklists and boilerplate language. In diagnosing these patients, do not dismiss schizophrenia because:

- “He is doing too well for schizophrenia.” This stems from the perception that all patients with schizophrenia must have a chronic, debilitating illness with clear, residual symptoms. This assumption is simply untrue.
- The patient is not psychotic when interviewed. I am treating many patients whom I have never seen psychotic because they have stayed on maintenance antipsychotics after their first episode and never have relapsed.
- The patient seems to be a good “historian” (a useful, albeit obviously incorrect term unless that patient has a university degree in history [11]) and convinces you that previous psychiatrists were incorrect about the diagnosis. “I never heard voices” is not an uncommon statement where lack of insight into symptoms and poor memory can distort the recollection of past events and internal mental states.

Key Point

Most of the time, most patients with *treated* schizophrenia are not psychotic or only have minimal symptoms unless they are treatment-refractory. (I admit that there is a bit of circular reasoning here.)

Common Diagnostic Mistakes

Psychiatric diagnoses are based on cross-sectional *and longitudinal* symptom review. I think most mistakes are made when a diagnosis is based on acute presentations only. Admittedly, unless you live with your patients in a state hospital (like the alienists used to), you will, in fact, have only rather incomplete knowledge about longitudinal symptoms. What is more, patients are almost never completely untreated; therefore, you see fully or partially treated syndromes. Nevertheless, strive to avoid these mistakes:

- Schizophrenia is not diagnosed because of prominent mood symptoms during an exacerbation of schizophrenia, even though mood symptoms are not prominent during the longitudinal course of the illness.
- Schizophrenia is not diagnosed because the disorder seems to not have been present long enough (e.g., 6 months in DSM-5). In reality, most patients have been ill for many months or even years ones they reach you. The prodromal period prior to the onset of frank psychosis counts toward illness duration.
- Schizophrenia is missed because symptoms are falsely attributed to drug use. Conversely, schizophrenia is diagnosed even though substance use alone can explain the presentation.
- Schizophrenia is diagnosed because dissociative symptoms and transient psychotic experiences (e.g., mild paranoid ideation or stress-induced hallucinations) are misinterpreted as evidence for schizophrenia.
- “Cultural” explanations are proffered to falsely reject schizophrenia or to inappropriately invoke schizophrenia. In people from other cultures or with other

religions, you are occasionally unable to judge if psychosis is present: ask somebody from within the culture in order to avoid misdiagnosis in either direction. However, the syndrome of schizophrenia is usually easily recognizable, regardless of where the patient is from, and the “cultural” aspect is a mere distraction. Anyone who has traveled to other countries and evaluated patients with schizophrenia there will confirm that patients with schizophrenia look strikingly similar. Nevertheless, “pathoplastic” (illness-shaping) influences of culture on diseases and their symptoms can lead to lack of congruity with DSM categories (e.g., *bouffée délirante* of Haiti: an acute, confusional disorder that resolves quickly – one example of a “culture-bound” syndrome).

- Racial stereotypes and fears may bias your diagnostic assessment. Overdiagnosis of schizophrenia in African Americans has been attributed to an overemphasis on psychotic symptoms, while depressive symptoms are missed [12].
- The patient is diagnosed with schizophrenia because the patient looks psychiatrically ill even though there is no evidence for psychosis (criteria are not met).
- Peculiarities in thinking and in interests are viewed as delusional. Consider the possibility of autism.

Let me add one last diagnostic mistake: schizophrenia is diagnosed because of psychotic symptoms for which no cause can be found, even though the person is otherwise well. Psychotic symptoms without clinical significance were surprisingly common in a community survey in the Netherlands (The Netherlands Mental Health Survey and Incidence Study, or NEMESIS), in which almost two out of ten people endorsed some form of psychotic symptom, an observation consistent with a psychosis continuum concept [13]. The epigraph to this chapter expresses the insight that severe psychosis like the psychosis of schizophrenia creates suffering for those who experience symptoms (e.g., even if society benefits from writings created during episodes of illness).

Common Diagnostic Omissions

Your goal at the end of the interview is not only to establish a diagnosis of schizophrenia but also to clearly rule in or rule out other psychiatric diagnoses.

Key Point

Do not just stop once you have diagnosed schizophrenia, but consider other additional diagnoses that can complicate treatment or are amenable to treatment. Schizophrenia can be overbearing, often seeming to tower above other problems. However, once psychosis is controlled, it is the “minor” diagnoses and the patient’s cognitive style (to paraphrase David Shapiro [14]) that matter most in treatment. Do not just subsume all problems under “schizophrenia,” but also do not create unnecessary diagnoses.

Specifically, consider the following psychiatric diagnostic questions:

- Is a personality disorder present? Cognitive styles and temperamental dispositions matter; in particular, recognize antisocial or borderline traits, which greatly complicate your clinical management.
- Is cognitive impairment so severe that dementia could be diagnosed?
- Are other diagnoses present that require treatment in their own right (may be subsyndromal)? Consider separate diagnoses for depression, post-traumatic stress disorder, panic disorder, or social phobia instead of subsuming them under schizophrenia.
- Is there obsessive-compulsive disorder (OCD) which can lead to diagnostic error? In some patients, cognitive inflexibility rather than obsessions is the problem. It remains to be seen if “schizo-obsessive disorder” is a valid subtype of co-occurring OCD plus schizophrenia [15].
- Are there autistic features that explain some oddities in behavior and peculiarities in thinking?

Comprehensive Assessment

Merely making a categorical diagnosis schizophrenia (yes or no) is not particularly informative per se and cannot guide your treatment. Instead, a comprehensive psychiatric and medical assessment is the basis for treatment planning and successful treatment. In addition to psychiatric diagnoses, substance use and medical diseases need to be noted as they may require major modifications of your treatment plan. No psychiatric evaluation is complete without a risk assessment for violence and suicide (see Chaps. 30 and 33). Threats to prognosis, particularly insight and adherence, are critical (see Chap. 31). Last, without understanding very real and concrete social needs and adversity, your best laid-out treatment plan may never get implemented (see Chap. 32 for a psychosocial assessment). Table 8.2 summarizes the elements of a comprehensive assessment. Pace yourself: there is no need to complete all the elements all at once.

In order to select the best treatments and develop treatment goals, you need to keep the end in mind. Pay attention to three related but separate elements of patient outcomes: symptom level, functional achievements, and quality of life. Figure 8.1 depicts graphically (using data from a first-episode cohort study in Europe [17]) how those three outcome measures capture different aspects of the goals of schizophrenia care. Note that only a minority of patients (less than one in three patients) in this good-prognosis cohort achieve the optimal outcome: freedom from symptoms, good function, and high quality of life *at the same time*. (See next chapter for a longer discussion of treatment goals.)

Table 8.2 Comprehensive assessment of schizophrenia

Diagnostic psychiatric assessment
Presence of psychosis (disorganization, delusions/hallucination) ^a
Nonpsychotic symptoms (motor, negative, affective symptoms) ^a
Neurocognition (cognitive symptoms) ^a
Additional psychiatric syndromes
Risk assessment
Violence and legal history
Suicide history
Substance use assessment
Current and past substance use
Smoking status
Diagnostic medical assessment
History of head injuries
Antipsychotic-associated side effects
Medical diseases relevant for psychiatric diagnosis and treatment
Wellness assessment (weight, physical activity, diet)
In females: assessment of childbearing potential
Assessment of functional capacities
Treatment motivation
Neurocognition
Assessment of quality of life
Assessment of psychosocial adjustment
Assessment of threats to prognosis
History of treatment adherence
Insight into illness including capacity to accept or reject treatment

Based on [16]

^aDimensional assessment of psychopathology for six symptom clusters: motor, disorganization, paranoid-hallucinatory, negative, cognition, affective

Dimensional Assessment

Patients with schizophrenia can have different combinations of symptoms, and no two patients look alike (although there are striking similarities between schizophrenia patients across cultures, as noted earlier). Depending on the exact admixture of symptoms, different historical subtypes have been described – i.e., catatonic, disorganized (hebephrenic), paranoid, simple, undifferentiated, or residual [18]. The subtypes are neither stable over time nor very useful, in part because most patients fall into the undifferentiated or residual categories with no prognostic relevance. As a result, the classic subtypes were dropped from DSM-5 and ICD-11 and replaced by a dimensional approach.

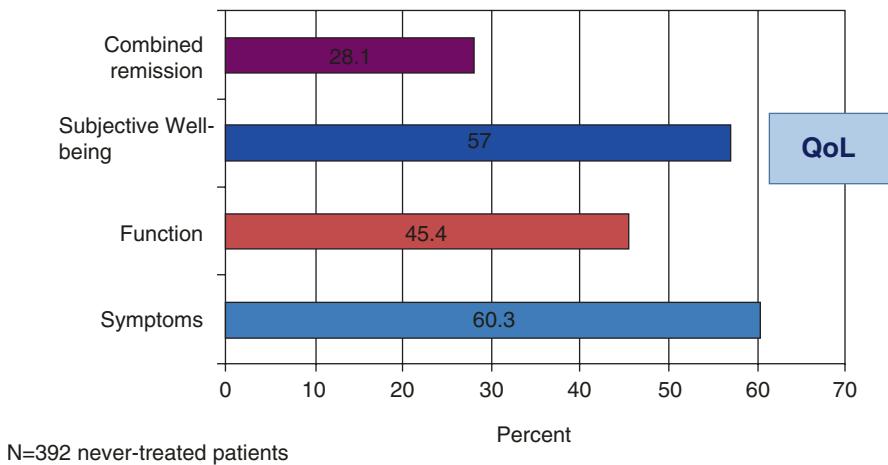


Fig. 8.1 Assessment of outcome. (Based on the SOHO (Schizophrenia Outpatients Health Outcomes) study [17])

Instead of assigning patients to a subtype, describe their symptom cluster profile, that is, which of the following six symptom clusters dominate in a given patient: motor symptoms (abnormal movements and catatonia), positive symptoms (separated into disorganization and a paranoid-hallucinatory cluster), negative symptoms, or cognitive symptoms; an affective symptom cluster (a “misery” cluster with dysphoria, depression, anxiety, and suicidality but also including disinhibition or other maniform symptoms) rounds up the six-symptom cluster dimensional assessment (see Fig. 8.2 for an example of a patient with prominent negative and cognitive symptoms and movements consistent with tardive dyskinesia). Using such a dimensional approach is also encouraged in the DSM-5 (Sect. 3) and ICD-11. (If you split up the paranoid-hallucinatory cluster and the affective symptom cluster into mania and depression, you end up with eight dimensions used in DSM-5.) Putting together a symptom profile based on the six clusters does not require additional work as it is merely a reconceptualization of your mental status exam. For any given patient, the symptom profile (e.g., minimal psychosis with prominent negative and cognitive symptoms) will guide your treatment, particularly on the outpatient side. You should consider measuring cross-sectional symptom severity with a rating scale – for example, the Brief Psychiatric Rating Scale (BPRS) for psychosis [19] in order to track progress.

Functional Assessment

You understand a patient very poorly if all you know are his symptoms but not how he is managing life in the real world. Does he independently shower? Can he use public transportation and manage his money? Does he work? Capturing real-world

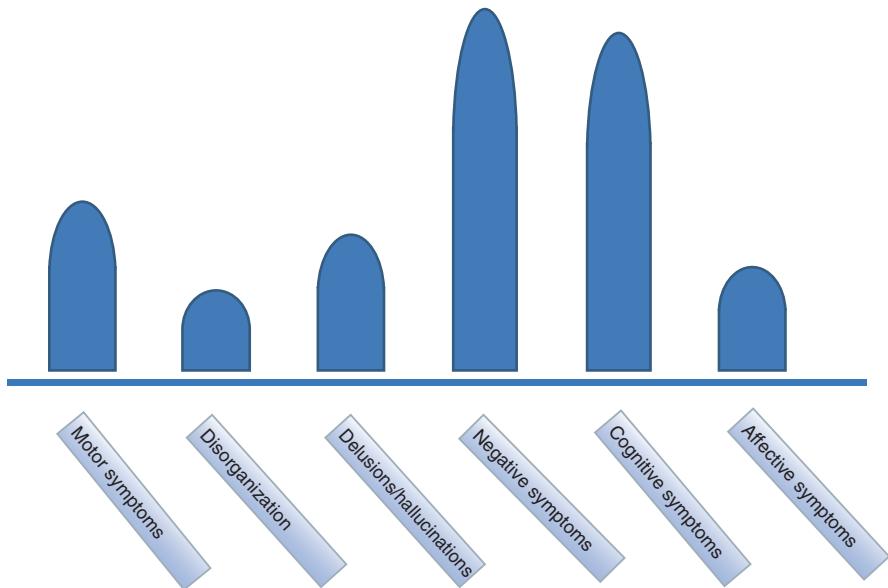


Fig. 8.2 Six symptom clusters of schizophrenia. Example for a symptom profile for a patient with predominance of negative and cognitive symptoms and some motor symptoms consistent with tardive dyskinesia. (Based on [20])

Table 8.3 Functional assessment

Understanding and communicating (e.g., concentrating, learning, problem-solving)
Getting around (e.g., mobility)
Self-care (e.g., hygiene, dressing, eating, independence)
Getting along with people (e.g., friendships, sexual activities)
Life activities (household, work, school)
Participation in society (e.g., community activities, leisure, effects of illness burden)

Based on the World Health Organization Disability Assessment Schedule (WHODAS) 2.0 [22]

function (disability) is important for treatment planning as your treatment will need to focus on rehabilitation rather than medicines alone (see Chap. 24). The Global Assessment of Functioning (GAF) scale which was used widely in the past tried to capture functioning with one number [21]. This limiting and not very informative approach has since been replaced by examining various functional domains separately. The World Health Organization's Disability Assessment Schedule (WHODAS) 2.0, for example, suggests looking at six domains (see Table 8.3) [22].

Table 8.4 Four domains of quality of life

Domain	Facets
Physical health	Pain, sleep, mobility, energy
Psychological	Self-esteem, anxiety and depression, body image, spiritual life
Social relationships	Personal relationships, social support, sex life
Environment	Financial resources, safety, housing, access to healthcare, opportunities for leisure and learning

Based on reference [23]

Assessment of Quality of Life

Consider using a brief scale (e.g., the brief version of the World Health Organization Quality of Life scale [23]) to engage patients in a discussion of their treatment goals with emphasis on life satisfaction and to identify areas of discontent, particularly unmet needs. Paying careful attention to all domains of QOL (see Table 8.4) may increase patient satisfaction with your treatment and better communication even if your clinical intervention's impact on symptoms, function, or unmet needs may be limited [24]. Ultimately, the patient needs to define what "recovery" or "the good life" means for him or her.

Use of Rating Scales

Rating scales are routinely used in research settings but less commonly in routine clinical care even though their use is typically endorsed. Such "measurement-based psychiatry" is currently mostly aspirational, although information technology will inevitably move our field toward measuring more and better [25]. At a minimum, look at commonly used research instruments, and include some questions into your assessment.

Some clinics require the use of particular scales as a quality measure, often in the form of screening tools. The Patient Health Questionnaire (PHQ-9), for example, is commonly used to screen for depression in many treatment settings [26]. Keep in mind one important principle of screening: only screen if you know what do to with the result. Also, do not ask patients to fill out rating scales without giving immediate feedback as there is a nocebo effect [24]. Have you ever been annoyed about filling out all these forms and checklists on a clipboard while waiting for your primary care doctor, only to realize that nobody ever looked at them? Immediate feedback, on the other hand, can strengthen your treatment alliance and improve patient satisfaction as patients recognize that you are paying attention to their concerns.

Tip

Self-rating scales are a quick and easy engagement tool that helps you practice patient-centered care and improve communication. Beyond the total score, pay attention to individual items (e.g., a suicide item) and how a patient approaches a scale (e.g., obsessively, with clear difficulties) [27].

References

1. Miller H. The cosmological eye. New York: New Directions; 1939.
2. World Health Organization. International classification of diseases 11th revision (ICD-11). Available from: <https://icd.who.int/en/>. Accessed on 7/1/2019.
3. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Arlington: American Psychiatric Association; 2013.
4. Freudenreich O, Querques J, Kontos N. Checklist psychiatry's effect on psychiatric education. *Am J Psychiatry*. 2004;161:930; author reply 930.
5. Hyman SE. The diagnosis of mental disorders: the problem of reification. *Annu Rev Clin Psychol*. 2010;6:155–79.
6. Keshavan MS, Morris DW, Sweeney JA, Pearson G, Thaker G, Seidman LJ, et al. A dimensional approach to the psychosis spectrum between bipolar disorder and schizophrenia: the Schizo-Bipolar scale. *Schizophr Res*. 2011;133:250–4.
7. Heckers S. Is schizoaffective disorder a useful diagnosis? *Curr Psychiatry Rep*. 2009;11:332–7.
8. Kontos N, Freudenreich O, Querques J. Thoughtful diagnoses: not checklist psychiatry [Pearls series]. *Curr Psychiatry*. 2007;6:112.
9. Westen D. Prototype diagnosis of psychiatric syndromes. *World Psychiatry*. 2012;11:16–21.
10. de Leon J. Is psychiatry only neurology? Or only abnormal psychology? Deja vu after 100 years. *Acta Neuropsychiatr*. 2015;27:69–81.
11. Tiemstra J. The poor historian. *Acad Med*. 2009;84:723.
12. Gara MA, Minsky S, Silverstein SM, Miskimen T, Strakowski SM. A naturalistic study of racial disparities in diagnoses at an outpatient behavioral health clinic. *Psychiatr Serv*. 2019;70:130–4.
13. Verdoux H, van Os J. Psychotic symptoms in non-clinical populations and the continuum of psychosis. *Schizophr Res*. 2002;54:59–65.
14. Shapiro D. Neurotic styles. New York: Basic Books; 1965.
15. Scotti-Muzzi E, Saide OL. Schizo-obsessive spectrum disorders: an update. *CNS Spectr*. 2017;22:258–72.
16. Freudenreich O, Viron M, Shtasel D. Serious mental illness. In: Stern TA, Fava M, Wilens TE, Rosenbaum JF, editors. Massachusetts general hospital comprehensive clinical psychiatry. 2nd ed. London: Elsevier; 2016. p. 703–8.
17. Lambert M, Naber D, Schacht A, Wagner T, Hundemer HP, Karow A, et al. Rates and predictors of remission and recovery during 3 years in 392 never-treated patients with schizophrenia. *Acta Psychiatr Scand*. 2008;118:220–9.
18. McGlashan TH, Fenton WS. Classical subtypes for schizophrenia: literature review for DSM-IV. *Schizophr Bull*. 1991;17:609–32.
19. Overall JE, Gorham DR. The brief psychiatric rating scale. *Psychol Rep*. 1962;10:799–812.
20. Freudenreich O. Schizophrenia? Target 6 symptom clusters [Pearls series]. *Curr Psychiatry*. 2009;8:74.
21. Goldman HH. Do you walk to school, or do you carry your lunch? [editorial]. *Psychiatr Serv*. 2005;56:419.

22. World Health Organization. WHO disability assessment schedule 2.0 (WHODAS 2.0). Available from: <https://www.who.int/classifications/icf/whodasii/en/>. Accessed on 7/1/2019.
23. World Health Organization. The World Health Organization Quality of Life (WHOQOL). Available from: https://www.who.int/mental_health/publications/whoqol/en/. Accessed on 7/1/2019.
24. Boyer L, Lancon C, Baumstarck K, Parola N, Berbis J, Auquier P. Evaluating the impact of a quality of life assessment with feedback to clinicians in patients with schizophrenia: randomised controlled trial. Br J Psychiatry. 2013;202:447–53.
25. Aboraya A, Nasrallah HA, Elswick DE, Ahmed E, Estephan N, Aboraya D, et al. Measurement-based care in psychiatry-past, present, and future. Innov Clin Neurosci. 2018;15:13–26.
26. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16:606–13.
27. Freudenberg O. Self-rating scales tell you more than the score [Pearls series]. Curr Psychiatry. 2008;7:110.

Additional Resources

Websites

https://www.who.int/mental_health/publications/whoqol/en/ – Good introduction to the importance of quality of life for patient care and how to assess it quickly yet comprehensively, using a rating scale developed by the World Health Organization.

Books

North C, Yutzy S. Goodwin and Guze's psychiatric diagnosis. 7th ed. New York: Oxford University Press; 2019. – Published originally in 1974, this book (particularly the preface to the first edition which is included in the 7th edition) is a must read for any psychiatrist who wants to critically examine the diagnostic validity of many of our current psychiatric diagnoses. The late Donald Goodwin and Samuel Guze (together with Eli Robins and George Winokur) belonged to an influential group of psychiatrists at the University of Washington in St. Louis that aligned psychiatric diagnosis with medical practice by introducing diagnostic criteria, ultimately resulting in the publication of DSM-III in 1980.

Article

Jansson LB, Parnas J. Competing definitions of schizophrenia: what can be learned from polydiagnostic studies? Schizophr Bull. 2007;33:1178–200. – Read this article to understand the vexing problem of validity of psychiatric diagnosis (and the limitations of our current approach to diagnosing schizophrenia). The issues raised over a decade ago are as pertinent today as they were then.

Chapter 9

Prevention and Clinical Staging



Essential Points

- The prevention of psychosocial toxicities due to untreated illness (job loss, interrupted education, criminal record) is an overarching goal of psychiatric treatment.
- Eliminating cannabis use during the vulnerable period is an example of primary prevention in schizophrenia.
- Early intervention (detection) and first-episode services are trying to bend the trajectory of schizophrenia toward a more benign illness course, with fewer chronic symptoms and better function.
- Reducing the duration of untreated psychosis (DUP) below 3 months is needed for optimal negative symptoms remission. In the United States, the typical DUP is between 1 and 2 years.
- Secondary prevention during the prodromal period in order to prevent the development of the full syndrome of schizophrenia is an area of great interest. Universal screening in the prepyschotic phase based on clinical ultra high-risk criteria is not sensitive or specific enough to predict transition to schizophrenia.
- Indicated prevention (signs of illness already apparent) for high-risk persons is already a form of treatment and consists of individual therapy and family support.
- Preventing psychotic relapse as an example of tertiary prevention may be one of the most important psychiatric treatment goals for patients with schizophrenia (treatment as prevention), including first-episode patients. Frequent relapse disrupts rehabilitation efforts and hinders sustained remission and eventual recovery.

- Approach the prevention of the next episode in “last-episode psychosis” patients with the same urgency as you would in preventing the second episode in first-episode psychosis patients.
- A natural outgrowth of a prevention framework is clinical staging to guide clinical care decisions with stage-specific interventions (one size does not fit all). Clinical staging emphasizes early detection, early treatment, and sustained treatment in order to avoid a progression toward higher (chronic) illness stages.
- Treatment during later illness stages (i.e., acute phase, stabilization phase, and stable maintenance phase) tries to achieve symptoms response, symptom resolution, and (sustained) symptom remission plus functional recovery, respectively. A first episode of schizophrenia is already a later illness stage as cognitive and negative symptoms develop prior to the onset of psychosis.
- Symptomatic remission in schizophrenia is defined as a relative absence of positive and negative symptoms, not a complete freedom from symptoms, for at least 6 months. Many patients are not truly asymptomatic.
- Functional recovery is only possible for a minority of patients (less than 20%).
- Always focus on rehabilitation and optimal functioning, even in the presence of symptoms (freedom from symptoms might not be possible).

“Nach dem Spiel ist vor dem Spiel.” [1]

(After the game is before the game.)

— Josef “Sepp” Herberger (1897–1977); fabled coach of 1954
West German soccer team

A prevention mind-set and clinical staging are two frames of reference that inform our care for patients with schizophrenia. Clinical staging which is a translation of prevention principles into clinical care defines stage-specific treatment goals and helps select stage-specific interventions in order to achieve the best possible treatment outcome, within the limitations of biology. Principles from this chapter are taken up in more detail in several other chapters. Optimal treatment for likely prodromal schizophrenia and a first episode of psychosis is covered in Chap. 11; treatment for severe and unremitting (treatment-resistant) illness in Chap. 12; treatment with clozapine in Chap. 17; and treatment with long-acting injectable antipsychotics in Chap. 18. The prevention of medical morbidity and mortality is such an important goal of schizophrenia treatment that I dedicate a separate chapter to it as well (Chap. 25).

Psychosocial Toxicities

Let us start with the end in mind: what constitutes a “bad outcome” of schizophrenia and what are factors leading to it? You probably would list, in addition to experiencing unpleasant symptoms, downstream social consequences of having a psychiatric illness such as unemployment, interrupted schooling, homelessness, being victimized, a criminal history, or loss of your reputation. These outcomes could be subsumed under the term “psychosocial toxicities.” Many factors can lead to them: arriving to treatment late or not at all, not receiving optimal treatment once in treatment, substance use, or poor engagement in or persistence with treatment [2]. Substance use and medical comorbidities are additional contributors. Psychotic relapses are responsible for much of the social damage that patients with schizophrenia accrue over time.

Key Point

Schizophrenia is a progressive social disease with accrued disability over time if no treatment is provided. For most, it is not a progressive brain disease with inevitable clinical outcomes.

Except for the small group of truly treatment-resistant patients who have nonresponsive biology, many of these “psychosocial toxicities” could be prevented with optimal psychiatric treatment. While we are currently not able to prevent schizophrenia, we can do a lot to mitigate the ramifications of having schizophrenia (its psychosocial toxicities) by providing care that is timely and optimal for the patient (one size does not fit all). In the language of HIV medicine: treatment as prevention.

Key Point

Preventing premature death and psychosocial toxicities *from having schizophrenia* (joblessness, loneliness, homelessness, victimization, and criminalization) is within the realm of possibilities for many patients who have schizophrenia. While a societal commitment is needed to achieve some goals, optimal clinical care is the foundation for living well despite schizophrenia.

Prevention in Schizophrenia

Public health traditionally differentiates between primary, secondary, and tertiary prevention activities [3]. Primary prevention aims to prevent a disease from ever occurring in a population (e.g., vaccinations, limiting environmental exposures by creating

a clean environment); secondary prevention uses screening to detect a disease early (before the onset of symptoms) when treatments are more effective and potentially curative (e.g., cancer screening); tertiary prevention are treatment efforts that try to limit the impact of a disease (e.g., surgery and rehabilitation). Using a prevention framework increases our repertoire of interventions beyond providing treatment [4].

Primary Prevention

The holy grail of prevention is primary prevention by removing risk factors for an illness so that the illness never develops in the first place. Preventing prenatal nutrient deficiencies [5] and improving obstetric care to avoid birth complications [6] are examples in schizophrenia care. Preventing all cannabis use during early adolescence and adulthood, if it were possible, would constitute primary prevention as cannabis is considered a component cause of schizophrenia (see Chap. 4 on drug-induced psychosis). Increasing resilience (at the individual and at the community level) is another promising primary prevention intervention as it can neutralize risk factors like social stress and protects normal brain development [7].

Early Intervention

The past decades have seen a renewed interest in identifying people at high-risk for developing schizophrenia and intervening in order to prevent the full syndrome of schizophrenia. The term “early intervention” is often used to capture screening (early detection) and treatment activities around the onset of full-blown psychosis [8]. In recognition of the important first few years around and after the onset of psychosis, a “critical illness period” has been postulated during which the provision of optimal treatment would have a positive effect on the long-term outcome. Many countries started specialized first-episode programs to provide stage-appropriate care.

Universal, selective, and indicated prevention is terminology that is more helpful than primary/secondary/tertiary prevention to characterize early intervention efforts (Table 9.1). All three efforts attempt to prevent new cases of schizophrenia. Note that indicated prevention straddles the border to clinical treatment, reflective of our inability to delineate exactly where a “case” in a neurodevelopmental disorder begins. Indicated prevention already constitutes treatment, despite its name.

Table 9.1 Prevention in early psychosis and first-episode psychosis

	Target group	Examples
Universal prevention	Whole population	Folic acid supplementation
		Improving obstetric care
Selective prevention	Symptom-free but high-risk	Support to reduce stress
Indicated prevention	Already showing signs of illness	Specialty “early intervention” care

Based on Ref. [4]

Early Detection

Unfortunately, a quite lengthy period of untreated psychosis precedes the initiation of psychiatric treatment. In the first-episode RAISE cohort, the median time from onset of psychotic symptoms to treatment was 74 weeks [9]. Shortening this so-called duration of untreated psychosis (DUP) is an example of early intervention as it may improve a patient's prognosis [10, 11]. As opposed to the signs of a heart attack, most people would be hard-pressed to identify the signs of an acute psychotic episode, resulting in lengthy treatment delays on the patient side. Community efforts like education about psychosis combined with easy access and outreach can shorten the DUP. In one region in Scandinavia that implemented such a community-wide and multipronged early detection effort, the DUP was shortened from 4 months (which is already quite short) to about 1 month [12], which resulted in improved negative symptoms [13]. Unfortunately, the gains were lost once the educational campaign came to an end [14]. Treatment delays happen on the patient and family side (not seeking treatment) but also on the treatment system side when patients are not given easy access to seeing a psychiatrist, ideally somebody with expertise in early psychosis [15]. Any delay within the treatment system itself should be unacceptable; we do not accept it in oncology. Reducing DUP below 3 months appears to be critical for negative symptoms remission [16]. A particular challenge is identifying patients with a very insidious illness onset as treatment is greatly delayed.

I want to emphasize that early detection of a first episode of psychosis is a very late disease stage if viewed from the point of schizophrenia as a neurodevelopmental disorder. Treatment at this stage is already tertiary prevention – you are merely trying to blunt the effect of illness! Similarly, identifying people at high-risk during a putatively prodromal period is probably too late since neurocognitive problems develop many years before schizophrenia declares itself by the onset of psychosis (see Chap. 7 on natural history) [17]. The time for truly early intervention with the goal of changing a young person's trajectory away from schizophrenia must therefore come much earlier than our current efforts. Children at high genetic risk because of a parent with schizophrenia, for example, may benefit from identification in pediatric care and close follow-up, including the avoidance of additional risk factors like cannabis use [7].

While the early intervention movement has clearly reinvigorated psychiatry, we cannot forget that chronic patients also benefit from optimal treatment. Moreover, long-term studies that have followed optimally treated first-episode patients (e.g., the OPUS cohort) have found that long-term support is needed to maintain gains made [18].

Tertiary Prevention

Tertiary prevention is the key concern for clinicians treating patients with established schizophrenia. Optimal disease management with the tools of our profession (pharmacotherapy, rehabilitation) can make the difference between a good life despite a serious illness and a life of homelessness or early death.

Key Point

Like multiple sclerosis, schizophrenia can be viewed as a relapsing-remitting disease, *with accrued psychosocial toxicity over time due to relapse*. Preventing psychotic relapse as an example of tertiary prevention may be one of the most important psychiatric treatment goals for patients with schizophrenia outside managing an acute psychotic episode.

Preventing Relapse

Keeping patients in long-term symptomatic remission is one of the most important treatment goals for patients with schizophrenia. This cannot be overemphasized, as the foundation for any functional improvement hinges on the ability to participate in treatment and rehabilitation. Preventing relapse is not only a goal in first-episode patients but should also be a goal in multi-episode patients. View these patients as “last-episode” psychosis patients – dedicate your efforts to preventing the next episode, just like you would dedicate your energies in first-episode patients trying to prevent a second episode [19]. Decades of clinical experience have clearly established antipsychotics to be highly effective medication in reducing the risk of relapse [20], comparable in efficacy to other medical treatments.

Key Point

The psychotic relapse risk after discontinuing antipsychotics is very high for both first-episode and multi-episode patients. In unselected first-episode patients, only a minority of 20% does not experience a second episode. Unfortunately, we are currently not able to tell who will not need further treatment. A seminal research study of first-episode patients showed a broadly defined relapse rate (re-emergence of symptoms, not necessarily hospitalization) approaching 100% after 2 years [21].

In clinical reality, most patients will want to stop their medications at some point. This is true for both first-episode and multi-episode patients. It is prudent to plan for this contingency since early detection of relapse is possible and a full relapse can often (but not always) be averted if treatment is reinstated in time [21]. If a decision is made to stop antipsychotics, try to do the following to minimize the risk of a major relapse:

- Taper antipsychotics over many months, if feasible (to reduce withdrawal effects). The optimal rate of dose reduction is unknown.
- Develop an individualized relapse signature based on the knowledge about how previous episodes have developed. The idea is to reinstate antipsychotics early

when relapse is just beginning. While this works in some people, others will lose insight once they develop symptoms and not return to antipsychotics. In some patients, the relapse is rather sudden, without much warning (see Chap. 7 on natural history).

- If your patient is asking for a treatment-free period, argue for antipsychotic continuation until a major milestone is reached (e.g., finishing college). I admit that there might never be a good time to relapse.
- Inform patients that relapse risk is stable and does not decrease with time: relapse risk is a constant (i.e., your propensity to relapse does not change with time, regardless of the number of symptom-free years on treatment). A stable relapse risk unrelated to the duration of remission is counterintuitive for patients. Biologically, the vulnerability toward relapse is constant as antipsychotics do not address the underlying biology of a relapse, merely its expression.
- Have a frank discussion about the risks of relapse and the risks and benefits of treatment. In some cases, advise against discontinuation if psychosis was dangerous, and document that discontinuing the antipsychotic is against your medical advice.
- Inform patients that they may not recover from their next episode as well as to the previous one. The difference may be particularly important between the first and second episode [22]. Warn them that they may become more treatment-resistant with each psychotic episode.
- Point out the survival benefit from treating schizophrenia with antipsychotics. In one very large Swedish register-based cohort study, the use of antipsychotics compared to no use reduced mortality by 50% [23]. The most benefit was seen for oral aripiprazole and second-generation long-acting injectable antipsychotics.

Given the nature of schizophrenia (relapsing-remitting illness) and the established benefit from maintenance treatment with antipsychotics (relapse prevention), I cannot overstate the prevention rational for using long-acting injectable antipsychotic for all patients who need antipsychotic maintenance treatment (see Chap. 18 on LAIs).

Intermittent treatment (treatment with antipsychotics only during acute illness phases) is not as effective as continuous treatment, at least not for multi-episode patients, and is discouraged for most patients [24]. It is sometimes the only type of treatment, however, that patients agree to. One patient told me that she preferred an annual hospitalization for psychosis during which treatment is provided to the long-term side effects from maintenance antipsychotics.

Key Point

The goal of maintenance treatment with antipsychotics for schizophrenia is prevention of relapse to reduce the impact of schizophrenia (tertiary prevention). For almost all patients with schizophrenia, antipsychotics are the foundation for sustained symptomatic remission which is the basis for functional remission and recovery.

STAGE	Definition	Clinical features
0	Asymptomatic subjects	Not help seeking No symptoms but risk
1a	“Help-seeking” subjects with symptoms	Non-specific anxiety/depression Mild-to-moderate severity
1b	“Attenuated syndromes”	More specific syndromes incl. mixed At least moderate severity
2	Discrete disorders	Discrete syndromes Moderate-to-severe symptoms
3	Recurrent or persistent disorder	Incomplete remission Recurrent episodes
4	Severe, persistent and unremitting illness	Chronic deteriorating No remission for 2 years

Fig. 9.1 Clinical staging of schizophrenia. (Adapted from Refs. [25, 26])

Clinical Staging

A natural outgrowth of a prevention framework is illness staging to guide clinical care decisions. Clinical staging makes sense for disorders where early detection is possible and where different stages suggest different treatments and different outcomes. A good example in medicine is cancer. Cancer screening efforts attempt to identify disease early, when treatment can be less aggressive or even curative. Later disease stages may merely be amendable to palliation. Only fairly recently has a staging paradigm been applied to schizophrenia care (see Fig. 9.1).

The fundamental goal implicit in clinical staging is to prevent a progression to higher, more severe illness stages. Several important treatment principles can be derived from this overarching goal:

- *Early treatment:* diseases are generally more responsive earlier, and treatments can be less aggressive. Early detection programs are trying to reduce the duration of untreated psychosis (DUP) in order to treat schizophrenia as early as possible, before psychosocial toxicities (and a more ill-defined biological damage visible in negative symptoms) pile up from untreated psychosis.
- *Phase-specific treatment:* one size does not fit all, but treatment needs to be tailored to the specific needs for patients in a particular illness phase. Chapter 11 applies this principle to first-episode patients.
- *Stepped treatment:* if a particular treatment is not working, treatment is changed and escalated until there is the desired outcome (treatment to target). The latter principle is often violated in psychiatry, where “being on medicine” often becomes a goal in and of itself, even though a patient might not benefit. Not using clozapine in a treatment-resistant patient would be an example.

Tip

If your patient's symptoms are not responding well to your treatment, think of ways to step up care: change to a different antipsychotic (LAI or clozapine), or add psychological treatments (CBT for psychosis). Do not forget that work is salutogenic, and encourage some activities, if tolerated; symptoms may improve.

Clinical staging allows us to be precise when we define treatment goals. Two concrete treatment goals are (1) to achieve symptomatic remission and (2) to keep a patient in prolonged symptomatic remission by preventing relapse (already discussed earlier).

Symptomatic Remission

Consensus criteria for what constitutes “remission” have been developed and validated in many treatment samples since their inception (Table 9.2) [27].

Importantly, the consensus working group decided to define remission as remission with regard to symptoms only (i.e., symptomatic remission), and not with regard to function. Separating symptomatic and functional remission is conceptually helpful since it brings into clear focus our task as psychiatrists: to optimally treat symptoms *until remission*, as defined (minimal symptoms in three core symptom areas). After all, medications which are our most important tool only address symptoms; functional gains require rehabilitation. According to the consensus definition, complete freedom from symptoms is not necessary (nor usually possible). This may not be a small, academic point as only a minority of patients is truly asymptomatic (using a different metric using clinical global impression), even if they fulfill remission criteria as defined by the working group [28]. Remission as commonly understood in medicine may not be as easily achieved in schizophrenia.

The second critical decision made by the consensus working group was to stipulate that symptomatic remission had to be sustained. While psychiatrists are also interested in a medication response (reduction in symptoms) and an early remission,

Table 9.2 Consensus criteria for symptomatic remission in schizophrenia

-
1. Focus on three core psychopathologic symptom dimensions (delusions and hallucinations; disorganization; negative symptoms)
 2. Symptom severity below clinically significant threshold for all core domains (i.e., mild or less)
 3. Sustained symptomatic remission for at least 6 months
-

Adapted from Ref. [27]

Notes: Remission does not require complete freedom from symptoms

Remission focuses on symptomatic, not functional recovery

particularly in acute treatment settings, the real work of putting lives back together requires sustained symptomatic remission. Without sustained freedom from symptoms, rehabilitation efforts are very difficult to implement. Functional improvement accrues over time, and each psychotic relapse disrupts this process, possibly negating gains made. Consider how damaging a hospitalization is if a patient has just started working again, after many months of vocational rehabilitation and trying to find a job. Each relapse potentially adds the afore-mentioned psychosocial toxicity.

Functional Remission and Recovery

Ultimately, patients need to rebuild their lives after a psychiatric hospitalization. Liberman and Kopelowicz [29], two rehabilitation specialists from the University of California in Los Angeles (UCLA), have proposed specific recovery criteria, including four domains that must be met for at least 2 years: symptom remission (positive as well as negative symptoms); appropriate role function (part-time work or school, homemaker); ability to perform day-to-day living tasks without supervision; and social interactions with people outside the family.

Statistically, the odds for such defined full recovery are not good. In one trial of first-episode patients, only 14% met the above UCLA recovery criteria 5 years later [30]. For some patients, freedom from symptoms and independence in a complex society are illusory treatment goals. Imposing the idea of full “recovery,” often equated with being “cured” (and not needing medications as a corollary) by patients and families, on partially refractory patients and their families is cruel. Refer to Chap. 8 for functional assessment and Chap. 24 for more thoughts about recovery.

References

1. Wikipedia. Herberger, Sepp. Available from: https://en.wikipedia.org/wiki/Sepp_Herberger. Accessed on 7/1/2019.
2. Zipursky RB, Reilly TJ, Murray RM. The myth of schizophrenia as a progressive brain disease. Schizophr Bull. 2013;39:1363–72.
3. CDC. Prevention. Available from: https://www.cdc.gov/pictureofamerica/pdfs/picture_of_america_prevention.pdf. Accessed on 7/1/2019.
4. Institute of Medicine (US) Committee on Prevention of Mental Disorders. Reducing risks for mental disorders: frontiers for preventive intervention research. Washington, DC: National Academies Press; 1994. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK236319/>. Accessed on 7/1/2019.
5. Freedman R, Hunter SK, Hoffman MC. Prenatal primary prevention of mental illness by micronutrient supplements in pregnancy. Am J Psychiatry. 2018;175:607–19.
6. Warner R. The prevention of schizophrenia: what interventions are safe and effective? Schizophr Bull. 2001;27:551–62.
7. Sommer IE, Bearden CE, van Dellen E, Breetvelt EJ, Duijff SN, Majjer K, et al. Early interventions in risk groups for schizophrenia: what are we waiting for? NPJ Schizophr. 2016;2:16003.

8. Srihari VH, Tek C, Pollard J, Zimmet S, Keat J, Cahill JD, et al. Reducing the duration of untreated psychosis and its impact in the U.S.: the STEP-ED study. *BMC Psychiatry.* 2014;14:335.
9. Addington J, Heinssen RK, Robinson DG, Schooler NR, Marcy P, Brunette MF, et al. Duration of untreated psychosis in community treatment settings in the United States. *Psychiatr Serv.* 2015;66:753–6.
10. Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Arch Gen Psychiatry.* 2005;62:975–83.
11. Penttila M, Jaaskelainen E, Hirvonen N, Isohanni M, Miettunen J. Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: systematic review and meta-analysis. *Br J Psychiatry.* 2014;205:88–94.
12. Melle I, Larsen TK, Haahr U, Friis S, Johannessen JO, Oajordsmoen S, et al. Reducing the duration of untreated first-episode psychosis: effects on clinical presentation. *Arch Gen Psychiatry.* 2004;61:143–50.
13. Melle I, Larsen TK, Haahr U, Friis S, Johannessen JO, Oajordsmoen S, et al. Prevention of negative symptom psychopathologies in first-episode schizophrenia: two-year effects of reducing the duration of untreated psychosis. *Arch Gen Psychiatry.* 2008;65:634–40.
14. Joa I, Johannessen JO, Auestad B, Friis S, McGlashan T, Melle I, et al. The key to reducing duration of untreated first psychosis: information campaigns. *Schizophr Bull.* 2008;34:466–72.
15. Cotter J, Zabel E, French P, Yung AR. Prolonged duration of untreated psychosis: a problem that needs addressing. *Early Interv Psychiatry.* 2017;11:263–8.
16. Dama M, Shah J, Norman R, Iyer S, Joober R, Schmitz N, et al. Short duration of untreated psychosis enhances negative symptom remission in extended early intervention service for psychosis. *Acta Psychiatr Scand.* 2019;140:65–76.
17. Seidman LJ, Shapiro DI, Stone WS, Woodberry KA, Ronzio A, Cornblatt BA, et al. Association of neurocognition with transition to psychosis: baseline functioning in the second phase of the North American Prodrome Longitudinal Study. *JAMA Psychiatry.* 2016;73:1239–48.
18. Secher RG, Hjorthoj CR, Austin SF, Thorup A, Jeppesen P, Mors O, et al. Ten-year follow-up of the OPUS specialized early intervention trial for patients with a first episode of psychosis. *Schizophr Bull.* 2015;41:617–26.
19. Munk-Jorgensen P, Nielsen J, Nielsen RE, Stahl SM. Last episode psychosis. *Acta Psychiatr Scand.* 2009;119:417–8.
20. Leuchi S, Tardy M, Komossa K, Heres S, Kissling W, Salanti G, et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *Lancet.* 2012;379:2063–71.
21. Gitlin M, Nuechterlein K, Subotnik KL, Ventura J, Mintz J, Fogelson DL, et al. Clinical outcome following neuroleptic discontinuation in patients with remitted recent-onset schizophrenia. *Am J Psychiatry.* 2001;158:1835–42.
22. Takeuchi H, Siu C, Remington G, Fervaha G, Zipursky RB, Foussias G, et al. Does relapse contribute to treatment resistance? Antipsychotic response in first- vs. second-episode schizophrenia. *Neuropsychopharmacology.* 2019;44:1036–42.
23. Taipale H, Mittendorfer-Rutz E, Alexanderson K, Majak M, Mehtala J, Hoti F, et al. Antipsychotics and mortality in a nationwide cohort of 29,823 patients with schizophrenia. *Schizophr Res.* 2018;197:274–80.
24. Sampson S, Mansour M, Maayan N, Soares-Weiser K, Adams CE. Intermittent drug techniques for schizophrenia. *Cochrane Database Syst Rev.* 2013;(7):CD006196.
25. Hickie IB, Scott EM, Hermens DF, Naismith SL, Guastella AJ, Kaur M, et al. Applying clinical staging to young people who present for mental health care. *Early Interv Psychiatry.* 2013;7:31–43.
26. Hickie IB, Scott J, McGorry PD. Clinical staging for mental disorders: a new development in diagnostic practice in mental health. *Med J Aust.* 2013;198:461–2.

27. Andreasen NC, Carpenter WT Jr, Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. *Am J Psychiatry*. 2005;162:441–9.
28. Schennach R, Obermeier M, Spellmann I, Seemuller F, Musil R, Jager M, et al. Remission in schizophrenia - what are we measuring? Comparing the consensus remission criteria to a CGI-based definition of remission and to remission in major depression. *Schizophr Res*. 2019;209:185.
29. Liberman RP, Kopelowicz A, Ventura J, Gutkind D. Operational criteria and factors related to recovery from schizophrenia. *Intern Rev Psychiatry*. 2002;14:256–72.
30. Robinson DG, Woerner MG, McMeniman M, Mendelowitz A, Bilder RM. Symptomatic and functional recovery from a first episode of schizophrenia or schizoaffective disorder. *Am J Psychiatry*. 2004;161:473–9.

Additional Resources

Articles

Andreasen NC, Carpenter WT Jr, Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. *Am J Psychiatry*. 2005;162:441–9. – A seminal article as it provides a consensus view of what constitutes remission in schizophrenia, providing you with a goal post for your treatment efforts.

McGorry PD, Nelson B, Goldstone S, Yung AR. Prevention: a heuristic and practical strategy for new research and better health and social outcomes for psychotic and related mood disorders. *Can J Psychiatr*. 2010;55:486–97. – A visionary article about how staging can be applied to improve psychosis care.

Munk-Jorgensen P, Nielsen J, Nielsen RE, Stahl SM. Last episode psychosis. *Acta Psychiatr Scand*. 2009;119:417–8. – This is one of the articles that changed how I practice: any episode in a patient with schizophrenia should be approached with the same urgency to make it this patient's last episode. It does not matter if it is the first, second or tenth episode. The epigraph reflects this sentiment.

Chapter 10

Emergency Management of Acute Psychosis



Essential Concepts

- During all steps of the emergency evaluation of a psychotic patient, ensure the safety of the patient, staff, and other patients in the emergency department (ED).
- Agitation is a behavioral emergency that needs to be treated aggressively. Even better: recognize who is at risk for agitation and offer medications early (before agitation) to prevent further behavioral escalation and violence. However, the ultimate goal of the emergency evaluation is diagnosis, so avoid oversedation.
- The most important determination in the ED will be if a psychotic patient is medically ill or delirious; intoxicated or withdrawing; or if the patient suffers from a primary psychiatric illness. The three are not mutually exclusive.
- Verbal de-escalation should be the first-line, gold-standard approach to agitation.
- There is no one best medication or medication combination that treats all agitation. The best choice depends on the acuity of the agitation, its etiology, and patient cooperativeness.
- Oral antipsychotic preparations (including rapidly acting preparations) or inhaled loxapine should be offered prior to moving to short-acting intramuscular antipsychotics.
- Do not use antipsychotics if there is concern for catatonia or NMS.
- Physical restraints should never be used lightly, but they can be lifesaving if needed.
- For acutely manic patients, valproate loading is a safe and effective strategy to quickly control mania. Treatment can be initiated in the emergency department.

- Do not discharge a patient with psychosis from the ED unless you are confident about your diagnosis and the feasibility of your follow-up plan.

“Coolness and absence of heat and haste indicate fine qualities.” [1]

– Ralph Waldo Emerson, American transcendentalist, 1803–1882

The emergency evaluation and treatment of a psychotic patient has several goals that I discuss in this chapter: (1) excluding medical etiologies for symptoms; (2) rapid stabilization of the acute crisis; (3) avoiding coercion; (4) treating in the least restrictive setting; (5) forming a therapeutic alliance; and (6) appropriate disposition and after-care plan [2]. In the emergency setting, you might have to treat psychotic patients before you have a firm (or any) diagnosis. Consider diagnosis to be a reiterative process, and the process outlined below is not necessarily linear and sequential. At all times, remember Emerson’s quote and approach psychotic patients calmly and without haste. Leadership matters: the way you compose yourself in the emergency room impacts the patient and your team. Managing agitation optimally and fast is critical to avoid complications (patient injury, staff injury).

Initial Stabilization for Safety

First, you need to decide where in the ED acutely psychotic patients need to go: Can they simply wait in the general waiting area with a family member until they can be seen, should they be secured in a locked room, do they need to be restrained, do they need an observer to monitor them, or do they need to go to the medical side (if the psychiatric ED is separate from the medical ED)?

Symptoms of psychosis are often very disturbing to patients and may lead to poor judgments regarding safe behavior. Agitation is a combination of physical signs involving aimless movements that suggest internal emotional distress. Staring intensely, hand wringing, fidgeting, pacing, clenched fists, shadowboxing, posturing, and pounding on doors or walls are all signs of agitation. Some patients may arrive agitated or combative, whereas others are calm until they recognize that their families have coaxed them into going to the ED under false pretenses. Patients might agree to an evaluation if they perceive that you are at least considering “letting them go” after the evaluation. Never promise that you will let a patient go if the patient talks with you, but inform the patient that talking with you is a sine qua non for possible release. Pleading the 5th in the ED is not a good choice for a patient!

Tip

A psychotic patient in the ED should be viewed as potentially violent until proven otherwise. To gauge potential for violence, review all accompanying materials before you go to see the patient.

The best management of agitation is preventing it in the first place. A series of interventions can be offered to decrease a patient's distress and avoid further behavioral escalation. Offers of food and drink, warm blankets, a trip to the restroom, or a more comfortable place to wait may decrease anxiety and help you to form an alliance. As importantly, consider offering medications very early, perhaps at first contact to prevent agitation to begin with. Most patients who come to the ED are distressed, so low-dose oral lorazepam or a low-dose of an oral antipsychotic may settle patients. Acknowledge the patient's power to make (some) decisions and provide information about the ED process in a calm voice. Clear limit-setting about safe behaviors in the ED also sets the stage for offers of medication if the patient is unable to behave in a safe manner. Verbal de-escalation should be standard practice [3]. If a patient appears agitated, keep yourself safe by maintaining at least an arm's distance from the patient, meet in a location where you can leave the room quickly, and limit the items in the room that could be picked up or thrown.

If a patient requires medication, follow the principles below in the next paragraph for acute treatment with medications. If done correctly, medications are a safe way to protect patients, caregivers, and other patients from injury. Appropriate use of medication also reduces the time that a patient might spend in physical restraints. Unfortunately, the ill-advised term "chemical restraint" is still used rather than emphasizing that medications are used to *treat* agitation. Physical restraint, a last resort in the management of acute agitation, can be necessary and lifesaving for extremely agitated patients *and for the protection of your staff*. In a typical ED, physical restraints are mostly needed for young patients under the influence of drugs or older, confused patients [4]. Many EDs have made progress in reducing the need for physical restraint which is a quality of care measure [5]. As a matter of respect for patients, follow protocols as they are a safeguard against overuse of the physical restraint tool.

Whenever possible, use oral medications including rapidly dissolving preparations in cooperative patients. Sublingual asenapine is a fast-acting alternative to an injection, if an oral medication is accepted [6]. The mid-potency antipsychotic loxapine is available as an aerosol that patients inhale using a small device [7]. Inhaled loxapine leads to rapid reduction of agitation, faster than intramuscular aripiprazole in one study that compared those two approaches [8]. Like oral medications, the loxapine spray requires a cooperative patient who can inhale the medicine correctly (it is not widely used in our geographic area). It should not be used in settings where patients cannot be intubated should bronchospasm occur from the inhalation. A show of force might convince patients to cooperate and accept oral medications or the loxapine inhaler, and not risk a fight. If intramuscular medication administration is required, many emergency room clinicians use haloperidol together with a benzodiazepine (and diphenhydramine for prophylaxis against dystonia) as a first-line treatment for agitated, psychotic patients, unless benzodiazepines are specifically contraindicated [9]. Intramuscular droperidol is quite effective for agitation [10] but has fallen out of favor because of concerns about QTc prolongation [11]. Several second-generation antipsychotics are available as short-acting intramuscular (IM) preparations (aripiprazole, olanzapine, and ziprasidone). Olanzapine in particular is quite effective in acute settings. (Do not confuse the short-acting intramuscular

preparations with the long-acting injectables for maintenance treatment!) They offer good efficacy and, compared to haloperidol, a lower risk for acute dystonic reactions and akathisia [12]. The culture of the ED you are working in more so than the clinical picture is going to determine which antipsychotics are available. Increasingly, ketamine is used for the initial control of severe agitation [13]. I am more likely to use second-generation antipsychotic in the ED setting if schizophrenia is the reason for agitation (consistent with Lukens et al.) [14]. Olanzapine is a good choice because of its sedative-ataractic qualities (avoid concurrent benzodiazepines). Otherwise, I use the haloperidol-lorazepam combination, which has an excellent track record regarding both safety and efficacy for any acute behavioral emergency. In some situations, it is probably safer to use benzodiazepines alone – e.g., antipsychotics increase risks for neuroleptic malignant syndrome (NMS) in patients with amphetamine intoxication.

Key Point

Do not use antipsychotics if catatonia or NMS is a diagnostic possibility.

Agitation due to intoxications from unknown causes is sometimes managed initially with only benzodiazepines in order to avoid added cardiac toxicity from antipsychotics [15]. Agitated, alcohol-intoxicated patients, however, are often better treated with antipsychotics to avoid respiratory depression. Benzodiazepines are needed for alcohol withdrawal. Note that agitated patients in alcohol or benzodiazepine withdrawal might need substantially higher doses of benzodiazepines than commonly recommended for acute agitation from other causes. If patients are psychotic, however, benzodiazepines are often insufficient as they merely sedate without treating the psychotic state. Severe, nonresponsive agitation such as you can see in refractory mania may require a transfer to an intensive care unit for sedation using anesthetics (e.g., propofol) [16]. Do not use “rapid neuroleptization” (i.e., the use of large loading doses of antipsychotic), as this strategy does not confer any benefit and you end up giving unnecessarily high antipsychotic doses [17].

Key Point

There is no one best medication or medication combination for the management of agitation [11]. The best approach hinges on the clinical situation (acuity, etiology, cooperativeness).

The following are common mistakes that I have seen in the use of medications for acute agitation:

- An initial dose is given but not repeated in a timely fashion, even though the patient is not calm. Agitation is a behavioral emergency and must be treated like any medical emergency: with close follow-up *until the emergency situation is resolved*.

Table 10.1 Psychopharmacology of acute agitation

<i>First-line oral options</i>
Diazepam 5–10 mg PO ^a
Lorazepam 1–2 mg PO/SL
Olanzapine 5–10 mg PO ^b
Risperidone 1–2 mg PO ^c
Asenapine 5–10 mg SL
<i>First-line parenteral options</i>
Haloperidol 5 mg plus lorazepam 2 mg plus diphenhydramine 50 mg IM ^d
Olanzapine 10 mg IM
<i>Second-line options</i>
Inhaled loxapine 10 mg (give only if respiratory distress can be managed)
Chlorpromazine 25–50 mg IM (never IV; IM more potent than oral)
Droperidol 5–10 mg IM (QTc prolongation)
<i>Third-line options</i>
Benzodiazepines given as IV slow bolus injection (give only if respiratory depression can be managed)
Haloperidol IV (give only if arrhythmias can be managed)

^aOral onset almost as fast as IV onset. Also available as liquid. Do not give IM because of erratic absorption

^bAlso available as orally disintegrating tablet

^cAlso available as liquid or orally disintegrating tablet

^dRepeat every 20 minutes if no effect. Once haloperidol 20 mg TD is given use only benzodiazepines. Give only two doses of diphenhydramine per 24 hours (anticholinergic delirium). Use higher doses of lorazepam (e.g., more than 6 mg) only in setting where flumazenil and ventilation are available

- Patients are given too much medication and are put to sleep. Your goal is to examine the patient to arrive at a diagnosis that will guide treatment, not to have a patient sleep in the ED.
- The standard cocktail (of haloperidol plus lorazepam plus benztrapine) is repeated until the patient has developed anticholinergic toxicity and/or akathisia.
- Patients are given benzodiazepines to the point of a benzodiazepine intoxication delirium.

Table 10.1 provides a few options for acutely agitated, healthy adult patients who need immediate treatment of agitation in an emergency department setting. Choice and doses need to be modified based on the clinical situation.

Initial Diagnosis and Differential Diagnosis

Once the patient is calm, perform a physical examination, a mental status examination, and order some initial labs. A delirium is a medical emergency and always has a medical cause that needs to be identified and treated, if possible (see Chap. 3 on delirium work-up and treatment). In textbook cases, a delirious patient with

psychosis is inattentive and has obvious memory problems, whereas a psychiatrically psychotic patient has no problems in those realms. In reality, I have examined many psychotic patients who have great difficulties relating their history coherently or who do not cooperate sufficiently with my examination. Sometimes sedating medications were given, which obfuscate the picture further. You will have to rely on your overall impression and serial examinations. Severe mania can appear delirious, hence the term “delirious mania.”

There is no generally agreed upon “medical clearance” that every psychotic patient must have in the ED, but I think it is reasonable to obtain routine labs to exclude intoxication, withdrawal, or common, treatable medical illnesses as the cause of psychosis, supplemented by lumbar puncture, electroencephalogram (EEG), and computed tomography/magnetic resonance imaging (CT/MRI) of the brain, if indicated clinically (use Table 3.3 as a guide for what to include in your work-up). The history that accompanies a patient, vital signs, your mental status examination, and initial labs should allow you to triage patients who are referred to the ED for “acute psychosis” into one of these subgroups:

Young, combative patients, possibly psychotic Any combative patient should be considered as potentially being psychotic. Common diagnoses in the differential include intoxication (e.g., PCP), withdrawal from a substance (e.g., alcohol), delirium, or a personality disorder. History and a urine drug screen (UDS) might help. Note, however, that the UDS does not screen for all drugs of abuse (e.g., LDS, ketamine, designer drugs). Paranoid patients can be violent, particularly if drug use is involved. Irritable mania can also lead to a very volatile presentation.

Older patient with recent onset of psychosis Until proven otherwise, any patient without a psychiatric history who presents with psychosis after the age of 40 should be considered medically ill, most likely delirious. The older the patient, the less likely this will be in initial presentation of a schizophrenia spectrum disorder. Elderly, delirious patients can be quietly psychotic and withdrawn. Always perform a urinalysis for these patients, because a urinary tract infection is a major risk factor for mental status change in older patients [18]. Other diagnoses to consider are dementia with psychosis, psychotic depression, or psychotic mania.

Young patient with first episode of psychosis: “first-episode patient” A typical history will show a college student with a decline in psychosocial function over several months or sometimes even years, who has become acutely psychotic. These patients commonly refer to their psychotic symptoms as “anxiety” when they first present to the ED. Question the specific feelings and experiences associated with the anxiety and listen for new-onset paranoia. Look for a family history of psychotic illness. Although drug use is often present (particularly cannabis use), it is often incidental, and the psychotic episode does not resolve spontaneously after drug use is stopped.

Patients with long-standing history of psychotic illness (schizophrenia or bipolar disorder): “acute on chronic” *For most patients, schizophrenia is a chronic illness with acute exacerbations, even with treatment. Although an acute illness exacerbation is the most likely cause in this scenario, the reason for the exacerbation must be clarified. Important factors can include antipsychotic medication partial adherence or nonadherence, alcohol and drug use, or significant environmental changes (e.g., a new staff member at the group home). Some patients will be marginally compensated to begin with, and any worsening will put them at the hospital level of care. Psychogenic polydipsia is a complication in 10% of patients with chronic schizophrenia who periodically develop dangerously low sodium levels from drinking water [19]. Hyponatremia can cause mental status changes and seizures; ask the group home of families about excessive water intake. An intercurrent medical illness (e.g., urinary tract infection, pneumonia) must always be considered as a potential cause for worsening of a patient’s psychotic symptoms, and a careful review of medical history and examination (e.g., chest X-ray) is necessary. If the patient is homeless, he or she may be at higher risk for new medical illnesses or exacerbation of chronic ones (e.g., skin infections, tuberculosis, diabetes), either from limited access to general care or the living conditions on the street or in a shelter [20]. A thorough physical examination should be done, including a skin examination, and one should have a low threshold for any indicated tests and laboratory studies.*

“Frequent flyer” with “psychosis” *All emergency rooms have a handful of patients who visit the ED frequently. Such patients often have borderline or antisocial personality disorder and usually misuse drugs. Psychosis could be present (e.g., from drug use) or malingered (including by patients which schizophrenia who have nowhere to go). You might not be able to clarify this in the ED setting (see Chap. 2 for malingering).*

Initiation of Treatment Specific for Diagnosis

In some EDs, “definite treatment” will be initiated if the diagnosis has become clear during the evaluation. Restarting previously effective antipsychotics in patients with schizophrenia who have become non-adherent is often reasonable; note that you might have to give a lower dose, depending on the duration of missed antipsychotics. If psychosis is thought to be drug-induced (e.g., cocaine-induced psychosis), consider delaying treatment with an antipsychotic to clarify the diagnosis, unless the patient is exhibiting agitated or dangerous behavior. However, providing symptomatic treatment with an antipsychotic may reduce the risk for violence and allow a patient to re-compensate quickly and go home. In some cases (e.g., chronic use of crystal methamphetamine or cocaine), the drug-induced psychosis may continue

even after the period of intoxication. In these cases, antipsychotic medications can be helpful. Acutely manic patients will benefit from the sedating effects of benzodiazepines and can also receive a loading dose of valproate (20 mg/kg) almost immediately upon arrival at the ED [21].

Appropriate Disposition

When can you discharge a patient with psychosis from the ED? The answer to this question has to do more with risk and social factors than with psychiatric diagnosis per se. The correct disposition requires clinical experience and should not be done without consultation with a physician experienced in emergency psychiatry. Consider the following situations as a starting point for your considerations:

- If psychosis from drug use (e.g., cocaine use) resolves in the ED in the expected time course, discharge and referral to a substance use outpatient program might be reasonable.
- If a chronically psychotic patient seems calm and cooperative in the ED after a behavioral incident in a group home, work with the group home to resolve the issue that got the patient upset; at a minimum, clarify what a brief psychiatric admission is supposed to accomplish.
- Do not overburden family (and patients) with clinical responsibilities; in most cases, a potentially dangerous patient with psychosis should be admitted to the hospital even if the family is willing to take the patient home (with some education, most families will agree with your recommendation to hospitalize even if they were initially against a hospitalization).
- Psychiatric hospitalizations are not without risks (i.e., stigma, traumatic experience, legal ramifications, loss of a job) [22]. If possible, avoid hospitalization for first-episode patients but initiate treatment in an outpatient setting, *unless this is unsafe or follow-up is unlikely or cannot be arranged in the ED*.
- Hospitalize any psychotic patient who is dangerous or gravely disabled even if the patient does not agree to the admission (refer to the civil commitment laws in your state regarding involuntary admission).
- You might have to admit a patient who seeks admission and whom you suspect of malingering psychosis. Don't take it personally.
- Think twice before you discharge a psychotic patient who was brought to the ED because of violence, simply because the patient is calm during the evaluation and seems to have a good explanation for everything that happened.
- Think twice before you discharge a manic patient unless mania is just beginning and family members are confident that they can supervise medications. Patients with acute mania have no appreciation of their illness and the need for treatment.

References

1. Emerson RW. *Manners. Essays, first and second series, English traits representative men addresses.* New York: Hearst's International Library Co., Inc; 1914.
2. Holloman GH Jr, Zeller SL. Overview of project BETA: best practices in evaluation and treatment of agitation. *West J Emerg Med.* 2012;13:1–2.
3. New A, Tucci VT, Rios J. A modern-day fight club? The stabilization and management of acutely agitated patients in the emergency department. *Psychiatr Clin North Am.* 2017;40:397–410.
4. Beynard N, Yersin B, Carron PN. Mechanical restraint in an emergency department: a consecutive series of 593 cases. *Intern Emerg Med.* 2018;13:575–83.
5. Knox DK, Holloman GH Jr. Use and avoidance of seclusion and restraint: consensus statement of the American association for emergency psychiatry project Beta seclusion and restraint workgroup. *West J Emerg Med.* 2012;13:35–40.
6. Pratts M, Citrome L, Grant W, Leso L, Opler LA. A single-dose, randomized, double-blind, placebo-controlled trial of sublingual asenapine for acute agitation. *Acta Psychiatr Scand.* 2014;130:61–8.
7. Pollack CV Jr. Inhaled loxapine for the urgent treatment of acute agitation associated with schizophrenia or bipolar disorder. *Curr Med Res Opin.* 2016;32:1253–60.
8. San L, Estrada G, Oudovenko N, Montanes F, Dobrovolskaya N, Bukhanovskaya O, et al. PLACID study: a randomized trial comparing the efficacy and safety of inhaled loxapine versus intramuscular aripiprazole in acutely agitated patients with schizophrenia or bipolar disorder. *Eur Neuropsychopharmacol.* 2018;28:710–8.
9. Allen MH, Currier GW, Carpenter D, Ross RW, Docherty JP, Expert Consensus Panel for Behavioral Emergencies 2005. The expert consensus guideline series. Treatment of behavioral emergencies 2005. *J Psychiatr Pract.* 2005;11(Suppl 1):5–108; quiz 110–102.
10. Isbister GK, Calver LA, Page CB, Stokes B, Bryant JL, Downes MA. Randomized controlled trial of intramuscular droperidol versus midazolam for violence and acute behavioral disturbance: the DORM study. *Ann Emerg Med.* 2010;56:392–401 e391.
11. Wilson MP, Pepper D, Currier GW, Holloman GH Jr, Feifel D. The psychopharmacology of agitation: consensus statement of the American association for emergency psychiatry project Beta psychopharmacology workgroup. *West J Emerg Med.* 2012;13:26–34.
12. Citrome L, Volavka J. The psychopharmacology of violence: making sensible decisions. *CNS Spectr.* 2014;19:411–8.
13. Riddell J, Tran A, Bengamin R, Hendey GW, Armenian P. Ketamine as a first-line treatment for severely agitated emergency department patients. *Am J Emerg Med.* 2017;35:1000–4.
14. Lukens TW, Wolf SJ, Edlow JA, Shahabuddin S, Allen MH, Currier GW, et al. Clinical policy: critical issues in the diagnosis and management of the adult psychiatric patient in the emergency department. *Ann Emerg Med.* 2006;47:79–99.
15. Hays H, Jolliff HA, Casavant MJ. The psychopharmacology of agitation: consensus statement of the American association for emergency psychiatry project BETA psychopharmacology workgroup. *West J Emerg Med.* 2012;13:536.
16. Cluver JS, Hardesty SJ. Propofol for severe, refractory mania: a case report. *J Clin Psychiatry.* 2006;67:165–6.
17. Coffman JA, Nasrallah HA, Lyskowski J, McCalley-Whitters M, Dunner FJ. Clinical effectiveness of oral and parenteral rapid neuroleptization. *J Clin Psychiatry.* 1987;48:20–4.
18. Gual N, Morandi A, Perez LM, Britez L, Burbano P, Man F, et al. Risk factors and outcomes of delirium in older patients admitted to postacute care with and without dementia. *Dement Geriatr Cogn Disord.* 2018;45:121–9.
19. Illowsky BP, Kirch DG. Polydipsia and hyponatremia in psychiatric patients. *Am J Psychiatry.* 1988;145:675–83.

20. Aldridge RW, Story A, Hwang SW, Nordentoft M, Luchenski SA, Hartwell G, et al. Morbidity and mortality in homeless individuals, prisoners, sex workers, and individuals with substance use disorders in high-income countries: a systematic review and meta-analysis. *Lancet.* 2018;391:241–50.
21. Keck PE Jr, McElroy SL, Tugrul KC, Bennett JA. Valproate oral loading in the treatment of acute mania. *J Clin Psychiatry.* 1993;54:305–8.
22. Paksarian D, Mojtabai R, Kotov R, Cullen B, Nugent KL, Bromet EJ. Perceived trauma during hospitalization and treatment participation among individuals with psychotic disorders. *Psychiatr Serv.* 2014;65:266–9.

Additional Resources

Articles

- Holloman GH Jr, Zeller SL. Overview of Project BETA: best practices in evaluation and treatment of agitation. *West J Emerg Med.* 2012;13:1–2. – Introduction to the Project BETA from the American Association for Emergency Psychiatry (AAEP) who, in October 2010, embarked on developing guidelines for the assessment and management of agitation in acute care settings. (BETA stands for Best practices in Evaluation and Treatment of Agitation). Working groups tackled several topics (medical evaluation and triage, psychiatric evaluation, verbal de-escalation, psychopharmacology, use and avoidance of seclusion and restraint), all published in the Western Journal of Emergency Medicine.
- Wilson MP, Pepper D, Currier GW, Holloman GH Jr, Feifel D. The psychopharmacology of agitation: consensus statement of the American Association for Emergency Psychiatry Project Beta psychopharmacology workgroup. *West J Emerg Med.* 2012;13:26–34. – The psychopharmacology recommendations from Project BETA.

Chapter 11

First-Episode Psychosis



Essential Concepts

- In most cases of first-episode patients, the diagnosis is clear once the longitudinal course is reviewed: most patients have been ill for more than 6 months if the prodromal period and duration of untreated psychosis are included. Diagnostic uncertainty during the first episode of psychosis should not delay schizophrenia-specific treatment.
- Using clinical staging (prodromal phase, acute and stabilization phase, stable (maintenance) phase), phase-specific treatment goals guide clinicians in the selection of the best treatment tools for each phase.
- Preventing medical morbidity and mortality is important across all illness phases and needs to be taken into account in parallel to achieving symptom control and remission.
- Patients at ultra high-risk for psychosis require close follow-up and integrated psychological and family interventions. Antipsychotics should not be used for the purpose of schizophrenia prevention.
- First-line antipsychotics achieve a response and *symptomatic* remission in most first-episode patients (around 60–70%). The choice of antipsychotic is guided by side effect considerations, including extrapyramidal symptoms (EPS) and long-term metabolic safety. Avoid haloperidol and olanzapine, respectively. Anticipating maintenance treatment, consider selecting an antipsychotic that can, after initial stabilization, be given as a long-acting injectable formulation.
- Treatment response to antipsychotic medications is much better in first-episode patients compared to chronic, multi-episode patients. The antipsychotic dose should be on the lower half of the dose range.
- Move to clozapine as soon as treatment-resistant schizophrenia becomes apparent. The majority of first-episode patients who are treatment-resistant

(70–80% of all treatment-resistant patients) are refractory from the get-go (i.e., they do not develop resistance over time); changing antipsychotics prior to a clozapine trial is of limited benefit for those patients.

- A long-acting antipsychotic would keep almost 100% of patients in sustained symptom remission for 1–2 years and prevent the psychosocially toxic relapse.
- While ultimately the patient and family will decide about maintenance treatment after a first psychotic episode, I always emphasize a higher risk of death during untreated illness and loss of responsiveness with each subsequent episode as key considerations in favor of maintenance treatment. At a minimum, patients should continue treatment for 18 months after full resolution of positive symptoms.
- Multicomponent-coordinated specialty care can improve short-term outcomes for first-episode schizophrenia but is not widely available.
- While symptomatic remission can be achieved in the majority of patients, functional recovery remains an elusive goal that is only achieved for a minority.
- Currently, only about 15% of patients achieve symptomatic and functional recovery 10 years after their first episode. Extended treatment beyond 2 years of specialized services may be needed.

“Même la nuit la plus sombre prendra fin et le soleil se lèvera.”
(Even the darkest night will come to an end, and the sun will rise.)

— Victor Hugo (1802–1885), French writer of the of the Romantic period;
Les Misérables [1]

In medicine, treatment during earlier disease stages, before a disease causes complications, is often more successful [2]. In psychiatry, intervening early in the course of schizophrenia, before prolonged psychosis causes wide-ranging disruption of people’s lives and before the illness becomes chronic, is a more recent and promising approach [3]. In addition, the early years after the diagnosis of schizophrenia are marred by high mortality due to accidents, drug use, and suicide [4]. The mortality risk in young first-episode patients is comparable to the risk of death in a cohort of geriatric patients over age 70. Optimal treatment of a first episode of psychosis may therefore improve some short-term and long-term outcomes, if we dedicate societal resources to it (see epigraph). In this chapter, I will outline the competent management of patients who present with a first episode of schizophrenia, with emphasis on the psychopharmacological management. I include a brief section on the prodromal (prepsychotic) period even though most psychiatrists will only encounter patients that are already in the psychotic phase. Reducing the duration of untreated psychosis, an important public health goal of schizophrenia care [5], is discussed in Chap. 9 as it represents an issue that can only be solved at a larger systems level, not by individual clinicians. First episode of psychosis and first episode of schizophrenia is used interchangeably.

Table 11.1 Acronyms in early intervention

<i>Terms for putatively prodromal states</i>	
UHR	Ultra high-risk
CHR	Clinically high-risk
ARMS	At risk mental state
APS	Attenuated psychosis syndrome (DSM-5 term) [6]
<i>Assessment tools</i>	
SIPS/SOPS	Structured interview for prodromal syndromes/scale of prodromal symptoms
CAARMS	Comprehensive assessment for at risk mental states
<i>Clinical states</i>	
DUP	Duration of untreated psychosis
DUI	Duration of untreated illness
<i>Cohorts</i>	
NAPLS	North American Prodrome Longitudinal Study [7]
Tips ^a	Early Treatment and Intervention in Psychosis [8]
Opus ^b	
<i>Clinical trials</i>	
EUFEST	European First-Episode Schizophrenia Trial [9]
CAFÉ	Comparison of Atypicals in First-Episode Psychosis [10]
RAISE	Recovery After an Initial Schizophrenia Episode [11]
OPTiMiSE	Optimization of Treatment and Management of Schizophrenia in Europe [12]

^aThe acronym stands for the Norwegian Tidlig Oppdagelse Og Behandling Av Psykoser (early discovery and treatment of psychoses)

^bDoes not appear to be an acronym

The early intervention and first-episode movement have created a large number of acronyms. Table 11.1 lists common acronyms that you will encounter when you read this chapter.

Diagnosis

The correct diagnosis of a first episode of schizophrenia hinges on the combination of typical symptoms on cross-sectional mental status exam and the longitudinal development of symptoms over time and the exclusion of “organic” factors that would explain the presentation (see Chap. 5). The onset of symptoms is usually in late adolescence or early adulthood although earlier and later onsets are possible. Many first episodes seem to be tied to the stress of leaving home for the first time (e.g., going to college or joining the military). The phenomenology of the early symptom course is discussed in greater detail in Chap. 7.

Several points about the symptom progression in early course schizophrenia are worth re-emphasizing (see Fig. 11.1):

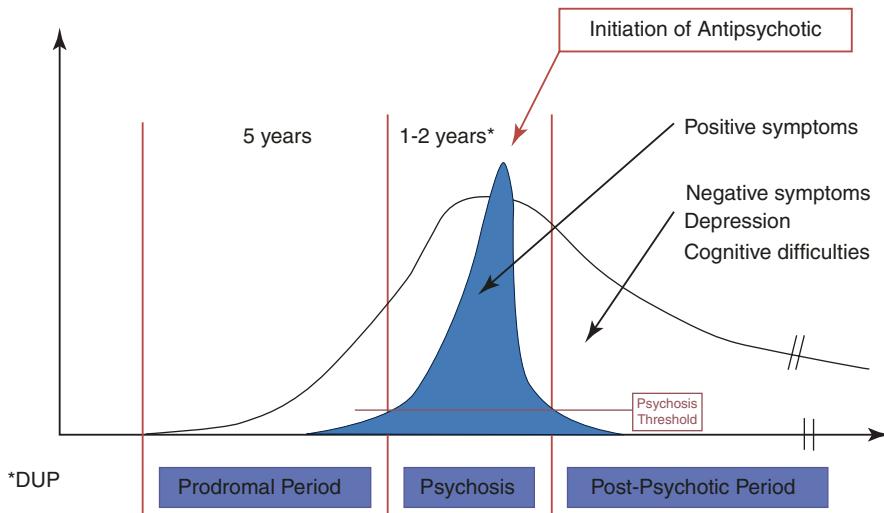


Fig. 11.1 Course of first-episode psychosis

- Before the onset of frank psychosis, patients experience a mixture of affective, negative, and cognitive prodromal symptoms, social withdrawal, and role failure.
- A period of attenuated positive symptoms turns into first-episode psychosis once an admittedly arbitrary syndromal psychosis threshold is crossed.
- The onset of frank psychosis is a late event. Once patients are psychotic, they have often been ill for many years. Both duration of untreated illness (DUI, when, in hindsight, there were signs that schizophrenia began) and duration of psychosis (DUP, when frank psychosis began) are measured in years.
- Treatment initiation in first-episode patients leads to a rapid reduction in positive symptoms but an incomplete response in negative and cognitive symptoms.

The depicted course represents a prototypical course. In reality, there can be significant differences, particularly with regard to the rapidity of onset. A minority have no discernible prodromal period and a rather sudden onset of psychosis. A manic episode with psychosis or an acute and transient psychotic disorder is strong differential diagnostic consideration in such cases. Sudden onset cases indicate a good prognosis, in part because they are brought to treatment early – something is clearly wrong. In contrast, patients with a very long prodromal period characterized by slow social withdrawal and a long period of unrecognized psychosis have a worse prognosis.

Tip

A common diagnostic mistake is only counting acute psychosis and not an often clearly discernible prodromal period toward the duration of the illness.

Many patients have clearly been ill for more than 6 months when you encounter them in the emergency room or during their first psychiatric hospitalization. The 6-month duration requirement in DSM-5 for a diagnosis of schizophrenia reflects illness duration, not merely active psychosis. Quite often, the duration of untreated psychosis alone is long enough to make the diagnosis.

Medical Examination

A medical examination and first-episode psychosis work-up is needed in order to achieve several goals: (1) to make sure that the psychosis is not secondary, (2) to detect medical comorbidities that may influence your treatment choice (e.g., ECG), and (3) to establish a baseline for some markers that are influenced by your treatment (e.g., weight and metabolic baseline). Refer to Table 5.1 in Chap. 5 for a proposed work-up.

Diagnostic Uncertainty

Tolerating uncertainty is hard, and communicating diagnostic uncertainty is an important clinical skill [13]. Patients and families are often left wondering if “everything was excluded.” They may focus on incidental laboratory abnormalities or pursue potentially quite dangerous treatments (e.g., for chronic Lyme disease). They wonder if drug use alone explains the psychotic episode. We need to acknowledge the distress but also tactfully explain why schizophrenia is the likely diagnosis in order to implement the correct treatment. At the same time, convey openness to changing your diagnosis as new facts become available. It is humbling to realize that our current knowledge is always incomplete and that new diseases are going to be discovered. When I attended medical school, hepatitis C was not yet discovered and known as non-A, non-B hepatitis, and NMDA receptor encephalitis was an unknown entity. For some family progress represents hope, and I encourage patients to consider participating in innovative research. Gluten-free diet may be helpful for some aspects of schizophrenia, for example, but only more clinical trials will identify those patients who can benefit from it. Some patients and families will never quite accept a psychiatric diagnosis and remain on some quest for the eventual discovery of the “real” cause of their symptoms.

Phase-Specific Treatment Goals

The treatment of schizophrenia can be thought of as proceeding through phases, not necessarily sharply demarcated, with each phase having different prevention and treatment goals (Table 11.2). The stabilization phase in particular is continuous with

Table 11.2 Phase-specific treatment goals for early course schizophrenia

Prodromal phase	Prevent progression to full syndrome Limit social and functional harm KEY QUESTION: Use antipsychotic?
Acute phase ^a	Keep duration of untreated psychosis (DUP) short Prevent harm and control psychotic behavior Achieve initial <i>symptom response</i> (reduce symptom severity) KEY QUESTION: Which antipsychotic and what dose?
Stabilization phase ^a	Achieve <i>early symptom remission (symptom resolution)</i> Prevent early relapse Early readjustment to community living Monitor and address side effects KEY QUESTION: When to switch if there is a poor response?
Stable (maintenance) phase ^b	Achieve <i>sustained symptom remission</i> Improve function and quality of life Monitor and address long-term iatrogenic morbidity Monitor and address demoralization and suicidality Achieve <i>recovery</i> (meaningful life despite illness) KEY QUESTION: For how long do you treat after remission?

^aAcute psychotic episode

^bSometimes called post-psychotic phase

the acute phase, but since both phases are managed in different settings (outpatient versus inpatients, respectively), there separation has conceptual value. For each phase, there is a one key question regarding the use of antipsychotics.

(Putatively) Prodromal Phase

Great hopes have been pinned on identifying the prodromal phase *prospectively* in order to intervene and either delay or prevent the full syndrome of schizophrenia. Following the pioneering work of Patrick McGorry in Australia [14], many academic centers all over the world have in the last 20 years developed “early intervention” services to identify such putatively prodromal, clinically high-risk or ultra high-risk (UHR) patients, as they are called. The Australian group delineated three groups of patients that were at high-risk of transition to psychosis within 1 year: patients with attenuated psychotic symptoms, patients with stuttering psychotic experiences (also known as BLIPS, for brief limited intermittent psychotic symptoms [15]), and patients with genetic risk (a family history of schizophrenia in first-degree relatives, schizotypal features) whose function declined; this general delineation of three UHR states is still used today [16]. In German-speaking coun-

tries, a different path based on basic symptoms was taken to identify UHR patients [17]. Basic symptoms are subtle (nonpsychotic) disturbances in thinking and perception that are believed to be the subjective experiencing of the changing brain in the prepsychotic period [18]. Examples are the experience of thought pressure or interference (difficulties giving thoughts direction) or difficulties reading as words and sentences make no sense (akin to reading a foreign language where you can sound out the words but they have no meaning to you). Phenomenologically, the prodromal period is rich with anomalous experiences of the self [19].

While the idea of identifying people during the prodromal phase of schizophrenia has been fruitful and energizing for psychiatry (including the creating of a huge list of acronyms, see Table 11.1), ushering in modern preventive psychiatry, several hard lessons were learned.

Most importantly, casting a large net to identify adolescents seemingly at risk for schizophrenia will result in catching many young people with social difficulties and non-specific symptoms. It turns out that psychotic-like experiences (transient sub-clinical phenomena like perceptual abnormalities or delusion-like ideas) or isolated frank psychotic symptoms are surprisingly common in children and adolescents, occurring in almost 10% of adolescents, for example [20]. The field had come to grapple with the problem that many young people seeking help in specialized “early intervention” centers have attenuated syndromes that defy a clear syndromal diagnosis [21], with only a minority (one third in 3 years) moving on the schizophrenia [22]. Transition rates around 10% in current CHR cohorts are now common which hinders research into effective interventions [23]. (In comparison, in the early years of studying high-risk cohorts, one-year transition rates were as high as 40% [24].) Most help-seeking patients today are “probably at risk, but certainly ill.” Increasingly, the pleiotropic nature of clinical symptoms of developing brains is appreciated, with no direct line from high-risk states to schizophrenia. As many as one third of CHR patients completely remit within 2 years [25]. The medical “high-risk” and “transition” approach may even be misplaced and needs replacing with a trans-diagnostic public health approach that provides interventions in youth-specific settings [26].

Current high-risk criteria based on clinical symptoms are insufficient for screening in unselected populations although risk calculators to predict transition risk in *identified CHR patients* have been developed [27]. Efforts are underway to increase the positive predictive value of clinical risk models by including biological markers [28] as well as neuroimaging and machine-learning [29].

Perhaps the biggest disappointment in the early intervention field was the failure of the multi-site NEURAPRO trial [23] to replicate positive result from an earlier indicated prevention trial using omega-3 polyunsaturated fatty acids to prevent transition to psychosis [30]. Omega-3 fatty acids would have been an ideal medication from a prevention perspective due to their safety. Neuroprotective agents like N-acetylcysteine (NAC) remain an interesting consideration for another indicated prevention trial [31]. One of the few intervention trials in the prodromal phase with antipsychotics, conducted in the NAPLS network, was inconclusive [32]. While olanzapine reduced positive symptoms and had fewer conversions to psychosis, this trial could not answer the fundamental question if the natural course of schizophre-

Table 11.3 Treatment recommendations for UHR patients

Assess and treat syndromes (anxiety, depression)
Do not treat pseudo-ADD with stimulants ^a
Benign interventions to delay conversion
CBT should be first-line treatment
Integrated psychological interventions (individual plus family therapy)
Omega-3 fatty acids are ineffective; consider N-acetylcysteine
Education about the importance of avoiding cannabis
Use of antipsychotics
Use low-dose second-generation antipsychotics <i>if clinically indicated</i> ^b
Do not use long-term for primarily preventive purpose to delay/prevent conversion ^c
Provide long-term follow-up ^d

^aNew-onset attentional difficulties that are consistent with prodromal schizophrenia [39]

^bLack of improvement despite treatment, including symptom-targeted pharmacotherapy for depression and anxiety; worsening clinical status including suicidal ideation; concern that psychosis is no longer subthreshold

^cCould consider to use for UHR patient and *clear* attenuated psychosis (i.e., clinically close to frank psychotic state)

^dAt least 3 years; the transition risk decreases with time

nia was merely delayed or in any way altered. Other antipsychotic trials were similarly inconclusive, particularly as patients also received non-medication interventions that alone may be effective [33]. The role of antipsychotics in managing CHR states as primary prevention remains to be studied [34] and is currently not recommended for indicated prevention. Strengthening those cognitive weaknesses that increase the risk for transition offers one possible non-medication intervention [35].

Management of young patients believed to be at high-risk for a transition of psychosis is summarized in Table 11.3. The most important aspect of care is close follow-up in order to intervene as new symptoms develop and supportive care [36]. Reducing stress with integrated psychological and family interventions is usually included in the management of high-risk patients [37] although no one intervention alone has been shown to be effective [38].

Acute Phase

Usually, but not always, initial treatment for an acute psychotic episode is provided in the hospital, where antipsychotics are initiated with the expectation of a *response*. In a meta-analysis, 50% of patients showed a 50% reduction in psychopathology

with acute treatment for their first episode of schizophrenia, with a better treatment response in female patients, in more severely ill patients, in antipsychotic naive patients, or in patients with a shorter illness duration [40].

Key Point

The overarching treatment goal for the first episode of psychosis is the timely initiation of a first-line antipsychotic (keeping DUP as short as possible) and a timely move to clozapine in treatment-refractory schizophrenia patients. A reformulated goal would be the initiation of *effective* treatment.

Ancillary medications (e.g., benzodiazepines or valproate) are often prescribed to reduce the severity of the patient's psychopathology. Create a good drug experience. All my older patients remember their first acute dystonic reaction from first-generation antipsychotics. Add-on therapies for presumed neuroinflammation or free radical production during acute psychosis are sometimes added by adventurous clinicians (e.g., N-acetylcysteine (NAC) 600 mg twice daily) [41].

Antipsychotic Choice

One seminal trial to answer the question which antipsychotic to initiate was the European First-Episode Schizophrenia Trial (EUFEST) [42]. EUFEST was a 1-year trial that compared low-dose haloperidol (mean dose 3.0 mg/d) with several second-generation antipsychotics (amisulpride (not available in the United States), ziprasidone (mean dose 110 mg/d), olanzapine (mean dose 12.5 mg/d), and quetiapine (mean dose 500 mg/d)) for the treatment of first-episode patients with minimal antipsychotic exposure. While low-dose haloperidol had the highest all-cause discontinuation rate (a common outcome measure since the CATIE trial), all antipsychotics had virtually identical symptom reduction [9]. A similar trial, CAFÉ, that compared olanzapine, quetiapine, and risperidone for first-episode schizophrenia confirmed comparable effectiveness between the three antipsychotics tested in this trial [10]. A network meta-analysis that compared all antipsychotics studied in randomized trials found little efficacy or tolerability differences between second-generation antipsychotics [43]. Haloperidol, however, was poorly tolerated. Since creating a good drug experience influenced adherence, it is prudent to avoid high-potency first-generation antipsychotics. Second-generation antipsychotics are clearly preferred today. In most patients, olanzapine could be avoided (although there are advantages on the inpatient side given its good efficacy and calming effect). There is no evidence that clozapine is advantageous for treatment-responsive first-episode patients (i.e., clozapine does not have disease-modifying properties [44]).

Key Point

The selection of the antipsychotic is guided by side effects as all first-line antipsychotics are about equally effective [43]. Given the need for maintenance treatment and comparable efficacy, a metabolically safe antipsychotic should be selected, preferentially one that is also available as a long-acting injectable. First-generation antipsychotics, particularly haloperidol, should not be used due to a higher risk of EPS.

Antipsychotic Dose

First-episode patients represent an unselected group of patients of which most will not (yet) be treatment-resistant. Antipsychotic-naïve patients respond very well to lower doses of antipsychotics compared to chronic patients, as initially shown for haloperidol [45]. They are also more sensitive to EPS which increases the risk for dystonias and weight gain which increases the risk for non-adherence. As a rule of thumb, the dose for first-episode patients should be closer to the lower half of the dose range, the exception being quetiapine which still requires around 500 or 600 mg/d, probably because of its weak D2 receptor binding [46]. The first-episode dose for the commonly used first-line second-generation antipsychotic risperidone is between 2 and 4 mg/day, with many patients achieving a good response at 2 mg already [47]; the mean dose in RAISE was 3 mg/d [48] (Table 11.4).

Stabilization Phase

During this illness phase, the main focus remains on symptoms while not ignoring long-term medical safety (i.e., health monitoring and active management of metabolic complications needs to occur in parallel with symptom management – do not defer until a patient is psychiatrically stable). When patients are discharged today, they are often still rather symptomatic. However, given time (and assuming adherence as well as an antipsychotic-responsive form of schizophrenia), positive symptoms are expected to remit completely, while other problems, particularly side

Table 11.4 Antipsychotic target dose for first-episode schizophrenia

Haloperidol	2–4 mg/d
Aripiprazole	10 mg/d
Olanzapine	10 mg/d
Paliperidone	6 mg/d
Quetiapine	500 mg/d
Risperidone	2–4 mg/d
Ziprasidone	80 mg/d

Based on EUFEST [9], CAFÉ [10], and RAISE [48]

Table 11.5 Fading of psychosis

Stage	Characteristics
1. Psychotic catastrophe	No doubt; hostility if questioned
2. Physically accessible psychosis	Admits to somatic symptoms; discussion of sleep
3. Discussable psychosis	Allows alternatives; able to do “double bookkeeping”
4. Blurring psychosis	Experience nebulous, less important
5. Psychotic remnants	Memory of psychosis; subjective certainty
6. Disease insight	Acknowledges past psychosis

Based on Ref. [50]

effects, negative symptoms, and depression, become the focus of treatment. For many first-episode patients, this early adjustment period following a psychiatric hospitalization will last anywhere from 3 months to 1 year.

Similar to Conrad's stages of beginning psychosis [49], psychosis recedes in a predictable pattern as summarized in Table 11.5. Not all patients, however, reach the last stage where they gain insight into the abnormal nature of their experiences.

Switching Antipsychotics due to Non-response

While a good response is achieved by the majority of first-episode patients quickly, a small group of patients requires longer treatment for a response to become apparent [51]. While 50% of patients show a response within 2 weeks and 80% within 4 weeks, 10% of patients have a delayed response that takes 8 weeks to develop. In first-episode patients, an early non-response does not predict a later non-response [52]. Note that this time course is different than chronic patients where lack of an early response predicts lack of a later response.

The OPTiMiSE trial [12] showed directly that simply waiting rather than switching antipsychotics after 4 weeks leads to the same degree of symptom reduction. In the first part of this European trial, patients received amisulpride for 4 weeks, followed by 6 weeks of either amisulpride or olanzapine. About 2/3 of patients remitted after 10 weeks, with no difference between the two treatments; put differently, simply waiting would have worked just as well compared to switching. In reality, most patients had already remitted after 4 weeks of treatment.

In a second part of this trial, patients who had not responded to 10 weeks of anti-psychotic treatment commenced on clozapine for 12 weeks, with at least some benefit from the switch. OPTiMiSE thus confirmed clozapine's efficacy for treatment-refractory first-episode patients. Given that most refractory patients are refractory from the get-go (i.e., only a minority becomes treatment-resistant over time) [53], OPTiMiSE raises the question if additional antipsychotic trials are needed once treatment-resistance has been established (see Chap. 12).

Key Point

Switch to clozapine early once treatment-refractoriness has been confirmed. Expect to see a meaningful response in up to 75% of patients after the switch [54].

Although many first-episode patients achieve short-term resolution of symptoms to the point of full symptomatic remission initially, the goal of sustained remission is often elusive because patients relapse after prematurely stopping antipsychotics. For example, fewer than 50% of first-episode patients (in a Finish study) continued their treatment after discharge for more than 30 days [55]. Partial adherence and intermittent (or ongoing) drug use are key factors in relapse that could greatly be mitigated by offering treatment with long-acting injectable antipsychotics (see also Chap. 18 on long-acting antipsychotic). In one open label trial of first-episode patients who were treated with a long-acting antipsychotic and who achieved remission (about two thirds of all patients), almost 100% *remained well* for 2 years while taking the LAI [56]. Once the LAI was withdrawn, almost 100% of the sample relapsed within 3 years [57]. Particularly concerning is the finding that 16% of relapsed patients no longer responded to treatment reinitiation [58]. In a 12-month, randomized trial comparing oral risperidone with risperidone LAI, only very few LAI patients relapsed (5%) in contrast to the oral treatment group (33%) [59]. Any treatment in oncology with such an effect size would make the news. In addition to efficacy, LAIs are also beneficial for families and the function of the family system. Being on an LAI eliminates the daily struggle about taking medication and concerns about adherence. And when family stress is reduced, the patient does better.

Key Point

Long-acting antipsychotics are a good first-line choice for first-episode patients. They should be routinely offered (opt-out) to all patients and already initiated in the hospital, not deferred to the outpatient team.

Stable Phase (Maintenance Phase)

In this phase, you move beyond symptom management to improving function and quality of life and to preventing the ultimate bad outcome: premature death. Preventing relapse to maintain the symptomatic remission achieved in the earlier treatment phases is the sine qua non of rehabilitation and recovery. Long-term health issue, such as preventing or addressing medical morbidity, is rising to the forefront of clinical management (monitoring and judicious antipsychotic selection already started during the acute phase), necessitating attention to metabolic monitoring and unhealthy lifestyles (diet, exercise, drug use, cigarette smoking) (see

Chap. 25). Demoralization and suicide can become urgent matters if patients are unable to adjust to a life different from the one envisioned (see Chap. 30).

Duration of Antipsychotic Treatment

One of the truly difficult and ultimately unresolved clinical decision in psychiatry is the question of how long to continue antipsychotic treatment for patients after a first episode of psychosis [60]. Given the high relapse risk and all its associated risks (including mortality and reduced or lack of response with each episode), a strong argument can be made for maintenance treatment after a first episode of psychosis increases. There is also no good evidence that providing no treatment leads to better outcomes. Quite the contrary, continuous treatment after a first episode of psychosis increases survival compared to patients with no or stuttering treatment. Naturalistic cohort studies do not support medication discontinuation even after full symptomatic and functional recovery has been achieved for a year as recovery appears to be more difficult once a patient has relapsed [61].

Key Point

Preventing a second psychotic episode is ideal since the response to the first episode is always superior to second episode [62]. In addition, each relapse contributes to emerging treatment resistances [63]. One wonders what the outcome of schizophrenia would look like if patients did not relapse [64].

Why risk it then? Patients will have two arguments: First, treatment has a side effect burden, including the possibility that it may hinder functional recovery [65]. Second, maintenance treatment is unneeded in those 20% of patients who will never have a second psychotic episode. Currently, we have no biological or clinical markers that can tell us which patient falls in this 20% category.

Regardless of any careful risk-benefit deliberations, I believe that maintenance treatment after a first episode is utterly unrealistic: most patients vote with their feet and eventually stop their antipsychotic, some as early as immediately after discharge, regardless of your views. Drug use, particularly cannabis, further reduces optimal adherence in many patients. Practically, a careful risk-benefit discussion with all involved parties and relapse prevention planning is needed. Relapse prevention needs to acknowledge (1) the difficulties of implementing it in some patients when they become psychotic and (2) the risk of a poor or no response even if treatment is reinstated early (see Chap. 9 regarding relapse prevention planning). Shared decision-making empowers the patient and his family to determine what they are most comfortable with. You could mention that the Canadian Schizophrenia Guidelines recommend treatment for *at least 18 months following resolution of positive symptoms* [66] if families want to stop the medicine immediately after hospital discharge. Eighteen months provide a helpful initial time frame for bargaining

and psychoeducation. It sets realistic expectations about the speed of recovery and commitment to treatment.

Tip

While ultimately the patient and family will decide about maintenance treatment after a first psychotic episode, I always emphasize increased survival and loss of responsiveness with each subsequent episode as key considerations in favor of maintenance treatment. Treatment despite its downsides appears to still offer the best hope for good clinical outcomes.

Prognosis

The outcome of first-episode psychosis is often described optimistically. This view is correct if we only focus on short-term symptom improvement in patients who had only one episode. For those patients, full symptomatic remission is within reach for the majority of patients, as noted earlier, particularly if LAI were used. One we factor in relapses and the development of some treatment-resistance, the outlook as less positive. Excellent long-term functional outcomes remain difficult to achieve. OPUS was an attempt in Denmark to provide specialized and comprehensive treatment (assertive community treatment, family involvement, social skills training) to first-episode patients for 2 years after onset of psychosis in order to change the long-term trajectory of the illness [67]. Patients benefited from the intensive interventions offered but only in the short run: the benefits observed after 2 years had disappeared after 5 years [68]. When participants in OPUS were followed up 10 years later, a mere 14% of patients met the study criteria for symptomatic and psychosocial recovery [69]. It may be that sustained treatment involvement over many years is needed otherwise benefits that had been achieved while actively involved in treatment are lost [70]. Negative symptoms in particular play a role in hindering recovery [71]. A recent meta-analysis based on 10,000 first-episode patients estimated a pooled remission rate of 58% and a pooled recovery rate of 38% (recovery rates were higher in North America); while remission rates had improved, recovery rates had remained stable [72]. The mean follow-up in this analysis was 5 years which is shorter than the OPUS 10-year follow-up. Even in well-resourced settings, achieving functional recovery for the majority of patients remains an elusive goal.

First-Episode Services

A first-episode service needs to be organized well to provide optimal care which needs to be integrated and comprehensive. Medications alone are not going to address the psychological and family needs at a time of feeling more or less “lost.”

Table 11.6 Treatment components for first-episode psychosis

Individual medication treatment
Family education program
Individual resilience training
Supported employment/education

Based on the multimodal NAVIGATE treatment components [74]

Patients and their families are going to struggle with diagnostic uncertainty, deny illness or its ramifications, and be demoralized about the slow or incomplete return to prior function. Milestones are going to be missed, and children are moving back home instead of taking further steps toward independence. The non-medication psychological treatment and rehabilitation components are as critical as the (correct) use of medications.

Compared to other countries, particularly in Europe and Australia, the United States was late in establishing a model of comprehensive coordinated specialty care for first-episode patients. To remedy this gap, the National Institute of Mental Health initiated the Recovery After an Initial Schizophrenia Episode (RAISE)-Early Treatment Program to develop a care delivery model that could be implemented in routine mental healthcare settings (i.e., not just academic centers) in the United States [73]. RAISE created an exemplary multimodal treatment package called NAVIGATE that integrates psychopharmacology with several psychosocial and family interventions (see Table 11.6) [74]. Compared to usual community care, NAVIGATE treatment had greater improvement in quality of life (the main outcome variable in this trial), particularly for patients with lower duration of untreated psychosis [11].

While developing NAVIGATE was an encouraging first step, its widespread implementation in poorly resourced settings remains challenging, particularly if one wants to add outcome measures to guide further improvements [75]. Our current system is unable to get those patients with very long DUP into treatment earlier [76], and early detection efforts need to account for our fragmented care system and its many entry points [77]. Further, while the provision of the NAVIGATE package may lead to the best possible short-term outcome, it has become clear that extended services and long-term support are going to be needed (see OPUS trial above). Any first-episode service needs to be optimally integrated and continuous with other services. Strengthening our public sector to include first-episode services may offer one solution [78].

Key Point

Team-based coordinated specialty care that can provide integrated and comprehensive care is necessary to optimize the chances for a good outcome of first-episode psychosis [79]. For many patients, services need to be provided beyond the first 2 years after diagnosis as the benefits from program participation are otherwise lost.

References

1. Hugo V. *Les Misérables*. Belgium: A. Lacroix, Verboeckhoven & Cie; 1862.
2. McGorry PD, Hickie IB, Yung AR, Pantelis C, Jackson HJ. Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. *Aust N Z J Psychiatry*. 2006;40:616–22.
3. Nordentoft M, Jeppesen P, Petersen L, Bertelsen M, Thorup A. The rationale for early intervention in schizophrenia and related disorders. *Early Interv Psychiatry*. 2009;3(Suppl 1):S3–7.
4. Schoenbaum M, Sutherland JM, Chappel A, Azrin S, Goldstein AB, Rupp A, et al. Twelve-month health care use and mortality in commercially insured young people with incident psychosis in the United States. *Schizophr Bull*. 2017;43:1262–72.
5. Murru A, Carpinello B. Duration of untreated illness as a key to early intervention in schizophrenia: a review. *Neurosci Lett*. 2018;669:59–67.
6. Fusar-Poli P, De Micheli A, Cappucciati M, Rutigliano G, Davies C, Ramella-Cravaro V, et al. Diagnostic and prognostic significance of DSM-5 attenuated psychosis syndrome in services for individuals at ultra high risk for psychosis. *Schizophr Bull*. 2018;44:264–75.
7. Seidman LJ, Giuliano AJ, Meyer EC, Addington J, Cadenhead KS, Cannon TD, et al. Neuropsychology of the prodrome to psychosis in the NAPLS consortium: relationship to family history and conversion to psychosis. *Arch Gen Psychiatry*. 2010;67:578–88.
8. Melle I, Larsen TK, Haahr U, Friis S, Johannessen JO, Opjordsmoen S, et al. Reducing the duration of untreated first-episode psychosis: effects on clinical presentation. *Arch Gen Psychiatry*. 2004;61:143–50.
9. Kahn RS, Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet IP, et al. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizopreniform disorder: an open randomised clinical trial. *Lancet*. 2008;371:1085–97.
10. McEvoy JP, Lieberman JA, Perkins DO, Hamer RM, Gu H, Lazarus A, et al. Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison. *Am J Psychiatry*. 2007;164:1050–60.
11. Kane JM, Robinson DG, Schooler NR, Mueser KT, Penn DL, Rosenheck RA, et al. Comprehensive versus usual community care for first-episode psychosis: 2-year outcomes from the NIMH RAISE Early Treatment Program. *Am J Psychiatry*. 2016;173:362–72.
12. Kahn RS, Winter van Rossum I, Leucht S, McGuire P, Lewis SW, Leboyer M, et al. Amisulpride and olanzapine followed by open-label treatment with clozapine in first-episode schizophrenia and schizopreniform disorder (OPTiMiSE): a three-phase switching study. *Lancet Psychiatry*. 2018;5:797–807.
13. Rosenbaum L. Communicating uncertainty—Ebola, public health, and the scientific process. *N Engl J Med*. 2015;372:7–9.
14. Yung AR, McGorry PD. The initial prodrome in psychosis: descriptive and qualitative aspects. *Aust N Z J Psychiatry*. 1996;30:587–99.
15. Fusar-Poli P, Cappucciati M, De Micheli A, Rutigliano G, Bonoldi I, Tognin S, et al. Diagnostic and prognostic significance of brief limited intermittent psychotic symptoms (BLIPS) in individuals at ultra high risk. *Schizophr Bull*. 2017;43:48–56.
16. Schultze-Lutter F, Michel C, Schmidt SJ, Schimmelmann BG, Maric NP, Salokangas RK, et al. EPA guidance on the early detection of clinical high risk states of psychoses. *Eur Psychiatry*. 2015;30:405–16.
17. Klosterkötter J, Hellmich M, Steinmeyer EM, Schultze-Lutter F. Diagnosing schizophrenia in the initial prodromal phase. *Arch Gen Psychiatry*. 2001;58:158–64.
18. Schultze-Lutter F. Subjective symptoms of schizophrenia in research and the clinic: the basic symptom concept. *Schizophr Bull*. 2009;35:5–8.
19. Moller P, Husby R. The initial prodrome in schizophrenia: searching for naturalistic core dimensions of experience and behavior. *Schizophr Bull*. 2000;26:217–32.
20. Kelleher I, Connor D, Clarke MC, Devlin N, Harley M, Cannon M. Prevalence of psychotic symptoms in childhood and adolescence: a systematic review and meta-analysis of population-based studies. *Psychol Med*. 2012;42:1857–63.

21. Hickie IB, Scott EM, Hermens DF, Naismith SL, Guastella AJ, Kaur M, et al. Applying clinical staging to young people who present for mental health care. *Early Interv Psychiatry*. 2013;7:31–43.
22. Fusar-Poli P, Bonoldi I, Yung AR, Borgwardt S, Kempton MJ, Valmaggia L, et al. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. *Arch Gen Psychiatry*. 2012;69:220–9.
23. McGorry PD, Nelson B, Markulev C, Yuen HP, Schafer MR, Mossaheb N, et al. Effect of omega-3 polyunsaturated fatty acids in young people at ultrahigh risk for psychotic disorders: the NEURAPRO randomized clinical trial. *JAMA Psychiatry*. 2017;74:19–27.
24. Yung AR, Phillips LJ, Yuen HP, Francey SM, McFarlane CA, Hallgren M, et al. Psychosis prediction: 12-month follow up of a high-risk (“prodromal”) group. *Schizophr Res*. 2003;60:21–32.
25. Simon AE, Borgwardt S, Riecher-Rossler A, Velthorst E, de Haan L, Fusar-Poli P. Moving beyond transition outcomes: meta-analysis of remission rates in individuals at high clinical risk for psychosis. *Psychiatry Res*. 2013;209:266–72.
26. van Os J, Gulozsuz S. A critique of the “ultra-high risk” and “transition” paradigm. *World Psychiatry*. 2017;16:200–6.
27. Cannon TD, Yu C, Addington J, Bearden CE, Cadenhead KS, Cornblatt BA, et al. An individualized risk calculator for research in prodromal psychosis. *Am J Psychiatry*. 2016;173:980–8.
28. Schmidt A, Cappucciat M, Radua J, Rutigliano G, Rocchetti M, Dell’Osso L, et al. Improving prognostic accuracy in subjects at clinical high risk for psychosis: systematic review of predictive models and meta-analytical sequential testing simulation. *Schizophr Bull*. 2017;43:375–88.
29. Koutsouleris N, Kambeitz-Illankovic L, Ruhrmann S, Rosen M, Ruef A, Dwyer DB, et al. Prediction models of functional outcomes for individuals in the clinical high-risk state for psychosis or with recent-onset depression: a multimodal, multisite machine learning analysis. *JAMA Psychiatry*. 2018;75:1156–72.
30. Amminger GP, Schafer MR, Papageorgiou K, Klier CM, Cotton SM, Harrigan SM, et al. Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. *Arch Gen Psychiatry*. 2010;67:146–54.
31. Schmidt SJ, Hurlemann R, Schultz J, Wasserthal S, Kloss C, Maier W, et al. Multimodal prevention of first psychotic episode through N-acetyl-l-cysteine and integrated preventive psychological intervention in individuals clinically at high risk for psychosis: protocol of a randomized, placebo-controlled, parallel-group trial. *Early Interv Psychiatry*. 2019. (in press).
32. McGlashan TH, Zipursky RB, Perkins D, Addington J, Miller T, Woods SW, et al. Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. *Am J Psychiatry*. 2006;163:790–9.
33. Stafford MR, Jackson H, Mayo-Wilson E, Morrison AP, Kendall T. Early interventions to prevent psychosis: systematic review and meta-analysis. *BMJ*. 2013;346:f185.
34. Joa I, Gisselgard J, Bronnick K, McGlashan T, Johannessen JO. Primary prevention of psychosis through interventions in the symptomatic prodromal phase, a pragmatic Norwegian ultra high risk study. *BMC Psychiatry*. 2015;15:89.
35. Seidman LJ, Shapiro DI, Stone WS, Woodberry KA, Ronzio A, Cornblatt BA, et al. Association of neurocognition with transition to psychosis: baseline functioning in the second phase of the North American Prodrome Longitudinal Study. *JAMA Psychiatry*. 2016;73:1239–48.
36. Schmidt SJ, Schultze-Lutter F, Schimmelmann BG, Maric NP, Salokangas RK, Riecher-Rossler A, et al. EPA guidance on the early intervention in clinical high risk states of psychoses. *Eur Psychiatry*. 2015;30:388–404.
37. McFarlane WR, Levin B, Travis L, Lucas FL, Lynch S, Verdi M, et al. Clinical and functional outcomes after 2 years in the early detection and intervention for the prevention of psychosis multisite effectiveness trial. *Schizophr Bull*. 2015;41:30–43.
38. Davies C, Cipriani A, Ioannidis JPA, Radua J, Stahl D, Provenzani U, et al. Lack of evidence to favor specific preventive interventions in psychosis: a network meta-analysis. *World Psychiatry*. 2018;17:196–209.

39. Freudenreich O, Cather C, Holt D. Stimulant misuse in college for “pseudo-attention deficit disorder” during schizophrenia prodrome. *Am J Psychiatry*. 2006;163:2019.
40. Zhu Y, Li C, Huhn M, Rothe P, Krause M, Bighelli I, et al. How well do patients with a first episode of schizophrenia respond to antipsychotics: a systematic review and meta-analysis. *Eur Neuropsychopharmacol*. 2017;27:835–44.
41. Chen AT, Chibnall JT, Nasrallah HA. Placebo-controlled augmentation trials of the antioxidant NAC in schizophrenia: a review. *Ann Clin Psychiatry*. 2016;28:190–6.
42. Fleischhacker WW, Keet IP, Kahn RS, Committee ES. The European First Episode Schizophrenia Trial (EUFEST): rationale and design of the trial. *Schizophr Res*. 2005;78:147–56.
43. Zhu Y, Krause M, Huhn M, Rothe P, Schneider-Thoma J, Chaimani A, et al. Antipsychotic drugs for the acute treatment of patients with a first episode of schizophrenia: a systematic review with pairwise and network meta-analyses. *Lancet Psychiatry*. 2017;4:694–705.
44. Girgis RR, Phillips MR, Li X, Li K, Jiang H, Wu C, et al. Clozapine v. chlorpromazine in treatment-naïve, first-episode schizophrenia: 9-year outcomes of a randomised clinical trial. *Br J Psychiatry*. 2011;199:281–8.
45. McEvoy JP, Hogarty GE, Steingard S. Optimal dose of neuroleptic in acute schizophrenia. A controlled study of the neuroleptic threshold and higher haloperidol dose. *Arch Gen Psychiatry*. 1991;48:739–45.
46. Buchanan RW, Kreyenbuhl J, Kelly DL, Noel JM, Boggs DL, Fischer BA, et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr Bull*. 2010;36:71–93.
47. McGorry PD, Cocks J, Power P, Burnett P, Harrigan S, Lambert T. Very low-dose risperidone in first-episode psychosis: a safe and effective way to initiate treatment. *Schizophr Res Treatment*. 2011;2011:631690.
48. Robinson DG, Schooler NR, Correll CU, John M, Kurian BT, Marcy P, et al. Psychopharmacological treatment in the RAISE-ETP study: outcomes of a manual and computer decision support system based intervention. *Am J Psychiatry*. 2018;175:169–79.
49. Mishara AL. Klaus Conrad (1905–1961): delusional mood, psychosis, and beginning schizophrenia. *Schizophr Bull*. 2010;36:9–13.
50. Felber W, Reuster T. The fading of psychosis. *Psychopathology*. 2001;34:219–20.
51. Emsley R, Rabinowitz J, Medori R. Time course for antipsychotic treatment response in first-episode schizophrenia. *Am J Psychiatry*. 2006;163:743–5.
52. Gallego JA, Robinson DG, Sevy SM, Napolitano B, McCormack J, Lesser ML, et al. Time to treatment response in first-episode schizophrenia: should acute treatment trials last several months? *J Clin Psychiatry*. 2011;72:1691–6.
53. Lally J, Ajnakina O, Di Forti M, Trotta A, Demjaha A, Kolliakou A, et al. Two distinct patterns of treatment resistance: clinical predictors of treatment resistance in first-episode schizophrenia spectrum psychoses. *Psychol Med*. 2016;46:3231–40.
54. Kane JM, Agid O, Baldwin ML, Howes O, Lindenmayer JP, Marder S, et al. Clinical guidance on the identification and management of treatment-resistant schizophrenia. *J Clin Psychiatry*. 2019;80:pii: 18com12123.
55. Tiihonen J, Haukka J, Taylor M, Haddad PM, Patel MX, Korhonen P. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. *Am J Psychiatry*. 2011;168:603–9.
56. Emsley R, Oosthuizen P, Koen L, Niehaus DJ, Medori R, Rabinowitz J. Remission in patients with first-episode schizophrenia receiving assured antipsychotic medication: a study with risperidone long-acting injection. *Int Clin Psychopharmacol*. 2008;23:325–31.
57. Emsley R, Oosthuizen PP, Koen L, Niehaus DJ, Martinez G. Symptom recurrence following intermittent treatment in first-episode schizophrenia successfully treated for 2 years: a 3-year open-label clinical study. *J Clin Psychiatry*. 2012;73:e541–7.
58. Emsley R, Oosthuizen P, Koen L, Niehaus D, Martinez L. Comparison of treatment response in second-episode versus first-episode schizophrenia. *J Clin Psychopharmacol*. 2013;33:80–3.

59. Subotnik KL, Casaus LR, Ventura J, Luo JS, Hellermann GS, Gretchen-Doorly D, et al. Long-acting injectable risperidone for relapse prevention and control of breakthrough symptoms after a recent first episode of schizophrenia. A randomized clinical trial. *JAMA Psychiatry*. 2015;72:822–9.
60. Sommer IEC, Oomen PP, Hasan A. Maintenance treatment for patients with a first psychotic episode. *Curr Opin Psychiatry*. 2019;32:147–56.
61. Mayoral-van Son J, de la Foz VO, Martinez-Garcia O, Moreno T, Parrilla-Escobar M, Valdizan EM, et al. Clinical outcome after antipsychotic treatment discontinuation in functionally recovered first-episode nonaffective psychosis individuals: a 3-year naturalistic follow-up study. *J Clin Psychiatry*. 2016;77:492–500.
62. Takeuchi H, Siu C, Remington G, Fervaha G, Zipursky RB, Foussias G, et al. Does relapse contribute to treatment resistance? Antipsychotic response in first- vs. second-episode schizophrenia. *Neuropsychopharmacology*. 2019;44:1036–42.
63. Catts SV, O'Toole BI. The treatment of schizophrenia: can we raise the standard of care? *Aust N Z J Psychiatry*. 2016;50:1128–38.
64. Zipursky RB. Imagining schizophrenia without relapses. *Aust N Z J Psychiatry*. 2017;51:764–5.
65. Wunderink L, Nieboer RM, Wiersma D, Sytema S, Nienhuis FJ. Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy: long-term follow-up of a 2-year randomized clinical trial. *JAMA Psychiatry*. 2013;70:913–20.
66. Remington G, Addington D, Honer W, Ismail Z, Raedler T, Teehan M. Guidelines for the pharmacotherapy of schizophrenia in adults. *Can J Psychiatr*. 2017;62:604–16.
67. Petersen L, Jeppesen P, Thorup A, Abel MB, Ohlenschlaeger J, Christensen TO, et al. A randomised multicentre trial of integrated versus standard treatment for patients with a first episode of psychotic illness. *BMJ*. 2005;331:602.
68. Bertelsen M, Jeppesen P, Petersen L, Thorup A, Ohlenschlaeger J, le Quach P, et al. Five-year follow-up of a randomized multicenter trial of intensive early intervention vs standard treatment for patients with a first episode of psychotic illness: the OPUS trial. *Arch Gen Psychiatry*. 2008;65:762–71.
69. Austin SF, Mors O, Secher RG, Hjorthoj CR, Albert N, Bertelsen M, et al. Predictors of recovery in first episode psychosis: the OPUS cohort at 10 year follow-up. *Schizophr Res*. 2013;150:163–8.
70. Secher RG, Hjorthoj CR, Austin SF, Thorup A, Jeppesen P, Mors O, et al. Ten-year follow-up of the OPUS specialized early intervention trial for patients with a first episode of psychosis. *Schizophr Bull*. 2015;41:617–26.
71. Austin SF, Mors O, Budtz-Jorgensen E, Secher RG, Hjorthoj CR, Bertelsen M, et al. Long-term trajectories of positive and negative symptoms in first episode psychosis: a 10-year follow-up study in the OPUS cohort. *Schizophr Res*. 2015;168:84–91.
72. Lally J, Ajnakina O, Stubbs B, Cullinane M, Murphy KC, Gaughran F, et al. Remission and recovery from first-episode psychosis in adults: systematic review and meta-analysis of long-term outcome studies. *Br J Psychiatry*. 2017;211:350–8.
73. Kane JM, Schooler NR, Marcy P, Correll CU, Brunette MF, Mueser KT, et al. The RAISE early treatment program for first-episode psychosis: background, rationale, and study design. *J Clin Psychiatry*. 2015;76:240–6.
74. Mueser KT, Penn DL, Addington J, Brunette MF, Gingerich S, Glynn SM, et al. The NAVIGATE program for first-episode psychosis: rationale, overview, and description of psychosocial components. *Psychiatr Serv*. 2015;66:680–90.
75. Dixon L, Jones N, Loewy R, Perkins D, Sale T, Huggins W, et al. Recommendations and challenges of the clinical services panel of the PhenX Early Psychosis Working Group. *Psychiatr Serv*. 2019;70:514–7.
76. O'Donoghue B, Lyne J, Kinsella A, Turner N, O'Callaghan E, Clarke M. Detection and characteristics of individuals with a very long duration of untreated psychosis in an early intervention for psychosis service. *Early Interv Psychiatry*. 2014;8:332–9.

77. Srihari VH, Tek C, Pollard J, Zimmet S, Keat J, Cahill JD, et al. Reducing the duration of untreated psychosis and its impact in the U.S.: the STEP-ED study. *BMC Psychiatry*. 2014;14:335.
78. Srihari VH, Tek C, Kucukgoncu S, Phutane VH, Breitborde NJ, Pollard J, et al. First-episode services for psychotic disorders in the U.S. public sector: a pragmatic randomized controlled trial. *Psychiatr Serv*. 2015;66:705–12.
79. Correll CU, Galling B, Pawar A, Krivko A, Bonetto C, Ruggeri M, et al. Comparison of early intervention services vs treatment as usual for early-phase psychosis: a systematic review, meta-analysis, and meta-regression. *JAMA Psychiatry*. 2018;75:555–65.

Additional Resources

Website

<https://www.nimh.nih.gov/health/topics/schizophrenia/raise/raise-resources-for-patients-and-families.shtml> – The RAISE website by the NIMH. It contains information and resources for first-episode patients.

Articles

Schmidt SJ, Schultze-Lutter F, Schimmelmann BG, Maric NP, Salokangas RK, Riecher-Rossler A, et al. EPA guidance on the early intervention in clinical high risk states of psychoses. *Eur Psychiatry*. 2015;30:388–404. – Guidance from the European Psychiatric Association regarding the management of UHR patients.

Schultze-Lutter F. Subjective symptoms of schizophrenia in research and the clinic: the basic symptom concept. *Schizophr Bull*. 2009;35:5–8. – An introduction to the basic symptom construct that reflects the continued interest of German psychiatry in phenomenology.

Remington G, Addington D, Honer W, Ismail Z, Raedler T, Teehan M. Guidelines for the pharmacotherapy of schizophrenia in adults. *Can J Psychiatry*. 2017;62:604–16. – Check your practice against the Canadian Schizophrenia Guidelines which contains 5 recommendations regarding first-episode patients (use an antipsychotic, chose one with the patient based on risk-benefit preference, treat for 4 weeks and then change if there is no response, use doses on lower dose range, and treat for at least 18 months after symptom resolution). This book chapter is consistent with their recommendations.

Chapter 12

Treatment-Resistant Schizophrenia



Essential Concepts

- Not all patients with schizophrenia have a meaningful response to antipsychotics: one patient in four or one patient in three benefits little from first-line antipsychotics; half of the treatment-refractory patients have no response to any antipsychotic, including clozapine.
- Make sure you are not dealing with “pseudo-refractoriness”: wrong or missed medical diagnoses, unrecognized adherence problems, or drug use.
- Before switching antipsychotics, optimize the dose of the antipsychotic that the patient is already taking, including using therapeutic blood monitoring.
- The timely use of clozapine for treatment-resistant schizophrenia is important as most patients (70%) are treatment refractory from the get-go, when they present for psychiatric treatment. For this group, first-line antipsychotics are not effective and constitute ineffective treatment.
- Consider a (time-limited) clozapine after two or even just one failed, adequate antipsychotic trial; a long-acting injectable antipsychotic trial is ideal given the importance of ruling out partial or full antipsychotic nonadherence.
- The goal of a clozapine trial is to determine if your patient is a good clozapine responder. 50% of treatment-refractory patients benefit little from clozapine.
- Augmentation strategies for poor clozapine responders include ECT. Other add-on medication strategies may confer some benefit, but none yields impressive results.
- Patients with treatment-resistant schizophrenia require longitudinal care beyond medications, including asylum-like spaces where they can humanely make the best of their situation.

“The tragedy of life is what dies inside a man while he lives – the death of genuine feeling, the death of inspired response, the death of the awareness that makes it possible to feel the pain or the glory of other men in oneself.” [1]

– Albert Schweitzer, 1875–1965, Noble Prize for Peace 1952

Most patients with schizophrenia, about 70–80%, have a meaningful reduction in positive symptoms from first-line antipsychotics [2]. Unfortunately, the tragedy of life, to paraphrase Schweitzer, leaves 20–30% of patients treatment-resistant, with little to no symptomatic response to first-line antipsychotics [3]. Among nonresponders, about half may show only a limited response even to clozapine [4]. At least 10% of patients are therefore currently not responsive to antipsychotics including clozapine. Of note, the majority of treatment-refractory patients (70%) are refractory from the get-go [5]; it is only a minority of patients who becomes treatment refractory over time. In this chapter, I describe a systematic approach to establish treatment-resistant schizophrenia and its treatments. The clinical use of clozapine which is the treatment of choice for treatment resistance is covered in greater depth in its own chapter (Chap. 17).

Terminology

For my clinical purposes, I use “treatment-resistant schizophrenia” (TRS) (or “refractory schizophrenia”) for those patients who do not have a clinically meaningful reduction in impairing *positive* symptoms despite two adequate (in dose and duration) antipsychotic trials except clozapine. Those patients who are refractory to all antipsychotics including clozapine fall into a category of themselves (“ultra-treatment-resistant”). Since treatment-resistant patients fail to respond to dopamine-blocking antipsychotics, they may have a different biology compared to non-refractory patients. Sometimes, “resistant” is used to suggest some responsiveness (albeit not good), while “refractory” is reserved for those patients with no response at all, but clinicians use the terms interchangeably.

Being refractory usually implies being refractory with regard to positive symptoms (for which we have treatment in the form of antipsychotics, it is merely not working *for this patient*) but not with regard to cognitive or negative symptoms (for which we have no treatment). Patients with refractory schizophrenia are usually profoundly disabled. Technically, the functional impairment that you may associate with “refractory” patients stems from negative and cognitive symptoms and not from merely disruptive positive symptoms. It is of course the illness that is refractory, not the patient; put differently, it is our treatment that is ineffective for a patient.

A recent consensus document by the Treatment Response and Resistance in Psychosis (TRRIP) Working Group delineates treatment-resistant schizophrenia (TRS) more precisely (see Table 12.1) [6]. Their effort will help clinical research as many studies in refractory patients are now quite old (often conducted with first-generation antipsychotics) and difficult to compare in meta-analyses.

Table 12.1 Treatment-refractory schizophrenia (TRS): consensus definition

<i>Persistent symptoms</i>
Moderate severity for specific symptom domain ^a
Ill for longer than 12 weeks
Moderate functional impairment
<i>Despite adequate treatment</i>
At least two adequate failed trials ^b
Duration: at least 6 weeks
Dosage: at least 600 CPZ-EQ = chlorpromazine equivalents
Adherence: at least 80%
Minimal response ^c

Based on reference [6]

^aSpecify if positive, negative, or cognitive symptoms

^bIdeally, at least one prospective treatment trial conducted specifically to establish nonresponse

^cTreatment response: at least 20% response
CPZ-EQ chlorpromazine equivalents

Rule-Out Pseudo-refractoriness

The key concept of treatment-resistant schizophrenia assumes a correct diagnosis of schizophrenia, adequate pharmacological treatment, and persistence of symptoms despite treatment. A mistaken assumption of treatment refractoriness has grievous consequences. It leads to polypharmacy, higher than necessary medication doses, poor treatment choices, and more side effects. Patients with intermittent compliance do not get used to side effects, and they might even run the risk of dangerous problems from starting a medication at full dose after missing a week of medications. Mistaken assumptions of nonresponse to a particular medication can lead the clinician to give up on a potentially valuable medication for the rest of the patient's life. Last, prolonged trials with an ineffective treatment do not allow a patient to develop a "positive drug attitude" as he or she never experiences any benefit, hindering adherence in the long run. Moreover, the longer the period of psychosis, the more difficult eventual reintegration into society becomes. A longer duration of untreated psychosis in first-episode patients is associated with worse outcomes [7]; I consider ineffective treatment to be equivalent to no treatment at all.

Before you label a patient treatment refractory, make therefore sure that you have considered two questions: do you have the correct diagnoses, and do you know that the patient had at least one *adequate* antipsychotic trial?

Is the Patient's Diagnosis Correct and Complete?

Patients who have a secondary psychosis due to a medical or neurological disease (e.g., psychosis due to Alzheimer's dementia) may not respond well or not at all to antipsychotics. A poor treatment response should alert you to a missed medical or

neurological diagnosis. Other psychiatric conditions may also hinder an optimal response if only treated with an antipsychotic (e.g., comorbid OCD or psychotic depression). The presence of catatonic symptoms may require significant treatment modifications (e.g., using benzodiazepines and clozapine or ECT), both to achieve symptomatic improvement and to prevent a transition to lethal catatonia [8]. The most common reason for a poor response, however, is comorbid drug use. While a substance-induced psychotic disorder responds to antipsychotics, you rarely get a full response in the face of ongoing use, particularly if substance use is accompanied by poor adherence [9].

Has the Patient Had an Adequate Antipsychotic Trial?

Assuming you are confident that your diagnosis is correct and that drug use is not to blame for continuing symptoms, review past treatment trials with regard to adequacy. Table 12.1 summarizes the consensus definition of what constitutes an “adequate trial.” In reality, you are often left with some guess work regarding adequacy of past trials. Rarely do you have good documentation of dose, duration, and response; in almost all cases (unless the trial included a long-acting injectable antipsychotic), you should question adherence. A patient might report, “I was on risperidone and it did not work,” without further knowledge of dose, duration, adherence, and response.

Key Point

It is often necessary to conduct one adequate antipsychotic trial *yourself* in order to prospectively establish TRS. Such a trial should assure adherence (at least 80%), adequate duration (at least 6 weeks), and adequate dose (at least 600 CPZ-EQ). One adequate trial with a dopamine antagonist is probably sufficient to establish treatment-refractory biology.

First, the aforementioned TRRIP Working Group decreed that a good trial duration ought to be at least 6 weeks, which seems reasonable. You should expect some clearly detectable clinical response after 2–4 weeks of treatment (not counting a titration). In first-episode patients, however, time to response varies [10], with a small group of patients responding only after 8–16 weeks [11]. If there is a clear response, simply wait! It is important to allow symptoms to resolve and not to switch prematurely: time on (the right) medication is as important as the dose of medication since psychosis needs to be given time to resolve which will take several weeks. Similarly, functional benefits of adequate symptom control will accrue only with time; here we are measuring progress in months, not weeks. Giving more medication cannot accelerate this process. It is a mistake to “push the dose” after 1 week

of hospitalizations, with little change in core psychotic symptoms. In other words, optimizing a medication can mean decreasing the dose for tolerability or adding something symptomatically or to counteract side effects. Most patients will in fact show signs of improvement as early as week 1 (or even after a single antipsychotic dose) (e.g., in sleep, in agitation) [12]. It is simply unrealistic to expect the resolution of a delusional system during a brief hospitalization.

Second, a dose of at least 600 CPZ-EQ should be used according to the Working Group. Some patients, however, might require a higher antipsychotic dose because of drug interactions (e.g., a patient on carbamazepine) or idiosyncrasies in drug metabolism, so do not just rely on the prescribed dose: therapeutic drug monitoring (TDM) is a critical aspect of managing patients who are considered treatment refractory (see Chap. 20 for TDM).

Tip

Check antipsychotic drug levels routinely to help with optimal dosing of antipsychotics but particularly in patients who appear treatment refractory. A non-detectable or very low antipsychotic level at the usual dose suggests either an adherence problem or unusual metabolism [13] and not true treatment resistance.

A higher than usual antipsychotic dose (higher than FDA-approved maximum dose) does not usually lead to further meaningful improvement. While clinicians often deploy a high-dose strategy, the only antipsychotics where clinical studies have shown a possible benefit is olanzapine [14]. Before giving up on olanzapine, consider therefore an olanzapine trial at a dose of 30 mg/day or more, particularly if clozapine is not an option. Note that this dose is higher than the Food and Drug Administration (FDA)-approved dose of 20 mg/day. An additional dose increase beyond 40 mg/d is unlikely to add more benefit in refractory patients [15]. With some antipsychotics, it has been confirmed in clinical trials that a higher dose is in fact not more effective than standard doses. Examples include ziprasidone (up to 320 mg/d) [16] and quetiapine (up to 1200 mg/d) [17, 18]. Keep in mind potentially dangerous problems when you exceed usual doses (e.g., dose-related QTc prolongation with quetiapine or ziprasidone).

Third, the Working Group proposed to use a cutoff of 80% adherence in order to be considered adequately adherent. If there is any chance that partial adherence might be the problem (I believe this is a very realistic possibility in almost all patients) and for a definitive conclusion of true treatment refractoriness, you may need to conduct a trial with a long-acting antipsychotic. This approach assures 100% adherence and, when coupled with TDM, confirms treatment-resistant schizophrenia if there is no response. I do not believe that oral trials with outpatients are sufficient.

Tip

Recommend (i.e., insist on) a time-limited trial of a long-acting injectable antipsychotic before moving to clozapine to eliminate that possibility of pseudo-refractoriness due to partial adherence, even in patients where adherence seems to be unproblematic.

Last, most guidelines, including the TRRIP Working Group guideline, recommend two well-conducted trials of an antipsychotic before moving to clozapine for refractory patients. I like to have one of the trials to be an antipsychotic with “tight” D2-binding like risperidone since you want to establish resistance to dopamine blockade. I hesitate to count quetiapine because of its transient and weak dopamine-2 (D2)-binding which could render it less effective for some patients toward a failed drug trial. If the two antipsychotics have not included olanzapine, I will often try olanzapine as it seems to be more effective than other first-line treatments [19]. The clinical task of establishing treatment resistance might not call for therapeutic adventures with newer antipsychotics where less is known clinically.

Important new information regarding the number of trials required in order to establish treatment resistance comes from a European trial called OPTiMiSE (which stands for Optimization of Treatment and Management of Schizophrenia in Europe) [20]. In OPTiMiSE, first-episode patients were treated according to a three-step algorithm. In the first phase, everybody received 4 weeks of initial treatment with the tight D2-blocking second-generation antipsychotic amisulpride (not available in the United States). In a double-blind randomized second phase, participants received either 6 more weeks with amisulpride, or they were switched to olanzapine. In the third phase, nonresponders received clozapine. The second phase asked the important question if switching antipsychotics is a useful strategy. The trial confirmed what we already knew: that first-episode patients as a group show a good response to antipsychotics – 2/3 of participants remitted after the end of the 10-week treatment with amisulpride or amisulpride and olanzapine [21]. The trial further showed that there was no additional benefit from switching to olanzapine; the patient who stayed on amisulpride did just as well. Finally, nonresponders benefited from switching to clozapine, but the response was not as robust as responders. What this trial basically shows is that some first-episode patients are refractory from the get-go, and the best intervention for this subgroup is a clozapine trial once it has been established that they are refractory to a first-line antipsychotic. This result confirms work by a Canadian group who has used a similarly stepped approach in their first-episode clinic. Like OPTiMiSE, patients who did not respond to their first antipsychotic benefited little from a switch to a second antipsychotic but showed a robust response once clozapine was offered [22]. Moving to clozapine after only one antipsychotic trial, particularly if treatment resistance was clearly established, may be something to discuss with your patient.

Clozapine Trial

In a stepped-care paradigm, a more effective treatment is used when a lower-level intervention has failed to lead to improvement (see Chap. 9 regarding stage-based treatment). Once you have established treatment resistance in a schizophrenia patient, you need to propose a clozapine trial. Clozapine is not a cure by any means. About 50% of TRS patients benefit little from clozapine [23]. The goal of a clozapine trial therefore is to establish if your patient is a good clozapine responder.

Key Point

Clozapine should be part of your treatment algorithm for patients with schizophrenia. Given its superior efficacy for refractory patients, it is inexcusable to not at least strongly recommend (some patients will not agree) and nudge treatment-resistant patients toward a clozapine trial, perhaps as early as after one adequate trial with a first-line antipsychotic. Clozapine for TRS should be the default (opt-out) option. Unless you try it, you will never know if your patient is a good clozapine responder.

Unfortunately, clozapine remains underused: many patients never receive clozapine even though they have had more than enough failed antipsychotic trials. Many patients will be wary of what they might have heard about clozapine, its host of potential side effects, and the need for regular blood work. However, physician attitude and barrier are real impediments [24]. First, convince yourself that clozapine is the next step, then convince the patient, and then make it happen. In a shared decision paradigm, you need to make patients aware of a clozapine trial, including the benefits, not just the downside. What you want to impress on the patient is that he or she deserves a chance to try a more effective medication to get better. Many patients will acknowledge after trying clozapine that clozapine is the best medicine they have taken, both with regard to efficacy and, in cases of patients with sensitivity to EPS, with regard to tolerability.

For most patients, a switch to clozapine is unproblematic: different switch strategies (abrupt vs gradual discontinuation of the non-clozapine antipsychotic) can be used [25]; I discuss the possibilities with the patient and let him chose.

Tip

I always tell the patients that I recommend a *time-limited* trial of clozapine: trying it does not mean taking it “for the rest of your life.” It gives the patient some control and might avert a refusal of a clozapine trial (which requires the cooperation of the patient; clozapine cannot be given parenterally). Many patients who improved elect to continue on it.

I want to make one last point about the timely use of clozapine. While clozapine should be used as early as needed (i.e., for refractory patients once this fact is established), unselected first-episode patients have an excellent chance to respond well to any first-line antipsychotics which are much safer and better tolerated than clozapine; for most patients, clozapine is not needed. Clozapine as a first-line treatment would only be justified if there were a disease-modifying benefit in the long run from using it. This hypothesis was not confirmed in one randomized trial in China that treated first-episode patients with either chlorpromazine or clozapine for 1 year [26] who were then followed up a decade later [27]. Both treatments worked similarly well, with no differences in symptoms or function.

Clinical Vignette

A young man, Alfred, came to my clinic after over 2 years of treatment for schizophrenia without much improvement. He had initially received risperidone but was switched to quetiapine after a few weeks when he did not get better. When I evaluated him, he experienced constant Schneiderian first-rank symptoms, preventing him from reading and concentrating on what people were saying to him; the distractions were so severe that he had been unable to work even part-time. There was not drug use, and (despite lack of efficacy) he had faithfully taken his prescribed antipsychotic. I switched him to olanzapine, which reduced his positive symptoms to the point that he could work again. We then negotiated a time-limited trial of clozapine to see if his positive symptoms would completely remit. Because clozapine led to complete symptom remission, he opted to continue with clozapine despite the need for blood monitoring. I have followed him now for many years, and he continues to be symptom-free on clozapine.

This story is unfortunately all too common; patients are left with residual symptoms of psychosis even though the most effective antipsychotics, olanzapine and particularly clozapine, have not been tried (for 2 years, Alfred was left on an antipsychotic that was entirely ineffective for him). Importantly, do not reserve clozapine only for the most seriously ill patients. For this patient, clozapine brought additional benefit compared to olanzapine. It is my personal view that you should treat schizophrenia only if you are able to offer a clozapine trial to your patient.

Clozapine Nonresponse

Among clozapine responders, I have had patients with an excellent response (full *restitutio ad integrum*), but most patients can realistically only expect a partial response [21]. About 50% of patients show no response to clozapine and are considered clozapine nonresponders [4]. Regardless of the degree of response, augmentation strategies are often pursued.

Electroconvulsive Therapy

The best clinical evidence is for offering electroconvulsive therapy (ECT) which is a rapidly effective albeit rarely used treatment for psychosis [28]. A meta-analysis estimated that between one half and two third of patients improve with the addition of ECT to clozapine treatment [29]. In one randomized trial, 50% of patients met response criteria (40% reduction in positive symptoms) after ECT was added to clozapine, while no patient assigned to clozapine alone responded [30]. In a cross-over phase of this trial, about 50% of nonresponders who had initially not received ECT improved when they were given ECT. It is unclear if ECT truly augmented clozapine or if ECT alone would have achieved the same results. While ECT may offer symptomatic improvement for TRS, it is unclear if the benefit extends to better function [31]. Even if you work in a healthcare system where ECT can be administered acutely for treatment-resistant schizophrenia, it does not solve the vexing management issue of needing some treatment after the course of ECT is finished. ECT maintenance treatment may be the best option for patients who had a robust response to ECT [32]. In clinical reality, patients are simply switched back to previous regimens – probably not an ideal strategy as those were ineffective – otherwise ECT would not have been pursued. Newer brain stimulation therapies like repetitive transcranial magnetic stimulation (rTMS) are promising but not routinely available [33].

Clozapine Augmentation

While combining clozapine with other antipsychotics or with other psychotropics is often pursued when clinicians and families get desperate, a Cochrane review found no high-quality studies that will help you make evidence-based treatment decisions [34]. Refer to the clozapine chapter (Chap. 17) for a longer discussion of clozapine augmentation with medications.

Sometimes, clinicians repurpose already available medications that are approved for other indications. For example, a small case series reported the successful treatment of ten treatment-resistant patients with 34 mg of pimavanserin which is a non-antidopaminergic antipsychotic (inverse 5-HT2a agonist) approved at the time of this writing only for the psychosis of Parkinson's disease [35]. For most patients in this series, pimavanserin was added onto clozapine treatment. While this clinical observation needs to be confirmed in a controlled clinical trial, it offers hope that we may eventually have better treatments for this group of patients. I will not get my hopes up, however, as using 5-HT2a antagonists for schizophrenia is not a new idea and previous trials have failed.

Families often will ask you about particular approaches, some merely off-label uses of FDA-approved medication, other more on the fringes. Adjunctive treatments are legion (e.g., neurosteroids, purinergic agents, glutamatergic agents, vitamins).

An example of a recent compound reported in a controlled trial to have some benefit is sodium benzoate (a D-amino acid oxidase inhibitor) at a dose of 1–2 mg/d added onto clozapine treatment [36]. Some of you will be more therapeutic enthusiasts, some more skeptics with regard to trying a new compound [37]. I believe given the seriousness of the situation, flexibility is needed on my part, as long as the primary treatment that I try to offer is not jeopardized and as long as the proposed intervention is not outright dangerous. Unfortunately, I often see patients spending large amounts of money on unhelpful pills and interventions.

Key Point

You cannot augment a nonresponse. While desperate times may require desperate measures, keep in mind that you are “skating on thin ice” [38] when it comes to evidence-supported treatments for treatment-resistant schizophrenia. The best evidence is for ECT.

There is a fine line between “snowing the patient” and “treating the patient.” Overly aggressive use of medications with limited efficacy has many risks for the patient. On the other hand, undertreating a violent, out-of-control patient brings suffering not only to society but ultimately to the patient. A desperate trial of an old drug, reserpine, can sometimes work, particularly in an excited psychosis [39]. At some point, however, rather than continuing to pile on medication, you may need to decide to abort a clozapine trial, including attempts at augmentation, and switch the patient back to a previous best medication regimen or even try an antipsychotic they have never taken. I have cared for treatment-resistant patients who ultimately did better on a non-clozapine regimen compared to clozapine. Keep in mind that “no response” in seriously ill patients does not mean that a patient would be better off completely untreated. In most patients, medications provide some benefit (e.g., less agitation) even if a patient remains ill at the syndromal level.

Cognitive-Behavioral Therapy

Non-medication interventions should be part of comprehensive care for patients with refractory psychosis. Cognitive-behavioral therapy (CBT) is a well-established add-on psychological treatment modality with a good evidence base for residual psychosis (see Chap. 22). More recently, avatar therapy represents an interesting new approach to improve positive symptom, specifically controlling, persecutory, and negative voices [40]. In this therapy, patients use software to create an avatar of the voice (an image or an embodiment of the voice, the way the patient hears the voice and imagines his or her tormenter to look). Creating an avatar works best if the voice has a clear and complex identity that the patient can engage with and is not just some “spirit” or something vaguely “mean.” By putting a face to the voice, a

dialogue becomes possible between the patient and his or her voice. In fact, the therapy is a trialogue as the therapist assumes the role of the therapist (to guide the patient) and also pretends to be the voice (to expose the patient to what is feared and avoided). The goal of avatar therapy is for the patient to assertively reestablish control and not feel powerless vis-à-vis an entity that feels omnipotent. This therapy uses exposure to something that is difficult: to be in dialogue with and talk to a powerful entity that uses threats and intimidation. A recent controlled trial of seven-session avatar therapy showed that when compared to supportive counseling it can rapidly (within a few weeks) reduce the severity of auditory hallucination [41]. Avatar therapy represents a rapid-onset, voice-specific treatment for medication-resistant auditory hallucinations with a good effect size (0.8).

Need for an Asylum

Given the reality of the existence of clozapine-refractory schizophrenia, a health-care system is needed to humanely manage this very disabled group of patients. Such places would be staffed by people well versed in nonmedical approaches (e.g., behavioral treatment) to manage difficult behaviors. We need to remain realistic, however, what we can achieve for this small group of seriously ill patients. In one very well-resourced clinical trial, severely ill patients did not improve from the treatment and rehabilitation efforts from well-trained staff that were offered in the intervention arm, compared to the treatment-as-usual group [42]. Some patients require long-term psychiatric care, and they may not improve much, despite our best efforts. Such patients require an “asylum,” a place from which they cannot be expelled; they cannot be discharged to a “lower level of care” which is often the streets [43]. Families alone, without the support of the public sector, can only care for their seriously ill relative up to a point. We do not need to bring back asylum care in front of the gates of our cities, but we need to create enough asylum-like spaces in the community that provide the appropriate level of supervision, concrete help, and protection for that group of patients that relies on us as a society. Not a single one of my patients chose to develop treatment-resistant schizophrenia to be difficult.

References

1. Cousins ND. Schweitzer of Lambaréné. New York: Harper & Brothers; 1960.
2. Meltzer HY. Treatment-resistant schizophrenia—the role of clozapine. Curr Med Res Opin. 1997;14:1–20.
3. Kane JM, Agid O, Baldwin ML, Howes O, Lindenmayer JP, Marder S, et al. Clinical guidance on the identification and management of treatment-resistant schizophrenia. J Clin Psychiatry. 2019;80:pii: 18com12123.
4. Mouaffak F, Tranulis C, Gourevitch R, Poirier MF, Douki S, Olie JP, et al. Augmentation strategies of clozapine with antipsychotics in the treatment of ultraresistant schizophrenia. Clin Neuropharmacol. 2006;29:28–33.

5. Lally J, Ajnakina O, Di Forti M, Trotta A, Demjaha A, Kolliakou A, et al. Two distinct patterns of treatment resistance: clinical predictors of treatment resistance in first-episode schizophrenia spectrum psychoses. *Psychol Med.* 2016;46:3231–40.
6. Howes OD, McCutcheon R, Agid O, de Bartolomeis A, van Beveren NJ, Birnbaum ML, et al. Treatment-resistant schizophrenia: treatment response and resistance in psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology. *Am J Psychiatry.* 2017;174:216–29.
7. Penttila M, Jaaskelainen E, Hirvonen N, Isohanni M, Miettunen J. Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: systematic review and meta-analysis. *Br J Psychiatry.* 2014;205:88–94.
8. England ML, Ongur D, Konopaske GT, Karmacharya R. Catatonia in psychotic patients: clinical features and treatment response. *J Neuropsychiatry Clin Neurosci.* 2011;23:223–6.
9. Schoeler T, Petros N, Di Forti M, Klamerus E, Foglia E, Murray R, et al. Poor medication adherence and risk of relapse associated with continued cannabis use in patients with first-episode psychosis: a prospective analysis. *Lancet Psychiatry.* 2017;4:627–33.
10. Emsley R, Rabinowitz J, Medori R. Time course for antipsychotic treatment response in first-episode schizophrenia. *Am J Psychiatry.* 2006;163:743–5.
11. Gallego JA, Robinson DG, Sevy SM, Napolitano B, McCormack J, Lesser ML, et al. Time to treatment response in first-episode schizophrenia: should acute treatment trials last several months? *J Clin Psychiatry.* 2011;72:1691–6.
12. Agid O, Seeman P, Kapur S. The “delayed onset” of antipsychotic action—an idea whose time has come and gone. *J Psychiatry Neurosci.* 2006;31:93–100.
13. Horvitz-Lennon M, Mattke S, Predmore Z, Howes OD. The role of antipsychotic plasma levels in the treatment of schizophrenia. *Am J Psychiatry.* 2017;174:421–6.
14. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med.* 2005;353:1209–23.
15. Lindenmayer JP, Czobor P, Volavka J, Lieberman JA, Citrome L, Sheitman B, et al. Olanzapine in refractory schizophrenia after failure of typical or atypical antipsychotic treatment: an open-label switch study. *J Clin Psychiatry.* 2002;63:931–5.
16. Goff DC, McEvoy JP, Citrome L, Mech AW, Bustillo JR, Gil R, et al. High-dose oral ziprasidone versus conventional dosing in schizophrenia patients with residual symptoms: the ZEBRAS study. *J Clin Psychopharmacol.* 2013;33:485–90.
17. Honer WG, MacEwan GW, Gendron A, Stip E, Labelle A, Williams R, et al. A randomized, double-blind, placebo-controlled study of the safety and tolerability of high-dose quetiapine in patients with persistent symptoms of schizophrenia or schizoaffective disorder. *J Clin Psychiatry.* 2012;73:13–20.
18. Lindenmayer JP, Citrome L, Khan A, Kaushik S. A randomized, double-blind, parallel-group, fixed-dose, clinical trial of quetiapine at 600 versus 1200 mg/d for patients with treatment-resistant schizophrenia or schizoaffective disorder. *J Clin Psychopharmacol.* 2011;31:160–8.
19. Lieberman JA, Tolleson G, Tohen M, Green AI, Gur RE, Kahn R, et al. Comparative efficacy and safety of atypical and conventional antipsychotic drugs in first-episode psychosis: a randomized, double-blind trial of olanzapine versus haloperidol. *Am J Psychiatry.* 2003;160:1396–404.
20. Leucht S, Winter-van Rossum I, Heres S, Arango C, Fleischhacker WW, Glenthøj B, et al. The optimization of treatment and management of schizophrenia in Europe (OPTiMiSE) trial: rationale for its methodology and a review of the effectiveness of switching antipsychotics. *Schizophr Bull.* 2015;41:549–58.
21. Kahn RS, Winter van Rossum I, Leucht S, McGuire P, Lewis SW, Leboyer M, et al. Amisulpride and olanzapine followed by open-label treatment with clozapine in first-episode schizophrenia and schizophreniform disorder (OPTiMiSE): a three-phase switching study. *Lancet Psychiatry.* 2018;5:797–807.

22. Agid O, Arenovich T, Sajeev G, Zipursky RB, Kapur S, Foussias G, et al. An algorithm-based approach to first-episode schizophrenia: response rates over 3 prospective antipsychotic trials with a retrospective data analysis. *J Clin Psychiatry*. 2011;72:1439–44.
23. Porcelli S, Balzarro B, Serretti A. Clozapine resistance: augmentation strategies. *Eur Neuropsychopharmacol*. 2012;22:165–82.
24. Kelly DL, Freudenreich O, Sayer MA, Love RC. Addressing barriers to clozapine underutilization: a national effort. *Psychiatr Serv*. 2018;69:224–7.
25. Takeuchi H, Lee J, Fervaha G, Foussias G, Agid O, Remington G. Switching to clozapine using immediate versus gradual antipsychotic discontinuation: a pilot, double-blind, randomized controlled trial. *J Clin Psychiatry*. 2017;78:223–8.
26. Lieberman JA, Phillips M, Gu H, Stroup S, Zhang P, Kong L, et al. Atypical and conventional antipsychotic drugs in treatment-naïve first-episode schizophrenia: a 52-week randomized trial of clozapine vs chlorpromazine. *Neuropsychopharmacology*. 2003;28:995–1003.
27. Girgis RR, Phillips MR, Li X, Li K, Jiang H, Wu C, et al. Clozapine v. chlorpromazine in treatment-naïve, first-episode schizophrenia: 9-year outcomes of a randomised clinical trial. *Br J Psychiatry*. 2011;199:281–8.
28. Tharyan P, Adams CE. Electroconvulsive therapy for schizophrenia. *Cochrane Database Syst Rev*. 2005;2:CD000076.
29. Lally J, Tully J, Robertson D, Stubbs B, Gaughran F, MacCabe JH. Augmentation of clozapine with electroconvulsive therapy in treatment resistant schizophrenia: a systematic review and meta-analysis. *Schizophr Res*. 2016;171:215–24.
30. Petrides G, Malur C, Braga RJ, Baille SH, Schooler NR, Malhotra AK, et al. Electroconvulsive therapy augmentation in clozapine-resistant schizophrenia: a prospective, randomized study. *Am J Psychiatry*. 2015;172:52–8.
31. Sinclair DJ, Zhao S, Qi F, Nyakyma K, Kwong JS, Adams CE. Electroconvulsive therapy for treatment-resistant schizophrenia. *Cochrane Database Syst Rev*. 2019;3:CD011847.
32. Ward HB, Szabo ST, Rakesh G. Maintenance ECT in schizophrenia: a systematic review. *Psychiatry Res*. 2018;264:131–42.
33. Wagner E, Wobrock T, Kunze B, Langguth B, Landgrebe M, Eichhammer P, et al. Efficacy of high-frequency repetitive transcranial magnetic stimulation in schizophrenia patients with treatment-resistant negative symptoms treated with clozapine. *Schizophr Res*. 2019;208:370–6.
34. Ortiz-Orendain J, Castiello-de Obeso S, Colunga-Lozano LE, Hu Y, Maayan N, Adams CE. Antipsychotic combinations for schizophrenia. *Cochrane Database Syst Rev*. 2017;6:CD009005.
35. Nasrallah HA, Fedor R, Morton R. Successful treatment of clozapine-nonresponsive refractory hallucinations and delusions with pimavanserin, a serotonin 5HT-2A receptor inverse agonist. *Schizophr Res*. 2019;208:217–20.
36. Lin CH, Lin CH, Chang YC, Huang YJ, Chen PW, Yang HT, et al. Sodium benzoate, a D-amino acid oxidase inhibitor, added to clozapine for the treatment of schizophrenia: a randomized, double-blind, placebo-controlled trial. *Biol Psychiatry*. 2018;84:422–32.
37. Fogel BS, Duffy J, McNamara ME, Salloway S. Skeptics and enthusiasts in neuropsychiatry. *J Neuropsychiatry Clin Neurosci*. 1992;4:458–62.
38. Tracy DK, Joyce DW, Sarkar SN, Mateos Fernandez MJ, Shergill SS. Skating on thin ice: pragmatic prescribing for medication refractory schizophrenia. *BMC Psychiatry*. 2015;15:174.
39. Berlant JL. Neuroleptics and reserpine in refractory psychoses. *J Clin Psychopharmacol*. 1986;6:180–4.
40. Leff J, Williams G, Huckvale MA, Arbuthnot M, Leff AP. Computer-assisted therapy for medication-resistant auditory hallucinations: proof-of-concept study. *Br J Psychiatry*. 2013;202:428–33.
41. Craig TK, Rus-Calafell M, Ward T, Leff JP, Huckvale M, Howarth E, et al. AVATAR therapy for auditory verbal hallucinations in people with psychosis: a single-blind, randomised controlled trial. *Lancet Psychiatry*. 2018;5:31–40.

42. Killaspy H, Marston L, Green N, Harrison I, Lean M, Cook S, et al. Clinical effectiveness of a staff training intervention in mental health inpatient rehabilitation units designed to increase patients' engagement in activities (the Rehabilitation Effectiveness for Activities for Life [REAL] study): single-blind, cluster-randomised controlled trial. *Lancet Psychiatry*. 2015;2:38–48.
43. Sisti DA, Segal AG, Emanuel EJ. Improving long-term psychiatric care: bring back the asylum. *JAMA*. 2015;313:243–4.

Additional Resources

Book

Buckley PF, Gaughran F, editors. *Treatment-refractory schizophrenia : a clinical conundrum*. Heidelberg: Springer; 2014. – A whole book about TRS, with international authors from Australia, Europe, and the Americas.

Articles

Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry*. 1988;45:789–96. – Read this one, as it is one of only a handful of truly seminal articles on the treatment of schizophrenia. Note the excellent clinical trials methodology, with a prospective treatment period to establish non-response.

Kane JM, Agid O, Baldwin ML, Howes O, Lindenmayer JP, Marder S, et al. Clinical guidance on the identification and management of treatment-resistant schizophrenia. *J Clin Psychiatry*. 2019;80:pii: 18com12123. – Excellent review of treatment-resistant schizophrenia by John Kane who conducted the Kane trial over 20 years ago (see above).

Sisti DA, Segal AG, Emanuel EJ. Improving long-term psychiatric care: bring back the asylum. *JAMA*. 2015;313:243–4. – An important viewpoint that argues for the ethical imperative to provide the whole continuum of psychiatric care, including caring for those with serious illness that have been hurt the most from deinstitutionalization (or rather, transinstitutionalization). While the title is provocative, the authors do not argue for a return to the state of hospitals of late but simply to provide humane and safe spaces for those who cannot help themselves.

Chapter 13

Antipsychotics: Overview



Essential Concepts

- All current antipsychotics marketed for schizophrenia share varying degrees of dopamine-2 (D2) receptor blockade as the presumed main mechanism of action. However, the next generation of antipsychotics may no longer follow this rule.
- Primary symptom targets of antipsychotics are positive symptoms (disorganization, delusions, and hallucinations) and agitation, with limited efficacy for other symptom clusters (negative symptoms, cognition).
- For historical reasons, antipsychotics are grouped into first-generation antipsychotics – “typical” or conventional antipsychotics, which are all characterized by extrapyramidal symptom (EPS) liability – and second- and third-generation antipsychotics (with reduced EPS risk, hence “atypical” antipsychotics).
- Second-generation antipsychotics (clozapine, iloperidone, lurasidone, olanzapine, risperidone, and paliperidone, quetiapine, ziprasidone) and third-generation antipsychotics (aripiprazole, brexpiprazole, cariprazine) should not be considered interchangeable, as each drug has a unique receptor profile beyond shared 5-HT-2 – D2 antagonism, resulting in different side effects.
- The main risks for first-generation antipsychotics are neurologic side effects (dystonias, akathisia, Parkinsonism, and tardive dyskinesia). For most second- and third-generation antipsychotics, metabolic problems (weight gain, dyslipidemia, and hyperglycemia) have emerged as major problems in long-term management, in addition to ongoing concerns about neurological side effects.
- Non-dopaminergic antipsychotics are under development as they would be devoid of undesirable effects related to dopamine blockade.

- In preclinical models, antipsychotics have both neuroprotective and neurotoxic properties. Tardive dyskinesia is an example of neurotoxicity, but the clinical implications of many other observations (e.g., cortical thinning in imaging studies) remain unclear.

“The greater the ignorance, the greater the dogmatism.” [1]

-Sir William Osler, Father of Modern Medicine, 1849–1919

Antipsychotics are the mainstay of treatment for schizophrenia. Lumped together into one group based on dopamine blockade, there are clear differences between antipsychotics with regard to side effects, particular among the newer antipsychotics. All antipsychotics are about equally effective for non-refractory patients with schizophrenia. For pedagogical reasons, I have maintained the historical distinction between first-, second-, and third-generation antipsychotics which mostly reflects the time period when they were approved. This chapter introduces dopamine blockade as mechanism of action for all current antipsychotics and derives clinical points related to this basic property (e.g., dosing). Motor and non-motor side effects are then covered in greater detail in the next two chapters (Chaps. 14 and 15, respectively). Clozapine and long-acting antipsychotics have their own chapters (Chaps. 17 and 18, respectively).

Mechanism of Action

All currently marketed antipsychotics for schizophrenia block D2 receptors, albeit with different affinities. Dopamine blockade in the mesolimbic system is believed to be responsible for the clinical efficacy of antipsychotics. Unfortunately, antipsychotics do not have enough regional specificity and cause extrapyramidal symptoms from D2 blockade in the nigrostriatal motor system and prolactin elevation in the tuberoinfundibular system. Drug development has thus far failed to develop an antipsychotic that does not interact with the dopamine system, although a pure serotonergic agonist, pimavanserin, is approved for psychosis in Parkinson’s disease [2] and clinicians have started to use it for other forms of psychosis [3]. The next generation of antipsychotics may very well include an antipsychotic that does not target dopamine receptors, at least not directly and would be expected to be devoid of motor side effects.

Antipsychotics only treat symptoms believed to be related to a hyperdopaminergic state (“dopamine storm”) in mesolimbic brain areas: positive symptoms (disorganization, delusions, and hallucinations) and agitation [4]. Since dopamine release is part of the biological mechanism behind tagging events as personally important

for us, antipsychotics may be particularly effective for those symptoms where unconstrained dopamine release creates a state of aberrant salience: where everything becomes meaningful and connected to us – a state of self-referential thinking which is the core of paranoia [5]. On the other hand, symptoms of schizophrenia associated with other brain networks may be adversely affected by dopamine blockade (e.g., motivational systems and cognition). In addition to their acute efficacy for positive symptoms, antipsychotics can prevent psychotic relapse [6]. Just as antipsychotics are not a treatment for all aspects of the syndrome of schizophrenia, antipsychotics are not a treatment specific for schizophrenia: they are also effective for delirium, for mania, for depression, for anxiety, or for insomnia. In that sense, antipsychotics are broad-spectrum psychotropics (like broad-spectrum antipsychotics).

Key Point

Antipsychotics are not a treatment for all symptoms of schizophrenia which is a syndrome. They are effective for the positive symptoms of schizophrenia and to prevent relapse. Other symptom clusters are either not effectively treated (e.g., cognitive symptoms) or even worsened with dopamine blockade (e.g., negative symptoms).

For antipsychotics that are full antagonists, the clinical effective dose (65–80% of receptor occupancy) results in maximal efficacy: a higher dose will not lead to more efficacy, merely more side effects [7]. Antipsychotic side effects can be predicted from (1) the degree of D2 blockade (the more tightly bound the D2 is the antipsychotic, the higher the risk for EPS) and (2) the selectivity for dopamine receptor (see Table 13.1).

Clozapine, iloperidone, and quetiapine are the antipsychotics with the least “tightness” of binding to D2 (i.e., fastest dissociation from the receptor, with easy displacement by endogenous dopamine) and hence are the least likely to cause EPS,

Table 13.1 Receptors and side effects

Receptor	Side effect	Clinical manifestations
Alpha-1	Hypotension	Syncope
Dopamine-2	Extrapyramidal side effects	Akathisia, dystonia, Parkinsonism Tardive dyskinesia
	Hyperprolactinemia	Amenorrhea, galactorrhea Sexual side effects Osteoporosis
Histamine-1	Sedation	Secondary negative symptoms
	Weight gain	Obesity, metabolic syndrome
Muscarinic	Anticholinergic side effects	Confusion, dry mouth, constipation, blurred vision, tachycardia, urinary retention

even at high doses [8]. All antipsychotics are full D2 antagonists with the exception of the more recent aripiprazole, brexipiprazole, and cariprazine which are partial agonists at D2 (i.e., function as an antagonist in the presence of dopamine).

One word on nomenclature: first-generation (or conventional) antipsychotics (FGAs) are old medications that were approved in the 1950s and 1960s. All are effective, and all cause EPS. FGAs are also referred to as “typical” antipsychotics to differentiate them from the “atypical” antipsychotic clozapine, which was the first antipsychotic that did not cause EPS, hence “atypical.” Up until clozapine, the efficacy of antipsychotics was believed to be tied to their propensity to cause EPS. With clozapine, efficacy and EPS became dissociated. Its value was proven in a seminal trial in 1988 when John Kane showed superior efficacy in treatment-refractory patients over typical antipsychotics [9]. Since then, many other atypical or second- and third-generation antipsychotics have been marketed, beginning with risperidone in 1993. Antipsychotic is the term preferred over neuroleptic. This current nomenclature based on “generations” is unsatisfactory and more a reflection on history and attempts to market antipsychotics (“new” implying better) [10]. Importantly, all antipsychotics are about equally effective for non-refractory patients with schizophrenia, at least at the group level. It is also misleading to assume that only first-generation antipsychotics induced EPS, while second-generation are mostly free of EPS [11]. Antipsychotics, particularly those lumped together in the bin of second-generation antipsychotics, have very little in common: they are widely different drugs with regard to side effect profiles and tolerability. Moreover, antipsychotics despite their name have a much broader range of applicability, beyond their core efficacy for positive symptoms and aggression, as noted above. A science-based nomenclature for antipsychotics based on the mechanism of action has been proposed but has not found its way into the clinic yet [12]. It is only for pedagogical purposes that I continue to use the terms first-, second, and third-generation antipsychotics.

Key Point

There is no one definition of what renders an antipsychotic “atypical” [13]. A broad definition of “atypicality” merely denotes the absence of extrapyramidal side effects across its dose range. Put differently, a neuroleptic is considered typical if it causes EPS at usual clinical doses (which is what you would expect from a “neuroleptic” – a “neuron-grabber” that stiffens mice when administered during drug discovery). More narrow definitions of atypicality include in addition to the lack of EPS the absence of hyperprolactinemia and, importantly, broadened efficacy (which may be mediated by receptors other than dopamine [14]). Clozapine remains the only truly atypical antipsychotic if the most narrow definition is applied.

For most antipsychotics, once-a-day dosing would be appropriate with regard to efficacy because the serum half-life of the antipsychotic does not reflect drug action

on the brain (initiation-adaptation hypothesis [15]). Tolerability and safety considerations, however, may make more frequent necessary. More frequent dosing can be used if one wants to take advantage of the ataractic properties that many antipsychotics possess (e.g., quetiapine), but nightly dosing works for most patients. The safe starting dose and rapidity of titration depend on the clinical situation (e.g., age, gender, ethnicity, first-episode vs. multi-episode patient, acute vs. maintenance treatment phase). As a rule of thumb, start at the low end of the dose range for outpatients and increase the dose slowly. More aggressive dosing is possible in supervised inpatient settings.

First-Generation Antipsychotics

The first-generation antipsychotics (FGAs) can be broadly classed into low-potency antipsychotics, medium-potency antipsychotics, and high-potency agents. The prototype of a low-potency FGA is chlorpromazine (brand name Thorazine, after Thor, the one with the hammer), the first antipsychotic approved by the Food and Drug Administration (FDA) in 1954. Low-potency FGAs are not selective for the dopamine receptor; sedation, orthostatic hypotension, and anticholinergic side effects, as well as metabolic problems, are characteristic. Haloperidol and fluphenazine are high-potency agents, which are highly selective for the D2 receptor; predictably, side effects are largely restricted to the motor system (and the pituitary). The medium-potency FGAs, perphenazine and loxapine, have a side effect profile that falls in between chlorpromazine and haloperidol with regard to EPS and sedation. Perphenazine has had a renaissance after its good efficacy and tolerability were demonstrated in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE; see Chap. 16 for more information on this seminal trial) in which it was chosen as the FGA comparator medication. Loxapine may be an overlooked mid-potency antipsychotic that fell out of use not because of ineffectiveness or difficult side effects but simply because newer medications displace older ones, at least in a market-driven society. It may behave like a second-generation antipsychotic [16] but without pronounced metabolic liability; consider giving it a try for maintenance treatment, at a dose of 25–50 mg/day. (For loxapine developed as an aerosol for the treatment of agitation, see Chap. 10.) Several FGAs with prominent cardiac side effects (thioridazine, mesoridazine) are no longer marketed.

Key Point

For antipsychotic efficacy, about 65% of (striatal) D2 receptors need to be blocked [17]. Pushing the dose of tightly bound antipsychotics, such as all FGAs, beyond this point will not increase efficacy but will merely lead to EPS once a threshold of 80% occupancy is exceeded [18].

Table 13.2 Dosing of selected first-generation antipsychotics

	CPZ-Eq ^a (mg)	Dosing range ^b (mg/day)	Maximum dose (mg/day) ^c
<i>Low-potency</i>			
Chlorpromazine	100	300–600	800
<i>Mid-potency</i>			
Loxapine	10	25–100 ^d	200
Perphenazine	10	8–32 ^e	42
<i>High-potency</i>			
Trifluoperazine	5	15–30	35
Fluphenazine	2	5–10	20
Haloperidol	2	5–10	20

Adapted from [19, 20]

^aCPZ-Eq, chlorpromazine equivalent dose (or “chlorpromazine equivalents”) reflects the potency of antipsychotics relative to 100 mg of chlorpromazine (which is equivalent to 5 mg of olanzapine)

^bDose range is for chronic patients; first-episode patients require dosing at the lower end of the range; acute treatment doses may need to be higher (up to 1000 CPZ-Eq)

^cClinically recommended upper dose limit

^dClinically recommended dose range consistent with perphenazine dosing

^eClinically recommended dose range based on Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) where the dose range was 8–32 mg/day; mean dose was 20 mg/day

There is no advantage to switching between FGAs for better efficacy since they all share the same mechanism of tight D2 blockade. The optimal dosing of FGAs (Table 13.2) can be based on chlorpromazine equivalents (CPZ-Eq) by converting the dose of a given FGA to the corresponding chlorpromazine dose.

Pushing the dose of FGAs reliably increases EPS but does no translate into further efficacy. Use the “neuroleptic threshold,” which is the point at which you just begin to see EPS on exam for cogwheeling (and which corresponds to 80% D2 occupancy), to determine the optimal dose; exceeding the patient’s neuroleptic threshold does not increase efficacy [21]. The recommended CPZ-Eq correspond to the neuroleptic threshold doses.

The major long-term morbidity concern with FGAs is tardive dyskinesia. Haloperidol has a rather complex metabolism that includes the formation of a neurotoxic pyridinium analog (HP+) which has been proposed to explain its higher risk for tardive dyskinesia [22]. Haloperidol and fluphenazine are the only first-generation antipsychotics that are available in the United States as long-acting depot injections (“decanoates”) (see Chap. 18 on LAIs).

Tip

I suggest that you become familiar with at least one from each group of FGAs. Be very familiar with the high-potency haloperidol because of its known efficacy and toxicities and availability for parental use (in the emergency department and the medical hospital). Medium-potency agents if dosed carefully (e.g., perphenazine) remain an interesting treatment choice due to overall good tolerability. The occasional patient still takes chlorpromazine, and it can be a useful adjunctive option (also for second-line use in the emergency department).

Second-Generation Antipsychotics

Newer antipsychotics are a more heterogeneous group than the first-generation antipsychotics with regard to tightness of D2-binding, degree of partial dopamine agonism, and additional receptor affinities that mitigate against EPS, particularly 5-HT2 antagonism. As a consequence, the neuroleptic threshold method cannot be used, and the direct comparison using dose equivalents between second- and third-generation antipsychotics is less straightforward [23]. Approximations of CPZ-Eq for some second-generation antipsychotics have nevertheless been published [24]. In the author's estimation, 100 mg chlorpromazine corresponds to 2 mg risperidone (equipotent with haloperidol), 5 mg olanzapine, 75 quetiapine, 60 mg ziprasidone, and 7.5 mg aripiprazole. Table 13.3 summarizes typical clinical doses using data from published clinical trials and FDA-approved doses.

Following clozapine as the prototype of an atypical antipsychotic, risperidone became the first in a series of antipsychotics with added serotonin 5-HT2a antagonism after it was noted that this modification reduced neurologic side effects [29]. All SGAs share this property and are thus 5-HT2a-D2 antagonists. Risperidone is a first-line antipsychotic with well-established efficacy (at least comparable to FGAs) and well-characterized side effect profile (low EPS risk at typical doses below 6 mg/day but with clear EPS if you use higher doses [30]). The active risperidone metabolite 9-hydroxyrisperidone was renamed paliperidone and marketed as well. Both risperidone and paliperidone are available as long-acting injectable formulations.

Olanzapine is sometimes effective when other antipsychotics are not, and olanzapine would be a first-line agent were it not for its higher liability for weight gain and diabetes. The CATIE results and other trials [31] suggest that doses higher than the 20 mg FDA-approved dose (i.e., 30 mg or even 40 mg) have added efficacy compared to other antipsychotics except clozapine. Other than the well-recognized

Table 13.3 Dosing of second-generation antipsychotics

Antipsychotic	Typical dose range	Maximum TDD	Comments
Asenapine	5–20 mg/day	20 mg	Sublingual tablet
Clozapine	100–400 mg/day	900 mg	Dosing based on blood levels
Iloperidone	6–12 mg twice daily	24 mg	
Lurasidone	40–160 mg/day	160 mg	Take with food (350 kcal)
Olanzapine	5–20 mg/day	40 mg ^a	
Paliperidone	3–12 mg/day	12 mg	
Quetiapine	100–400 mg/day	800 mg ^b	
Risperidone	2–8 mg/day	16 mg ^c	
Ziprasidone	40–160 mg/day	320 mg ^d	Take with food (500 kcal)

TDD, total daily dose

^aHigher doses than FDA-approved dose of 20 mg/day have been studied in clinical trials; the CATIE dosing allowed up to 30 mg/day [25]

^bNo benefit from high-dose quetiapine (up to 1200 mg/day) was found in two controlled trials [26, 27]

^cThe optimal dose for risperidone was misjudged when it was approved in 1993. Since then, the doses used clinically have come down. A higher dose than 8 mg/day should rarely be needed

^dNo benefit from high-dose ziprasidone (up to 320 mg/day) was found in one controlled trial [28]

metabolic problems with olanzapine, sedation is a second factor that can prohibit the use of olanzapine if patients feel “drugged” all day and sleep 12 hours or more, a problem that compounds already existing negative symptoms.

Quetiapine and ziprasidone are effective antipsychotics, although doubt lingers about their efficacy in more refractory patients. Quetiapine is often considered a “milder” antipsychotic, with pronounced ataractic (from the Greek, “undisturbed,” describing a serene state of calm equanimity) properties. Accordingly, it is frequently used adjunctively and not as the mainstay of treatment. Ziprasidone is probably the metabolically safest antipsychotic, and it causes sedation only rarely. Instead, activation and insomnia can occur, which may be treated with benzodiazepines. Food doubles ziprasidone’s absorption, and it should be taken with a medium-calorie meal (500 kcal) [32]. The number of calories appears to be more important than the composition of the meal (e.g., fat content).

Newer antipsychotics approved in the past decade include lurasidone, iloperidone, and asenapine. Lurasidone is an effective antipsychotic that behaves in many ways like a FGA (i.e., EPS at higher doses); it appears to have a very favorable long-term safety profile, with minimal weight gain and low metabolic liability [33]. Like ziprasidone, it needs to be taken with food (at least 350 kcal, independent of fat content) [34]. To avoid EPS, it is important to keep the dose of lurasidone below 120 mg/day, if possible. In comparison, iloperidone has very low EPS liability including akathisia [35] but must be titrated due to alpha-blocking properties. Watch for priapism which may be increased because of alpha blockade [36]. Iloperidone also prolongs the QTc interval in a dose-dependent manner (9 ms at a dose of 12 mg twice daily). Asenapine is a potent dopamine antagonist that is quite effective in acute settings due to sedation [37]. Because of poor oral bioavailability of below 2%, asenapine is formulated for sublingual (oral mucosal) administration which increases bioavailability to 35% [38]. Patients should not eat or drink for 10 minutes after to assure best absorption. Some patients complain about dysgeusia (alteration in sense of taste) and oral hypoesthesia when taking asenapine. The sublingual mode of administration, however, has the advantage that it can be taken by patients who cannot swallow (e.g., patients in palliative care). Recently, asenapine has become available as a transdermal patch.

Clozapine is psychiatry’s specialty drug, and it is our most effective but also our most difficult to use, antipsychotic. Because of its importance, I dedicate a whole chapter to clozapine (Chap. 17).

Third-Generation Antipsychotics

Aripiprazole, followed by brexpiprazole and cariprazine, was the first of a new group of antipsychotics characterized by partial dopamine-2 receptor agonist properties. Partial agonists at the dopamine-2 receptor have interesting properties. They lower the ceiling for dopamine transmission, but they do not shut it down completely which may protect against Parkinsonism and other low-dopaminergic states.

In addition, partial agonists activate a hypoactive dopamine receptor [39]. Initial questions about their efficacy and risks of worsening psychosis compared to full dopamine blockers have been mostly put to rest since their introduction over a decade ago: they appear to be as effective as standard antipsychotics, both for the acute treatment of psychosis and for the long-term maintenance phase to prevent relapse. An observational population-based cohort study of patients who started aripiprazole did not find an increased risk of treatment failure (hospitalizations, self-harm, or suicide) compared to patients starting other antipsychotics [40]. Individual patients, of course, may differ in their response to partial agonist antipsychotic and can experience more symptoms if they are switched [41]. Agents in this class are widely used for other indications, particularly at a lower dose as add-on agents for depression. Partial dopamine agonist antipsychotics may also have a role in managing the many patients with schizophrenia who use substances, perhaps via reducing craving and normalizing reward circuitry [42]. Dopamine agonist medications used in the treatment of Parkinson's disease or restless legs have been linked to impulse control disorders (e.g., gambling, hypersexuality, increased spending, compulsive eating) [43]. Partial agonist antipsychotics, particularly aripiprazole have similarly been linked to new-onset gambling in particular [44].

The partial agonist receptor-binding property is probably responsible for fairly good tolerability – many of my patients prefer aripiprazole, for example, over other antipsychotics they have been taken before, as they do not seem to get the neuroleptic-induced dysphoria that characterizes full D2 blockade. Moreover, partial agonism may be better for negative symptoms, as shown in a trial directly comparing cariprazine with risperidone (see Chap. 28 on negative symptoms for a larger discussion). Some side effects of this antipsychotic class are attributable to their dopamine-2 agonist properties (nausea, insomnia, restlessness, lowering prolactin levels). The various third-generation antipsychotics differ in their intrinsic agonist properties (aripiprazole, e.g., has approximately 61% activity compared to dopamine; brexpiprazole has only 43% activity [39]). Differences in the overall receptor profile beyond the dopamine system are likely responsible for differences in side effects like akathisia or weight gain liability. To complicate matters further, cariprazine binding to D3 receptors exceeds its D2 binding which may explain some of clinical characteristics beyond its antipsychotic efficacy [45].

Aripiprazole has a very long half-life of 72 hours: changes will become apparent 2 weeks after the dose increase; there is no need to “push the dose” during an acute admission. There is another reason that pushing the dose is probably unnecessary for many patients: 15 mg/day occupies almost all dopamine receptors (tightly); higher doses cannot change the intrinsic agonist/antagonist ratio for this partial agonist. The registration trials have not found added benefits from 20 to 30 mg/day doses. Brexpiprazole has a similarly long half-life of several days [46]. Cariprazine has two active metabolites, with a combined half-life of the active moiety amounting to 1 week [47]. Table 13.4 compares the dosing for the partial agonist antipsychotics. Currently, aripiprazole is the only available long-acting antipsychotic in this group.

Table 13.4 Dosing of third-generation antipsychotics^a

	Titration	Dose range	Maximum dose
Aripiprazole	No	10–15 mg/day ^b	30 mg/day
Brexpiprazole	Start with 1 mg/day	1–4 mg/day	4 mg/day
Cariprazine	Start with 1.5 mg/day	1.5–6 mg/day ^c	6 mg/day

^aDose range and target doses are for adult patients with schizophrenia

^bClinical trials have not shown better efficacy from doses higher than 10 or 15 mg/day. Higher doses are often given unnecessarily because the dose is increased before steady-state was reached (2 weeks), particularly on the inpatient side

^cIn a negative symptom trial comparing cariprazine and risperidone, patients received an average dose of 4 mg/day [48]

Non-dopaminergic Antipsychotics

Current antipsychotics work at the end of a chain of events that lead to excessive dopamine release into the mesolimbic system, a final common biological pathway which is believed to underlie the clinical expression of psychosis. In this model of drug action, postsynaptic dopamine receptor blockade is rather distal to the pathology and not particularly selective. The holy grail of antipsychotic drug development has been to identify a compound that does not block dopamine receptors and yet treats psychosis. Such a compound would possibly be devoid of many undesirable side effects related to dopamine blockade, particularly extrapyramidal symptoms (it would be “atypical”) or interference with motivational systems that depend on dopamine. A non-dopaminergic antipsychotic may likely still need to be able to prevent or shut down unconstrained excessive mesolimbic dopamine release, but it could do so by targeting the proximal causes of such excessive dopamine release (e.g., via strengthening inhibitory neurotransmitter systems like NDMA receptors or reducing dopamine synthesis). To complicate matters, some forms of psychosis may not be related to dopamine. Treatment-refractory psychosis, for example, is clearly not a phenomenon related to excessive dopamine release that can be treated with dopamine blockade: if it were that simple, we would not see refractory patients since we have dopamine-blocking agents. Non-dopaminergic antipsychotics may also offer efficacy beyond the positive symptoms of schizophrenia and relapse prevention.

A serotonergic inverse agonist on the 5-HT1a receptor (i.e., functionally an antagonist), pimavanserin, has been found to be somewhat effective for the psychosis of Parkinson’s disease [2, 49]. Naturally, clinicians have started to try it out in their patients with schizophrenia, with some encouraging findings [3]. However, previous clinical schizophrenia trials of pure 5-HT1a antagonists have failed, so only time will tell if pimavanserin is different. Randomized, controlled clinical trials are ongoing to test if there are non-dopaminergic antipsychotics with broad efficacy for schizophrenia.

Neurotoxicity and Neuroprotection

In many preclinical studies, antipsychotics can be shown to be neurotoxic. For example, in one influential study of 18 macaque monkeys treated with haloperidol, olanzapine, or a placebo vehicle, the antipsychotic-treated monkeys had a 10% reduction in brain volume [50]. In humans, tardive dyskinesia is considered to be the outward clinical manifestation of neurotoxicity, in this case of damage to basal ganglia. Cortical thinning in patients treated with antipsychotics, a well-described dose-related phenomenon is often interpreted as evidence of neurotoxicity from antipsychotics (ignoring the complexity of measuring cortical thickness and the heterogeneity of treatment samples) [51]. Dopamine “supersensitivity psychosis” (upregulation of dopamine receptors in response to chronic dopamine blockade) which can be shown in animal models has been proposed as yet another iatrogenic mechanism leading to a more complex longitudinal illness course, particularly a greater sensitivity to psychotic relapse once antipsychotics are withdrawn [52]. These issues are further complicated by findings that antipsychotics, particularly atypical antipsychotics, are neuroprotective [53]. Some of these “off-target” effects (e.g., increasing hippocampal neurogenesis [14]) may turn out to be therapeutically as important as an antipsychotic’s affinity for dopamine receptors [54].

Where does this leave a clinician? Antipsychotics are clearly effective for an acute episode of psychosis and for the prevention of subsequent episodes. However, the long-term benefits and costs of taking antipsychotics are less clear, as illness-related brain changes, normal brain development, and antipsychotic effects interact in ways that are difficult to disentangle [55]. Some patients may indeed pay a price when they have to take antipsychotics in the long run, with an increased risk of antipsychotic-associated morbidity and mortality and but also with reduced functional achievements [56]. Like chemotherapy for cancer, it may be that undesired long-term consequences are an unavoidable aspect of our current treatment with dopamine-blocking antipsychotics that nevertheless, on balance, produce clinical outcomes that are better than no treatment. For narrowly defined schizophrenia, providing no treatment with antipsychotics is in most cohorts associated with the worst clinical outcomes (see the natural history of schizophrenia in Chap. 7). I suspect the issue will remain contentious until biomarker’s become available that help clinician’s determine who does not require long-term pharmacotherapy with antipsychotics after an episode of psychosis and until medications are developed that have a different mechanism of action to prevent relapse.

References

1. Wikiquote. William Osler. Available from: https://en.wikiquote.org/wiki/William_Osler. Accessed on 7/1/2019.
2. Sahli ZT, Tarazi FI. Pimavanserin: novel pharmacotherapy for Parkinson’s disease psychosis. Expert Opin Drug Discov. 2018;13:103–10.

3. Nasrallah HA, Fedora R, Morton R. Successful treatment of clozapine-nonresponsive refractory hallucinations and delusions with pimavanserin, a serotonin 5HT-2A receptor inverse agonist. *Schizophr Res.* 2019;208:217–20.
4. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III—the final common pathway. *Schizophr Bull.* 2009;35:549–62.
5. Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry.* 2003;160:13–23.
6. Leucht S, Tardy M, Komossa K, Heres S, Kissling W, Salanti G, et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *Lancet.* 2012;379:2063–71.
7. El-Mallakh RS. Receptor occupancy and drug response: understanding the relationship. *Curr Psychiatr Ther.* 2018;17:8–13.
8. Kapur S, Seeman P. Does fast dissociation from the dopamine d(2) receptor explain the action of atypical antipsychotics?: a new hypothesis. *Am J Psychiatry.* 2001;158:360–9.
9. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry.* 1988;45:789–96.
10. Kendall T. The rise and fall of the atypical antipsychotics. *Br J Psychiatry.* 2011;199:266–8.
11. Fischer-Barnicol D, Lanquillon S, Haen E, Zofel P, Koch HJ, Dose M, et al. Typical and atypical antipsychotics—the misleading dichotomy. Results from the Working Group “Drugs in Psychiatry” (AGATE). *Neuropsychobiology.* 2008;57:80–7.
12. Zohar J, Kasper S. Neuroscience-based nomenclature (NbN): a call for action. *World J Biol Psychiatry.* 2016;17:318–20.
13. Meltzer HY. What's atypical about atypical antipsychotic drugs? *Curr Opin Pharmacol.* 2004;4:53–7.
14. Kusumi I, Boku S, Takahashi Y. Psychopharmacology of atypical antipsychotic drugs: from the receptor binding profile to neuroprotection and neurogenesis. *Psychiatry Clin Neurosci.* 2015;69:243–58.
15. Hyman SE, Nestler EJ. Initiation and adaptation: a paradigm for understanding psychotropic drug action. *Am J Psychiatry.* 1996;153:151–62.
16. Glazer WM. Does loxapine have “atypical” properties? Clinical evidence. *J Clin Psychiatry.* 1999;60(Suppl 10):42–6.
17. Farde L, Wiesel FA, Halldin C, Sedvall G. Central D2-dopamine receptor occupancy in schizophrenic patients treated with antipsychotic drugs. *Arch Gen Psychiatry.* 1988;45:71–6.
18. Nord M, Farde L. Antipsychotic occupancy of dopamine receptors in schizophrenia. *CNS Neurosci Ther.* 2011;17:97–103.
19. Buchanan RW, Kreyenbuhl J, Kelly DL, Noel JM, Boggs DL, Fischer BA, et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr Bull.* 2010;36:71–93.
20. Gardner DM, Murphy AL, O'Donnell H, Centorrino F, Baldessarini RJ. International consensus study of antipsychotic dosing. *Am J Psychiatry.* 2010;167:686–93.
21. McEvoy JP, Hogarty GE, Steingard S. Optimal dose of neuroleptic in acute schizophrenia. A controlled study of the neuroleptic threshold and higher haloperidol dose. *Arch Gen Psychiatry.* 1991;48:739–45.
22. Fang J, McKay G, Song J, Remillrd A, Li X, Midha K. In vitro characterization of the metabolism of haloperidol using recombinant cytochrome p450 enzymes and human liver microsomes. *Drug Metab Dispos.* 2001;29:1638–43.
23. Leucht S, Samara M, Heres S, Patel MX, Furukawa T, Cipriani A, et al. Dose equivalents for second-generation antipsychotic drugs: the classical mean dose method. *Schizophr Bull.* 2015;41:1397–402.
24. Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. *J Clin Psychiatry.* 2003;64:663–7.
25. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med.* 2005;353:1209–23.

26. Honer WG, MacEwan GW, Gendron A, Stip E, Labelle A, Williams R, et al. A randomized, double-blind, placebo-controlled study of the safety and tolerability of high-dose quetiapine in patients with persistent symptoms of schizophrenia or schizoaffective disorder. *J Clin Psychiatry*. 2012;73:13–20.
27. Lindenmayer JP, Citrome L, Khan A, Kaushik S. A randomized, double-blind, parallel-group, fixed-dose, clinical trial of quetiapine at 600 versus 1200 mg/d for patients with treatment-resistant schizophrenia or schizoaffective disorder. *J Clin Psychopharmacol*. 2011;31:160–8.
28. Goff DC, McEvoy JP, Citrome L, Mech AW, Bustillo JR, Gil R, et al. High-dose oral ziprasidone versus conventional dosing in schizophrenia patients with residual symptoms: the ZEBRAS study. *J Clin Psychopharmacol*. 2013;33:485–90.
29. Meltzer HY. Serotonergic mechanisms as targets for existing and novel antipsychotics. *Handb Exp Pharmacol*. 2012;87–124.
30. Li C, Xia J, Wang J. Risperidone dose for schizophrenia. *Cochrane Database Syst Rev*. 2009;CD007474.
31. Volavka J, Czobor P, Sheitman B, Lindenmayer JP, Citrome L, McEvoy JP, et al. Clozapine, olanzapine, risperidone, and haloperidol in the treatment of patients with chronic schizophrenia and schizoaffective disorder. *Am J Psychiatry*. 2002;159:255–62.
32. Gandelman K, Alderman JA, Glue P, Lombardo I, LaBadie RR, Versavel M, et al. The impact of calories and fat content of meals on oral ziprasidone absorption: a randomized, open-label, crossover trial. *J Clin Psychiatry*. 2009;70:58–62.
33. Citrome L. Lurasidone for the acute treatment of adults with schizophrenia: what is the number needed to treat, number needed to harm, and likelihood to be helped or harmed? *Clin Schizophr Relat Psychoses*. 2012;6:76–85.
34. Preskorn S, Ereshesky L, Chiu YY, Poola N, Loebel A. Effect of food on the pharmacokinetics of lurasidone: results of two randomized, open-label, crossover studies. *Hum Psychopharmacol*. 2013;28:495–505.
35. Citrome L, Meng X, Hochfeld M, Stahl SM. Efficacy of iloperidone in the short-term treatment of schizophrenia: a post hoc analysis of pooled patient data from four phase III, placebo- and active-controlled trials. *Hum Psychopharmacol*. 2012;27:24–32.
36. Subeesh V, Maheswari E, Singh H, Beulah TE, Swaroop AM. Novel adverse events of iloperidone: a disproportionality analysis in US Food and Drug Administration Adverse Event Reporting System (FAERS) database. *Curr Drug Saf*. 2019;14:21–6.
37. Citrome L. Role of sublingual asenapine in treatment of schizophrenia. *Neuropsychiatr Dis Treat*. 2011;7:325–39.
38. Citrome L. Asenapine for schizophrenia and bipolar disorder: a review of the efficacy and safety profile for this newly approved sublingually absorbed second-generation antipsychotic. *Int J Clin Pract*. 2009;63:1762–84.
39. Goff DC. Brexpiprazole: a new antipsychotic following in the footsteps of aripiprazole. *Am J Psychiatry*. 2015;172:820–1.
40. Montastruc F, Nie R, Loo S, Rej S, Dell'Aniello S, Micallef J, et al. Association of aripiprazole with the risk for psychiatric hospitalization, self-harm, or suicide. *JAMA Psychiatry*. 2019;76:409–17.
41. Stroup TS, McEvoy JP, Ring KD, Hamer RH, LaVange LM, Swartz MS, et al. A randomized trial examining the effectiveness of switching from olanzapine, quetiapine, or risperidone to aripiprazole to reduce metabolic risk: comparison of antipsychotics for metabolic problems (CAMP). *Am J Psychiatry*. 2011;168:947–56.
42. Moreira FA, Dalley JW. Dopamine receptor partial agonists and addiction. *Eur J Pharmacol*. 2015;752:112–5.
43. Moore TJ, Glenmullen J, Mattison DR. Reports of pathological gambling, hypersexuality, and compulsive shopping associated with dopamine receptor agonist drugs. *JAMA Intern Med*. 2014;174:1930–3.
44. Giri YR, Peteru SR. Escalation of gambling associated with aripiprazole: a case report and literature review. *J Psychiatr Pract*. 2019;25:139–45.

45. Calabrese F, Tarazi FI, Racagni G, Riva MA. The role of dopamine D3 receptors in the mechanism of action of cariprazine. *CNS Spectr.* 2019;1:9–.
46. Citrome L. Brexpiprazole: a new dopamine D(2)receptor partial agonist for the treatment of schizophrenia and major depressive disorder. *Drugs Today.* 2015;51:397–414.
47. Nakamura T, Kubota T, Iwakaji A, Imada M, Kapas M, Morio Y. Clinical pharmacology study of cariprazine (MP-214) in patients with schizophrenia (12-week treatment). *Drug Des Devel Ther.* 2016;10:327–38.
48. Nemeth G, Laszlovszky I, Czobor P, Szalai E, Szatmari B, Harsanyi J, et al. Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial. *Lancet.* 2017;389:1103–13.
49. Cummings J, Isaacson S, Mills R, Williams H, Chi-Burris K, Corbett A, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. *Lancet.* 2014;383:533–40.
50. Dorph-Petersen KA, Pierri JN, Perel JM, Sun Z, Sampson AR, Lewis DA. The influence of chronic exposure to antipsychotic medications on brain size before and after tissue fixation: a comparison of haloperidol and olanzapine in macaque monkeys. *Neuropsychopharmacology.* 2005;30:1649–61.
51. Lesh TA, Tanase C, Geib BR, Niendam TA, Yoon JH, Minzenberg MJ, et al. A multimodal analysis of antipsychotic effects on brain structure and function in first-episode schizophrenia. *JAMA Psychiatry.* 2015;72:226–34.
52. Yin J, Barr AM, Ramos-Miguel A, Procyshyn RM. Antipsychotic induced dopamine supersensitivity psychosis: a comprehensive review. *Curr Neuropharmacol.* 2017;15:174–83.
53. Chen AT, Nasrallah HA. Neuroprotective effects of the second generation antipsychotics. *Schizophr Res.* 2019;208:1–7.
54. Bowling H, Santini E. Unlocking the molecular mechanisms of antipsychotics – a new frontier for discovery. *Swiss Med Wkly.* 2016;146:w14314.
55. Goff DC, Falkai P, Fleischhacker WW, Girgis RR, Kahn RM, Uchida H, et al. The long-term effects of antipsychotic medication on clinical course in schizophrenia. *Am J Psychiatry.* 2017;174:840–9.
56. Wunderink L, Nieboer RM, Wiersma D, Sytema S, Nienhuis FJ. Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy: long-term follow-up of a 2-year randomized clinical trial. *JAMA Psychiatry.* 2013;70:913–20.

Additional Resources

Articles

- Freudenreich O. Dosing units help avoid medication errors [Pearl]. *Curr Psychiatry.* 2008;7:80–8. – From the Pearls Series, this one-page summary provides a simple scheme to remember typical dosing of antipsychotics, using clinical reference dosing units. This approach is helpful to spot unusual antipsychotic doses if you look over medications lists for example.
- Goff DC, Falkai P, Fleischhacker WW, Girgis RR, Kahn RM, Uchida H, et al. The long-term effects of antipsychotic medication on clinical course in schizophrenia. *Am J Psychiatry.* 2017;174:840–9. – Leaders in the field of schizophrenia research summarize what is known about antipsychotic neurotoxicity and the possible negative effects on the long-term course of illness.
- Kontos N, Querques J, Freudenreich O. The problem of the psychopharmacologist. *Acad Psychiatry.* 2006;30:218–26. – Mandatory remedial reading if you consider yourself a “psychopharmacologist”.

Chapter 14

Antipsychotics: Motor Side Effects



Essential Concepts

- Motor side effects associated with antipsychotic treatment include acute and early extrapyramidal syndromes (acute dystonic reaction, akathisia, Parkinsonism) and long-term complications (tardive dyskinesia (TD)).
- Acute dystonic reactions (usually limited to the head and neck, including oculogyric crisis) are early antipsychotic side effects that you will see mostly in antipsychotic-naïve patients commencing treatment for the first time.
- The sine qua non of akathisia is subjective restlessness with objective manifestations becoming apparent with increasing severity, possibly leading to bad clinical outcomes (suicide attempts, nonadherence).
- The symptoms of antipsychotic-induced Parkinsonism and idiopathic Parkinson's disease are the same. Consider subtle forms of Parkinsonism in blunted and slowed patients.
- Tardive dyskinesia (TD) can occur with all antipsychotics. Once it develops, it is almost always irreversible which makes prevention critical. Treatment options for TD used to be very limited, but the approval of two vesicular monoamine transporter 2 (VMAT-2) inhibitors, deutetrabenazine and valbenazine, offers effective and safe treatments.
- Use the well-established Abnormal Involuntary Movement Scale (AIMS) to record and follow the severity of abnormal movements (at least annually in low-risk patients but more frequently if the TD risk is higher).
- Neuroleptic malignant syndrome (NMS) is a potentially fatal neurologic emergency characterized by a triad of fever, lead-pipe rigidity, and mental status changes.

“Never mistake motion for action.”

Often attributed to Ernest Hemingway, Nobel Prize for Literature 1954, 1899–1961

Antipsychotics can cause a range of motor syndromes, and a good motor exam for acute/early extrapyramidal symptoms (EPS) and chronic tardive dyskinesia is a core skill for a psychiatrists. In addition, neuroleptic malignant syndrome (NMS) is a rare psychiatric emergency related to antipsychotic use that must be recognized quickly. Drug-induced EPS cause a wide spectrum of motor symptoms, some hypokinetic (e.g., Parkinsonism) and some hyperkinetic (e.g., dystonia or choreiform movements). The common motor syndromes can also be organized according to time course: early symptoms that occur as quickly as after one dose include acute dystonias and akathisia, Parkinsonism takes a few weeks to develop, and finally, tardive dyskinesia emerges as a feared long-term complication after several months or even years of treatment.

Correctly diagnosing movement disorders requires experience. Figure 14.1 depicts a simplified organizing scheme for the clinic. Main decisions to make are the following: Is there too much (hyperkinetic) or too little (hypokinetic) movement? Are there rhythmic movements (tremor)? How fast are the hyperkinetic movements?

Patients may experience several motor symptoms at the same time as schematically depicted in Fig. 14.2 which is based on a survey in chronically institutionalized patients in Estonia [1]. In this cohort, 60% of patients experienced at least one motor disorder and 40% were motor disease-free. Unfortunately, despite wider use of newer antipsychotics compared to their original survey, the prevalence of disease-free patients remained around 40% when the same authors reexamined their original patient cohort 8 years later [2]. Anyone working with schizophrenia patients will confirm my observation that newer antipsychotics have clearly reduced the rate and

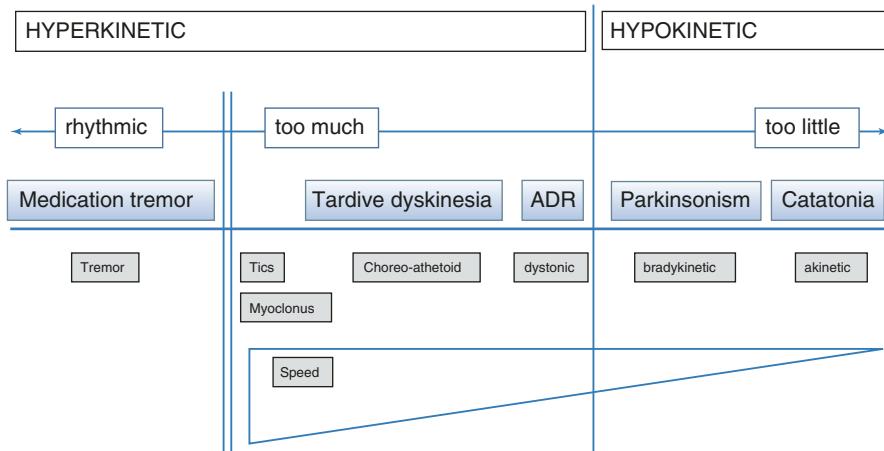
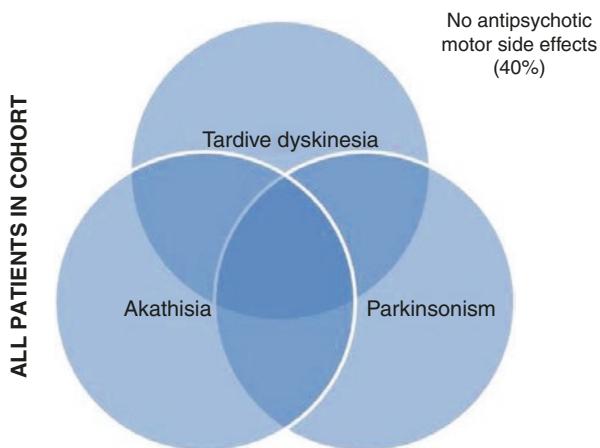


Fig. 14.1 Clinical organizing scheme of movement disorders

Fig. 14.2 Antipsychotic-induced motor side effects.
(Based on [1])



severity of EPS and tardive dyskinesia, without solving the problem completely. Depending on your practice setting, you will also care for older patients with legacy TD from previous treatment with older antipsychotics, including much higher doses than we would use today. With an organized approach described in this chapter, you will be able to reduce the risk for EPS and TD, delineate the nature of motor problems should they arise during treatment, and manage them competently.

Although antipsychotic-induced motor disorders are more common with first-generation antipsychotics (FGAs) compared to newer antipsychotics, they can occur with any currently available antipsychotic as they all share the same mechanism of action (dopamine-2 receptor blockade). Dystonia, akathisia, and Parkinsonism are considered extrapyramidal side effects or symptoms (EPS) as they result from dopamine blockade in the posterior part of the basal ganglia (the motor loop) [3]. Many symptoms of EPS are dose-related and occur once dopamine receptor occupancy exceeds 80%, as described in the previous chapter. Antipsychotics with loose D2-binding (quetiapine and clozapine) have the lowest risk of causing EPS as they are easily displaced by endogenous dopamine. The distressing nature of EPS can lead patients to discontinue antipsychotic treatment. The relative risk for EPS has been estimated as follows (from highest risk to lowest risk): high-potency FGA > mid-potency FGA = risperidone > low-potency FGA > olanzapine = ziprasidone > quetiapine > clozapine [4]. This ranking did not include the newest antipsychotics but provides an initial orientation. There are great differences between antipsychotics and their propensity to cause EPS, particularly between antipsychotics from the second- and third-generation groups (see Chap. 13 for individual antipsychotics). EPS is usually reversible once the antipsychotic is stopped. Permanent damage to the basal ganglia may occur with chronic use, however, resulting in irreversible hyperkinetic movements (tardive dyskinesia but also tardive akathisia and tardive dystonia).

Tip

A motor exam can easily be done as part of any routine office visit. The key is to observe the patient sitting, talking, and walking. Look for evidence of tremor, bradykinesia, restlessness, or abnormal movements, and specifically ask about inner sense of restlessness. To look for tremor, ask patients to hold out their hands, and examine for increased muscle tone and cogwheeling at every visit. Your observation is augmented by activation tasks in selected cases where you are unsure. For simplicity, motor findings can be considered part of your mental status examination (MSE) and noted there.

Acute Dystonic Reaction

An acute dystonic reaction (ADR; involuntary, intermittent, sustained muscle contractions) is an early-onset EPS and can occur after a single dose of an antipsychotic, particularly in antipsychotic-naïve patients. Half of cases occur within 2 days of starting treatment and almost all within 1 week. While an ADR is much more likely with high-potency FGAs, this side effect can occur with all antipsychotics, including loose D2-binding ones like clozapine or quetiapine.

Key Point

The acute onset of involuntary, sustained muscle contractions (dystonias) in the right setting (within a few days of starting a dopamine antagonist) should suggest an ADR. An ADR can also occur in nonpsychiatric settings with anti-emetics like metoclopramide [5].

Patients complain about “cramping,” their “head turning,” problems with their eye “rolling back,” or a “thick” or protruding tongue. More dramatic manifestations, such as opisthotonus (body arching), torticollis, oculogyric crises (eyes rolling backwards), or trismus (lockjaw), can occur. Patients can be distressed and overwhelmed with anxiety, but are not confused. Although distressing, dystonia is usually not dangerous except in the cases of laryngeal-pharyngeal dystonia, which can result in respiratory compromise.

The clinical presentation of an ADR is usually acute and dramatic, and the diagnosis should not be difficult. Treatment with parenteral benztrapine or diphenhydramine is highly effective.

Tip

If there is no response to treatment as usual, consider other etiologies. Phencyclidine (PCP) intoxication can cause dystonia, and cocaine increases the dystonia risk for patients treated with antipsychotics. Although rare, anti-cholinergics can be misused, and patients may fake an ADR to obtain them.

ADR is preventable by giving prophylactic anticholinergics to high-risk patients [6]. Do not forget to discharge patients who had an acute dystonic reaction that brought them to the emergency room (ED) with a brief course of anticholinergics. If no further antipsychotic treatment is planned, 2 or 3 days of benztropine (Cogentin) 1–2 mg qid or diphenhydramine (Benadryl) 25–50 mg qid is sufficient. I have seen patients return to the ED the next day with another episode of ADR because they did not receive prophylaxis. The Pisa syndrome is a variant of dystonia that you should consider in a sideways-leaning patient due to persistent truncal dystonia.

Akathisia

Akathisia literally means “unable to sit still.” It is an extremely unpleasant sense of inner restlessness that compels patients to move about to relieve tension. As akathisia becomes more severe, you can observe the motor restlessness as patients may pace around and jiggle their feet or are unable to sit in your office or watch television for more than a few minutes at a time. It is one of the acute side effects, and I expect it to occur early in the course of treatment, sometimes as early as after the first antipsychotic dose. Although FGAs, particularly high-potency antipsychotics like haloperidol or fluphenazine, can easily bring on akathisia, higher doses of second-generation antipsychotics and the third-generation antipsychotics (partial agonists) can also cause it. The antipsychotics least likely to cause akathisia include quetiapine, iloperidone, and clozapine. Among the third-generation antipsychotics, brexpiprazole seems to have a very low akathisia risk [7].

The diagnosis of akathisia is usually straightforward. In the right clinical setting (i.e., after initiation of an antipsychotic), you should be alert for evidence of motor restlessness and always ask about an inner sense of restlessness. Some patients (usually more impaired patients with chronic disease) are objectively restless but deny the subjective component. In these circumstances I prefer to treat presumptively for akathisia. Note that the Barnes Akathisia Rating Scale (BARS) which is considered the gold standard in clinical trials labels such patients as having “pseudoakathisia” [8]. A diagnostic dilemma can occur when agitation in a very psychotic patient is either due to akathisia, requiring a reduction in antipsychotic treatment, or psychotic agitation, where increased medication is needed.

Key Point

Akathisia has a subjective aspect (reported by the patient) and an objective (observable by the clinician) aspect. In mild cases, the patient only feels restless and distressed, and in more severe cases, the patient becomes physically unable to tolerate the restlessness and feels compelled to move about.

Akathisia is not a side effect that patients should have to live with in the long run. You have some fiduciary responsibility to recognize akathisia in impaired patients who cannot describe their inner distress. If possible, lower the antipsychotic and

hope the akathisia resolves. Otherwise, you might have to switch antipsychotics, including switching to clozapine in patients who are very sensitive to extrapyramidal symptoms. Whatever you do, always treat akathisia symptomatically as well. Beta-blockers are considered the treatment of choice, and patients should be followed closely after initiation in case higher doses are required (start with propranolol 10 mg twice daily and titrate upward to up to 120 mg total daily dose). Mirtazapine which is a strong 5-HT_{2a} antagonist antidepressant may be as effective as propranolol but easier to use and better tolerated [9, 10]. Simply add 15 mg at night. You should see a rapid effect, without the need to increase the dose. If there is marked distress, you can add a benzodiazepine (e.g., diazepam 5–15 mg/day). In cases with concurrent Parkinsonism, anticholinergics may be tried although they are probably not particularly good antiakathisia agents.

Tip

Akathisia can be very acute and severe. In a peracute case (which is an emergency), 10 mg diazepam brings instant relief. Even in less urgent cases, initiate treatment for akathisia, and have the patient come for a follow-up in a few days to adjust the dose for efficacy.

Parkinsonism

In its extreme form, drug-induced Parkinsonism is difficult to miss: patients can be observed shuffling along the corridor, almost falling, without arm swing. During a visit to your office, they may sit with their mouth open, drool, have a coarse resting tremor, or need help getting out of the chair. Parkinsonism is usually symmetrical in the drug-induced form and is characterized by a triad of resting tremor, cogwheel rigidity, and akinesia/bradykinesia, just like idiopathic Parkinsonism. Subtle manifestations, however, are easy to overlook or misdiagnose, such as an apparent lack of facial expression being described as “blunted affect” and attributed to primary negative symptoms instead of the masked facies of Parkinsonism, a secondary negative symptom. Signs and symptoms of Parkinsonism usually appear within the first month of treatment, and, as this side effect is often dose-related, reducing the dose of antipsychotic may solve the problem. If not, anticholinergic medications can be used, but attempts should be made to taper them after 3 months (see Chap. 19 for a more detailed discussion of why).

In clinical trials, the gold standard for the assessment of drug-induced Parkinsonism is the Simpson-Angus Rating Scale (SARS) [11]. Using the scale will help you assess a patient systematically for evidence of EPS, including examining a patient for clinical manifestations of rigidity and bradykinesia (e.g., drooling).

Tardive Dyskinesia

The most feared, long-term (hence “tardive,” which means late) consequence of treatment with dopamine-blocking agents is TD, a potentially irreversible movement disorder characterized by involuntary, choreiform movements. Less common, tardive akathisia or tardive dystonia is seen. Clinicians need to appreciate that TD is almost always irreversible once it develops, contrary to the hopeful view held by some clinicians that it remits if detected early and antipsychotics are stopped [12].

Key Point

The risk for developing TD with FGAs is estimated to be 6.5% per year (annual incidence rate) for the first few years of treatment in young adults [13]. The risk is much higher for older patients (at least 25% per year). Use of newer antipsychotics reduces the new-onset TD risk by about half, to 2.6% per year. There may be real differences between individual antipsychotics; clozapine has the least TD liability. Consider TD irreversible once it develops.

Depending on the clinical population treated with antipsychotics, you can expect to find a cross-sectional TD prevalence of around 20–30% [14]. The lowest prevalence (less than 10%) was seen in populations who had never been exposed to first-generation antipsychotics. These rates suggest two possibilities: (a) not all patients are at risk for TD (they are somehow protected biologically) and/or (b) TD can remit (which occurs in a small minority of patients, around 5%). One long-term study of 20 years found that most patients had TD at some time point during the course of their illness and it remains of concern to all patients. It is also notable that abnormal movements were present in 10% of patients with schizophrenia who had never been exposed to antipsychotic medications [15] suggesting that some cases of presumed drug-induced TD might be from the disease process itself, as already noted by Kraepelin in the pre-neuroleptic era. Taken together, these studies suggest that TD is a dynamic disorder, with the natural course interacting with antipsychotics in susceptible individuals. Risk factors for TD include non-modifiable risk factors like age (older patients are more sensitive), female gender, and a history of early EPS [16]. Some modifiable risk factors are diabetes, smoking, alcohol use, and the cumulative exposure to antipsychotics.

Tip

Sensitivity to EPS may be the most important risk factor for the later development of TD. View it as a biological warning sign of a high-risk patient and pay attention to it: TD rarely (in 5% or less) remits once established but instead becomes a permanent problem.

Diagnosis

TD is an iatrogenic disorder, and treatment with a dopamine-blocking agent (usually antipsychotics but do not forget antiemetics like metoclopramide) is a condition sine qua non. “Tardive” implies a sufficient duration of exposure, in most cases at least a few months, but I would still diagnose TD after briefer antipsychotic exposure if a patient develops new-onset motor symptoms consistent with TD.

Tardive movements from antipsychotics are choreiform (rapid and irregular; you cannot predict when the next movement is coming, like in chorea Huntington), although athetoid (slow and writhing) or even dystonic movements (more sustained postures) are sometimes seen. Movements can be confined to the face (e.g., tongue protrusions, chewing movements, eye blinking, or “grimacing”), but other areas can also be affected. Patients may seem to be moving their fingers as if playing the piano or truncal involvement can give patients the appearance of “dancing.” A tremor is not a symptom of TD! Most cases of TD are mild with a waxing and waning course, and as noted earlier, around 5% even remit spontaneously despite ongoing treatment. Severely afflicted patients can be incapacitated by constant, severe movements that interfere with talking, eating, breathing (respiratory TD affecting the diaphragm), or walking. Dramatic withdrawal dyskinesias can occur when patients are abruptly withdrawn from chronic antipsychotics, possibly due to the mechanism of dopamine receptor supersensitivity [17]. Those movements can last a few weeks but should eventually remit as the dopamine system resets itself.

Key Point

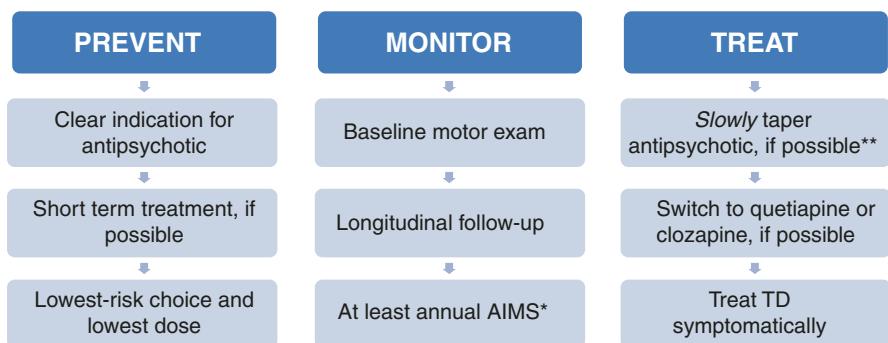
TD is a hyperkinetic movement disorder, and typical cases are easy to spot. It requires experience, however, to correctly delineate the precise nature of abnormal patient movements or recognize subtle TD (which can appear volitional – see epigraph to this chapter). Lateral jaw movements may be an early sign of TD that patients often dismiss as a habit.

TD is only one of many hyperkinetic movement disorders to be considered (Table 14.1); get a neurologist to help sort it out. Note that antipsychotics can mask TD, which may become apparent only when reducing the dose (or stopping medications).

Once you have detected abnormal movements and made the clinical diagnosis of TD, you can then use the well-established abnormal involuntary movement scale (AIMS) [18] to record and follow the severity of abnormal movements. The AIMS is not a diagnostic tool! View the AIMS as a checklist that reminds you to be comprehensive: you need to rate the severity of abnormal movements in seven body areas (grouped into facial and oral movements, extremity movements, and trunk movements). Adding up the seven individual scores gives you the total AIMS severity score. See Additional Resources for the standard reference about how to use the AIMS correctly.

Table 14.1 Differential diagnosis of tardive dyskinesia

Old age (edentulous patients; orobuccal dyskinesias of old age)
Meige syndrome
Blepharospasm
Stereotypies and dyskinesias of (never-treated) schizophrenia
Withdrawal dyskinesia (after removing dopamine blockade)
Neurological syndromes
Choreas (prototype Huntington's disease)
Fahr's syndrome (idiopathic basal ganglia calcification)
Wilson's disease
Dystonias
Tourette's syndrome and other tic disorders
Restless leg syndrome
Toxins
Medications
Postanoxic or postencephalitic
Hypoparathyroidism
Systemic lupus erythematosus
Chorea gravidarum
Central nervous system neoplasm



*In low-risk patients; more frequent monitoring in higher risk patients

**Stop anticholinergics; based on Bergman H. and Soares-Weiser K. Cochrane Database Syst Rev. 2018 Jan 17; 1: CD000204.

Fig. 14.3 Prevention and treatment of TD. (Based on [19])

Management

Figure 14.3 summarizes the management of tardive dyskinesia, including primary prevention, secondary prevention (monitoring), and treatment.

The best treatment (like pretty much always in medicine) is prevention: use the lowest possible dose of any antipsychotic, but particularly an FGA, and minimize lifetime exposure; or strongly consider a second-generation antipsychotic with

lower TD risk. Antipsychotics are now more widely used for indications other than schizophrenia which puts larger groups of patients at risk for it. Periodically reassess the need for an antipsychotic if you use them for indications other than maintenance treatment of schizophrenia. Do not overlook antidopaminergic agents used for medical reasons (e.g., the antiemetic metoclopramide). The frequency of monitoring is guided by the risk for TD. Remember, however: TD is almost always irreversible once it develops [12]. The best hope for reversing TD may be in young people, if discovered very early.

Tip

For obvious medicolegal reasons, document specifically that the patient's informed consent included a discussion of TD when discussing the need and choice for any antipsychotic, regardless of indication. Clearly document your baseline assessment of motor problems (which might be present), and monitor regularly. I check for EPS every patient visit and specifically note "no abnormal movement" in the MSE if patients show no signs of TD, but also fill out an official AIMS form every 6–12 months (depending on the risk even more frequently).

If TD should develop, decide (again) if an antipsychotic is clearly needed, and discontinue the antipsychotic, if possible. Consider a switch to quetiapine or clozapine, which have the least likelihood of causing TD if antipsychotic discontinuation is not an option [19]. Clozapine may improve abnormal movements in parallel with overall symptom improvement. I may add vitamin E (1600 IU/day) as soon as I notice TD, as this might prevent further worsening of symptoms when given early. In well-established cases of TD, vitamin E has no effect [20]. Alternatively, a relatively benign, high-yield intervention to try is giving 400 mg/day of vitamin B6 for a few months [21]. If there is no response, however, do not forget to stop high-dose vitamin B6 as it can cause a sensory neuropathy. I am unsure about the benefits of benzodiazepine although some reviews suggest benefit; you are also introducing the problems associated with a controlled substance. Anticholinergics are ineffective for tardive dyskinesia. In some patients, there is a seeming worsening of TD once an anticholinergic is added. This may be an artifact of treating Parkinsonism and as an unintended consequence "freeing" TD from its Parkinsonian corset. Several medications are available to treat established TD symptomatically, including two new medications that are FDA-approved specifically for TD, valbenazine and deutetrabenazine (Table 14.2).

Until recently, there was no clearly effective and well-tolerated medication to treat TD. The most effective medication, tetrabenazine, was repurposed from Huntington's disease treatment. Tetrabenazine belongs to a class of so-called vesicular monoamine transporter 2 (VMAT-2) inhibitors. VMAT-2 inhibitors effectively deplete dopamine in presynaptic striatal nerve terminals which is believed to underlie their efficacy for hyperkinetic movement disorders. However, the need for

Table 14.2 Medications to treat TD

<i>Treatment of choice</i>
Deutetrabenazine ^a
Valbenazine ^a
<i>Other agents with some support</i>
Tetrabenazine
Benzodiazepines ^b
<i>Ginkgo biloba</i>
Amantadine
Vitamin E (early course TD)
Branched-chain amino acids
Vitamin B6
<i>For intractable TD</i>
Botulinum toxin type A (focal dystonia)
Pallidal deep brain stimulation

Based on [22, 23]

^aFDA-approved for treatment of TD

^bControlled substance

frequent dosing (three times daily) and poor tolerability (Parkinsonism, risk for suicidality) limited tetrabenazine's use for tardive dyskinesia. Deutetrabenazine and valbenazine are derivates of tetrabenazine that were developed to improve tolerability and allow for less frequent dosing. Valbenazine is a prodrug that leads to one active metabolite of tetrabenazine and a half-life that allows once-daily dosing [24]. Deutetrabenazine is an example of the successful application of deuteration (replacing selected hydrogen atoms in the drug with heavier deuterium isotopes) to change the pharmacokinetic properties of a drug [25]. Carbon-deuterium bonds are stronger than carbon-hydrogen bonds and therefore more resistant to being broken up during drug metabolism which leads to a longer half-life (twice-daily dosing in the case of deutetrabenazine). Deuterated drugs have pharmacodynamic properties identical to the unmodified mother drug as the 3-D structure of the molecule, and hence their receptor binding profile remains the same. Both deutetrabenazine and valbenazine have demonstrated safety and efficacy in modern clinical trials, leading to FDA approval [26]. The risk for Parkinsonism and suicidal ideation appears to be low [27]. However, only long-term experience in routine clinical populations can delineate the full benefits from VMAT-2 inhibitors, optimal dosing, and risks not identified during short-term registration trials. Unfortunately, the hope that time-limited use of VMAT-2 inhibitors may reverse neurological damage underlying tardive dyskinesia has not materialized. Once stopped, TD symptoms return, and long-term treatment is needed. Given the substantial yearly cost for these new medications, the choice is often determined by insurance coverage and not by clinical considerations (e.g., dosing).

Botulinum injections [28] and deep brain stimulations [23] are therapies that may offer relief in otherwise non-responsive TD patients. In some situation (e.g., a case of severe withdrawal dyskinesia) a high-affinity dopamine antagonist like haloperidol can be used to suppress tardive dyskinesia. While not a preferred long-term

strategy as it may worse the overall course of TD, it is an effective short-term intervention.

Neuroleptic-Induced Dysphoria

Neuroleptic-induced dysphoria (NID), another rather distressing and frequently overlooked subjective side effect, was thought to be a variant of EPS as it accompanies residual akathisia [29], but it may better be regarded as its own spectrum of disorders of subjective antipsychotic tolerability [30]. Patients describe a sense of listlessness and lack of motivation occurring after the first dose of an antipsychotic and lasting several weeks. NID is likely the result of dopamine blockade not in the nigrostriatal motor pathway but in the nucleus accumbens, a key structure in reward and motivation pathways. NID is related to the concept of “subjective well-being on neuroleptics” and a risk factor for treatment discontinuation [31]. Newer antipsychotics may be preferred by patients as they are less likely to cause this particular problem [32].

Neuroleptic Malignant Syndrome (NMS)

NMS can be regarded as a severe form of EPS with systemic manifestation. It can also be regarded a drug-induced variant of malignant catatonia [33]. It is an iatrogenic and potentially fatal complication of antipsychotic use [34]. Patients with current catatonia or a history of catatonia are at higher risk for developing NMS, so proceed cautiously with antipsychotics in such patients. NMS develops almost always (in 96% of patients in one study) within 30 days of starting an antipsychotic, although it can also rarely occur even years after initiating neuroleptics. It can also occur after withdrawal from a dopamine agonist. The clinical picture develops rapidly (hours to days) and resolves (barring complications) within 30 days. NMS is characterized by a classic triad of fever (in all cases), lead-pipe muscular rigidity, and mental status changes. In addition to the aforementioned triad, vital signs are unstable, and patients are diaphoretic. Laboratory values show an increased creatine phosphokinase (CPK) from widespread myonecrosis and an increase in white blood cells. See Table 14.3 for a summary of the full spectrum of symptoms and how they evolve in NMS.

NMS can only be diagnosed if CNS infections, systemic infections, seizures, or drug intoxications (e.g., PCP) have been ruled out. Also differentiate NMS from other conditions accompanied by fever and motor symptoms, including serotonin syndrome, malignant catatonia, malignant hyperthermia (after general anesthesia) [36], and heat stroke [37]. The motor hallmark of serotonin syndrome is hyperre-

Table 14.3 Spectrum of symptoms in NMS

<i>Core triad</i>
Fever
Rigidity
Mental status changes: agitation, confusion
<i>Clinical presentation (in order of symptom appearance)</i>
Confusion and fluctuating level of consciousness
Rigidity (typically lead pipe, other motor symptoms are possible)
Diaphoresis
Mutism
Autonomic instability (tachycardia; hypertension/hypotension; tachypnea)
Hyperthermia
Elevated serum creatine phosphokinase (CPK) (>1000 IU/L)
Onset within 2 weeks of starting antipsychotic
Low iron is a state-dependent sensitive but not specific marker

Based on [35]

flexia/myoclonus [38] and not the lead-pipe rigidity of NMS which may help distinguish those two syndromes. Atypical presentations without EPS or rigidity are possible with second-generation antipsychotics [39] although most presentations of NMS with atypical antipsychotics are typical (i.e., with rigidity) [40]. Clozapine can cause typical NMS [41]! It remains unclear if asymptomatic creatine phosphokinase (CPK) elevation represents a forme fruste of NMS.

Key Point

NMS is a neurologic emergency. If you suspect NMS based on the classic triad of fever, lead-pipe rigidity, and mental status changes, hold all antipsychotics and refer the patient to the emergency room. In inpatient settings, assuring good hydration can prevent some cases of NMS.

After stopping all antipsychotics, the treatment of NMS is symptomatic and resolves within 30 days, unless the course is complicated. Rhabdomyolysis and myoglobinuria can lead to kidney damage. A careful reintroduction of a second- or third-generation antipsychotic is usually possible once the episode of NMS has been resolved, after waiting for at least 2 weeks [42]. If treated early and optimally, the mortality from NMS should today be below 10% [43].

References

1. Janno S, Holi M, Tuisku K, Wahlbeck K. Prevalence of neuroleptic-induced movement disorders in chronic schizophrenia inpatients. *Am J Psychiatry*. 2004;161:160–3.
2. Parksepp M, Ljubajev U, Taht K, Janno S. Prevalence of neuroleptic-induced movement disorders: an 8-year follow-up study in chronic schizophrenia inpatients. *Nord J Psychiatry*. 2016;70:498–502.
3. Glazer WM. Extrapyramidal side effects, tardive dyskinesia, and the concept of atypicality. *J Clin Psychiatry*. 2000;61(Suppl 3):16–21.
4. Buchanan RW, Kreyenbuhl J, Kelly DL, Noel JM, Boggs DL, Fischer BA, et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr Bull*. 2010;36:71–93.
5. Freudenberg O. Atypical laryngeal dystonia caused by an antiemetic. *Am Fam Physician*. 2004;69:1623.
6. Arana GW, Goff DC, Baldessarini RJ, Keepers GA. Efficacy of anticholinergic prophylaxis for neuroleptic-induced acute dystonia. *Am J Psychiatry*. 1988;145:993–6.
7. Citrome L. Brexpiprazole: a new dopamine D(2)receptor partial agonist for the treatment of schizophrenia and major depressive disorder. *Drugs Today*. 2015;51:397–414.
8. Barnes TR. A rating scale for drug-induced akathisia. *Br J Psychiatry*. 1989;154:672–6.
9. Poyurovsky M, Pashinian A, Weizman R, Fuchs C, Weizman A. Low-dose mirtazapine: a new option in the treatment of antipsychotic-induced akathisia. A randomized, double-blind, placebo- and propranolol-controlled trial. *Biol Psychiatry*. 2006;59:1071–7.
10. Poyurovsky M, Bergman J, Pashinian A, Weizman A. Beneficial effect of low-dose mirtazapine in acute aripiprazole-induced akathisia. *Int Clin Psychopharmacol*. 2014;29:296–8.
11. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand Suppl*. 1970;212:11–9.
12. Correll CU, Kane JM, Citrome LL. Epidemiology, prevention, and assessment of tardive dyskinesia and advances in treatment. *J Clin Psychiatry*. 2017;78:1136–47.
13. Widschwendter CG, Hofer A. Antipsychotic-induced tardive dyskinesia: update on epidemiology and management. *Curr Opin Psychiatry*. 2019;32:179–84.
14. Carbon M, Hsieh CH, Kane JM, Correll CU. Tardive dyskinesia prevalence in the period of second-generation antipsychotic use: a meta-analysis. *J Clin Psychiatry*. 2017;78:e264–78.
15. Gervin M, Browne S, Lane A, Clarke M, Waddington JL, Larkin C, et al. Spontaneous abnormal involuntary movements in first-episode schizophrenia and schizopreniform disorder: baseline rate in a group of patients from an Irish catchment area. *Am J Psychiatry*. 1998;155:1202–6.
16. Solmi M, Pigati G, Kane JM, Correll CU. Clinical risk factors for the development of tardive dyskinesia. *J Neurol Sci*. 2018;389:21–7.
17. Chouinard G, Samaha AN, Chouinard VA, Peretti CS, Kanahara N, Takase M, et al. Antipsychotic-induced dopamine supersensitivity psychosis: pharmacology, criteria, and therapy. *Psychother Psychosom*. 2017;86:189–219.
18. Guy W. ECDEU assessment manual for psychopharmacology: revised (DHEW publication number ADM 76-338). Rockwill: US Department of Health, Education and Welfare, Public Health Service, Alcohol, Drug Abuse and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976. p. 534–7.
19. Ricciardi L, Pringsheim T, Barnes TRE, Martino D, Gardner D, Remington G, et al. Treatment recommendations for tardive dyskinesia. *Can J Psychiatr*. 2019;64(6):388–99.
20. Adler LA, Rotrosen J, Edson R, Lavori P, Lohr J, Hitzemann R, et al. Vitamin E treatment for tardive dyskinesia. Veterans Affairs Cooperative Study #394 Study Group. *Arch Gen Psychiatry*. 1999;56:836–41.

21. Adelufosi AO, Abayomi O, Ojo TM. Pyridoxal 5 phosphate for neuroleptic-induced tardive dyskinesia. *Cochrane Database Syst Rev.* 2015;CD010501.
22. Bhidayasiri R, Fahn S, Weiner WJ, Gronseth GS, Sullivan KL, Zesiewicz TA, et al. Evidence-based guideline: treatment of tardive syndromes: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology.* 2013;81:463–9.
23. Bhidayasiri R, Jitkritsadakul O, Friedman JH, Fahn S. Updating the recommendations for treatment of tardive syndromes: a systematic review of new evidence and practical treatment algorithm. *J Neurol Sci.* 2018;389:67–75.
24. Freudenberg O, Remington G. Valbenazine for tardive dyskinesia. *Clin Schizophr Relat Psychoses.* 2017;11:113–9.
25. Timmins GS. Deuterated drugs; updates and obviousness analysis. *Expert Opin Ther Pat.* 2017;27:1353–61.
26. Tarakad A, Jimenez-Shahed J. VMAT2 inhibitors in neuropsychiatric disorders. *CNS Drugs.* 2018;32:1131–44.
27. Solmi M, Pigato G, Kane JM, Correll CU. Treatment of tardive dyskinesia with VMAT-2 inhibitors: a systematic review and meta-analysis of randomized controlled trials. *Drug Des Devel Ther.* 2018;12:1215–38.
28. Jankovic J. An update on new and unique uses of botulinum toxin in movement disorders. *Toxicon.* 2018;147:84–8.
29. Newcomer JW, Miller LS, Faustman WO, Wetzel MW, Vogler GP, Csernansky JG. Correlations between akathisia and residual psychopathology: a by-product of neuroleptic-induced dysphoria. *Br J Psychiatry.* 1994;164:834–8.
30. Voruganti L, Awad AG. Neuroleptic dysphoria: towards a new synthesis. *Psychopharmacology.* 2004;171:121–32.
31. Naber D, Karow A, Lambert M. Subjective well-being under the neuroleptic treatment and its relevance for compliance. *Acta Psychiatr Scand Suppl.* 2005;111:29–34.
32. Naber D, Moritz S, Lambert M, Pajonk FG, Holzbach R, Mass R, et al. Improvement of schizophrenic patients' subjective well-being under atypical antipsychotic drugs. *Schizophr Res.* 2001;50:79–88.
33. Casamassima F, Lattanzi L, Perlis RH, Litta A, Fui E, Bonuccelli U, et al. Neuroleptic malignant syndrome: further lessons from a case report. *Psychosomatics.* 2010;51:349–54.
34. Addonizio G, Susman VL, Roth SD. Neuroleptic malignant syndrome: review and analysis of 115 cases. *Biol Psychiatry.* 1987;22:1004–20.
35. Gurrera RJ, Caroff SN, Cohen A, Carroll BT, DeRoos F, Francis A, et al. An international consensus study of neuroleptic malignant syndrome diagnostic criteria using the Delphi method. *J Clin Psychiatry.* 2011;72:1222–8.
36. Berman BD. Neuroleptic malignant syndrome: a review for neurohospitalists. *Neurohospitalist.* 2011;1:41–7.
37. Lazarus A. Differentiating neuroleptic-related heatstroke from neuroleptic malignant syndrome. *Psychosomatics.* 1989;30:454–6.
38. Sternbach H. The serotonin syndrome. *Am J Psychiatry.* 1991;148:705–13.
39. Trollor JN, Chen X, Chitty K, Sachdev PS. Comparison of neuroleptic malignant syndrome induced by first- and second-generation antipsychotics. *Br J Psychiatry.* 2012;201:52–6.
40. Trollor JN, Chen X, Sachdev PS. Neuroleptic malignant syndrome associated with atypical antipsychotic drugs. *CNS Drugs.* 2009;23:477–92.
41. Sachdev P, Kruk J, Kneebone M, Kissane D. Clozapine-induced neuroleptic malignant syndrome: review and report of new cases. *J Clin Psychopharmacol.* 1995;15:365–71.
42. Rosebush PI, Stewart TD, Gelenberg AJ. Twenty neuroleptic rechallenges after neuroleptic malignant syndrome in 15 patients. *J Clin Psychiatry.* 1989;50:295–8.
43. Modi S, Dharaiya D, Schultz L, Varelas P. Neuroleptic malignant syndrome: complications, outcomes, and mortality. *Neurocrit Care.* 2016;24:97–103.

Additional Resources

Web Site

<https://www.mhause.org> – The Malignant Hyperthermia Association of the United States (MHAUS) also hosts the Neuroleptic Malignant Syndrome Information service (NMSIS) which offers many resources related to NMS, including a hotline for professionals.

Book Chapter

Freudenreich O, Flaherty AW. Patients with abnormal movements. In: Stern TA, Freudenreich O, Smith FA, Fricchione GL, Rosenbaum JF, editors. Massachusetts General Hospital handbook of general hospital psychiatry. 7th ed. Edinburgh: Elsevier; 2018. p. 231–29. – A more detailed book chapter that I wrote with a colleague from neurology about the assessment of patients with abnormal movements, including tremors and psychogenic movement disorder which I did not discuss here.

Articles

Gurrera RJ, Caroff SN, Cohen A, Carroll BT, DeRoos F, Francis A, et al. An international consensus study of neuroleptic malignant syndrome diagnostic criteria using the Delphi method. *J Clin Psychiatry*. 2011;72:1222–8. – Consensus criteria using the Delphi method (a RAND cooperation-developed method to establish expert consensus) for a diagnosis of NMS.

Munetz MR, Benjamin S. How to examine patients using the Abnormal Involuntary Movement Scale. *Hosp Community Psychiatry*. 1988;39:1172–7. – The standard reference, with clear instructions about how to correctly use the AIMS.

Chapter 15

Antipsychotics: Nonmotor Side Effects



Essential Concepts

- Nonmotor side effects of antipsychotics such as sedation or weight gain can reduce quality of life and lead to nonadherence.
- Weight gain and its associated metabolic side effects (i.e., diabetes mellitus and dyslipidemias) are a major long-term clinical concern and management issue. Olanzapine and clozapine are metabolically high-risk medications.
- First-generation antipsychotics and several second-generation antipsychotics (risperidone, paliperidone, lurasidone) reliably increase prolactin at usual doses. Clozapine, quetiapine, ziprasidone, iloperidone, and all partial agonists are “prolactin-sparing.”
- Assess side effects related to hyperprolactinemia clinically, as they are not associated with the degree of prolactin elevation. Typical side effects include erectile dysfunction and galactorrhea in males and irregular or absent menses and galactorrhea in females.
- Osteoporosis can be a long-term complication from prolactin elevation if it is accompanied by hypoestrogenemia.
- Antipsychotics cause sexual side effects, and many patients are sexually active.
- Antipsychotics can increase the risk for torsades de pointes if they prolong the QTc interval. Assess the cardiac risk in all patients and monitor the electrocardiogram (ECG), if possible, but always in selected clinical situations (e.g., intravenous haloperidol use).
- Encourage regular eye and dental care as patients with serious mental illness often have risk factors for cataracts and poor dentition, with antipsychotics possibly contributing.

- Antipsychotic use is associated with increased mortality in patients with dementia but also with sudden death in other patient groups. Careful monitoring and managing cardiovascular risk factors is a critical component of care for schizophrenia patients who receive antipsychotics.

“Was mich nicht umbringt, macht mich härter.” [1]

(“What does not kill me, makes me stronger.”)

Friedrich Nietzsche, 1844–1899, Götzen-Dämmerung

Nonmotor side effects such as sedation or weight gain are as important to patients as motor side effects and are in part responsible for non-adherence to second-generation antipsychotics – I think most patients would disagree with Nietzsche and not view side effects as character building but as a nuisance that reduces your quality of life. Imagine you were asked to take a medicine long-term that makes you feel sluggish for most of your waking hours or that reminds you of your younger normal-weight self every time you look into the mirror. Knowing about and addressing these nonmotor side effects to increase “subjective well-being under neuroleptic treatment” are important to optimize adherence [2]. Moreover, cardiac side effects and metabolic problems associated with antipsychotics (glucose intolerance or weight gain) contribute to high rates of cardiovascular disease and premature mortality in patients with schizophrenia. Metabolic monitoring and weight management are discussed in more detail in Chap. 25. Clozapine has a host of nonmotor side effects that are described in more detail in Chap. 17.

Sedation

Sedation can be rather severe and cause patients to sleep most of the day. For patients who have a problem with negative symptoms, this adds insult to injury. Clozapine, olanzapine, and quetiapine are clearly rather sedating for most patients, whereas aripiprazole and ziprasidone can lead to insomnia and are often poorly tolerated by chronic patients who have gotten used to the ataractic effects of their antipsychotic. Sedation depends in part on the degree to which histamine receptors are blocked by the antipsychotic.

With patients who have a “hangover” in the morning from a high nightly antipsychotic dose, you can try splitting up the dose or lowering the total daily dose. Short of changing the antipsychotic, coffee in the morning is sometimes sufficient (I think this is as effective as and safer than prescription stimulants or modafinil). Some medications can be activating (akathisia) and sedating at the same time [3]. I tell all patients that antipsychotics used to be called “major tranquilizer” and that they may feel tired when taking them. It is a patient’s responsibility to pay attention if their medication impairs their ability to drive.

Weight Gain and Metabolic Side Effects

Weight gain has always been a problem for patients taking antipsychotics, but the second-generation antipsychotics have turned the spotlight even more on this particular side effect. In 1999, a very influential meta-analysis of weight gain propensity of antipsychotics showed that not all antipsychotics are created equal when it comes to weight gain [4]. Clozapine and olanzapine had the biggest liability for weight gain estimated to be more than 4 kg in 10 weeks of treatment, compared to 2 kg with risperidone. Ziprasidone was weight neutral in this analysis, which did not include aripiprazole and quetiapine; molindone which is no longer available was associated with weight loss. In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), olanzapine led to a weight gain of 2 lbs per months, risperidone and quetiapine had comparable weight gains of 0.5 lbs per month, whereas patients assigned to ziprasidone or perphenazine lost weight [5]. In 2009, the Schizophrenia Patient Outcomes Research Team (PORT) guidelines [6] provided the following helpful ranking of weight gain liability (from highest to lowest risk): clozapine = olanzapine > low-potency first-generation antipsychotics > risperidone = paliperidone = quetiapine > mid-potency first-generation antipsychotics > high-potency antipsychotics = aripiprazole = ziprasidone. A more recent meta-analysis of weight gain in first-episode patients found weight gain for all antipsychotics except ziprasidone [7]. Note that not all newer antipsychotics were available for this analysis. Among more recently approved antipsychotics, lurasidone [8], brexpiprazole [9], and cariprazine appear to have excellent metabolic safety profiles [10].

Antipsychotic-induced weight gain is undesirable not only for reasons of esthetics but because of the many medical complications that are associated with being overweight or obese. Metabolic derangement is most critical: as weight and body fat increases, insulin resistance increases, which can lead to a cluster of metabolic findings known as metabolic syndrome (syndrome X), that is, impaired glucose tolerance, hypertension, and dyslipidemia. The relevance of the metabolic syndrome lies in its predictive value for cardiovascular disease and diabetes, making it all the more worrisome that four out of ten patients in the CATIE cohort, for example, had the metabolic syndrome [11]. The typical patient develops diabetes as a late complication, in the setting of creeping but steady weight gain and increasing insulin resistance. It is intra-abdominal (central) fat that is responsible for the metabolic derangements: it matters where fat is deposited, and not all obese patients based on BMI calculations have the same metabolic risk. The pear-shaped abdomen seen in many chronic schizophrenia patients is the outward sign of central obesity and an ominous sign. One surrogate measure of metabolic risk is waist circumference which better reflects abdominal fat deposition than absolute weight. Waist circumference is the best anthropomorphic marker of insulin resistance for clozapine patients [12]. It is for this reason that metabolic monitoring guidelines include waist circumference as a parameter to follow (see Chap. 25 for metabolic monitoring guidelines). Insulin resistance develops rapidly, within a few weeks of treatment, with more pronounced effects of olanzapine compared to risperidone or aripiprazole.

[13]. Note that in patients treated with high-risk antipsychotics, particularly olanzapine and clozapine, insulin resistance can also develop in the absence of clinical obesity [14], and patients can present with diabetic ketoacidosis as the first clinical sign of a metabolic problem. Clozapine and olanzapine also have the highest risk for increasing triglycerides (one of the parameters of the metabolic syndrome). Very high triglycerides increase the risk for pancreatitis, although no clear cutoff value exists.

To summarize, the past decades of experience with second- and third-generation antipsychotics have established several facts about antipsychotic-associated weight gain:

- The liability to cause weight gain differs between antipsychotics. High-risk antipsychotics include clozapine and olanzapine, and low-risk antipsychotics include haloperidol, fluphenazine, lurasidone, ziprasidone, brexpiprazole, and cariprazine. The other antipsychotics fall somewhere in-between.
- Young, first-episode patients who are antipsychotic-naïve are at higher risk of weight gain than older and previously treated patients [15].
- Not all weight gain is equal. In one cohort study of young patients who started taking one of four antipsychotics (aripiprazole, risperidone, quetiapine, olanzapine), all antipsychotics caused weight gain, but only aripiprazole did not have accompanying metabolic derangements [16].
- Antipsychotic-associated weight gain is unfortunately not clearly dose-related. Even a low dose of quetiapine for insomnia can cause weight gain and metabolic problems. Similarly, lowering olanzapine from 20 to 10 mg/day, if clinically possible, will be disappointing with regard to weight loss.

Key Point

No antipsychotic should be considered “weight neutral.” Antipsychotic-naïve patients treated with antipsychotics will invariably gain weight, the amount depending on individual sensitivity to this side effect and the specific antipsychotic. Do not promise your patient that he or she will not gain weight but emphasize what countermeasures *they* can take to mitigate the weight gain.

See Chap. 25 for details regarding guideline-based weight and metabolic monitoring.

Hyperprolactinemia and Sexual Side Effects

Recall from medical school that the prolactin inhibitory factor (PIF) turned out to be dopamine. Consequently, dopamine antagonists (i.e., antipsychotics) can increase prolactin. The first-generation antipsychotics and those second-generation antipsy-

chotics with tight D₂-binding predictably lead to hyperprolactinemia; antipsychotics with loose D₂-binding and the partial agonist antipsychotics are considered “prolactin-sparing” (see Fig. 15.1).

Almost all patients treated with usual doses of risperidone and paliperidone will experience hyperprolactinemia (but usually below 100 ng/mL, females have relatively higher levels). It is important to know that patients with increased prolactin levels do not automatically experience prolactin-related side effects; Table 15.1 presents a list of side effects. Although prolactin elevation is correlated with antipsychotic dose, clinical symptoms do not correlate with prolactin levels.

For those patients who have symptoms attributable to hyperprolactinemia, I would first check the prolactin level and then consider switching to a prolactin-sparing antipsychotic. If the hyperprolactinemia is higher than you are comfortable with (e.g., above 100 ng/mL) or does not resolve after switching to a prolactin-

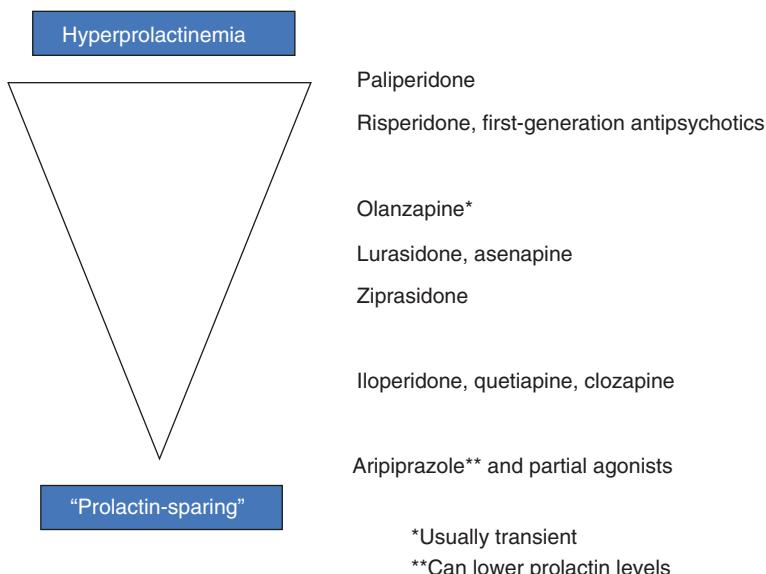


Fig. 15.1 Prolactin-sparing antipsychotics

Table 15.1 Side effects related to hyperprolactinemia

Decreased libido
Anorgasmia
Gynecomastia and galactorrhea
In men: erectile dysfunction
In women: irregular menses or amenorrhea (with secondary infertility)

Based on Ref. [17]

sparing antipsychotic, further work-up will be necessary to make sure your patient does not have a prolactinoma [18]. Visual field testing and brain imaging may be needed. In cases where it is clinically necessary to continue a prolactin-elevating antipsychotic (e.g., a first-generation long-acting injectable), adding aripiprazole will normalize prolactin levels.

The long-term effects of (asymptomatic) elevation of prolactin are unclear. However, prolactin-induced hypoestrogenemia can lead to osteoporosis, and I would consider monitoring (in collaboration with the patient's primary care doctor) bone density in premenopausal women with antipsychotic-induced amenorrhea [19]. For some women, hormone replacement therapy should be considered. An observed increased breast cancer risk in female patients with schizophrenia has raised concerns about antipsychotic-induced prolactin elevation as prolactin plays a role in mammary carcinogenesis [20]. However, most patients have other breast cancer risk factors (nulliparity, obesity, diabetes, smoking) that are probably more relevant. This is similar to patients with osteoporosis who have risk factors other than hyperprolactinemia that would need to be taken into account as well [21].

Tip

Warn your female patient with amenorrhea from antipsychotics that their menses (and fertility!) might return when they are switched to prolactin-sparing antipsychotics. Discuss contraception with your female patient of childbearing age.

Clinical Vignette

I had known a female patient with schizophrenia and alcoholism for many years. A severe drinker, her adherence to antipsychotics was marginal at best, and she went in and out of detoxification units, homeless shelters, and psychiatric hospitals until long-acting risperidone led to a period of psychiatric stability followed by cessation of drinking. She developed hyperprolactinemia but not have symptoms associated with it other than amenorrhea, which did not bother her. Because she was clinically stable and she did not want to have more tests, we decided together to continue risperidone while monitoring prolactin levels. Her initial prolactin level (while on risperidone) was 147 ng/mL, which has remained stable for the past 2 years. Serial prolactin levels are useful in excluding a prolactinoma (where levels should rise) if a referral to endocrinology and brain imaging is not possible.

Many patients struggle with loss of libido as a function of dopamine blockade and hyperprolactinemia [22]. Sexual side effects of antipsychotics are usually missed as nobody (I am guilty myself) ever asks but simply assumes patients to be “asexual,” particularly your middle-aged and older, chronic patient [23]. This is

untrue: patients with schizophrenia are sexually active, and this means that female patients can get pregnant and that all patients are at risk for sexually transmitted disease, including human immunodeficiency virus (HIV). It is worthwhile not to assume anything, so you should have a discussion about sexual topics with your patients, regardless of age. Simply ask: “Are you sexually active?” and take it from there. Erectile dysfunction from antipsychotics might respond to a trial of sildenafil [24].

Priapism is a potentially serious adverse reaction to antipsychotics with prominent alpha-1 blockade: risperidone, olanzapine, and clozapine [25]. Warning signs are prolonged erections that last several hours.

Cardiac Toxicity

Although rare, antipsychotics, particularly thioridazine (no longer on the market), have been implicated in sudden death since the introduction of antipsychotics. Pimozide, sometimes touted as the best treatment for delusional disorder, has calcium channel-blocking properties and should only be used if you can monitor the ECG. Personally, I never used thioridazine (or its metabolite mesoridazine) much or pimozide because safer options that are as effective are available. Many emergency departments avoid droperidol because of (an admittedly controversial) black-box warning about QTc prolongation. Intravenous haloperidol should only be used if ECG monitoring is possible. Unfortunately, newer antipsychotics do not appear to be safer with regard to the risk for sudden death than older antipsychotics [26].

Antipsychotics can cause arrhythmias via prolongation of the action-potential phase of the cardiac cycle, by delaying ventricular repolarization and thereby increasing the risk for lethal ventricular arrhythmias, such as torsades de pointes (TdP) [27]. This effect on repolarization is reflected in a prolonged QT interval on the ECG which is a precondition for the development of torsades. Since the QT interval is inversely correlated with the heart rate, it needs to be heart-rate corrected. A common method for a corrected QTc interval uses the Bazett formula, which is calculated by dividing the QT interval by the square root of the R-R interval [28] although other corrections are available.

The propensity to prolong the QTc interval is different for different antipsychotics and tied to their potency to block particular potassium channels. Ziprasidone went through the FDA-approval process when the issue of antipsychotics and QTc prolongation had become a concern. As a result, the company that makes ziprasidone had to conduct a trial that directly compared the propensity of ziprasidone to increase QTc at peak levels with several other antipsychotics. Thioridazine came out as the clear winner (or loser, if you will), increasing QTc by 36 ms, followed by ziprasidone which demonstrably increased QTc by about 20 ms. Other antipsychotic showed less QTc prolongation. It is reassuring that QTc prolongation greater than 500 ms is very rare with ziprasidone [29] and that there is no dose-related QTc prolongation with ziprasidone [30]. The latter is important because it suggests that

blocking the metabolism of ziprasidone should not increase cardiac risk beyond the small, expected QTc prolongation. It is further reassuring that the modest QTc prolongation with ziprasidone appears to not translate into a higher risk of sudden death when compared to other antipsychotics. After ziprasidone was approved, a large cohort study of almost 20,000 patients (named ZODIAC, for Ziprasidone Observational Study of Cardiac Outcomes) that randomized participants to either ziprasidone or olanzapine found no difference between those two treatments with regard to serious cardiac events [31]. This trial confirmed the observation of a very low yet increased risk of sudden death for schizophrenia patients. ZODIAC is a good example of a “large simple trial” that focuses on detecting small differences between outcomes that are important in routine clinical care [32]. Quetiapine and iloperidone are newer antipsychotics that prolong the QTc interval in a dose-dependent manner. The evidence, however, for clinically meaningful QT prolongation with most classes of psychiatric agents remains minimal [27].

I would nevertheless prefer a baseline ECG in all my patients. True, the measurement of the QTc interval is fraught with measurement errors, and its predictive value for important clinical end points is imperfect, as seen in ZODIAC above [33]. However, ECG monitoring is the only way to identify patients at higher risk for sudden cardiac death from an arrhythmia on the basis of QTc prolongation. The threshold for QTc interval screening with follow-up ECG monitoring should be lower in patients on polypharmacy or patients from special populations (e.g., methadone patients [34]). The most important risk-reducing intervention may be a careful search for risk factor for QT prolongation before prescribing psychiatric medications [27].

Key Point

While an imperfect tool, a group of European schizophrenia experts listed EKG monitoring as a key parameter of good patient care in order to reduce the risk of catastrophic outcomes from an arrhythmia [35]. If obtaining a baseline ECG is not possible, a careful family and personal history of heart disease (sudden death, syncope) and a review of all medications, particularly heart medications, will help determine increased risk. While for many clinicians who work in traditional, nonmedical psychiatric outpatient settings, securing an ECG is no small task, good practice requires us overcoming obstacles in obtaining ECGs, at a minimum for all patients who are identified as higher risk. The risk for sudden death per year (3 deaths per 1000 patient-years) may be tenfold higher than the risk of death from clozapine-related agranulocytosis (0.2 deaths per 1000 patients-years) for which we have a strict risk-management program in place [36].

Medications with alpha-blocking properties (i.e., low-potency antipsychotics and clozapine) can cause orthostatic hypotension and need to be titrated at the beginning of treatment. Consider orthostasis if your patient complains about

dizziness or reports falls at home. Clozapine stands out with a unique and particularly dangerous cardiac side effect, myocarditis, which can develop shortly after starting clozapine (see Chap. 17 on clozapine).

Anticholinergic Side Effects

Antipsychotics that are anticholinergic can be expected to cause a dry mouth, blurry vision, and constipation, but more serious side effects are possible (e.g., toxic megacolon, particularly well described with clozapine). The low-potency first-generation antipsychotic chlorpromazine is strongly anticholinergic, as is clozapine. Paradoxically, clozapine can cause sialorrhea, mostly due to a decrease in swallowing and not because of an increase in saliva flow. Quetiapine can cause anticholinergic-like side effect via adrenergic mechanisms, including constipation and dry mouth.

Eye and Dental Care

With some older medications, eye problems can develop. Chlorpromazine can cause pigment changes affecting the retina (it also causes general pigmentation of the skin and photosensitivity), and thioridazine causes a pigmentary retinopathy at doses greater than 800 mg/day [37]. The most relevant eye concern in my patient population is cataracts. Patients with schizophrenia have many risk factors for cataracts (e.g., smoking and diabetes), so it is not clear if medications are additional risk factors [38]. The concern that quetiapine causes cataracts (which led to mentioning the need for serial slit-lamp examinations in the package insert) is based on animal studies in Beagles and has not been confirmed in humans. Fraunfelder [39] considers slit exam unnecessary for patients on quetiapine.

Tip

Given the lack of eye care in the population of patients with serious mental illness, it might not be a bad idea to refer your patient for a basic eye examination, as part of caring for them medically [40]. To kill two birds with one stone (reduce your medicolegal liability and provide preventive eye care), I would encourage any patient including those who are going to take quetiapine *long-term* to see an ophthalmologist.

Similar to poor eye care, dental care is often not prioritized, which results in poor dentition in patients with serious mental illness [41]. Poor self-care from negative symptoms does not stop with not taking showers: patients may not brush their teeth regularly, leading to caries and eventually losing teeth and even requiring dentures.

Many patients in my clinic have missing teeth or frequent dental infections from poor oral hygiene, for example. Antipsychotics compound problems with teeth and gums in a variety of ways. Tardive dyskinesia is one obvious mechanism that can damage teeth through mechanical grinding. Changes in salivary flow and saliva composition including pH are a second mechanism that contributes to tooth decay. Antipsychotics that cause sialorrhea (more so than antipsychotics that cause xerostomia) also contribute to periodontal disease [42].

Other Side Effects

Antipsychotics can lower the seizure threshold and increase the risk for seizures, with clozapine having the highest risk, followed by chlorpromazine [43]. In a population-based study from Taiwan, haloperidol had a slightly higher seizure risk and aripiprazole a slightly lower seizure risk when compared to risperidone [44]. The overall seizure risk in this cohort was 9.6 per 1000 person-years (12-month incidence rate). The risk for an antipsychotic-induced seizure increases with dose (or rather, blood level), rapidity of dose escalation, and susceptibility of the brain (e.g., organic brain disease).

Antipsychotics are generally not nephrotoxic, and usually not hematotoxic or hepatotoxic. What this means is that routine blood work to monitor renal function, blood cells, or liver function is usually neither necessary nor done. There are exceptions: clozapine can lead to agranulocytosis (hence the requirement for registry-based prescribing), and many antipsychotics can lead to mild liver function test abnormalities at the start of treatment [45]. Chlorpromazine can be hepatotoxic, with cholestasis the typical finding [46]. Consider fatty liver in patients treated with metabolically high-risk antipsychotics if mild liver function tests abnormalities are detected [47]. More recently, an increased risk of acute kidney injury from second-generation antipsychotics was described in a cohort study of elderly patients [48]. However, any possible risk is probably restricted to older patients who are vulnerable to kidney disease [49]. Consult the package insert to see if an antipsychotic needs to be adjusted in the presence of significant liver or kidney disease.

Mortality From Antipsychotics

I already mentioned earlier that schizophrenia patients have a higher risk of sudden death [26]. In most cases, a sudden and otherwise unexplained death is due to ventricular fibrillation, usually as a consequence of existing coronary artery disease and only rarely due to an arrhythmia in a structurally normal heart [50]. However, the exact cause is often not known, particularly when a patient dies alone. In psychiatric patients treated with antipsychotics who die suddenly, it is often assumed that

antipsychotics contributed directly via triggering an arrhythmia. This assumption may not be correct for the majority of cases. In a consecutive cohort of 100 psychiatric patients with unexplained, sudden deaths, a root cause analysis found no support for the direct role of antipsychotics via QTc prolongation but instead pointed toward acute coronary events and diabetes or dyslipidemia as the main causes of death [51]. Managing hypertension and the metabolic syndrome optimally may be the best way to prevent sudden deaths in psychiatric patients. Many other side anti-psychotic effects can directly cause the death of a patient (e.g., neuroleptic malignant syndrome, seizures, agranulocytosis, myocarditis). Thankfully, those are rare occurrences that mostly can be prevented with careful monitoring. However, always keep in mind that *untreated* patients with schizophrenia have a higher mortality than patients who are treated with antipsychotics [52] (see Chap. 16).

I already noted in Chap. 5 (secondary schizophrenia) that antipsychotics are quite problematic for older patients with dementia-related psychosis: they are neither particularly effective nor safe. All antipsychotics carry a class black-box warning about an increased risk of death in geriatric patients who receive them for dementia-related psychosis, a risk that appears to be a dose-related [53]. The risk for cerebrovascular events, such as a stroke, may also be increased if dementia patients are treated with antipsychotics although this risk may be limited to specific antipsychotics [54]. A risk-benefit assessment might still justify a time-limited antipsychotic trial if no treatment is believed to be even more dangerous and after non-pharmacological interventions have failed [55].

References

1. Nietzsche F. Götzen-Dämmerung, oder, wie man mit dem Hammer philosophirt. Leipzig: C.G. Naumann; 1889.
2. Naber D, Karow A, Lambert M. Subjective well-being under the neuroleptic treatment and its relevance for compliance. Acta Psychiatr Scand Suppl. 2005;111:29–34.
3. Citrome L. Activating and sedating adverse effects of second-generation antipsychotics in the treatment of schizophrenia and major depressive disorder: absolute risk increase and number needed to harm. J Clin Psychopharmacol. 2017;37:138–47.
4. Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry. 1999;156:1686–96.
5. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005;353:1209–23.
6. Buchanan RW, Kreyenbuhl J, Kelly DL, Noel JM, Boggs DL, Fischer BA, et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. Schizophr Bull. 2010;36:71–93.
7. Tek C, Kucukgoncu S, Guloksuz S, Woods SW, Srihari VH, Annamalai A. Antipsychotic-induced weight gain in first-episode psychosis patients: a meta-analysis of differential effects of antipsychotic medications. Early Interv Psychiatry. 2016;10:193–202.
8. Meyer JM, Mao Y, Pikalov A, Cucchiaro J, Loebel A. Weight change during long-term treatment with lurasidone: pooled analysis of studies in patients with schizophrenia. Int Clin Psychopharmacol. 2015;30:342–50.

9. Kane JM, Skuban A, Hobart M, Ouyang J, Weiller E, Weiss C, et al. Overview of short- and long-term tolerability and safety of brexpiprazole in patients with schizophrenia. *Schizophr Res.* 2016;174:93–8.
10. Durgam S, Greenberg WM, Li D, Lu K, Laszlovszky I, Nemeth G, et al. Safety and tolerability of cariprazine in the long-term treatment of schizophrenia: results from a 48-week, single-arm, open-label extension study. *Psychopharmacology.* 2017;234:199–209.
11. McEvoy JP, Meyer JM, Goff DC, Nasrallah HA, Davis SM, Sullivan L, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. *Schizophr Res.* 2005;80:19–32.
12. Henderson DC, Fan X, Sharma B, Copeland PM, Borba CP, Freudenreich O, et al. Waist circumference is the best anthropometric predictor for insulin resistance in nondiabetic patients with schizophrenia treated with clozapine but not olanzapine. *J Psychiatr Pract.* 2009;15:251–61.
13. Nicol GE, Yingling MD, Flavin KS, Schweiger JA, Patterson BW, Schechtman KB, et al. Metabolic effects of antipsychotics on adiposity and insulin sensitivity in youths: a randomized clinical trial. *JAMA Psychiatry.* 2018;75:788–96.
14. Henderson DC, Cagliero E, Copeland PM, Borba CP, Evins E, Hayden D, et al. Glucose metabolism in patients with schizophrenia treated with atypical antipsychotic agents: a frequently sampled intravenous glucose tolerance test and minimal model analysis. *Arch Gen Psychiatry.* 2005;62:19–28.
15. Bak M, Fransen A, Janssen J, van Os J, Drukker M. Almost all antipsychotics result in weight gain: a meta-analysis. *PLoS One.* 2014;9:e94112.
16. Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA.* 2009;302:1765–73.
17. Bostwick JR, Guthrie SK, Ellingrod VL. Antipsychotic-induced hyperprolactinemia. *Pharmacotherapy.* 2009;29:64–73.
18. Ali S, Miller KK, Freudenreich O. Management of psychosis associated with a prolactinoma: case report and review of the literature. *Psychosomatics.* 2010;51:370–6.
19. Naidoo U, Goff DC, Klibanski A. Hyperprolactinemia and bone mineral density: the potential impact of antipsychotic agents. *Psychoneuroendocrinology.* 2003;28(Suppl 2):97–108.
20. De Hert M, Peuskens J, Sabbe T, Mitchell AJ, Stubbs B, Neven P, et al. Relationship between prolactin, breast cancer risk, and antipsychotics in patients with schizophrenia: a critical review. *Acta Psychiatr Scand.* 2016;133:5–22.
21. De Hert M, Detraux J, Stubbs B. Relationship between antipsychotic medication, serum prolactin levels and osteoporosis/osteoporotic fractures in patients with schizophrenia: a critical literature review. *Expert Opin Drug Saf.* 2016;15:809–23.
22. Park YW, Kim Y, Lee JH. Antipsychotic-induced sexual dysfunction and its management. *World J Mens Health.* 2012;30:153–9.
23. Burke MA, McEvoy JP, Ritchie JC. A pilot study of a structured interview addressing sexual function in men with schizophrenia. *Biol Psychiatry.* 1994;35:32–5.
24. Schmidt HM, Hagen M, Kriston L, Soares-Weiser K, Maayan N, Berner MM. Management of sexual dysfunction due to antipsychotic drug therapy. *Cochrane Database Syst Rev.* 2012;11:CD003546.
25. Freudenreich O. Exacerbation of idiopathic priapism with risperidone-citalopram combination. *J Clin Psychiatry.* 2002;63:249–50.
26. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med.* 2009;360:225–35.
27. Beach SR, Celano CM, Sugrue AM, Adams C, Ackerman MJ, Noseworthy PA, et al. QT prolongation, torsades de pointes, and psychotropic medications: a 5-year update. *Psychosomatics.* 2018;59:105–22.
28. Lester RM, Paglialunga S, Johnson IA. QT assessment in early drug development: the long and the short of it. *Int J Mol Sci.* 2019;20:pii: E1324.

29. Miceli JJ, Tensfeldt TG, Shiovitz T, Anziano R, O'Gorman C, Harrigan RH. Effects of oral ziprasidone and oral haloperidol on QTc interval in patients with schizophrenia or schizoaffective disorder. *Pharmacotherapy*. 2010;30:127–35.
30. Doyle M, Rosenthal LJ. Psychotropic medications, associated QTc prolongation, and sudden cardiac death: a review for clinicians. *Psychiatr Ann*. 2013;43:58–65.
31. Strom BL, Eng SM, Faich G, Reynolds RF, D'Agostino RB, Ruskin J, et al. Comparative mortality associated with ziprasidone and olanzapine in real-world use among 18,154 patients with schizophrenia: the Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC). *Am J Psychiatry*. 2011;168:193–201.
32. Stroup TS. What can large simple trials do for psychiatry? *Am J Psychiatry*. 2011;168:117–9.
33. Al-Khatib SM, LaPointe NM, Kramer JM, Califf RM. What clinicians should know about the QT interval. *JAMA*. 2003;289:2120–7.
34. Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MC. QTc interval screening in methadone treatment. *Ann Intern Med*. 2009;150:387–95.
35. Kerwin R. Connecting patient needs with treatment management. *Acta Psychiatr Scand Suppl*. 2009;119:33–9.
36. Schneeweiss S, Avorn J. Antipsychotic agents and sudden cardiac death--how should we manage the risk? *N Engl J Med*. 2009;360:294–6.
37. Richa S, Yazbek JC. Ocular adverse effects of common psychotropic agents: a review. *CNS Drugs*. 2010;24:501–26.
38. Chou PH, Chu CS, Lin CH, Cheng C, Chen YH, Lan TH, et al. Use of atypical antipsychotics and risks of cataract development in patients with schizophrenia: a population-based, nested case-control study. *Schizophr Res*. 2016;174:137–43.
39. Fraunfelder FW. Twice-yearly exams unnecessary for patients taking quetiapine. *Am J Ophthalmol*. 2004;138:870–1.
40. Anthony SA. Focus on eye care in schizophrenia. *Clin Exp Optom*. 2019;102(4):385–93.
41. Yang M, Chen P, He MX, Lu M, Wang HM, Soares JC, et al. Poor oral health in patients with schizophrenia: a systematic review and meta-analysis. *Schizophr Res*. 2018;201:3–9.
42. Eltas A, Kartalcı S, Eltas SD, Dundar S, Uslu MO. An assessment of periodontal health in patients with schizophrenia and taking antipsychotic medication. *Int J Dent Hyg*. 2013;11:78–83.
43. Hedges D, Jeppson K, Whitehead P. Antipsychotic medication and seizures: a review. *Drugs Today*. 2003;39:551–7.
44. Wu CS, Wang SC, Yeh IJ, Liu SK. Comparative risk of seizure with use of first- and second-generation antipsychotics in patients with schizophrenia and mood disorders. *J Clin Psychiatry*. 2016;77:e573–9.
45. Howland RH. Psychotropic medication use: what will it do to my liver? *J Psychosoc Nurs Ment Health Serv*. 2014;52:23–6.
46. Anthierieu S, Bachour-El Azzi P, Dumont J, Abdel-Razzak Z, Guguen-Guilouzo C, Fromenty B, et al. Oxidative stress plays a major role in chlorpromazine-induced cholestasis in human HepaRG cells. *Hepatology*. 2013;57:1518–29.
47. Soliman HM, Wagih HM, Algaidi SA, Hafiz AH. Histological evaluation of the role of atypical antipsychotic drugs in inducing non-alcoholic fatty liver disease in adult male albino rats (light and electron microscopic study). *Folia Biol (Praha)*. 2013;59:173–80.
48. Hwang YJ, Dixon SN, Reiss JP, Wald R, Parikh CR, Gandhi S, et al. Atypical antipsychotic drugs and the risk for acute kidney injury and other adverse outcomes in older adults: a population-based cohort study. *Ann Intern Med*. 2014;161:242–8.
49. Jiang Y, McCombs JS, Park SH. A retrospective cohort study of acute kidney injury risk associated with antipsychotics. *CNS Drugs*. 2017;31:319–26.
50. Priori SG, Aliot E, Blomstrom-Lundqvist C, Bossaert L, Breithardt G, Brugada P, et al. Task Force on sudden cardiac death of the European Society of Cardiology. *Eur Heart J*. 2001;22:1374–450.
51. Manu P, Kane JM, Correll CU. Sudden deaths in psychiatric patients. *J Clin Psychiatry*. 2011;72:936–41.

52. Torniainen M, Mittendorfer-Rutz E, Tanskanen A, Bjorkenstam C, Suvisaari J, Alexanderson K, et al. Antipsychotic treatment and mortality in schizophrenia. *Schizophr Bull.* 2015;41:656–63.
53. Maust DT, Kim HM, Seyfried LS, Chiang C, Kavanagh J, Schneider LS, et al. Antipsychotics, other psychotropics, and the risk of death in patients with dementia: number needed to harm. *JAMA Psychiatry.* 2015;72:438–45.
54. Hsu WT, Esmaily-Fard A, Lai CC, Zala D, Lee SH, Chang SS, et al. Antipsychotics and the risk of cerebrovascular accident: a systematic review and meta-analysis of observational studies. *J Am Med Dir Assoc.* 2017;18:692–9.
55. Stevens JR, Jarrahzadeh T, Brendel RW, Stern TA. Strategies for the prescription of psychotropic drugs with black box warnings. *Psychosomatics.* 2014;55:123–33.
56. Beach SR, Celano CM, Noseworthy PA, Januzzi JL, Huffman JC. QTc prolongation, torsades de pointes, and psychotropic medications. *Psychosomatics.* 2013;54:1–13.

Additional Resources

Article

- Beach SR, Celano CM, Sugrue AM, Adams C, Ackerman MJ, Noseworthy PA, et al. QT prolongation, torsades de pointes, and psychotropic medications: a 5-year update. *Psychosomatics.* 2018;59:105–22. – A colleague of mine from my hospital's CL service has published a seminal review in 2013 of QT prolongation that he updated in 2018. While geared towards medically ill patients seen in the hospital, the review summarizes what is known about QT prolongation and makes pragmatic suggestions how to manage this risk.
- Lester RM, Paglialunga S, Johnson IA. QT assessment in early drug development: the long and the short of it. *Int J Mol Sci.* 2019;20:1324. – More than you ever wanted to know about the QT interval, including its measurement variability.
- Naber D, Moritz S, Lambert M, Pajonk FG, Holzbach R, Mass R, et al. Improvement of schizophrenic patients' subjective well-being under atypical antipsychotic drugs. *Schizophr Res.* 2001;50:79–88. – An article that introduces the idea of “subjective well-being under neuroleptic treatment,” a construct that reminds us of the central importance of a patient's experience with our medications (including side effects).

Chapter 16

Antipsychotics: Clinical Effectiveness



Essential Concepts

- Good clinicians know the clinical trials literature in their area of practice in order to provide evidence-based care wherever possible. Meta-analyses and network meta-analyses are important tools that summarize the evidence base from clinical trials. Guidelines are another source of information that synthesized the literature. You still need clinical judgment to determine how a particular guideline recommendation applies to the patient in front of you.
- Large pragmatic trials such as the seminal Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) have ushered in a new appreciation of antipsychotics, both of what they can achieve and also their limitations.
- Treatment goals directly related to antipsychotics include reducing the symptoms of schizophrenia, increasing quality of life, and preventing iatrogenic morbidity and mortality.
- Antipsychotics are selected based on individualized risk-benefit assessments (balancing psychiatric stability with day-to-day tolerability and long-term medical morbidity, particularly cardiovascular risk). To find the best medication for a patient usually requires sequential trials in a collaborative manner.
- Include long-acting antipsychotics in the list of first-line choices to routinely offer your patients, not only to those who refuse medications.
- Switching antipsychotics to reduce long-term cardiovascular risk can be an appropriate clinical decision, albeit at the risk of psychiatric instability. Both immediate drug discontinuation and gradual discontinuation over several weeks are possible strategies during a switch.
- Knowing how to stop an antipsychotic is as important as knowing how to start one. Antipsychotic discontinuation syndromes are not as well described as SSRI withdrawal.

- Shared decision-making empowers your patient to be an active participant in treatment decisions. However, not all decisions are created equal, and physicians need to differentiate between life-or-death decision, best-choice decisions, and preference-sensitive decision and act accordingly. Coercion is only acceptable in life-or-death decision.
- Quality of life is an independent treatment target that is determined by clinical variables (depression, medication side effects) and unmet needs (financial insecurity, lack of housing, loneliness unemployment).
- Our patients deserve the safest treatment possible. Minimizing iatrogenic morbidity and mortality from our treatments is an important treatment goal.

“Plus ça change, plus c'est la même chose.”

(“The more things change, the more they stay the same.”)

— Alphonse Karr, French critic, journalist, writer, editor of *Les Guêpes* where the epigram was published in 1849 [1]

The previous three chapters introduced the antipsychotics and reviewed their motor and nonmotor side effects. In this chapter, I summarize clinical lessons learned from the last 20 years of clinical antipsychotic trials, particularly regarding their clinical effectiveness and how these lessons inform important clinical decision such as the choice of antipsychotics or switching antipsychotics. “Clinical effectiveness” contrasts with efficacy. You can view efficacy as working under ideal conditions with homogeneous subjects (in a clinical trial), whereas effectiveness is working under real conditions with real patients (in the clinic). Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) was the first effectiveness trial for antipsychotics that enrolled typical clinic patients with as few exclusions as possible [2]. I will describe CATIE in more detail as it became the model for subsequent trials in schizophrenia that try to answer real-world questions and are not mostly conducted for regulatory approval [3].

Evidence-Based Prescribing

The arrival of second-generation antipsychotics (SGAs) in the early 1990s led to great excitement among both patients and psychiatrists. Although this optimism might seem naïve and unbridled today, it is important to remember that psychiatric drug development had made little (some would say no) progress beyond chlorpromazine at that time, even though the limits of dopamine antagonists, both in terms of efficacy and side effects (i.e., tardive dyskinesia), had become painfully clear. SGAs quickly became the treatment of choice. However, almost all data supporting the superiority of SGAs over FGAs (according to the adage, newer must be better) had

come from industry-sponsored drug trials, and some become convinced that the claims of superiority of SGAs were the result of comparing SGAs to what are today considered excessive haloperidol doses [4]. Others found somewhat better efficacy for some (clozapine, olanzapine, and risperidone), but not all SGAs, compared to FGAs, consistent with the heterogeneity of SGAs [5]. Clinicians also started to notice that SGAs (while having a lower risk for tardive dyskinesia) had shifted the side effect burden to metabolic problems.

Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)

To remedy the lack of independent and generalizable data, the National Institute of Mental Health (NIMH) decided to sponsor a large, randomized trial, CATIE, comparing the SGAs available at the time (olanzapine, quetiapine, risperidone; ziprasidone was added after the trial was at about the midway point; aripiprazole as the first third-generation partial dopamine agonist was not yet available) with each other and with a fairly low dose of the mid-potency antipsychotic perphenazine (Phase I). In all, 1493 patients were recruited from more than 50 representative sites in the United States and followed double-blind after randomization for 18 months. The main outcome variable was all-cause discontinuation, a summary measure combining efficacy and tolerability. The focus of CATIE on effectiveness (to understand how a drug performs in real-world settings in all-comers) was rather different than the typical pharmacologic efficacy trial (in which drug effects are studied under ideal conditions in highly selected, homogenous populations). CATIE patients who failed their initially assigned treatment because of lack of efficacy could go on to a second phase that included treatment with clozapine. The main results of Phase I were disappointing: only 26% of subjects completed the trial on their initially assigned antipsychotic, pointing toward major effectiveness problems with available antipsychotics [2]. Moreover, contrary to expectations SGAs were not better than perphenazine, including for cognition [6]. Phase II confirmed the superiority of clozapine over available SGAs [7].

Another effectiveness trial conducted in Europe, CUtLASS 1 (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study), similarly found older FGAs (in particular one not available in the United States, sulpiride) as effective and as well tolerated as SGAs [8]. In the end, the SGAs might not have been the major advance for all patients they were once hoped to be. In one treatment satisfaction survey, however, patients were more satisfied with their psychiatric care if they received more recent antipsychotics [9]. In an effectiveness trial named Neuroleptic Strategy Study or NeSSy that allowed some patient choice regarding their treatment, patient-reported quality of life was higher in patients taking SGAs compared to FGAs [10].

Key Point

Large, simple (practical) trials like CATIE attempt to answer *one* important clinical question by enrolling large numbers of subjects in randomized trials in typical treatment settings. Such trials are often generalizable as opposed to the subjects studied in clinical trials who are often unique and not representative of the world of real medicine (e.g., no substance use allowed).

Clinical Trials Beyond CATIE

Drug development and numerous clinical trials all over the world since CATIE have helped us to solidify our knowledge about antipsychotic efficacy, effectiveness, and side effects. Psychiatry has started to see clinical trials where the outcome variable is a *medical* outcome (metabolic parameter) in order to determine how to best address iatrogenic morbidity from antipsychotics [11, 12]. Such trials are going to become increasingly important, just as trials that use quality of life as an important patient-centered outcome measure are becoming more standard in psychiatry (see below). Summarizing the literature and my own involvement in clinical trials over the past 20 years, I can draw several broad conclusions for clinicians that are summarized in Table 16.1.

In addition to an explosion of the sheer number of clinical trials as psychiatry has become a truly international endeavor, major advances in our knowledge in the past 20 years have increasingly used the tool of meta-analyses and, more recently, network meta-analyses (“meta-analyses of meta-analyses”) [14]. Meta-analyses allow for the compilation of similar small trials to increase the power to detect a treatment effect. Network meta-analyses (or multiple treatment meta-analyses) go one step further and allow for the comparison of medications even if they were never directly tested against each other in any of the trials included in the analysis [15]. The resulting evidence is quite indirect, and no statistical maneuver can substitute for a well-conducted clinical trial of enough power that directly answers a specific clinical question. Meta-analyses provide you with a quick summary of the clinical trial literature but provide no guidance how the findings apply to your practice, if at all.

Let me add one comment about clinical psychopharmacology and evidence-based psychiatry. It is sometimes claimed that we know “nothing” in psychiatry since we do not know the pathophysiology of our illnesses. When it comes to clinical psychopharmacology, however, this is simply untrue (see above). I believe it is intellectual laziness to not know the clinical trials literature in your area of prescribing (see Table 16.2), including the gaps in our knowledge where no clinical trials were ever done. Almost more important, clinicians ought to know the trials that *were* actually conducted, including negative trials that refute a particular treatment (e.g., gabapentin was shown that it is very safe but unfortunately completely ineffective for bipolar disorder). It is true that there are many unanswered questions where randomized clinical trials (often considered the gold standard) have never

Table 16.1 Lessons from clinical antipsychotic trials

All antipsychotics have limitations in the real world with regard to efficacy, tolerability, or both; this leaves many patients unwilling to take them in the long run. It has been disappointing that drug development has failed to meet the unmet need with a medication for negative symptoms or cognition

Type and severity of side effects differ between all antipsychotics, particularly between second- and third-generation antipsychotics; they should therefore not be regarded as one class, and patients should have access to all of them to individualize their treatment since no single antipsychotic is optimal for all, or even most, patients [13]

Olanzapine and clozapine are the most effective antipsychotics but also the antipsychotics with the highest risk for metabolic side effects. Both continue to be needed, particularly clozapine which remains the only antipsychotic with efficacy in treatment-resistant schizophrenia (see Chap. 12)

Managing long-term metabolic side effects has become a key concern with second-generation antipsychotics. Switching antipsychotics to metabolically lower-risk antipsychotics [12] or adding metformin [11] has become a standard intervention to reduce iatrogenic cardiovascular risk (see Chap. 25)

Tardive dyskinesia (TD) has not disappeared albeit the risk with newer antipsychotics is lower. New treatments (VMAT-2 inhibitors) offer a better treatment option for patients with TD (see Chap. 14)

Preventing schizophrenia by intervening early (during the prodromal phase) has become an area of intense interest although no medication has been shown to alter the long-term trajectory of beginning schizophrenia. The optimal pharmacological management in first-episode patients has been characterized, particularly the importance of preventing a second episode of psychosis (see Chap. 11)

The mode of antipsychotic administration matters since potentially effective antipsychotics have no clinical effectiveness if not taken. Long-acting injectable antipsychotics have emerged as an important treatment tool for all patients (see Chap. 18)

Table 16.2 Treatment goals for schizophrenia

Domain	Treatment goal
Symptoms ^a	Sustained remission
Function	Optimal role function
Quality of life ^a	Comfortable life despite illness and treatment burden
Meaning	Purposeful life in society despite illness
Mortality ^a	Life expectancy of general population

^aDirectly influenced by antipsychotics

been conducted or where they were inclusive. “Evidence-based psychiatry,” however, is not limited to randomized clinical trials, particularly since psychiatric disorders are not homogeneous disease entities where a precise intervention changes prognosis [16]. Withholding treatment purely for lack of randomized clinical trials (a common reason by insurance companies to deny paying for treatment), as if there were no other evidence and as if we had solved problems of epistemology in psychiatry, should be considered unethical.

Tip

Good treatment guidelines summarize the literature based on the strength of the evidence and provide guidance for specific clinical questions. Guidelines differ depending on their purpose, but they represent one attempt to synthesize knowledge [17]. Know guideline recommendations, and follow them for most patients; know why you deviate from them when it becomes necessary for the individual patient in front of you. Several schizophrenia guidelines are listed in the additional resources.

Schizophrenia Treatment Goals

Conceptually, it helps to break down treatment goals into different domains as shown in Table 16.2. Antipsychotics directly influence three of the five treatment goals. First, they are necessary to achieve sustained symptomatic remission as the basis for functional recovery and reintegration into society. Second, antipsychotics contribute to increased quality of life (reduction of distressing symptoms) while at the same time reducing it (side effect burden). Last, antipsychotics reduce mortality from untreated illness while also adding the potential for iatrogenic morbidity and mortality.

Key Point

A psychiatric treatment plan needs to balance symptom control, quality of life, and patient safety. Quality of life may be more important than trying to “eradicate” symptoms. Selecting a safer medication may require a change in treatment.

Practical Considerations

Clinicians have three basic tasks when it comes to antipsychotic medications: they need to select an antipsychotic to start treatment, they need to switch to a different antipsychotic if there is no response or poor tolerability, or they need to discontinue antipsychotics. Augmenting antipsychotics is discussed in Chap. 19, and managing side effects without switching or discontinuing the antipsychotic in the previous two chapters.

Selecting Antipsychotics

Individual patients show marked differences in their clinical response and tolerability to any given antipsychotic. Because you cannot predict which medication is going to show the best benefit-risk ration for individual patients, you will have to do

sequential trials to empirically figure this out in collaboration with your patients. As noted in Chap. 20, pharmacogenetic testing is of limited value for antipsychotic selection. The side effect profile can help narrow your initial choices, based on patient preference; for example, for a patient who sleeps poorly, you might consider offering a more sedating antipsychotic first. For some patients, you can take into account personal or family medical history; for example, for an overweight patient with a family history of diabetes, ziprasidone would be one logical first choice. For others, the preference of avoiding a particular side effect (e.g., any degree of possible weight gain) weighs heavily for or against a particular drug. In one population-based study, oral aripiprazole (together with long-acting second-generation antipsychotics) showed the best reduction in mortality compared to no treatment [18] for those patients interested in mortality reduction.

Key Point

For many patients, the best (i.e., most effective) long-term antipsychotic will represent a compromise between efficacy and tolerability. The only way of tailoring your antipsychotic treatment to your patient is by trial and error in the form of sequential trials.

Other, important variables that will influence your choice of medication and dose are the following:

- Age – Children/adolescents and elderly patients require different antipsychotic doses. Children/adolescents are not little adults, and dosing needs to take into account stage and type of brain development (“neurotypical or neuroatypical”) in addition to high variability in metabolism. Antipsychotic dosing should start at the low end of the dose range, but due to the potential for increased liver metabolism in some youth, doses approximating what is given to adults may be needed. Children and adolescents are sensitive to side effects, including sedation, extrapyramidal symptoms, and weight gain [19]. Geriatric patients may only require or tolerate very low doses. Other than biological age, take into account the frailty of the elderly patient. The tardive dyskinesia risk increases with age [20].
- Gender – Female patients pose additional problems with family planning and side effects related to the reproductive system. Prolactin-elevating antipsychotics interfere with fertility and would need to be switched if pregnancy is a desired goal. Antipsychotic doses can generally be lower in female patients, particularly in premenopausal women [21]. Always remember that all women of childbearing age are potential new mothers [22].
- Ethnicity – Optimal antipsychotic doses might vary with ethnicity, in part from genetically determined differences in metabolism. As a rule of thumb, it is recommended to use a 20% lower antipsychotic dose for patients from East Asian countries (I am aware that this is a large and diverse region), compared to Caucasians [23].

In patients who sabotage their own treatment and rehabilitation with frequent relapses due to nonadherence to antipsychotics, the mode of administration becomes

as important as other considerations. I always include a long-acting antipsychotic as an excellent choice for all patients, given the chronic nature of the disease and the need for ongoing maintenance treatment with antipsychotics. If presented as one of the choices at the beginning of treatment, it becomes an easier sell when you become concerned about partial adherence (see Chap. 18 on long-acting antipsychotics for more).

Tip

The mode of administration matters greatly. Routinely offer long-acting antipsychotic to all patients including first-episode patients. This is not only an excellent clinical option but avoids the idea of getting punished with “a shot” if the patients “fails” oral medications.

Switching Antipsychotics

Switching antipsychotics should come up regularly in the outpatient setting, as the typical patient is burdened with side effects from only partially effective medications. Many questions about switching are judgment calls with no obviously right or wrong answer: what symptom level should trigger a switch? Should you switch for nonpsychotic symptoms (negative or cognitive symptoms)? Should you switch elderly patients who have missed the atypical revolution because of the possibility of tardive dyskinesia? Should you switch because of increased HbA1c? The decision is difficult, and risk-benefit discussions should involve all parties affected by the switch, which is often not just the patient but also family members or direct care providers in a group home as well.

Key Point

Switching antipsychotics on the outpatient side is rarely an emergency, and preparing a switch is time well spent. “Failed switches” are often the result of insufficient preparation and lack of buy-in by all parties involved.

Whenever possible, optimize the current antipsychotic first (e.g., ensure maximal compliance and optimal dosage, therapeutic drug monitoring) before switching. There is risk in any switch as seen in CATIE which was fundamentally a switch study. In the CATIE sample (of treatment-experienced, chronic patients), those who did not switch (i.e., they were randomly assigned to the same antipsychotic they had entered the trial on) fared somewhat better than those who were assigned to switch [24]. However, a switch is often quite possible, as seen in another switch study called CAMP (Comparison of Antipsychotics for Metabolic Problems) where patients were switched from olanzapine, quetiapine, or risperidone to the metaboli-

cally safer aripiprazole [12]. While patients assigned to stay on their original anti-psychotic had fewer treatment discontinuations, many patients also switched successfully.

These are common outpatient reasons for switching antipsychotics:

- Switching because of ongoing, residual positive symptoms, particularly if they are distressing or if they interfere with day-to-day functioning
- Switching because of secondary negative symptoms (including sedation)
- Switching because of distressing side effects that decrease quality of life (e.g., akathisia)
- Switching to a metabolically lower-risk antipsychotic because of concerns about long-term medical morbidity (i.e., weight gain, diabetes, dyslipidemia) (see Chap. 25)
- Switching because of tardive dyskinesia (see Chap. 14)
- Switching to a long-acting injectable antipsychotic because of nonadherence (see Chap. 18)
- Switching to clozapine because of treatment-resistant schizophrenia (see Chap. 17)
- Switching for administrative reasons (e.g., antipsychotic not covered by insurance)

The question of switching to “the new medication” comes up invariably when a new antipsychotic enters the market. Help patients understand that medications (or medication switches) are at best part of the solution. In some patients you encounter the opposite problem. Even though you think a switch makes sense because of lack of efficacy, the family or group home does not want to rock the boat, due to fears that “things could be worse.”

Tip

The question to ask about a newly approved drug is not how it is better but rather how it is different. Do not promise a cure but suggest that improvement in overall well-being without complete freedom from symptoms is probably a more realistic goal. Switching to reduce cardiovascular risk factors (as opposed to switching for psychiatric efficacy) has become an important strategy. However, do not sacrifice psychiatric stability on the altar of metabolic safety. There is no health without mental health!

The mechanics of switching are uncomplicated (and are often made more complicated than necessary), with the most conservative approach being never to leave patients uncovered (i.e., always make sure a patient is dopamine blocked) during a cross-titration to avoid acute withdrawal phenomena, including withdrawal psychosis (see also below). As a general approach, I leave the old antipsychotic aboard at full dose, initiate the new antipsychotic and titrate it to its full therapeutic target dose quickly, overlap for 2 weeks, and only then start tapering the old antipsychotic. Modify this schema based on individual tolerability to try to get the crossover done

in 1 month and to minimize environmental interference that could lead to clinical instability which will then erroneously be attributed to the switch. Some antipsychotics, particularly the third-generation antipsychotics, have a very long half-life, representing a built-in taper if stopped. Also, keep it simple to minimize room for medication error, and persist in switching over even if there is apparent improvement halfway through (to avoid the stalled-taper phenomenon). The literature does not suggest that gradual discontinuation over several weeks as part of a switch is even necessary in most patients. Immediate discontinuation of the old antipsychotic which limits the possibility of synergistic side effects does not appear have a higher risk of symptom exacerbation or other withdrawal effects [25]. Immediate discontinuation is also a feasible strategy when moving to clozapine [26]. Use clinical judgment, and include patient preference to decide on the best strategy.

Clinical Vignette

A patient whom I “inherited” had been clinically stable on olanzapine for many years, without psychosis, and had not required hospitalizations. Because he had developed the metabolic syndrome, the patient and his family, at the urging of the primary care physician, wanted his olanzapine switched to ziprasidone, a reasonable clinical decision, particularly because behavioral measures were unsuccessful in improving his health. Unfortunately, he became psychotic 1 month after the switch and required several hospitalizations over the course of 6 months, eventually stabilizing on olanzapine again.

While switching is often unproblematic, some patients do poorly because they are taken off a medication that worked best *for them*. Think of what clinicians do as an example of personalized medicine. Patients often had sequential antipsychotic trials ($N = 1$), conducted over years that, through trial-and-error established the best antipsychotic for this patient.

Since relapse during a switch is a real risk even in patients who have been asymptomatic for many years, always discuss the risks, benefits, and alternatives (including no change) of any switch. A switch is rarely an emergency and you have time to get everybody aboard before the switch (unless you want to get the blame for a failed switch, “You never told us he could end up in the hospital again.”). Recall that the psychotic relapse risk remains constant and does not decrease with time: even a decade of stability does not ensure a relapse-free switch [27]. This is not intuitive and requires psychoeducation. Relapse is discussed in more detail in Chap. 9.

Discontinuing Antipsychotics

Psychiatrists should have as much knowledge about stopping antipsychotics as about starting them. We often emphasize starting medication but de-emphasize the second. There are two clinical scenarios:

1. A patient needs to be off an antipsychotic for medical reasons or wants to be off by his or her choice.
2. A patient should be off an antipsychotic.(See Chap. 21.)

Unfortunately, as opposed to well-described withdrawal syndromes with antidepressants (SSRI withdrawal or discontinuation syndrome), antipsychotic withdrawal has not received much attention. No specific antipsychotic discontinuation syndrome has been delineated. In one survey of patients who stopped taking their medications, the majority reported a wide range of non-specific somatic and psychological symptoms [28]. Some problems can be anticipated: if you remove a sedating antipsychotic, a patient may have trouble sleeping (even if the sedation was merely the signal that triggered sleep). In most instances, however, stopping antipsychotics appears to be unproblematic and can usually be done quickly, within a couple of weeks. There is one exception: clozapine can cause gastrointestinal problems and a severe withdrawal delirium and psychosis when it is stopped abruptly, due in part to cholinergic rebound [29]. Consider adding an anticholinergic medication or an antipsychotic that is anticholinergic (like chlorpromazine) if clozapine needs to be stopped abruptly. Withdrawal catatonia is another recognized complication [30]. For all other antipsychotics, the best described complications are withdrawal (emergent) dyskinesias, occurring in 10–20% of patients [31]. In patients with suppressed tardive dyskinesia (TD), you can see worsening of TD.

However, long-standing concerns about supersensitivity psychosis (rebound psychosis due to previous dopamine blockade), the nonmotor pendant of the aforementioned withdrawal dyskinesias, remain unresolved [32]. If you accept the supersensitivity psychosis as an entity, a very slow reduction in antipsychotic dose would logically be necessary to avoid psychosis simply due to the withdrawal from dopamine blockade (as opposed to the spontaneous relapse from being untreated). Antipsychotic reduction and discontinuation, including the rapidity of dose changes, is an important area for future research, particularly as the best long-term treatment for some patients with schizophrenia may not require lifelong antipsychotics.

Tip

Patients will be more comfortable stopping a medication if you propose time-limited trials and if you introduce the idea of stopping *when you start*. This discussion is easier if the antipsychotic does not seem critical (e.g., if used for augmentation) or when you are merely switching between antipsychotics. For first-episode patients who want to stop their antipsychotic after clinical recovery, see Chap. 11.

Shared Decision-Making

Shared decision-making is an attempt to overcome the asymmetry in the patient-doctor relationship and increase patient autonomy. While shared decision-making is not limited to antipsychotic prescribing, discussions about medications exemplify

the spirit of it. Since *informed* consent is the basis for prescribing, patients should be truly informed if we respect their autonomy. I believe our informed consent discussions are often pro forma. Just consider these two questions: when discussing tardive dyskinesia, do you show patients a video of a patient with moderate TD? Is your organization giving you the resources (information materials appropriate for your patients or, the most important one, time) to do shared decision-making well?

Tip

For all medications, discuss their “risks, benefits, alternatives, including no treatment.” This does not mean to tell everything which amounts to providing no information at all (comparable to the incomprehensible contracts that you sign when you rent a car). The trick is to provide enough information in a way that a patient can understand to make his or her own, truly informed decision. Know when less is more. Information can also be provided over time. A risk-benefit analysis includes not just side effects (of which there are many) but also an emphatic emphasis on the benefits [33]. Do not forget to list them!

Shared decision is often misunderstood as providing the information and then letting the patient choose. However, not all decisions are created equal, and physician passivity only applies to decision where all choices are equally reasonable except that patients may prefer one choice over another (e.g., choosing an antipsychotic based on side effect profile). A helpful scheme differentiates between three scenarios where clinicians are more or less directive or nudging (see Table 16.3). It is quite important to make sure to not confuse these categories, particularly resorting to coercive measures because a patient rejects a best-choice decision.

Shared decision-making requires communication and negotiation skills [35]. Motivational interviewing includes techniques that can be helpfully employed in nudging a patient toward a best-choice decision. Perhaps psychiatry can also learn from the hospitality industry and work toward increasing patient satisfaction. You may want to be more critical about the “product” we offer and reflect on why patients reject our medications.

Ultimately, shared decision-making is an attitude. Be honest: do you want to let your patient chose? If your answer is yes, empower patients who have been socialized to be passive and invite them to be a more active participant in treatment decisions. You, however, need to be able to then tolerate what you believe to be a poor choice without escalating to more directive measures. This is asking a lot as

Table 16.3 Shared decision-making

Type of decision	Physician stance
1. Life or death	Directive, including coercive as only one outcome is acceptable ^a
2. Best choice	Active, “nudging” as one outcome is best and clearly preferred
3. Preference sensitive	Indifferent to outcome as all outcomes are equally acceptable

Based on [34]

^aMake sure that a best-choice decision does not become a life-or-death decision because it is easier

you undoubtedly will feel pressure (medicolegal liability) from a society increasingly unable to tolerate any risk, curtailing our patients' freedom to make poor choices in the process [36].

Quality of Life

Compared to healthy controls, patients with schizophrenia report lower quality of life across a wide range of domains [37]. While a patient's life satisfaction or subjective quality of life (QOL) is often related to psychiatric symptoms and real-world functioning, improving QOL can be viewed as a third goal of treatment *in its own right*, regardless of symptoms and function which are often seen as the two main psychiatric treatment targets [38]. Some patients may not require much vis-à-vis improvements in their quality of life. In the CATIE sample of chronic patients with schizophrenia, about 50% were generally satisfied with their lives despite ongoing symptoms and poor function [39]. In clinical trials for chronic conditions, QOL is increasingly used as a primary outcome variable and not as a mere afterthought. Among other variables (see below), QOL is influenced by both efficacy and side effects which matters more to patients than a mere reduction in positive symptoms. The CUTLASS trial [8] and the RAISE trial [40] are examples from psychiatry.

Comprehensive definitions of QOL include subjective and objective aspects [41]. The subjective component is sometimes equated with "life satisfaction," "well-being," or even "happiness." Objective markers include cultural expectations about what constitutes a good life, including financial security and in contemporary Western societies an emphasis on societal "function." How a patient rates his or her QOL depends on clinical variables (pain, depression, medication side effects) and perceived unmet needs (loneliness, housing, work) (see Table 8.4 in the Chap. 8 on diagnostic assessment). Depression is the most important clinical determinant of poor QOL that you may be able to directly address with psychiatric treatment. In medicine, QOL is intimately tight to medication side effects. Patients may forgo lifesaving cancer treatment if they believe that the treatment robs them of a good quality of life. Long-term well-being while taking antipsychotic medications is thus a critical consideration for patients with schizophrenia. Poor adherence can often be traced back to poor medication tolerability but also to lack of efficacy with regard to unmet needs like having housing or a job. Internalized societal expectations can lead to poor subjective quality of life when patients cannot carve out a life that is meaningful *to them*.

Morbidity and Mortality

Preventing psychiatric mortality with treatment ("treatment as prevention") while avoiding iatrogenic morbidity and mortality is an important balance to strike. This critically important topic is discussed in its own Chap. 25.

Key Point

Careful attention to iatrogenic contributions to morbidity and mortality from antipsychotic medications is a key consideration for safe antipsychotic prescribing. Guideline-concordant monitoring needs to be implemented (see Table 25.2 in Chap. 25).

References

1. Wiktionary. Plus ça change, plus c'est la même chose. Available from: https://en.wiktionary.org/wiki/plus_%C3%A7a_change,_plus_c%27est_la_m%C3%Aame_chose. Accessed on 7/1/2019.
2. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med.* 2005;353:1209–23.
3. Stroup TS, Alves WM, Hamer RM, Lieberman JA. Clinical trials for antipsychotic drugs: design conventions, dilemmas and innovations. *Nat Rev Drug Discov.* 2006;5:133–46.
4. Geddes J, Freemantle N, Harrison P, Bebbington P. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. *BMJ.* 2000;321:1371–6.
5. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. *Arch Gen Psychiatry.* 2003;60:553–64.
6. Keefe RS, Bilder RM, Davis SM, Harvey PD, Palmer BW, Gold JM, et al. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. *Arch Gen Psychiatry.* 2007;64:633–47.
7. McEvoy JP, Lieberman JA, Stroup TS, Davis SM, Meltzer HY, Rosenheck RA, et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry.* 2006;163:600–10.
8. Jones PB, Barnes TR, Davies L, Dunn G, Lloyd H, Hayhurst KP, et al. Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: cost utility of the latest antipsychotic drugs in schizophrenia study (CUtLASS 1). *Arch Gen Psychiatry.* 2006;63:1079–87.
9. Nordon C, Rouillon F, Barry C, Gasquet I, Falissard B. Determinants of treatment satisfaction of schizophrenia patients: results from the ESPASS study. *Schizophr Res.* 2012;139:211–7.
10. Grunder G, Heinze M, Cordes J, Muhlbauer B, Juckel G, Schulz C, et al. Effects of first-generation antipsychotics versus second-generation antipsychotics on quality of life in schizophrenia: a double-blind, randomised study. *Lancet Psychiatry.* 2016;3:717–29.
11. Jarskog LF, Hamer RM, Catellier DJ, Stewart DD, Lavange L, Ray N, et al. Metformin for weight loss and metabolic control in overweight outpatients with schizophrenia and schizoaffective disorder. *Am J Psychiatry.* 2013;170:1032–40.
12. Stroup TS, McEvoy JP, Ring KD, Hamer RH, LaVange LM, Swartz MS, et al. A randomized trial examining the effectiveness of switching from olanzapine, quetiapine, or risperidone to aripiprazole to reduce metabolic risk: comparison of antipsychotics for metabolic problems (CAMP). *Am J Psychiatry.* 2011;168:947–56.
13. Leucht S, Cipriani A, Spinelli L, Mavridis D, Orey D, Richter F, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet.* 2013;382:951–62.
14. Fleischhacker WW. A meta view on meta-analyses. *JAMA Psychiatry.* 2017;74:684–5.

15. Mills EJ, Ioannidis JP, Thorlund K, Schunemann HJ, Puhan MA, Guyatt GH. How to use an article reporting a multiple treatment comparison meta-analysis. *JAMA*. 2012;308:1246–53.
16. Gupta M. Does evidence-based medicine apply to psychiatry? *Theor Med Bioeth*. 2007;28:103–20.
17. Moore TA. Schizophrenia treatment guidelines in the United States. *Clin Schizophr Relat Psychoses*. 2011;5:40–9.
18. Taipale H, Mittendorfer-Rutz E, Alexanderson K, Majak M, Mehtala J, Hoti F, et al. Antipsychotics and mortality in a nationwide cohort of 29,823 patients with schizophrenia. *Schizophr Res*. 2018;197:274–80.
19. Krause M, Zhu Y, Huhn M, Schneider-Thoma J, Bighelli I, Chaimani A, et al. Efficacy, acceptability, and tolerability of antipsychotics in children and adolescents with schizophrenia: a network meta-analysis. *Eur Neuropsychopharmacol*. 2018;28:659–74.
20. Jeste DV, Caligiuri MP, Paulsen JS, Heaton RK, Lacro JP, Harris MJ, et al. Risk of tardive dyskinesia in older patients. A prospective longitudinal study of 266 outpatients. *Arch Gen Psychiatry*. 1995;52:756–65.
21. Seeman MV. Gender differences in the prescribing of antipsychotic drugs. *Am J Psychiatry*. 2004;161:1324–33.
22. Seeman MV. Clinical interventions for women with schizophrenia: pregnancy. *Acta Psychiatr Scand*. 2013;127:12–22.
23. Gardner DM, Murphy AL, O'Donnell H, Centorrino F, Baldessarini RJ. International consensus study of antipsychotic dosing. *Am J Psychiatry*. 2010;167:686–93.
24. Essock SM, Covell NH, Davis SM, Stroup TS, Rosenheck RA, Lieberman JA. Effectiveness of switching antipsychotic medications. *Am J Psychiatry*. 2006;163:2090–5.
25. Takeuchi H, Kantor N, Uchida H, Suzuki T, Remington G. Immediate vs gradual discontinuation in antipsychotic switching: a systematic review and meta-analysis. *Schizophr Bull*. 2017;43:862–71.
26. Takeuchi H, Lee J, Fervaha G, Foussias G, Agid O, Remington G. Switching to clozapine using immediate versus gradual antipsychotic discontinuation: a pilot, double-blind, randomized controlled trial. *J Clin Psychiatry*. 2017;78:223–8.
27. Leucht S, Tardy M, Komossa K, Heres S, Kissling W, Salanti G, et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *Lancet*. 2012;379:2063–71.
28. Salomon C, Hamilton B, Elsom S. Experiencing antipsychotic discontinuation: results from a survey of Australian consumers. *J Psychiatr Ment Health Nurs*. 2014;21:917–23.
29. Shiovitz TM, Welke TL, Tighe PD, Anand R, Hartman RD, Sramek JJ, et al. Cholinergic rebound and rapid onset psychosis following abrupt clozapine withdrawal. *Schizophr Bull*. 1996;22:591–5.
30. Boazak M, Cotes RO, Potvin H, Decker AM, Schwartz AC. Catatonia due to clozapine withdrawal: a case report and literature review. *Psychosomatics*. 2019;60(4):421–7.
31. Chouinard G, Chouinard VA. Atypical antipsychotics: CATIE study, drug-induced movement disorder and resulting iatrogenic psychiatric-like symptoms, supersensitivity rebound psychosis and withdrawal discontinuation syndromes. *Psychother Psychosom*. 2008;77:69–77.
32. Chouinard G, Samaha AN, Chouinard VA, Peretti CS, Kanahara N, Takase M, et al. Antipsychotic-induced dopamine supersensitivity psychosis: pharmacology, criteria, and therapy. *Psychother Psychosom*. 2017;86:189–219.
33. Correll CU, Rubio JM, Kane JM. What is the risk-benefit ratio of long-term antipsychotic treatment in people with schizophrenia? *World Psychiatry*. 2018;17:149–60.
34. Hamann J, Heres S. Adapting shared decision making for individuals with severe mental illness. *Psychiatr Serv*. 2014;65:1483–6.
35. Beitinger R, Kissling W, Hamann J. Trends and perspectives of shared decision-making in schizophrenia and related disorders. *Curr Opin Psychiatry*. 2014;27:222–9.
36. Ekberg M. The parameters of the risk society: a review and exploration. *Curr Sociol*. 2007;55:343–66.

37. Dong M, Lu L, Zhang L, Zhang YS, Ng CH, Ungvari GS, et al. Quality of life in schizophrenia: a meta-analysis of comparative studies. In: Psychiatr Q, vol. 90; 2019. p. 519–32.
38. Valiente C, Espinosa R, Trucharte A, Nieto J, Martinez-Prado L. The challenge of well-being and quality of life: a meta-analysis of psychological interventions in schizophrenia. Schizophr Res. 2019;208:16–24.
39. Fervaha G, Agid O, Takeuchi H, Foussias G, Remington G. Life satisfaction among individuals with schizophrenia in the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) study. Am J Psychiatry. 2013;170:1061–2.
40. Kane JM, Robinson DG, Schooler NR, Mueser KT, Penn DL, Rosenheck RA, et al. Comprehensive versus usual community care for first-episode psychosis: 2-year outcomes from the NIMH RAISE Early Treatment Program. Am J Psychiatry. 2016;173:362–72.
41. Fleury MJ, Grenier G, Bamvita JM, Tremblay J, Schmitz N, Caron J. Predictors of quality of life in a longitudinal study of users with severe mental disorders. Health Qual Life Outcomes. 2013;11:92.

Additional Resources

Web Site

<https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines> – The link to the practice guidelines for the American Psychiatric Association, including the updated schizophrenia guideline.

<https://www.nice.org.uk/guidance> – The link to NICE guidance, including various guidelines related to schizophrenia care. NICE which stands for National Institute for Health and Care Excellence is an independent organization in the UK that was established in 1999 to provide unbiased summaries of the literature to guide clinicians but also systems regarding healthcare funding. So-called NICE recommendations are often considered authoritative. Incidentally, their first clinical guideline was the schizophrenia guideline.

Article

Remington G, Addington D, Honer W, Ismail Z, Raedler T, Teehan M. Guidelines for the pharmacotherapy of schizophrenia in adults. Can J Psychiatry. 2017;62:604–16. – A very well organized and readable guideline from our colleagues and neighbors in Canada.

Chapter 17

Clozapine



Essential Points

- Clozapine is a broad-spectrum antipsychotics with course-stabilizing properties. It is our most effective antipsychotic that works in many patients (around 50% of chronic patients, almost 75% in first-episode patients) who are treatment resistant to first-line antipsychotics.
- Clozapine should be used early (as soon as treatment resistance has been established which may be during the first psychotic episode) in the course of schizophrenia and not be relegated to third-line status.
- Clinical indications for clozapine are not limited to the two FDA indications (treatment-resistant schizophrenia and suicidality in patients with psychosis). Patients who are sensitive to extrapyramidal symptoms are an important third group of patients who may benefit from clozapine (clozapine is “atypical” in not causing EPS). Other, less established, indications include aggression and substance use.
- The agranulocytosis risk (0.8%) is managed by registry-based prescribing. All patients need to be registered with the Clozapine REMS Program that stipulates the frequency of neutrophil monitoring. In the United States, monitoring is mandated as long as a patient is on clozapine.
- Clozapine is metabolized partly by cytochrome P450 1A2 which is an enzyme inducible by smoking. Smokers may require a higher clozapine dose as outpatients when they resume smoking after leaving the hospital.
- Therapeutic drug monitoring (TDM) is well-established for clozapine. TDM should be routinely used to avoid toxic drug levels (increase in seizure risk) and subtherapeutic blood levels. A blood level of at least 450 ng/mL is necessary in patients who show no response.
- Clozapine carries five black box warnings: agranulocytosis, myocarditis, seizures (which are dose related), orthostatic hypotension with syncope

and cardiorespiratory arrest, and increased mortality in elderly patients with dementia-related psychosis (class warning for all antipsychotics).

- Myocarditis is a side effect unusual for antipsychotics. Its risk is highest in the first month of treatment and requires a high index of suspicion (malaise, palpitations, chest pain).
- Constipation is very common and more than a nuisance side effect since it can lead to bowel obstruction. Constipation needs to be monitored and actively managed.
- The long-term medical management of clozapine is mainly focused on its metabolic problems (weight gain and diabetes) that require monitoring and proactive management.
- Clozapine augmentation strategies with medications to improve psychopathology are unimpressive. Consider, however, adding aripiprazole to blunt weight gain and reverses metabolic abnormalities associated with clozapine use.

“Per aspera ad astra.”
(Through hardship to the stars.)

Clozapine is psychiatry’s specialty drug, and it is our most effective but also our most difficult to use antipsychotic. Because of its importance, I dedicate a whole chapter to it, to have information about clozapine all in one place. Every psychiatrist who treats patients with psychosis needs to be able to prescribe clozapine. While more difficult to use than other antipsychotics, clozapine’s benefits are quite rewarding, as the Latin epigraph succinctly says. Clozapine may save a patient’s life – literally (reducing mortality from untreated or poorly treated illness [1]) and figuratively (allowing patients to pursue their life goals in the community as a result of clozapine’s illness course-stabilizing properties [2]). In our own hospital, we have a mandatory rotation in a clozapine clinic to prepare younger colleagues in the competent use of clozapine [3]. My teaching points from this clozapine rotation are the basis for this chapter. Establishing treatment-resistant schizophrenia which in most cases (including in first-episode patients) is the reason for a clozapine trial is discussed in detail in Chap. 12.

History

Clozapine’s unique “atypical” properties (i.e., antipsychotic efficacy without neurolepsis in animal models) were recognized already in the 1950s, but it was taken off the market in the 1970s after a series of deaths from agranulocytosis in Finland [4]. A handful of committed psychiatrists and pharmacologists from Sandoz AG (now

Novartis, after a merger with Ciba-Geigy in 1996) conducted a seminal clinical trial (see below) that convinced the FDA to reintroduce clozapine for refractory schizophrenia in 1990, albeit with the safeguard of mandatory registry-based prescribing to mitigate the risk of dying from agranulocytosis. Clozapine's side effects and administrative burden due to the registry lead too many patients and psychiatrists to forgo a clozapine trial. This is tragic: I cannot emphasize enough that clozapine can be life-saving and life-altering for patients who need it and that all psychiatrists ought to be able to offer it when indicated [3]. It should not be relegated to third-line status, but patients should receive it as early as needed for one of its clinical indications (which usually but not exclusively is treatment resistance [5]). Organizing care around a clozapine clinic may offer one solution to the ongoing low-prescribing rates of clozapine [6].

Efficacy for Refractory Psychosis

Clozapine is the most effective intervention for psychosis (other than ECT) that we have in our armamentarium. In the seminal study by Kane and colleagues [7], clozapine led to some improvement in 30% of patients who were prospectively treated with at least two antipsychotics (at the time, first-generation antipsychotics) and judged refractory. The superiority of clozapine has since been confirmed in several other trials, including in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) cohort which included patients who had failed second-generation antipsychotics [8]. In younger, first-episode patients, up to 75% may benefit from a switch to clozapine [9]. In more chronic populations, fewer patients will benefit, probably about 50% [10]. At least two meta-analyses [11, 12] confirm the clinical impression that clozapine is a different drug that can be helpful for those patients who respond poorly to other antipsychotics. One analysis estimated that 40% of patients have a clinically meaningful response to clozapine, with an average symptom reduction of 25% [13]. I suspect that part of its effectiveness is not based on pharmacology alone but stems from the need to provide good psychiatric care, with close and regular clinical follow-up of patients.

Indications

Clozapine can be considered a broad-spectrum antipsychotic with course-stabilizing properties. It is clearly indicated for patients who are treatment refractory to first-line antipsychotics in order to prevent chronicity (see Chap. 9). The timely use of clozapine in first-episode patients who are usually treatment resistant at the time of presentation cannot be overstated (see Chap. 11) [14]. Because clozapine can reduce suicidality [15] and aggression [16], you should also strongly consider it in those cases. You can use clozapine in psychiatric and neurological cases where other anti-

Table 17.1 Clinical indications for clozapine

Treatment-resistant schizophrenia ^a
Suicidality in the context of schizophrenia spectrum disorders ^a
Aggression in the context of schizophrenia spectrum disorders
Refractory mood disorders
EPS sensitivity to antipsychotics
Tardive dyskinesia
Psychogenic polydipsia
Schizophrenia with comorbid substance use
Psychosis in Parkinson's disease or other neurological conditions ^b
<i>EPS</i> extrapyramidal symptoms

^aFDA-approved indications^bIf other antipsychotics are not tolerated due to EPS

psychotics are not tolerated because of sensitivity to extrapyramidal side effects. Catatonic schizophrenia may be a subtype where clozapine is the antipsychotic of choice [17]. Clozapine has a low risk for tardive dyskinesia; consider it also for patient with established tardive dyskinesia if you are worried about progression [18]. “Softer” indications where clozapine might help are patients with comorbid substance use problems [19] and those with psychogenic polydipsia [20]. Often, clozapine is tried for patients who have a serious illness course due to a psychotic mood disorder. Table 17.1 lists clinical indications for clozapine.

Agranulocytosis and the Clozapine Registry

Clozapine has a risk of around 0.8% to cause agranulocytosis which is higher than seen with other antipsychotics [21]. Its mechanism may be due to an activation of the immune system that leads to altered neutrophil kinetics in susceptible patients [22]. In the United States, clozapine can only be dispensed by a pharmacist if a patient is registered with the nationwide Clozapine REMS Program (a unified clozapine case registry) and submits to regular blood draws (“no blood, no drug”) [23]. In 2015, a single registry replaced previous independent registries and databases and created one single access point for all clozapine products.

Management decisions with regard to agranulocytosis are solely based on the absolute neutrophil count (ANC) and not on the WBC or other parameters. Before starting clozapine, the ANC needs to be above an acceptable cut-off of at least 1500/ μ L. (For patients with benign ethnic neutropenia (BEN) other cut-offs apply, see below.) Subsequent frequency of ANC monitoring and interruptions for clozapine treatment depend on the ANC count (a monitoring table with detailed monitoring rules can be found on the Clozapine REMS website (see Additional Resources); Fig. 17.1 is a summary).

Consistent with the nonlinear agranulocytosis risk (highest at the beginning of treatment, with a decline over 6–12 months but never reaching a zero risk), ANC is

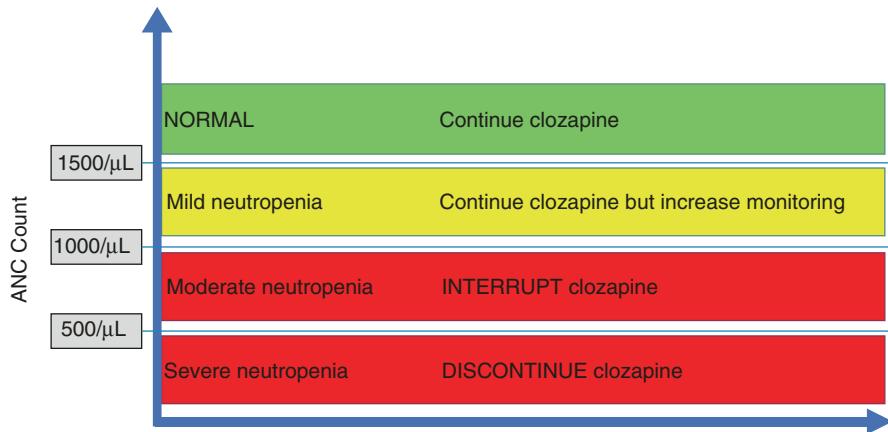


Fig. 17.1 Absolute neutrophil count (ANC) monitoring. Neutrophils refer to the neutrophilic granulocytes. The absolute neutrophil count is calculated by multiplying the WBC with the percentage of neutrophils (segs plus bands). (According to [23])

monitored weekly for 6 months, then every other week for 6 months, and then every 4 weeks indefinitely as long the patient continues on clozapine.

Tip

Emphasize to patients who are often worried about weekly blood work that they are only agreeing to a time-limited trial of a few months; they may not take clozapine in the long run unless there is benefit. Those patients who benefit usually put up gladly with the eventual monthly blood work. (Point-of-care testing using finger sticks is under development for routine clinical use which would be helpful to have as an option.)

If granulocytopenia develops during treatment, treatment either has to be monitored more frequently (for mild neutropenia, $\geq 1000/\mu\text{L}$ and $< 1500/\mu\text{L}$) or temporarily interrupted (for moderate neutropenia, $\geq 500/\mu\text{L}$ and $< 1000/\mu\text{L}$) until the granulocyte count recovers. For severe neutropenia, ($< 500/\mu\text{L}$) discontinue clozapine. Consult the REMS Programs' monitoring table for the exact rules if there are problems (see Additional Resources). With this blood-monitoring schedule, the risk of dying from agranulocytosis is low (obviously monitoring alone does not prevent bone marrow toxicity; it just detects it early enough so clozapine can be discontinued, and a patient can be monitored and treated for infections). Other countries with different risk tolerance have less stringent ANC monitoring requirements, particularly after the period of highest risk (the first 6–12 months) is over. Currently, no genetic marker combination is available to flag patients at high-risk for agranulocytosis [24]. Patients who developed clear-cut severe neutropenia or agranulocytosis due to clozapine (sometimes the etiology of a lower granulocyte count in a complex,

medically ill patient is not so clear) should probably not be rechallenged as the risk of recurrence is high [25]. However, the registry allows for a rechallenge with clozapine in those selected cases where the clinical outcome without clozapine is dire. Granulocyte colony-stimulating factor (G-CSF) is often used to reduce the duration of neutropenia in cases of clozapine-induced agranulocytosis [26]. Its role during a clozapine rechallenge is unclear [27].

Benign Ethnic Neutropenia

You will find patients with habitually (genetically) low ANC counts (benign ethnic neutropenia or BEN) [28]. BEN is not a pathological condition; you may see it in patients of African descent, for example. A diagnosis of BEN is made if, in a patient of appropriate ethnic background, mild and persistent (i.e., on repeated, spaced out blood draws) neutropenia is observed. Consider asking hematology for help if your patient with a low neutrophil count does not fit the ethnic background for BEN and if there are frequent infections which are not characteristic for BEN. Most BEN patients fluctuate around a neutrophil count above 1000/ μ L (in the mild neutropenia range) and can be safely managed with clozapine [29]. Patients in the BEN population follow a different monitoring schedule in order to be eligible to receive clozapine (e.g., a lower cut-off of at least 1000/ μ L is acceptable for routine clozapine prescribing). Prior to the unified registry which introduced special considerations for BEN patients, patients with BEN could either not receive clozapine or clinicians had to resort to bone marrow-stimulating approaches like adding lithium to boost a patient's granulocyte count – an example of structural unfairness in medicine [30].

Metabolism and Dosing

Clozapine has a complex receptor profile. It still features D2-5-HT2 antagonism which is typical for all second-generation antipsychotics. Of note, it has only loose dopamine-2 receptor binding which, together with being strongly anticholinergic, can explain its lack of extrapyramidal side effects. It is a very strong alpha antagonist which explains its cardiac effects (orthostatic hypotension). Its unique efficacy is likely related to other properties (e.g., NMDA).

Metabolism

Clozapine is metabolized by the cytochrome P450 enzymes 1A2 and 3A4, with smaller contributions from 2D6 and 2C19 [31]. The most important drug interactions are mediated via 1A2, either by drugs that block 1A2 (e.g., fluvoxamine) or

that induce it (e.g., cigarette smoking). Cigarette smoking has enough of an effect on clozapine blood levels that smoking status needs to be taken into account (see Chap. 20). Male smokers have the highest dose requirements. Severe infections via their inhibitory effect on drug metabolism may be an underappreciated risk of clozapine toxicity in hospitalized patients [32]. Norclozapine (desmethylclozapine) is clozapine's main metabolite. It has 10% of clozapine's activity, contributing thus very little to the active moiety. For most practical purposes, you can safely ignore it.

Dosing

Clozapine has a short half-life of less than 12 hours. While early clinical trials used three times daily dosing, most patients can be managed with nightly dosing to minimize the effects of sedation. Some patients prefer twice daily dosing to reduce a hang-over effect in the morning. More frequent dosing can be used for those patients who want to experience the ataractic effects of clozapine more directly.

Clozapine needs to be titrated slowly because of (1) the risk for seizures, (2) sedation, and (3) syncope. Predictable early side effects that most patients experience when they start clozapine are sedation and orthostatic hypotension.

On the outpatient side, I keep it simple and start with 25 mg/day (after a test dose of 12.5 mg to make sure there is not unusual sensitivity) and then increase the dose by 25 mg every week. Inpatient titration schedules can be more aggressive. No one titration schedule is set in stone: your main consideration is how a particular patient could compensate side effects, particularly orthostatic hypotension. Adjust your titration based on expected and observed tolerability. If clozapine treatment is interrupted, follow the REMS guidelines regarding restarting clozapine (see Additional Resources). Depending on the length of interruption, you may need to start from scratch; adherence to clozapine is therefore particularly critical. Patients, families, and group homes need to know that they cannot just restart clozapine at the full dose if several doses were missed.

With clozapine, dosing should be based on serum levels [33] as you cannot predict serum levels from the clozapine dose: the interindividual variability between achieved clozapine blood level for any given dose is large [34]. I check a clozapine level after reaching 100 mg/day. Assuming linear pharmacokinetics ("you double the dose, you double the level"), this first data point will give you some idea about the dose you will eventually need to achieve your target clozapine serum level range. One study found that a clozapine serum level range of 200–300 ng/mL was as effective as 350–450 ng/mL [34]. I therefore try to reach an initial target range of 200–300 ng/mL but increase the dose to above 450 ng/mL if there is no response, consistent with guidelines for refractory psychosis. Clozapine blood levels below 150 ng/mL are perhaps too low for most patients. I will add that an optimal highest dose for clozapine has not been established [35].

Key Point

Therapeutic drug monitoring (TDM) is well established for clozapine and a necessary component of prescribing clozapine safely and most effectively as there is very wide clozapine plasma level variability between patients for a given dose. TDM helps detect insufficient clozapine levels and avoid dangerously high levels, often assumed to be somewhere around 1000 ng/mL for the active moiety (clozapine plus norclozapine). Note, however, that the literature on clozapine TDM is based on clozapine alone, not on the active moiety.

Table 17.2 Clozapine black box warnings

Agranulocytosis
Myocarditis
Seizures
Orthostatic hypotension with syncope and cardiorespiratory arrest
Increased mortality in elderly patients with dementia-related psychosis ^a

^aClass warning for all antipsychotics, *not* specific to clozapine

Side Effects

Clozapine carries five black box warnings for serious side effects (see Table 17.2). Other antipsychotics can also cause agranulocytosis and seizures although they occur at a higher rate with clozapine. Some side effects are unusual for antipsychotics (myocarditis, pancreatitis); they are likely immune mediated. Ileus is an additional potentially lethal side effect of clozapine and may, though not a black box warning, be a more common cause of morbidity and mortality than agranulocytosis or myocarditis.

Unfortunately, there is often no tachyphylaxis with regard to sedation which is common, and patients need to learn how to manage it (e.g., drinking coffee). This can be challenging in patients with negative symptoms who simply sleep a lot more than they already would. For the long-term management, weight gain and metabolic complications are most critical. Motor side effects (tremor, tardive dyskinesia) are less than with other antipsychotics (hence, “atypical”) but not impossible. NMS in particular occurs and can present atypically, with less prominent rigidity [36].

Agranulocytosis

As already noted earlier, clozapine causes agranulocytosis in approximately 0.8% [21]. The risk of agranulocytosis is highest during the first few months of treatment, then drops off but never returns to zero and increases with age. Other blood dyscrasias (leukocytosis, low platelet count, increased eosinophil count, low red

blood cell count) have been described with clozapine use, but they usually do not prevent the use of clozapine.

Myocarditis

Myocarditis is a problem that is not usually associated with antipsychotics but that is clearly described with clozapine. Its frequency is a matter of some debate; it might be more common than agranulocytosis [37]. Following weekly markers of inflammation (CRP) and cardiac muscle damage (troponin) and obtaining an ECG in symptomatic patients during the high-risk period (4 weeks) are reasonable precautions [38] although there is no consensus about monitoring for myocarditis during treatment [39]. While a baseline ECG makes sense prior to starting clozapine (to have a comparison), obtaining a baseline echocardiograms like some have suggested would likely prevent the use of clozapine in many settings [40]. Clozapine has also been linked to cardiomyopathy during long-term treatment.

Key Point

Suspect myocarditis if malaise, chest pain, or palpitations develop during the initial clozapine titration phase (first month). A high clinical index of suspicion together with laboratory monitoring is needed as the non-specific symptoms of myocarditis overlap with typical side effects during the initiation of clozapine (fatigue, increased heart rate, light-headedness from orthostatic hypotension).

Seizures

Clozapine may cause EEG abnormalities [41] and seizures that are dose related [42]. The seizure risk increases steadily, and there is no cut-off dose (or blood level) that can be considered safe. Therapeutic blood monitoring is key to avoid unnecessarily high clozapine blood levels. Most seizures are of the grand mal type; myoclonus is a warning sign. It is usually unnecessary to prophylactically pretreat patients with an antiepileptic drug unless you think the patient has an increased seizure risk (e.g., organic brain injury). All broad-spectrum antiepileptic drugs are effective, but carbamazepine is relatively contraindicated because of its bone marrow toxicity.

Orthostatic Hypotension

Clozapine is a strong alpha-1 receptor blocker which explains orthostatic hypotension. Many patients will have some degree of tachycardia that can be managed with beta-blockers if desired. Titration is key to avoid complications, particularly in patients

who might not tolerate a drop in blood pressure. Benzodiazepine should be avoided particularly in this initial treatment phase because of the potential for severe interactions (that have resulted in deaths from cardiovascular collapse when clozapine was introduced), but clinical experience also shows that benzodiazepines can be safely used in patients without medical comorbidities like pulmonary compromise [43].

Constipation and Ileus

Clozapine decreases colonic transit time, and many patients complain about constipation. Bowel obstruction as a complication is common enough that we see one or two cases per year in our clozapine clinic, despite efforts to prevent it.

Key Point

Clozapine-induced constipation needs to be taken seriously and managed prospectively as it may result in ileus. More impaired and psychiatrically ill patients may not complain about constipation until they present with colon perforation and peritonitis [44]. Consider a standing order for a bowel regimen (see under Additional Resources).

Sialorrhea

The seemingly paradoxical problem of sialorrhea can emerge as a dose-limiting side effect. Sialorrhea is unexpected given the strong anticholinergic side effects of clozapine which ought to cause a dry mouth as a patient complaint. However, clozapine impairs swallowing akin to Parkinson patients, leading to drooling (“drool and pool hypothesis”) which explains that sialorrhea is usually worse at night (we swallow less during sleep) and why chewing gum works (we swallow more when chewing gum). I have sometimes used sublingual Atropine spray in order to avoid systemic side effects [45]. The most effective treatment for clozapine-induced sialorrhea, however, is probably glycopyrrolate 2 mg at night [46]. A dose reduction may help some patients, particularly if clozapine levels are unnecessarily high. For some patients, sialorrhea is more than a mere nuisance side effect as it can cause recurrent episodes of aspiration pneumonia [47].

Urinary Incontinence

This is another vexing side effect that can be difficult to manage when it occurs [48]. Make sure that you are not dealing with nocturnal seizures. In some cases, splitting up the clozapine dose may solve the problem if nocturnal incontinence is due to sedation

Table 17.3 Dangerous clozapine side effects

Side Effect	Management
Agranulocytosis	Granulocyte monitoring as per guidelines
Seizures	Titration Therapeutic drug monitoring to prevent seizures
Myocarditis	High index of suspicion Monitoring (CRP, troponin) for the first 4 weeks
Orthostatic hypotension	Titration
Neuroleptic malignant syndrome	High index of suspicion
Diabetic ketoacidosis	Metabolic monitoring including HbA1c prior to starting clozapine
Constipation and ileus	Proactive management of constipation
Pancreatitis	High index of suspicion
Pulmonary embolism	High index of suspicion Active lifestyle to prevent deep vein thrombosis
Aspiration pneumonia	Proactive management of sialorrhea

Table based on [50]

that does not wake patients up when they have to go to the bathroom (overflow incontinence). Patients should limit fluid intake in the evening and empty the bladder before going to bed. However, clozapine also has direct effects on bladder function (alpha-adrenergic blockade) that may respond to medical treatment with the alpha-adrenergic agonist ephedrine [49]. Consider a referral to urology to help you.

Table 17.3 summarizes dangerous clozapine side effects and their management.

Morbidity and Mortality

Weight gain and metabolic problems are quite pronounced with clozapine and must be taken into account when reviewing the risks and benefits of long-term clozapine treatment [51]. In our own clozapine cohort, about one third of patients were diagnosed with diabetes in a 5-year naturalistic cohort study [52]. Recognizing developing diabetes early may be important to prevent triggering an episode of diabetic ketoacidosis in clozapine-treated patients [53]. Metabolic monitoring is therefore a critical component of safe clozapine prescribing (see Table 17.4).

In an ideal world, all patients who commence on clozapine would participate in a behavioral program that teaches lifestyle interventions and fosters illness self-management in order to blunt clozapine-related weight gain [55]. Unfortunately, such programs are not universally available [56]. To complicate matters further, clozapine is typically used in rather ill patients where principles of illness self-management may be out of reach, necessitating a more proactive approach with medications to address the clozapine-associated reduction in insulin sensitivity [57]. The use of metformin is one such approach that has been shown to be quite effective [58], at least in the short run (see more on the use of metformin in Chap. 25). As

Table 17.4 Clozapine metabolic monitoring

<i>Prior to starting clozapine</i>
Metabolic bundle*
ECG
<i>During treatment</i>
Every visit: weight
Metabolic bundle* at least every 3–6 months

*Metabolic bundle consists of BMI, waist circumference^a, HbA1c, fasting glucose, fasting lipid profile
^aWaist circumference is the best anthropomorphic marker for insulin resistance in clozapine-treated patients [54]

second strategy is the addition of aripiprazole (an agonist at the 5-HT2c receptor) to counteract clozapine-related weight gain (driven in part by 5-HT-2c antagonism) [59, 60]. While early behavioral and early medication interventions with metformin or aripiprazole have face validity and support from the literature for short-term benefit, it remains to be established if they can reduce the increased long-term morbidity and mortality from cardiovascular disease that we have observed in our cohort of clozapine patients [61].

Despite long-term side effects from clozapine, you should also take into account the disastrous medical consequences from poorly controlled psychiatric illness, including the difficulties to stay healthy or manage medical illnesses well. Psychiatric instability is a poor basis for medical health which is reflected in better survival of patients who are treated with antipsychotics, including patients receiving clozapine, compared to untreated patients [1]. The highest risk of death in patients with schizophrenia stems from no treatment [62]. A healthy body requires a healthy mind, to paraphrase the Roman poet Juvenal.

Clozapine Augmentation

While I have seen clozapine super-responders (my term), the reality for most patients who do not respond to first-line antipsychotics is that they will only have a partial response to clozapine [63] or no response at all. My rule of thumb is that 50% of treatment-resistant patients will have some response to clozapine, and 50% will not benefit from it [10]. Given the clinical need, augmentation strategies are often employed in patients who are clozapine resistant [64], usually first with a second antipsychotic to increase dopamine binding (clozapine binds to D2 very loosely) [65]. I have spent a good decade of my research career to study various augmentation strategies, including risperidone [66] but also modafinil [67] or donepezil [68]. None of those strategies has panned out in our clinical trials, an observation that has since essentially been confirmed in meta-analyses (e.g., [69, 70]). Aripiprazole is one exception in that it may offer some symptomatic benefit and, as noted above, may also improve the metabolic abnormalities associated with clozapine use [60]. Recently, a second benefit was observed. In a Finnish cohort studies, the addition of

aripiprazole to clozapine reduced the risk for a psychiatric hospitalization by up to 25% compared to clozapine treatment alone [71].

Commonly used clozapine augmentation strategies that may offer some benefit include the addition of antiepileptic drugs, particularly valproate [70] and topiramate [72]. Topiramate has a high discontinuation rate due to side effects but may offer some added weight loss benefit, if tolerated [73]. I used to add lamotrigine after initial reports of its benefits but have been less enthusiastic about it after further work has failed to show benefit [74]. (See Chap. 19 on adjunctive medications for more details about the antiepileptic drugs.) Finally, a small case series reported the successful treatment of ten treatment-resistant patients with 34 mg of pimavanserin which is a non-antidopaminergic antipsychotic (inverse 5-HT_{2a} agonist) approved at the time of this writing only for the psychosis of Parkinson's disease [75]. It remains to be seen if pimavanserin is truly a new option for patients with treatment-resistant schizophrenia.

The failure of augmentation strategies is perhaps not surprising as clozapine already represents polypharmacy at the receptor level [76]. Adding a second agent might do nothing more than duplicate some of clozapine's actions, and, importantly, it does not address the biology that underlies treatment resistance [66]. More importantly, clozapine's shotgun approach at the receptor level appears to serendipitously represent a better receptor combination than other antipsychotics with regard to inducing a change in brain states (from psychotic to less psychotic). Without progress at the level of understanding the biology underlying treatment resistance, it is unlikely that a better antipsychotic than clozapine can be developed.

Key Point

Resist the tendency to continue to add medications when faced with a poor clozapine response: polypharmacy may do more harm than good (with the exception of adding aripiprazole to reverse metabolic abnormalities). Instead, refer a patient to electroconvulsive therapy for ongoing psychosis that does not respond to clozapine and optimize non-pharmacological interventions (see Chap. 12 on refractory psychosis).

References

1. Tiihonen J, Lonnqvist J, Wahlbeck K, Klaukka T, Niskanen L, Tanskanen A, et al. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet*. 2009;374:620–7.
2. Tiihonen J, Mittendorfer-Rutz E, Majak M, Mehtala J, Hoti F, Jedenius E, et al. Real-world effectiveness of antipsychotic treatments in a nationwide cohort of 29823 patients with schizophrenia. *JAMA Psychiatry*. 2017;74:686–93.
3. Freudenberg O, Henderson DC, Sanders KM, Goff DC. Training in a clozapine clinic for psychiatry residents: a plea and suggestions for implementation. *Acad Psychiatry*. 2013;37:27–30.
4. Crilly J. The history of clozapine and its emergence in the US market: a review and analysis. *Hist Psychiatry*. 2007;18:39–60.

5. Williams R, Malla A, Roy MA, Joober R, Manchanda R, Tibbo P, et al. What is the place of clozapine in the treatment of early psychosis in Canada? *Can J Psychiatr.* 2017;62:109–14.
6. Kelly DL, Freudenreich O, Sayer MA, Love RC. Addressing barriers to clozapine underutilization: a national effort. *Psychiatr Serv.* 2018;69:224–7.
7. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry.* 1988;45:789–96.
8. McEvoy JP, Lieberman JA, Stroup TS, Davis SM, Meltzer HY, Rosenheck RA, et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry.* 2006;163:600–10.
9. Kane JM, Agid O, Baldwin ML, Howes O, Lindenmayer JP, Marder S, et al. Clinical guidance on the identification and management of treatment-resistant schizophrenia. *J Clin Psychiatry.* 2019;80:pii: 18com12123.
10. Mouaffak F, Tranulis C, Gourevitch R, Poirier MF, Douki S, Olie JP, et al. Augmentation strategies of clozapine with antipsychotics in the treatment of ultraresistant schizophrenia. *Clin Neuropharmacol.* 2006;29:28–33.
11. Leucht S, Cipriani A, Spinelli L, Mavridis D, Orey D, Richter F, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet.* 2013;382:951–62.
12. Siskind D, McCartney L, Goldschlager R, Kisely S. Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. *Br J Psychiatry.* 2016;209:385–92.
13. Siskind D, Siskind V, Kisely S. Clozapine response rates among people with treatment-resistant schizophrenia: data from a systematic review and meta-analysis. *Can J Psychiatr.* 2017;62:772–7.
14. Agid O, Remington G, Kapur S, Arenovich T, Zipursky RB. Early use of clozapine for poorly responding first-episode psychosis. *J Clin Psychopharmacol.* 2007;27:369–73.
15. Meltzer HY, Alphs L, Green AI, Altamura AC, Anand R, Bertoldi A, et al. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry.* 2003;60:82–91.
16. Volavka J, Czobor P, Nolan K, Sheitman B, Lindenmayer JP, Citrome L, et al. Overt aggression and psychotic symptoms in patients with schizophrenia treated with clozapine, olanzapine, risperidone, or haloperidol. *J Clin Psychopharmacol.* 2004;24:225–8.
17. England ML, Ongur D, Konopaske GT, Karmacharya R. Catatonia in psychotic patients: clinical features and treatment response. *J Neuropsychiatr Clin Neurosci.* 2011;23:223–6.
18. Lieberman JA, Saltz BL, Johns CA, Pollack S, Borenstein M, Kane J. The effects of clozapine on tardive dyskinesia. *Br J Psychiatry.* 1991;158:503–10.
19. Krause M, Huhn M, Schneider-Thoma J, Bighelli I, Gutzsmiedl K, Leucht S. Efficacy, acceptability and tolerability of antipsychotics in patients with schizophrenia and comorbid substance use. A systematic review and meta-analysis. *Eur Neuropsychopharmacol.* 2019;29:32–45.
20. Spears NM, Leadbetter RA, Shutty MS Jr. Clozapine treatment in polydipsia and intermittent hyponatremia. *J Clin Psychiatry.* 1996;57:123–8.
21. Alvir JM, Lieberman JA, Safferman AZ, Schwimmer JL, Schaaf JA. Clozapine-induced agranulocytosis. Incidence and risk factors in the United States. *N Engl J Med.* 1993;329:162–7.
22. Ng W, Kennar R, Uetrecht J. Effect of clozapine and olanzapine on neutrophil kinetics: implications for drug-induced agranulocytosis. *Chem Res Toxicol.* 2014;27:1104–8.
23. Clozapine REMS Program. Available from <https://www.clozapinerems.com/CpmgClozapineUI/home.u>. Accessed on 7/1/2019.
24. Athanasiou MC, Dettling M, Cascorbi I, Mosyagin I, Salisbury BA, Pierz KA, et al. Candidate gene analysis identifies a polymorphism in HLA-DQB1 associated with clozapine-induced agranulocytosis. *J Clin Psychiatry.* 2011;72:458–63.

25. Manu P, Sarpal D, Muir O, Kane JM, Correll CU. When can patients with potentially life-threatening adverse effects be rechallenged with clozapine? A systematic review of the published literature. *Schizophr Res.* 2012;134:180–6.
26. Lally J, Malik S, Whiskey E, Taylor DM, Gaughran FP, Krivoy A, et al. Clozapine-associated agranulocytosis treatment with granulocyte colony-stimulating factor/granulocyte-macrophage colony-stimulating factor: a systematic review. *J Clin Psychopharmacol.* 2017;37:441–6.
27. Lally J, Malik S, Krivoy A, Whiskey E, Taylor DM, Gaughran FP, et al. The use of granulocyte colony-stimulating factor in clozapine rechallenge: a systematic review. *J Clin Psychopharmacol.* 2017;37:600–4.
28. Palmblad J, Hoglund P. Ethnic benign neutropenia: a phenomenon finds an explanation. *Pediatr Blood Cancer.* 2018;65:e27361.
29. Manu P, Sarvaiya N, Rogoza LM, Kane JM, Correll CU. Benign ethnic neutropenia and clozapine use: a systematic review of the evidence and treatment recommendations. *J Clin Psychiatry.* 2016;77:e909–16.
30. Nykiel S, Henderson D, Bhide G, Freudenreich O. Lithium to allow clozapine prescribing in benign ethnic neutropenia. *Clin Schizophr Relat Psychoses.* 2010;4:138–40.
31. Stevens JR, Freudenreich O, Stern TA. Elevated clozapine serum level after treatment with amiodarone. *Psychosomatics.* 2008;49:255–7.
32. Leung JG. Increasing the safety of clozapine management in hospitalized patients with or without infection: still much to learn ... and teach. *Psychosomatics.* 2018;59:102–4.
33. Freudenreich O. Clozapine drug levels guide dosing [Pearls series]. *Curr Psychiatry.* 2009;8:78.
34. VanderZwaag C, McGee M, McEvoy JP, Freudenreich O, Wilson WH, Cooper TB. Response of patients with treatment-refractory schizophrenia to clozapine within three serum level ranges. *Am J Psychiatry.* 1996;153:1579–84.
35. Remington G, Agid O, Foussias G, Ferguson L, McDonald K, Powell V. Clozapine and therapeutic drug monitoring: is there sufficient evidence for an upper threshold? *Psychopharmacology.* 2013;225:505–18.
36. Belvederi Murri M, Guaglianone A, Bugiani M, Calcagno P, Respino M, Serafini G, et al. Second-generation antipsychotics and neuroleptic malignant syndrome: systematic review and case report analysis. *Drugs R D.* 2015;15:45–62.
37. Ronaldson KJ, Fitzgerald PB, McNeil JJ. Clozapine-induced myocarditis, a widely overlooked adverse reaction. *Acta Psychiatr Scand.* 2015;132:231–40.
38. Ronaldson KJ, Fitzgerald PB, Taylor AJ, Topliss DJ, McNeil JJ. A new monitoring protocol for clozapine-induced myocarditis based on an analysis of 75 cases and 94 controls. *Aust N Z J Psychiatry.* 2011;45:458–65.
39. Knoph KN, Morgan RJ 3rd, Palmer BA, Schak KM, Owen AC, Leloux MR, et al. Clozapine-induced cardiomyopathy and myocarditis monitoring: a systematic review. *Schizophr Res.* 2018;199:17–30.
40. Freudenreich O. Clozapine-induced myocarditis: prescribe safely but do prescribe. *Acta Psychiatr Scand.* 2015;132:240–1.
41. Freudenreich O, Weiner RD, McEvoy JP. Clozapine-induced electroencephalogram changes as a function of clozapine serum levels. *Biol Psychiatry.* 1997;42:132–7.
42. Devinsky O, Honigfeld G, Patin J. Clozapine-related seizures. *Neurology.* 1991;41:369–71.
43. Bitter R, Demler TL, Opler L. Safety evaluation of the concomitant use of clozapine and benzodiazepines: a retrospective, cross-sectional chart review. *J Psychiatr Pract.* 2008;14:265–70.
44. Freudenreich O, Goff DC. Colon perforation and peritonitis associated with clozapine [letter]. *J Clin Psychiatry.* 2000;61:950–1.
45. Freudenreich O, Beebe M, Goff DC. Clozapine-induced sialorrhea treated with sublingual ipratropium spray: a case series. *J Clin Psychopharmacol.* 2004;24:98–100.
46. Man WH, Colen-de Koning JC, Schulte PF, Cahn W, van Haelst IM, Doodeman HJ, et al. The effect of glycopyrrolate on nocturnal sialorrhea in patients using clozapine: a randomized, crossover, double-blind, placebo-controlled trial. *J Clin Psychopharmacol.* 2017;37:155–61.

47. Kaplan J, Schwartz AC, Ward MC. Clozapine-associated aspiration pneumonia: case series and review of the literature. *Psychosomatics*. 2018;59:199–203.
48. Warner JP, Harvey CA, Barnes TR. Clozapine and urinary incontinence. *Int Clin Psychopharmacol*. 1994;9:207–9.
49. Fuller MA, Borovicka MC, Jaskiw GE, Simon MR, Kwon K, Konicki PE. Clozapine-induced urinary incontinence: incidence and treatment with ephedrine. *J Clin Psychiatry*. 1996;57:514–8.
50. Marcovitz D, Freudenreich O. Clozapine: talking about risks, benefits, and alternatives with patients [Pearls series]. *Curr Psychiatry*. 2014;13:65–6.
51. Hill M, Freudenreich O. Clozapine: key discussion points for prescribers. *Clin Schizophr Relat Psychoses*. 2013;6:177–85.
52. Henderson DC, Cagliero E, Gray C, Nasrallah RA, Hayden DL, Schoenfeld DA, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. *Am J Psychiatry*. 2000;157:975–81.
53. Henderson DC, Cagliero E, Copeland PM, Louie PM, Borba CP, Fan X, et al. Elevated hemoglobin A1c as a possible indicator of diabetes mellitus and diabetic ketoacidosis in schizophrenia patients receiving atypical antipsychotics. *J Clin Psychiatry*. 2007;68:533–41.
54. Henderson DC, Fan X, Sharma B, Copeland PM, Borba CP, Freudenreich O, et al. Waist circumference is the best anthropometric predictor for insulin resistance in nondiabetic patients with schizophrenia treated with clozapine but not olanzapine. *J Psychiatr Pract*. 2009;15:251–61.
55. Daumit GL, Dickerson FB, Wang NY, Dalcin A, Jerome GJ, Anderson CA, et al. A behavioral weight-loss intervention in persons with serious mental illness. *N Engl J Med*. 2013;368:1594–602.
56. Bartels SJ. Can behavioral health organizations change health behaviors? The STRIDE study and lifestyle interventions for obesity in serious mental illness. *Am J Psychiatry*. 2015;172:9–11.
57. Henderson DC, Cagliero E, Copeland PM, Borba CP, Evins E, Hayden D, et al. Glucose metabolism in patients with schizophrenia treated with atypical antipsychotic agents: a frequently sampled intravenous glucose tolerance test and minimal model analysis. *Arch Gen Psychiatry*. 2005;62:19–28.
58. Siskind DJ, Leung J, Russell AW, Wysoczanski D, Kisely S. Metformin for clozapine associated obesity: a systematic review and meta-analysis. *PLoS One*. 2016;11:e0156208.
59. Henderson DC, Kunkel L, Nguyen DD, Borba CP, Daley TB, Louie PM, et al. An exploratory open-label trial of aripiprazole as an adjuvant to clozapine therapy in chronic schizophrenia. *Acta Psychiatr Scand*. 2006;113:142–7.
60. Fan X, Borba CP, Copeland P, Hayden D, Freudenreich O, Goff DC, et al. Metabolic effects of adjunctive aripiprazole in clozapine-treated patients with schizophrenia. *Acta Psychiatr Scand*. 2013;127:217–26.
61. Henderson DC, Nguyen DD, Copeland PM, Hayden DL, Borba CP, Louie PM, et al. Clozapine, diabetes mellitus, hyperlipidemia, and cardiovascular risks and mortality: results of a 10-year naturalistic study. *J Clin Psychiatry*. 2005;66:1116–21.
62. Torniainen M, Mittendorfer-Rutz E, Tanskanen A, Bjorkenstam C, Suvisaari J, Alexanderson K, et al. Antipsychotic treatment and mortality in schizophrenia. *Schizophr Bull*. 2015;41:656–63.
63. Kahn RS, Winter van Rossum I, Leucht S, McGuire P, Lewis SW, Leboyer M, et al. Amisulpiride and olanzapine followed by open-label treatment with clozapine in first-episode schizophrenia and schizophreniform disorder (OPTiMiSE): a three-phase switching study. *Lancet Psychiatry*. 2018;5:797–807.
64. Goff DC, Freudenreich O, Evins AE. Augmentation strategies in the treatment of schizophrenia. *CNS Spectr*. 2001;6:904, 907–11.

65. Freudenreich O, Goff DC. Antipsychotic combination therapy in schizophrenia. A review of efficacy and risks of current combinations. *Acta Psychiatr Scand.* 2002;106:323–30.
66. Freudenreich O, Henderson DC, Walsh JP, Culhane MA, Goff DC. Risperidone augmentation for schizophrenia partially responsive to clozapine: a double-blind, placebo-controlled trial. *Schizophr Res.* 2007;92:90–4.
67. Freudenreich O, Henderson DC, Macklin EA, Evins AE, Fan X, Cather C, et al. Modafinil for clozapine-treated schizophrenia patients: a double-blind, placebo-controlled pilot trial. *J Clin Psychiatry.* 2009;70:1674–80.
68. Freudenreich O, Herz L, Deckersbach T, Evins AE, Henderson DC, Cather C, et al. Added donepezil for stable schizophrenia: a double-blind, placebo-controlled trial. *Psychopharmacology.* 2005;181:358–63.
69. Barber S, Olotu U, Corsi M, Cipriani A. Clozapine combined with different antipsychotic drugs for treatment-resistant schizophrenia. *Cochrane Database Syst Rev.* 2017;3:CD006324.
70. Siskind DJ, Lee M, Ravindran A, Zhang Q, Ma E, Motamarri B, et al. Augmentation strategies for clozapine refractory schizophrenia: a systematic review and meta-analysis. *Aust N Z J Psychiatry.* 2018;52:751–67.
71. Tiihonen J, Taipale H, Mehtala J, Vattulainen P, Correll CU, Tanskanen A. Association of antipsychotic polypharmacy vs monotherapy with psychiatric rehospitalization among adults with schizophrenia. *JAMA Psychiatry.* 2019;76:499–507.
72. Zheng W, Xiang YT, Yang XH, Xiang YQ, de Leon J. Clozapine augmentation with antiepileptic drugs for treatment-resistant schizophrenia: a meta-analysis of randomized controlled trials. *J Clin Psychiatry.* 2017;78:e498–505.
73. Correll CU, Maayan L, Kane J, Hert MD, Cohen D. Efficacy for psychopathology and body weight and safety of topiramate-antipsychotic cotermination in patients with schizophrenia spectrum disorders: results from a meta-analysis of randomized controlled trials. *J Clin Psychiatry.* 2016;77:e746–56.
74. Goff DC, Keefe R, Citrome L, Davy K, Krystal JH, Large C, et al. Lamotrigine as add-on therapy in schizophrenia: results of 2 placebo-controlled trials. *J Clin Psychopharmacol.* 2007;27:582–9.
75. Nasrallah HA, Fedora R, Morton R. Successful treatment of clozapine-nonresponsive refractory hallucinations and delusions with pimavanserin, a serotonin 5HT-2A receptor inverse agonist. *Schizophr Res.* 2019;208:217–20.
76. Freudenreich O, Goff DC. Polypharmacy in schizophrenia: a fuzzy concept [letter]. *J Clin Psychiatry.* 2003;64:1132.

Additional Resources

Websites

<https://www.clozapinerems.com/CpmgClozapineUI/home.u> – The homepage of the Clozapine REMS Program. You will find information, forms and tables about everything you need to know about prescribing clozapine to a patient.

<https://smiadviser.org/about/clozapine> – A collaboration between the APA and SAMSHA, the SMI Advisor initiative is a clinical support system for serious mental illness. The initiative includes a Clozapine Center of Excellence with clinical tips, FAQs, webinars, and guidelines (geared towards clinicians).

Articles

Cruz A, Freudenreich O. Clozapine-induced GI hypomotility: from constipation to bowel obstruction [Pearls series]. *Curr Psychiatry*. 2018;17:44. – Consult this one-page summary about the management of constipation in clozapine-treated patients. It may prevent ileus and a trip to the operating room for your patient.

Freudenreich O, Henderson DC, Sanders KM, Goff DC. Training in a clozapine clinic for psychiatry residents: a plea and suggestions for implementation. *Acad Psychiatry*. 2013;37:27–30. – A description of our long-standing clozapine clinic and its role in training the next generation of clinicians in the use of clozapine.

Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry*. 1988;45:789–96. Probably one of the best conducted and most impactful clinical trials in schizophrenia, leading to the resurrection of clozapine in the United States after it had been removed from the market because of agranulocytosis.

Kelly DL, Freudenreich O, Sayer MA, Love RC. Addressing barriers to clozapine underutilization: a national effort. *Psychiatr Serv*. 2018;69:224–7. – I included this article to emphasize the need to make clozapine available to everybody who may benefit from it. It behooves us to remove barriers, wherever we may practice.

Chapter 18

Long-Acting Injectable Antipsychotics



Essential Points

- Preventing psychotic relapse is one of the most important goals of treatment for schizophrenia. Antipsychotics are highly effective to prevent relapse (NNT = 3) but only if taken.
- Long-acting injectable antipsychotics (LAIs) reduce relapse and mortality in patients with schizophrenia. They should be the default option (i.e., patient need to opt out) for patients who require antipsychotic maintenance treatment in order to assure continuous care. Clinician attitude against LAIs more so than patient attitude is a major reason for the underuse of LAIs.
- Patients who should preferentially receive LAIs include first-episode patients and schizophrenia patients with forensic histories.
- There is benefit from making nonadherence readily transparent. It frees clinicians and families to focus on treatment issues other than adherence.
- Consider LAIs as a harm reduction strategy to delay the inevitable as long as possible for patients unlikely to adhere to psychiatric treatment.
- The LAI choice is determined by patient choice, taking into account side effects and injection frequency but not efficacy which is about equal between LAIs.
- LAIs are no substitute for rehabilitation or a clozapine trial in refractory patients.
- Make things convenient for patients but not too convenient. Rare contact with the treatment team risks treatment disengagement.
- Setting up “injection clinics” which may be virtual allows for population-based management and safe care (e.g., guideline-concordant monitoring).

“Der Ball ist rund, und das Spiel dauert 90 Minuten.” [1]

(The (soccer) ball is round and the game (of soccer) lasts 90 minutes.)

—Josef “Sepp” Herberger (1897–1977);
fabled coach of 1954 West German soccer team

Long-acting injectable antipsychotics (LAIs) are an important tool in the long-term management of schizophrenia so I dedicate a whole chapter to them. I already made the argument for the critical importance of relapse prevention for schizophrenia as an example of tertiary prevention in Chap. 9 on prevention and staging. While antipsychotics are highly effective in preventing relapse (NNT = 3) [2], the oral route of administration is often problematic, and many patients relapse because of insufficient adherence. In this chapter, I examine the benefits of long-acting preparations of antipsychotics over their oral pendants and make the case for the routine first-line use of LAIs for most patients with schizophrenia in order to assure continuous care [3] in the service of improved functional outcomes [4]. Despite the clear challenges with adherence to oral antipsychotics, many clinicians are ambivalent and persist in using oral antipsychotics, without offering LAIs to their patients [5]. Even if the resistance stems from patients, clinicians must learn communication skills to nudge patients toward a LAI [6]. Emphasizing procedure rather than benefit, for example, is a common mistake [5]. Sepp Herberger’s famous quote about the game of soccer (see epigraph) admonishes us to not lose sight of simple facts. In our case, that long-term management of schizophrenia is fundamentally simple: long-term remission matters, and LAIs are excellent tools to achieve this goal. Remembering what is at stake and being mentally prepared will allow you to effectively counter a patient’s arguments against the use of LAIs. If education is done well, the vast majority of patients will accept treatment with a LAI. In a clinical trial of LAI for first-episode patients termed PRELAPSE, only about 10% rejected study participation because of the injection, and over 90% of participants accepted the actual injection during the treatment phase [7].

Key Point

The more difficult and ultimately most important task for a psychiatrist is not the treatment of an acute episode of psychotic illness but keeping patients stable over time. LAIs are the most effective tool to achieve the goal of relapse-free remission and the best possible recovery. Clinicians need to convey this message to patients effectively.

Advantages over Oral Antipsychotics

To clinicians, it appears obvious that a monthly LAI offers an efficacy advantage with regard to relapse over oral pills that need to be taken daily (and can be forgotten daily). Several randomized trials have indeed confirmed the benefit of LAIs over

oral antipsychotics, for both chronic [8] and first-episode patients [9]. However, there have been many more studies that failed to show that LAIs are better than oral medications to prevent relapse [10], an apparent efficacy paradox. PROACTIVE (Preventing Relapse Oral Antipsychotics Compared to Injectables Evaluating Efficacy) was one such relapse prevention study that assigned patients to either LAI risperidone or an oral second-generation antipsychotic of the physician's choice [11]. In this large and well-conducted trial, there was no difference between the two groups with regard to relapse. Rather than questioning the value of LAIs, PROACTIVE perhaps simply shows that good clinical care (provided not just to the LAI intervention group but also to the oral control treatment arm) makes a difference in patient outcomes. In addition, it may very well be one example where a randomized trial may not be the gold standard to answer a particular clinical question [12]. Patients in a clinical trial do not represent the typical clinic patient who you would like to transition to a long-acting injectable. Mirror-image studies (a design where you contrast an outcome pre- and post-intervention, in this case before and after a transition to LAIs) conducted in real-world clinical populations have uniformly confirmed the superiority of LAIs over oral antipsychotics [13].

A nationwide study in Sweden found a reduction in mortality for schizophrenia patients treated with second-generation antipsychotics compared to no treatment [14]. With the exception of oral aripiprazole, LAIs were better than their oral counterparts, reducing mortality by about 33% more. The mode of administration matters: this survival benefit is a very strong argument for using LAIs routinely.

Key Point

LAIs are more effective in reducing relapse and mortality compared to oral antipsychotics. Put differently, the route of administration of antipsychotics has survival benefits which would be newsworthy were it a cancer treatment.

In addition to the obviously highly relevant benefits for relapse prevention and mortality reduction, LAIs have other advantages that are less apparent. Perhaps most importantly for all stakeholders, LAIs allow for an open discussion of adherence as nonadherence is readily apparent when a patient misses an injection. It frees families to be family and not the adherence police (an unthankful role for any parent), and it frees clinicians to focus on issues other than trying to figure out adherence. It allows for informed decisions if there are symptoms as opposed to trying to make a notoriously difficult guess about partial adherence. Many patients are quite receptive when they hear that there is a preparation of their medicine where they do not have to remember to take a pill every day. With longer preparations available or in development, LAIs are even more convenient (but see limitations below).

The REMIND trial reminded us that our usual tools to assist motivated patients remember taking oral medications for chronic conditions (i.e., a pillbox) are imperfect [15]. In this large, pragmatic trial, patients who were taking up to three medications for chronic conditions either received pillboxes (some with reminder functions)

or they did not. Only 15% of patients achieved optimal adherence, with no better adherence in the patients who were provided pillboxes. Even in motivated patients, LAIs may therefore be the practically better option if we want to avoid inadvertent adherence. Simple, low-cost reminders alone may not do it. Be careful transitioning patients back to oral medications “to increase autonomy” after they have been stabilized on LAIs. LAIs may just be what is needed to achieve stability.

Patient Selection

In the old days, first-generation LAI were reserved for patients who had failed oral medications. For many clinicians, LAIs represented a treatment of last resort, often reserved for patients with “no insight.” Patients often perceived the use of LAIs as punitive. This thinking is slowly shifting. The NICE Schizophrenia Guideline suggests offering LAIs to patient (1) who prefers such treatment after an acute episode and (2) where avoiding covert nonadherence (either intentional or unintentional) to antipsychotics is a clinical priority [16]. An even stronger argument can be made (see above) that LAIs should be the preferred mode of administration for *any* patient who requires maintenance treatment, given their established efficacy and survival advantages over oral medications. At a minimum, LAIs should be presented to all patients as a choice on par with oral antipsychotics. In addition, patient groups who are very likely to discontinue antipsychotics or who have much to lose if there is a psychotic relapse should be prioritized for LAIs. Examples are first-episode patients who are trying to piece their lives back together after their first psychiatric hospitalization or patients at high-risk for criminal offending when they are psychotic. Long-term follow-up studies [17, 18] and randomized trials [9] have clearly established that LAIs are effective medications to prevent early relapse in young first-episode patients. LAIs to assure medication persistence may be even more important for first-episode patients who use substances [19]. PRIDE (Paliperidone Palmitate Research in Demonstrating Effectiveness) showed the benefit on reducing arrest rates if patients with criminal histories were given a long-acting injection prior to hospital discharge [8]. Table 18.1 summarizes clinical indications for LAIs that have face validity.

Table 18.1 Indications for LAIs

Routine care for maintenance phase of schizophrenia
<i>Strong considerations</i>
First-episode schizophrenia
High-risk for forensic offending
Serious illness course
Partial adherence due to co-morbid drug use
Rule-out treatment-refractory schizophrenia
<i>Others</i>
Maintenance phase of bipolar disorder
Harm reduction in nonadherent patients
Court-ordered antipsychotic maintenance treatment

While lithium remains the most gold standard mood stabilizer for all phases of bipolar disorder, antipsychotics, including long-acting antipsychotics, are increasingly used to manage bipolar disorder [20]. Particularly second- and third-generation antipsychotics are now routinely used and recommended to manage acute mood episodes and to prevent relapse [21]. Perhaps not surprisingly, a large Finnish cohort study found that, in bipolar patients, long-acting injectables were more effective in reducing psychiatric (and medical) hospitalizations than their oral counterparts [22].

Key Point

Consider LAIs the treatment of choice for all patients, at all disease stages (first episode, chronic). LAIs should be the default option, where patients need to opt out.

Harm Reduction

Discharge patients unlikely to adhere to psychiatric treatment on a long-acting injectable antipsychotic. I had learned about this approach first when I visited a hospital in Addis Ababa where the very pragmatic psychiatrists described this as a common discharge plan when long-term follow-up could not be guaranteed in resource-poor settings of rural Ethiopia. In that way, it bought families a few months of normalcy.

Tip

LAIs can be used as a risk mitigation strategy [23]: if adherence is unlikely, a longer-acting antipsychotic preparation delays relapse after medication discontinuation.

If LAIs are not an option, consider an oral antipsychotic with a long half-life such as cariprazine which has an effective half-life of the active moiety of 1 week [24]. In one analysis of a cariprazine relapse prevention study where patients received either cariprazine or placebo after acute stabilization, placebo relapse was delayed by several weeks compared to antipsychotics with shorter half-lives. This property may buy clinicians more time to address adherence, particularly partial adherence [25].

Contraindications to LAIs

LAIs are not a good option for all patients with schizophrenia (see Table 18.2). LAIs are not a substitute for clozapine if patients have treatment-refractory schizophrenia. It turns out that clozapine has real-world effectiveness for relapse prevention

Table 18.2 Contraindications for LAIs

Tolerability not established
Treatment-refractory schizophrenia ^a
Sensitivity to extrapyramidal side effects
History of NMS ^b
History of catatonia ^c

^aLAI are not a substitute for clozapine
^bRelative contraindication. Very low risk in stabilized patients on second-generation LAIs
^cRelative contraindication. Avoid first-generation LAIs

that mirrors those of LAIs [26]. They also pose risks related to their long half-life: once administered, an injection cannot be taken away which can result in difficult-to-manage situations (e.g., if NMS develops or the patient experiences severe akathisia). LAIs can therefore only be given to patient known to tolerate the oral pendant which requires an oral treatment period prior to giving an injection. However, side effects may only become apparent weeks later. Be careful with loading strategies and avoid overshooting, particularly when using the decanoates as you may cause severe EPS [27]. NMS appears to be rare with second-generation LAIs. In a review of a clinical trials database for long-acting paliperidone, only 1 patient out of 5000 (which translates to less than 0.1% incidence per year) experienced an episode of NMS from which he recovered [28].

Choice of Long-Acting Antipsychotics

Long-acting preparations are available for several first-generation antipsychotics and for many second- and third-generation antipsychotics (see Table 18.3).

Efficacy is not a major consideration when selecting a LAI. ACCLAIMS (which stands for A Comparison of Long-Acting Injectable Medications for Schizophrenia) compared an older long-acting antipsychotic (haloperidol decanoate) with one of the second-generation LAIs (paliperidone palmitate) [29]. Similar to the CATIE findings for oral antipsychotic [30], there was no efficacy difference between the old and the newer LAI. Younger patients experienced longer relapse-free survival on haloperidol decanoate which suggests a possible modifying influence of age [31]. Individual patients may, however, do better on particular LAIs, including a first-generation LAI. The clinical question that comes up frequently whether to switch patients stabilized for many years on a first-generation LAI to a newer one (to reduce the risk of TD) was answered in a randomized switch trial [32]. More patients switched from haloperidol or fluphenazine decanoate to long-acting risperidone microspheres experienced treatment failure compared to patients who did not switch. Like in any medication switch, there is a group of patients that should have stayed on their treatment, something you unfortunately only know in hindsight.

As expected, the side effect profiles in the aforementioned ACCLAIMS trial differed depending on the LAI: patients experienced more metabolic problems with

Table 18.3 Long-acting injectable antipsychotics

Drug	Dose strengths	Dose (IM) and frequency	Notes
Haloperidol decanoate [HALDOL DECANOATE] [PROLIXIN DECANOATE]	Vials 50 mg/ml Vials 100 mg/ml	50–200 mg monthly Other dose intervals are possible	Initiation: overlap with oral antipsychotic Loading dose strategy possible Maintenance dose equals 10 to 15× oral dose 100 to 150 mg IM monthly corresponds to 10 mg/d oral
Fluphenazine decanoate [PROLIXIN DECANOATE]	Vials 25 mg/ml	6.25–25 mg every 2 weeks Other dose intervals are possible	Initiation: overlap with oral antipsychotic 12.5 mg IM every 2 weeks corresponds to 10 mg/d oral
Risperidone microspheres [RISPERDAL CONSTA] [INVEGA SUSTENNA]	12.5 mg, 25 mg, 37.5 mg, 50 mg	12.5–50 mg every 2 weeks	Initiation: 3-week overlap with oral antipsychotic Main release of drug occurs 3 weeks after injection 50 mg every 2 weeks corresponds to 4 mg/d oral (50 mg is highest IM dose)
Risperidone implant-like gel (PERSERIS) Paliperidone palmitate [INVEGA SUSTENNA]	90 mg, 120 mg 39 mg, 78 mg, 117 mg, 156 mg, 234 mg	90 mg or 120 mg SC monthly [NB: subcutaneous] 39–234 mg monthly	No overlap with oral antipsychotic needed Loading dose of 234 mg [deltoid] to initiate (no oral overlap needed), 2nd dose 1 week later, and then monthly
[INVEGA TRINZA] [OLANZAPINE PAMOATE [ZYPREXA RELPREVV] [ABILIFY MAINTENA]	273 mg, 410 mg, 546 mg, 819 mg 150 mg, 210 mg, 300 mg, 405 mg	273–819 mg every 3 months 150 or 300 mg every 2 weeks 405 mg monthly	156 mg monthly corresponds to 9 mg/d oral Every 3 months dose can be used after 4 months of monthly injections 546 mg corresponds to 9 mg/d oral No overlap with oral antipsychotic need (higher initiation doses) Monitor for 3 hours of observation for postinjection delirium/sedation syndrome (PDSS) ^a 300 mg monthly corresponds to 10 mg/d oral Initiation: 2-week overlap with oral antipsychotic 300 mg corresponds to 10 mg/d oral, 400 mg to 15 mg/d

(continued)

Table 18.3 (continued)

Drug	Dose strengths	Dose (IM) and frequency	Notes
Aripiprazole lauroxil [ARISTADA] ^a	441 mg, 662 mg, 882 mg, 1064 mg	441,662,882 mg every 4 weeks; 882 mg every 6 weeks 1064 mg every 2 months	Initiation: 3-week overlap with oral antipsychotic Loading dose strategy with AL _{NCD} possible Inject rapidly due to non-Newtonian fluid characteristics Only lowest dose of 441 mg dose can be given in deltoid 441 mg monthly corresponds to 10 mg/d oral 662 mg monthly or 1064 mg every 2 months corresponds to 15 mg/d oral 882 mg monthly corresponds to 20 mg/d oral (highest IM dose)

Oral test dose required for all antipsychotic if patient has never been exposed to IM antipsychotic

AL_{NCD} Aripiprazole Lauroxil NanoCrystal Dispersion

^aSee REMS website for olanzapine pamoate

paliperidone palmitate and more EPS with haloperidol decanoate [33]. Otherwise, the side effect profiles for long-acting antipsychotics are identical to their short-acting, oral pendants. Pharmacokinetic differences due to the “smoother” plasma level curve in LAI-treated patients do not seem to translate into clinical advantages such as fewer side effects.

Practical clinical considerations can limit the choice of LAI. An injection-related complication unique to olanzapine is the onset of severe sedation, confusion, slurred speech, or coma within a few minutes to a few hours after the injection (median time from injection to symptoms: 25 minutes). This is seen when olanzapine is inadvertently injected directly into the bloodstream [34]. The risk of this postinjection delirium/sedation syndrome (PDSS) prevents patients from receiving LAI olanzapine in many outpatient community settings unless they can comply with a mandated risk mitigation program (i.e., being able to offer a 3-hour postinjection observation and having ready access to emergency response services).

Key Point

The choice of LAI is determined by patient preference that takes into account the side effect profile, injection frequency, and some systems requirements (e.g., having qualified nurses to administer the injections correctly) but not efficacy. Antipsychotics are now available for administration as infrequently as every 2 or 3 months, with even longer-acting preparations under investigation, leading to more convenience and built-in forgiveness vis-à-vis a delayed injection due to a missed appointment.

The older “decanoate” antipsychotics (haloperidol and fluphenazine) are oil-based (they are more painful when injected), while all the newer antipsychotics are water-based. Having an experienced clinic nurse is critical as giving injections has become more complicated compared to the days when we only had the decanoates. As opposed to the slow decanoate injection, aripiprazole lauroxil, for example, must be injected very rapidly because of its unique, non-Newtonian fluid characteristics; otherwise, it clogs the needle. The choice of injection site (deltoid or gluteal muscle) depends on the particular LAI.

Optimal dosing of LAIs, including the best way to initiate them, similarly requires experience and is best done with help from a clinician well-versed in the use of LAIs in order to avoid dosing mistakes. For many but not all antipsychotics, loading dose strategies are possible that simplify initial dosing and reduce or eliminate the need for initial oral supplementation (see Table 18.3). Some loading dose strategies lead to plasma levels within a few days, which allows you to use LAIs for acute treatment. The long-acting risperidone microsphere preparation has a 3-week lag period between the injection and the release of medications from the microsphere into the bloodstream [35]. In this case, a loading dose strategy is not possible, but oral supplementation is needed instead. Aripiprazole lauroxil can be initiated with a 1-day initiation regimen (one-time oral aripiprazole dose plus a one-time nanoparticle-formulated aripiprazole injection given together with the LAI) [36].

A low-dose approach for maintenance dosing risks losing the benefit (i.e., protection against relapse) from LAIs. Haloperidol decanoate, for example, had 1-year relapse rates of 60% in a clinical trial when a low dose was given (25 mg every month) which was greatly reduced to 15% when a high dose of 200 mg was administered [37]. Intermediate doses of 50 mg and 100 mg were almost as effective as the highest dose, with relapse rates of 25 and 23%, respectively. Interestingly, a trial comparing fluphenazine dosing 25 mg IM every 2 weeks versus every 6 weeks did not find an efficacy difference if the injection interval was extended beyond the customary 2 weeks for this LAI [38]. Interval adjustments with the newer second-generation antipsychotics need to be approached carefully, if at all as the pharmacokinetic properties can differ from decanoates, depending on how the medication is released from its storage site.

Limitations OF LAIs

While the longer half-life of LAIs is a desired pharmacokinetic property, it comes at the price of less dosing flexibility and a longer time to reach steady state. Dose adjustments are more difficult to make, and you may inadvertently underdose or overshoot. TDM is possible for all available first- and second-generation LAIs which can help optimize dosing by checking trough levels (blood level just prior to the next injection) (for TDM see Chap. 20 on drug interactions).

LAIs are no panacea: they are only a tool to prevent relapse and do not constitute comprehensive treatment of schizophrenia [39]. They cannot replace clozapine for those patients refractory to first-line antipsychotics. They may also become an end in and of itself, replacing rehabilitations and other therapeutic offers. Rather than used as tools to increase patient autonomy, there is a risk to use LAIs as coercive tools. LAIs still require patient consent (or assent) to be given the injection unless involuntary administration is approved by a court and a mechanism exists to enforce the treatment plan. Patients do not start to like LAIs if they did not like them orally. Antipsychotics including LAIs are also not perfect: in the aforementioned ACCLAIMS trial [29], 1/3 of patients experienced efficacy failure. (In a meta-analysis, 10% of patients on antipsychotics are hospitalized over the course of 1 year because of efficacy failure [2].) Relapse prevention remains a clinical point of concern even for patients on LAIs.

Last, for some patients, decreasing the frequency of clinic visits (e.g., switching from a monthly to an every 3-month injectable) to make it more convenient for patients may result in treatment disengagement. Letting a visiting nurse administer LAI at a patient's home so the patient does not have to come to clinic may have the unintended consequences of fragmenting care and clinic oversight if injections are late or missed. To paraphrase Einstein, make things convenient but not more convenient. Emphasize to patients the benefits from regular psychiatric treatment. Tie clinic visits to other goals, both for your patients (e.g., access entitlement programs) and yourself (e.g., to provide safe medical care via guideline-concordant medical monitoring). Like clozapine treatment, part of the efficacy from LAIs may stem from regular contact with the treatment team.

Tip

Setting up an “injection clinic” (similar to a clozapine clinic) can facilitate population-based management and improve medical monitoring and follow-up for no-shows. The clinic can be virtual, starting with a spreadsheet.

References

1. Wikipedia. Herberger, Sepp. Available from: https://en.wikipedia.org/wiki/Sepp_Herberger. Accessed on 7/1/2019.
2. Leucht S, Tardy M, Komossa K, Heres S, Kissling W, Salanti G, et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *Lancet*. 2012;379:2063–71.
3. Lauriello J, Perkins DO. Enhancing the treatment of patients with schizophrenia through continuous care. *J Clin Psychiatry*. 2019;80(1): pii. al18010ah2c. <https://doi.org/10.4088/JCP.al18010ah2c>.
4. Olagunju AT, Clark SR, Baune BT. Long-acting atypical antipsychotics in schizophrenia: a systematic review and meta-analyses of effects on functional outcome. *Aust N Z J Psychiatry*. 2019;53(6):509–27. <https://doi.org/10.1177/0004867419837358>.
5. Weiden PJ, Roma RS, Velligan DI, Alphs L, DiChiara M, Davidson B. The challenge of offering long-acting antipsychotic therapies: a preliminary discourse analysis of psychiatrist recommendations for injectable therapy to patients with schizophrenia. *J Clin Psychiatry*. 2015;76:684–90.
6. Hamann J, Kissling W, Heres S. Checking the plausibility of psychiatrists arguments for not prescribing depot medication. *Eur Neuropsychopharmacol*. 2014;24:1506–10.
7. Kane JM, Schooler NR, Marcy P, Achtyes ED, Correll CU, Robinson DG. Patients with early-phase schizophrenia will accept treatment with sustained-release medication (long-acting injectable antipsychotics): results from the recruitment phase of the PRELAPSE trial. *J Clin Psychiatry*. 2019;80(3):18m12546.
8. Alphs L, Benson C, Cheshire-Kinney K, Lindenmayer JP, Mao L, Rodriguez SC, et al. Real-world outcomes of paliperidone palmitate compared to daily oral antipsychotic therapy in schizophrenia: a randomized, open-label, review board-blinded 15-month study. *J Clin Psychiatry*. 2015;76:554–61.
9. Subotnik KL, Casaus LR, Ventura J, Luo JS, Hellermann GS, Gretchen-Doorly D, et al. Long-acting injectable risperidone for relapse prevention and control of breakthrough symptoms after a recent first episode of schizophrenia. A randomized clinical trial. *JAMA Psychiatry*. 2015;72:822–9.
10. Kishimoto T, Robenzadeh A, Leucht C, Leucht S, Watanabe K, Mimura M, et al. Long-acting injectable vs oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials. *Schizophr Bull*. 2014;40:192–213.
11. Buckley PF, Schooler NR, Goff DC, Hsiao J, Kopelowicz A, Lauriello J, et al. Comparison of SGA oral medications and a long-acting injectable SGA: the PROACTIVE study. *Schizophr Bull*. 2015;41:449–59.
12. Kane JM, Kishimoto T, Correll CU. Assessing the comparative effectiveness of long-acting injectable vs. oral antipsychotic medications in the prevention of relapse provides a case study in comparative effectiveness research in psychiatry. *J Clin Epidemiol*. 2013;66:S37–41.
13. Kishimoto T, Nitta M, Borenstein M, Kane JM, Correll CU. Long-acting injectable versus oral antipsychotics in schizophrenia: a systematic review and meta-analysis of mirror-image studies. *J Clin Psychiatry*. 2013;74:957–65.
14. Taipale H, Mittendorfer-Rutz E, Alexanderson K, Majak M, Mehtala J, Hoti F, et al. Antipsychotics and mortality in a nationwide cohort of 29,823 patients with schizophrenia. *Schizophr Res*. 2018;197:274–80.

15. Choudhry NK, Krumme AA, Ercole PM, Girdish C, Tong AY, Khan NF, et al. Effect of reminder devices on medication adherence: the REMIND randomized clinical trial. *JAMA Intern Med.* 2017;177:624–31.
16. National Institute for Health and Care Excellence. Psychosis and schizophrenia in adults: prevention and management. 2014. Available from: <https://www.nice.org.uk/guidance/cg178>. Accessed on 7/1/2019.
17. Taipale H, Mehtala J, Tanskanen A, Tiihonen J. Comparative effectiveness of antipsychotic drugs for rehospitalization in schizophrenia-a nationwide study with 20-year follow-up. *Schizophr Bull.* 2018;44:1381–7.
18. Nielsen RE, Hessellund KB, Valentim JB, Licht RW. Second-generation LAI are associated to favorable outcome in a cohort of incident patients diagnosed with schizophrenia. *Schizophr Res.* 2018;202:234–40.
19. Abdel-Baki A, Thibault D, Medrano S, Stip E, Ladouceur M, Tahir R, et al. Long-acting antipsychotic medication as first-line treatment of first-episode psychosis with comorbid substance use disorder. *Early Interv Psychiatry.* 2019 (in press).
20. Chou YH, Chu PC, Wu SW, Lee JC, Lee YH, Sun IW, et al. A systemic review and experts' consensus for long-acting injectable antipsychotics in bipolar disorder. *Clin Psychopharmacol Neurosci.* 2015;13:121–8.
21. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord.* 2018;20:97–170.
22. Lahteenvirta M, Tanskanen A, Taipale H, Hoti F, Vattulainen P, Vieta E, et al. Real-world effectiveness of pharmacologic treatments for the prevention of rehospitalization in a Finnish nationwide cohort of patients with bipolar disorder. *JAMA Psychiatry.* 2018;75:347–55.
23. Weiden PJ, Kim E, Bermak J, Turkoz I, Gopal S, Berwaerts J. Does half-life matter after antipsychotic discontinuation? A relapse comparison in schizophrenia with 3 different formulations of paliperidone. *J Clin Psychiatry.* 2017;78:e813–20.
24. Nakamura T, Kubota T, Iwakaji A, Imada M, Kapas M, Morio Y. Clinical pharmacology study of cariprazine (MP-214) in patients with schizophrenia (12-week treatment). *Drug Des Devel Ther.* 2016;10:327–38.
25. Correll CU, Potkin SG, Zhong Y, Harsanyi J, Szatmari B, Earley W. Long-term remission with cariprazine treatment in patients with schizophrenia: a post hoc analysis of a randomized, double-blind, placebo-controlled, relapse prevention trial. *J Clin Psychiatry* 2019;80(2): pii. 18m12495. <https://doi.org/10.4088/JCP.18m12495>.
26. Tiihonen J, Mittendorfer-Rutz E, Majak M, Mehtala J, Hoti F, Jedenius E, et al. Real-world effectiveness of antipsychotic treatments in a nationwide cohort of 29823 patients with schizophrenia. *JAMA Psychiatry.* 2017;74:686–93.
27. Freudenberg O, McEvoy JP. How much haldol D does Larry really need? *J Clin Psychiatry.* 1995;56:331–2.
28. Kane JM, Correll CU, Delva N, Gopal S, Savitz A, Mathews M. Low incidence of neuroleptic malignant syndrome associated with paliperidone palmitate long-acting injectable: a database report and case study. *J Clin Psychopharmacol.* 2019;39:180–2.
29. McEvoy JP, Byerly M, Hamer RM, Dominik R, Swartz MS, Rosenheck RA, et al. Effectiveness of paliperidone palmitate vs haloperidol decanoate for maintenance treatment of schizophrenia: a randomized clinical trial. *JAMA.* 2014;311:1978–87.
30. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med.* 2005;353:1209–23.
31. Stroup TS, Bareis NA, Rosenheck RA, Swartz MS, McEvoy JP. Heterogeneity of treatment effects of long-acting injectable antipsychotic medications. *J Clin Psychiatry.* 2019;80:18m12109.
32. Covell NH, McEvoy JP, Schooler NR, Stroup TS, Jackson CT, Rojas IA, et al. Effectiveness of switching from long-acting injectable fluphenazine or haloperidol decanoate to long-acting injectable risperidone microspheres: an open-label, randomized controlled trial. *J Clin Psychiatry.* 2012;73:669–75.

33. Freudenreich O. Paliperidone depot is not different from haloperidol in relapse prevention of schizophrenia, but different side effects should be considered. *Evid Based Ment Health.* 2014;17:110.
34. Meyers KJ, Upadhyaya HP, Landry JL, Chhabra-Khanna R, Falk DM, Seetharama Rao B, et al. Postinjection delirium/sedation syndrome in patients with schizophrenia receiving olanzapine long-acting injection: results from a large observational study. *BJPsych Open.* 2017;3:186–92.
35. Harrison TS, Goa KL. Long-acting risperidone: a review of its use in schizophrenia. *CNS Drugs.* 2004;18:113–32.
36. Meyer J, Jain R, Wehr A, Rege B, von Moltke L, Weiden PJ. 27 a new method for initiating treatment with the long-acting antipsychotic aripiprazole lauroxil. *CNS Spectr.* 2019;24:188–9.
37. Kane JM, Davis JM, Schooler N, Marder S, Casey D, Brauzer B, et al. A multidose study of haloperidol decanoate in the maintenance treatment of schizophrenia. *Am J Psychiatry.* 2002;159:554–60.
38. Carpenter WT Jr, Buchanan RW, Kirkpatrick B, Lann HD, Breier AF, Summerfelt AT. Comparative effectiveness of fluphenazine decanoate injections every 2 weeks versus every 6 weeks. *Am J Psychiatry.* 1999;156:412–8.
39. Carpenter WT Jr. Evidence-based treatment for first-episode schizophrenia? *Am J Psychiatry.* 2001;158:1771–3.

Additional Resources

Book

Haddad P, Lambert T, Lauriello J. Antipsychotic long-acting injections. 2nd ed. Oxford: Oxford University Press; 2016. – Excellent book to have for your injection clinic.

References

- Correll CU, Citrome L, Haddad PM, Lauriello J, Olfson M, Calloway SM, et al. The use of long-acting injectable antipsychotics in schizophrenia: evaluating the evidence. *J Clin Psychiatry.* 2016;77:1–24. – Review of the substantial evidence that favors LAIs over oral antipsychotics.
- Sajatovic M, Ross R, Legacy SN, Byerly M, Kane JM, DiBiasi F, et al. Initiating/maintaining long-acting injectable antipsychotics in schizophrenia/schizoaffective or bipolar disorder – expert consensus survey part 2. *Neuropsychiatr Dis Treat.* 2018;14:1475–92. – An expert consensus guide to the use of LAIs. You will note a lack of agreement about many practical issues (e.g., how long to treat with an oral agent to establish tolerability or how to switch between LAIs).
- Weiden PJ, Roma RS, Velligan DI, Alphs L, DiChiara M, Davidson B. The challenge of offering long-acting antipsychotic therapies: a preliminary discourse analysis of psychiatrist recommendations for injectable therapy to patients with schizophrenia. *J Clin Psychiatry.* 2015;76:684–90. – A good read to educate yourself about how to better communicate with patients about LAI as a good treatment modality.

Chapter 19

Adjunctive Medications



Essential Concepts

- Avoid antidepressants during acute episodes of psychosis, but consider antidepressants in schizophrenia patients with positive symptom remission who then develop full, syndromal depression, who have subsyndromal depression or suicidality, or who have persistent negative symptoms. Antidepressant treatment may be lifesaving if there is depression or demoralization.
- Benzodiazepines are useful for ancillary problems such as insomnia and anxiety disorders, if used judiciously. They can be used to stave off relapse, instead of increasing antipsychotics.
- Lithium is not useful for psychosis per se, and it carries the risk of neurotoxicity when combined with antipsychotics. Long-term nephrotoxicity is a concern when using lithium in a patient group that often has additional risk factors for kidney disease (e.g., diabetes).
- Lamotrigine may have a role as adjunctive treatment for clozapine patients, particularly if there is dysphoria or depression.
- Valproate is useful adjunctively in acute psychosis to decrease agitation quickly. Its value in the long-term management of schizophrenia is less clear, except possibly in cases with chronic irritability or excitability. It should not be used in female patients with childbearing potential.
- Carbamazepine is probably most useful (if at all) for patients with schizophrenia and neurologic problems. Its use is hampered by enzyme induction and serious side effects (Stevens-Johnson syndrome, bone marrow toxicity).
- Added topiramate may improve global psychopathology with the added benefit of weight loss. In routine clinical practice, it may be one of the more effective approaches for weight loss.

- Anticholinergics should only be used short-term because of impairment of memory.
- Many patients will take herbal preparations and other supplements. Do not forget to inquire about them in order to determine if they are safe.

“At some point, you have to get off the sandbar and suggest some type of treatment to help those in distress.”

—George B. Murray, MD, Massachusetts General Hospital (personal communication)

As I have stated throughout the book, antipsychotics are not antischizophrenic medications; their main usefulness lies in reducing positive symptoms acutely and preventing psychotic relapse in the long run. Since schizophrenia is a syndrome with nonpsychotic symptom clusters (e.g., affective symptoms), psychiatrists use medications from many other drug classes adjunctively to treat these residual symptoms. The literature is only a partial guide for clinicians as most add-on trials, should they exist are small and not necessarily applicable to the clinical problem at hand. Given this lack of large and well-controlled trials in this area of psychiatry, a meta-analysis of 42 combination strategies was unable to strongly recommend one particular strategy over another [1]. Clinicians also add medications to improve antipsychotic tolerability. The typical intervention is the addition of anticholinergics to manage EPS which is covered in this chapter; medications added to manage antipsychotic-associated weight gain are described in more detail in the chapter on medical morbidity and mortality (Chap. 25). After reading this chapter, read the chapters on drug interactions (Chap. 20) and on polypharmacy (Chap. 21) to prescribe combinations safely and to guard against prescribing too much, respectively, but be willing to try new treatments to help your patient, as the Dr. Murray’s dictum suggests. Clozapine augmentation for refractory psychosis is covered in the clozapine chapter (Chap. 17).

Antidepressants

Antidepressants are widely used in schizophrenia because dysphoria and depressive symptoms are common problems for patients. Although antidepressants seem like a good idea in this clinical scenario, their usefulness has never been clearly established [2]. Much of the literature on antidepressants for schizophrenia stems from the era of first-generation antipsychotics and tricyclic antidepressants and is of dubious value today. This older literature suggests that tricyclic antidepressants added during an acute psychotic symptom exacerbation will in fact impede resolution of psychosis, whereas post-psychotic depressive episodes are helped with antidepressants, and some patients will relapse if antidepressants are discontinued. This field of inquiry is hampered by high placebo response rate to antidepressants, 50%

in one study that compared sertraline with placebo in patients with remitted schizophrenia who had a depressive episode [3].

I want to highlight two findings from the more recent clinical trials literature. First, in chronic patients, there may be clinical benefit from adding citalopram for subsyndromal depressive symptoms [4] and suicidal ideation [5]. This is an important finding as patients in this “mid-career” group are often struggling with residual symptoms while the treatment system (for whom they are stable) is no longer as invested as during earlier phases of illness. I suspect that suicidal ideation reflecting demoralization and subsyndromal depression are not uncommon in this patient group. Treating depression and demoralization with antidepressants may be lifesaving, as noted in an observational study [6]. Second, in first-episode patients, depression should be considered to be part and parcel of untreated psychosis that resolves in parallel with the improvement in psychosis once antipsychotics are initiated [7]. The benefit of adding antidepressants for residual depression after the first episode, while common practice, may be minimal [8]. Taken together, adjunctive antidepressant treatment may have an overall positive effect on depressive symptoms in schizophrenia, with a low risk of exacerbating psychosis or causing significant side effect [9]. The benefit may be clearer in chronic patients. One last point, a large comparative effectiveness study using US national Medicaid data found reduced risks for a psychiatric hospitalization when an antidepressant was added compared to an antipsychotic, a benzodiazepine, or a mood stabilizer [10]. This strategy was safe whereas the addition of benzodiazepines or mood stabilizers had worse clinical outcomes, including an increased risk for hospitalizations and increased mortality, respectively.

Tip

Avoid antidepressants in acutely psychotic patients with schizophrenia; an antipsychotic alone will usually lead to resolution of depressive symptoms as well. Consider adding an antidepressant in the post-psychotic or stable period if a full depressive episode develops in otherwise remitted patients or if patients experience persistent subsyndromal depressive symptoms or suicidality. Make sure you measure the severity of depression with a rating scale. (The specific Calgary Depression Scale for Schizophrenia, or CDSS [11], works satisfactorily, but I have found the patient-rated Beck Depression Inventory easy to use serially.)

There is a small literature that selective serotonin reuptake inhibitors (SSRIs) can be a useful adjunct to treat negative symptoms [9]. However, the effect size is small, and I am unsure if you can see a clinical difference in most patients. Nevertheless, given the lack of good treatment options, a time-limited trial can be justified. Last, low-dose mirtazapine (15 mg) has been shown in a controlled trial to be rather effective for the treatment of akathisia [12]. Remember to follow a patient’s weight if you

prescribe mirtazapine for long-term use. Last, antidepressants are often used for patients with schizophrenia and comorbid OCD. Patient in this “schizo-obsessive” subgroup are often difficult to treat [13].

Anxiolytics

Most psychiatrists who treat many patients with schizophrenia will agree with me that benzodiazepines are a very useful medication class for adjunctive use in selected patients with schizophrenia, both during the acute treatment phase and the chronic phase, even though very few pharmacology trials have been conducted. Benzodiazepines are devoid of many side effects that characterize antipsychotics, like weight gain or tardive dyskinesia. However, prescribe this class of medication judiciously as there are clear risks associated with benzodiazepines. For example, keep in mind the possibility if impairing cognition (but also the deleterious effects of untreated anxiety on performance). In elderly patients, benzodiazepines are one class that is reliably linked to falls [14]. Chronic use of benzodiazepines can lead to addiction, so always prescribe this class of medications with safeguards in place and only for short periods of time if possible. I admit that I care for patients where discontinuing benzodiazepines has been all but impossible, despite my best intentions to use them only briefly. An added concern is an association with increased mortality in schizophrenia patients who are chronically prescribed benzodiazepines [15], particularly high doses [6].

Table 19.1 gives indications for which benzodiazepines could be considered. Note that benzodiazepines are first-line treatments for catatonia. Their use with clozapine is a relative contraindication.

Tip

If your patients experiences some stress and you are worried about a psychotic relapse, add diazepam (Valium) 5–10 mg up to three times per day for a few days, instead of increasing the antipsychotic (to avoid side effects related to higher antipsychotic doses) [17].

Table 19.1 Clinical indications for benzodiazepines in schizophrenia

Acute agitation ^a
Hostility and aggression ^a
Nonspecific anxiety and specific anxiety syndromes
Early signs of psychotic relapse
Akathisia
Insomnia
Catatonic symptoms
Tardive dyskinesia

^aMay cause paradoxical behavioral disinhibition [16]

Clinical Vignette

Matthias suffers from schizophrenia with well-controlled positive symptoms but has difficulties getting around in the city because he avoids the subway (“people make me nervous”). Initially attributed to subtle paranoia and social uneasiness commonly seen in schizophrenia, you learn he also avoids escalators and bridges. On further questioning, he endorses clear and frequently panic attacks and avoidance of situations he fears could induce a panic attack. The addition of a benzodiazepine completely stopped the panic attacks, and he is venturing out more easily in the city. Comorbid, syndromal anxiety disorders, in particular panic disorder, are not uncommon in schizophrenia and can be easily missed, yet are very treatable with either benzodiazepines or SSRIs [18]. Consider treating panic attacks even if they occur in response to paranoia.

Sedative-Hypnotics

Sleep problems are very common in schizophrenia and usually multifactorial, defying one simple solution such as prescribing a hypnotic agent. Often, a specific, diagnosable sleep disorder is present. Common disorders are obstructive sleep apnea [19, 20] or simply poor sleep hygiene and sleep-wake cycle disturbances [21] for which benzodiazepines are of little to no use. Patients with no day structure, who sleep in until noon, are inactive during the rest of the day, and perhaps even take a nap, will simply not be tired before midnight. In those patients, prescribing a hypnotic will exacerbate rather than help the problem. Some more activating antipsychotics (i.e., antipsychotics who are not sedating) can cause insomnia, and adding a benzodiazepine at night remedies this problem. Insomnia can be a problem for patients who are used to sedating antipsychotic when they are switched to less sedating antipsychotics. If I need to symptomatically treat insomnia, I will consider a sedative-hypnotic (e.g., zolpidem) and not forego this medication class at the expense of more risky approaches (e.g., the antipsychotic quetiapine which causes weight gain and increases QTc). The American Society of Sleep Medicine published guidelines with recommendations for and against specific agents [22]. Other than confirming the value of the Z-drugs, they recommend doxepin (3 mg or 6 mg) or suvorexant for sleep maintenance insomnia and ramelteon for sleep onset insomnia. They specifically recommend against using low-dose trazodone, melatonin, or diphenhydramine which are all commonly used medications in community settings because of their perceived safety despite little to no evidence for their efficacy.

Lithium

Lithium alone is probably ineffective for the core symptoms of schizophrenia [23]. A trial of lithium is nevertheless reasonable in refractory cases with periodicity in the presentation or significant admixture of mood symptoms such as irritability with

aggression. Lithium add-on may be a consideration for patients who are depressed and suicidal. The risks from lithium use must be taken into consideration, particularly the higher side effect burden and the risk of neuroleptic malignant syndrome (NMS) and other neurotoxic effects (e.g., delirium, increased extrapyramidal symptoms, or EPS) from combining lithium with antipsychotics [24]. The risk for serious episodes of lithium intoxications is not negligible in complex patients, and the psychosocial situation has to be taken into account if one plans to use lithium for maintenance treatment of schizophrenia. Last, the long-term risk of lithium-related kidney damage needs to be taken into account, particularly as patients with serious mental illness often have other risk factors for kidney disease, like diabetes.

Antiepileptic Drugs

Lamotrigine

Lamotrigine has shown some promise in controlled clinical trials as an add-on medication for patients with schizophrenia [25]. I try it in patients with persistent psychosis, particularly if they have chronic dysphoria or dysthymia as well (remember, it is FDA-approved for maintenance treatment of bipolar disorder but seems to be mostly used as a treatment for bipolar depression [26]). Clinical trials in schizophrenia have generally used total daily doses of 200 to 400 mg per day. I have found lamotrigine to be one of the better-tolerated antiepileptic drugs used in psychiatry, with little sedation or weight gain. However, you must strictly follow titration guidelines to minimize the risk for Stevens-Johnson syndrome or similar cutaneous reactions [27]. After a decade or so of using it, I admit that my enthusiasm has waned. Two more recent clinical trials have been disappointing in that they failed to replicate earlier positive trials [28]. I mostly reserve its use now for patients with refractory psychosis on clozapine but may still use it for patients with prominent depressive symptoms who do not want to try lithium or an antidepressant.

Valproate

Valproate may be one of the most overused medications in the management of schizophrenia spectrum disorders, despite lack of evidence for its benefit [29]. It is somewhat useful for the acute management of psychosis by hastening a response [30], although its role in the long-term management of schizophrenia is questionable. When valproate is combined with an antipsychotic, acutely psychotic patients become calmer more quickly than with the antipsychotic alone, as early as on the third day; however, both approaches lead to the same degree of improvement after several weeks of treatment [31]. I think it is a common mistake to simply continue valproate with an outpatient if it was added in the hospital for faster behavior control (which in and of itself is not a bad idea given the risks of injury if there is agita-

tion and aggression during psychosis). For refractory and chronic irritability, valproate is frequently used (including by me), although the benefit of this approach is not well documented [29]. In one meta-analysis of antiepileptic drugs, valproate (and topiramate) was found to offer some benefit [32].

In my experience, valproate is not as well tolerated as many seem to think; sedation, worsened EPS, and weight gain are expectable problems (in addition to a host of potentially more severe problems such as pancreatitis). In women, take into account that valproate is associated with polycystic ovary syndrome (PCOS) and other endocrine abnormalities [33]. Worse, valproate is one of the most teratogenic agents psychiatrists prescribe, with well-documented risk for major congenital malformations [34]. Despite these risks, the adherence to guideline recommendations for valproate-treated female patients to prevent pregnancy (contraception) or poor pregnancy outcomes (folic acid supplementation) is low in patients with serious mental illness [35]. Taking into account these real-world difficulties in safely prescribing valproate, the best harm reduction approach may severely restrict the use of valproate in women of childbearing age (i.e., consider it contraindicated unless no other treatment exists). This stance was recently taken by the European Union's FDA, the European Medicines Agency [36].

Carbamazepine and Oxcarbazepine

Apart from unclear efficacy for schizophrenia [37], the clinical use of carbamazepine is limited by enzyme induction and a host of potentially quite dangerous side effects (allergic skin reactions, aplastic anemia, and agranulocytosis). It should not be combined with clozapine because of its bone marrow toxicity. Carbamazepine is a pan-inducer of P450 enzymes which can make it difficult to reach sufficient anti-psychotic drug levels. Stevens-Johnson syndrome and other toxic cutaneous reactions are well-established complications. Those are 10x more common in patients with a particular HLA genotype found in many Asian populations, and HLA genotyping is required before starting treatment in any patient who has Asian ancestry [38]. I consider carbamazepine a third-line add-on treatment unless there are electroencephalogram (EEG) abnormalities. Oxcarbazepine is sometimes used instead of carbamazepine as it has less, albeit not zero, enzyme induction [39]. Hyponatremia is a well-described long-term concern with both carbamazepine and oxcarbazepine, particularly in elderly patients, and more so for oxcarbazepine [40].

Topiramate

In one meta-analysis, topiramate was found to improve psychopathology globally while offering good tolerability when added to ongoing antipsychotic treatments [41]. In addition, patients lost weight. This is noteworthy as most medications used to treat schizophrenia are associated with weight gain. As noted earlier, topiramate

was one of two antiepileptic drugs in a different meta-analysis of clozapine augmentation with antiepileptic drugs (the other drug being valproate) that offered some global benefit for clozapine-treated patients [32]. In this second analysis, topiramate had a high discontinuation rate due to side effects.

I have found topiramate quite effective for some weight loss in some patients. There may be a dose effect, and I use between 100 and 200 mg/day. (For comparison, topiramate is marketed for weight loss in a combination pill with phentermine, with the highest dose strength containing 92 mg of topiramate.) Like always in medicine, “results may vary,” as they say on TV. I once treated a patient who experienced a dramatic weight loss and who underwent an extensive cancer work-up until I discovered that his PCP had added topiramate for migraine prophylaxis. While tolerability of topiramate seems good in my patient population, I remain worried about possible negative effects on cognition. In patients with serious mental illness, somewhat worse cognition may neither be reported by patients nor easily observed by staff but still have functional consequences that go unrecognized. On the other hand, patients with normal cognition may be more sensitive to the cognitive side effects of topiramate, an effect observed in a study with normal volunteers [42].

Anticholinergics

Chronic use of anticholinergics is very problematic: they impair memory and complex attention [43], both of which are impaired in schizophrenia to begin with (see Chap. 29). Other concerns include concerns for worsening tardive dyskinesia and increasing the peripheral side effect burden in the form of constipation or blurred vision. Some patients misuse anticholinergics for their psychoactive effects (to get a “buzz”) [44], but others perhaps in an attempt to treat unpleasant extrapyramidal side effects (EPS) caused by antipsychotic treatment [45].

The acute use of anticholinergic medications for a week or so (e.g., to prevent an acute dystonic reaction in high-risk cases of young patients who receive first-generation antipsychotics) can be a reasonable and effective clinical decision [46]. In selected cases, a trial with an anticholinergic to eliminate the possibility of secondary negative symptoms from subtle EPS can be considered. However, the World Health Organization (WHO) in an old yet still valid consensus statement strongly recommends against the routine, prophylactic use of anticholinergics [47]. Instead, anticholinergics should only be used in cases in which Parkinsonism actually develops and other measures prove ineffective. Even in those cases, attempts to discontinue the anticholinergic after 3 months are recommended. If EPS develop with an antipsychotic, try to switch to an antipsychotic that does not require the chronic use of anticholinergics. With the availability of many antipsychotics with different EPS propensity, this is usually possible unless there is severe sensitivity to EPS (in which case clozapine may be indicated). Alternatively, you could try adding the equally effective anti-Parkinson drug amantadine for milder cases of EPS instead of an anticholinergic [48]. Amantadine does not hinder new learning [49], and it

Table 19.2 Dosing guidelines for anticholinergics, diphenhydramine, and amantadine

Agent	Benztropine equivalents ^a	Typical dose range	Maximum dose/day
Benztropine (Cogentin) ^b	1 mg	0.5–2 mg bid	6 mg
Biperiden (Akineton) ^b	2 mg	1–2 mg bid/tid	16 mg
Trihexyphenidyl (Artane)	3.5 mg	2–5 mg bid/tid	15 mg
Diphenhydramine	30 mg	25–50 mg tid/qid	400 mg
Amantadine (Symmetrel)	N/A	100 mg bid/tid	300 mg
<i>For comparison:</i>			
Chlorpromazine	300 mg		
Clozapine	50–100 mg		

^aBased on Refs. [43, 51]^bAvailable for intramuscular use in the United States

might even have a positive effect on weight [50]. Table 19.2 presents dosing guidelines for anticholinergics and amantadine.

Herbal Remedies and Supplements

Often, patients and their families will pursue holistic treatments including taking herbal remedies and supplements that are perceived as “natural,” so be sure to ask about them. Many add-on dietary supplements may be reasonably safe, and if families value them, I will not get in the way. Given often poor diets and drug use in patients with serious mental disorders [52], taking vitamin supplements may not be unreasonable. I will occasionally advise against specific products, certainly if I believe they are medically unsafe (e.g., taking extra iron without having iron deficiency), if they interfere with my treatment, but particularly if patients spend a lot of money they do not have on snake oils. It requires some skill to help patients separate the hope from irresponsible reporting of small pilot trials to a realistic assessment of the chances that this particular supplement will be more effective than clozapine. Be particularly careful about wide-ranging claims of “neuroprotection” which is problematic as the inflationary use of terms renders them useless.

For selected patients, specific vitamins can be recommended [53], such as folate or L-methylfolate, for patients with negative symptoms, particularly if they carry the low-activity variant of methylene tetrahydrofolate reductase (MTHFR) enzyme (see Chap. 28). This is a good example of a biological subtype that guides your add-on treatment. Some dietary supplements have good support based on preclinical models of schizophrenia and even some clinical trials (e.g., antioxidants like NAC which stands for N-acetylcysteine) [54] or omega-3 polyunsaturated fatty acids [55]. In some instances, promising treatments have failed when subjected to scrutiny in well-conducted trials. A case in point is the failure of omega-3 fatty acids to prevent transition to psychosis in high-risk patients [56] (see Chap. 9). Among the herbal medicines, *Ginkgo biloba* is the most studied and is reported to have some

benefit for schizophrenia [57] and tardive dyskinesia [58]. In the case of *Ginkgo*, most trials have been conducted in China [59] which may limit generalizability. All in all, I have found the benefit of these add-on strategies for the unselected, average clinic patients usually rather disappointing.

Tip

Remain flexible and open to progress. I encourage my patients to send me information about what supplement they are taking or what they want to try so I can arrive at my own conclusions about its merits. Keep in mind that families today are often better informed than you about new research findings, particularly if they are not exactly in your area of interest. Families can become a resource to help you keep up with research that they find intriguing. You may learn something from them.

References

1. Correll CU, Rubio JM, Inczedy-Farkas G, Birnbaum ML, Kane JM, Leucht S. Efficacy of 42 pharmacologic cotreatment strategies added to antipsychotic monotherapy in schizophrenia: systematic overview and quality appraisal of the meta-analytic evidence. *JAMA Psychiatry*. 2017;74:675–84.
2. Freudenreich O, Goff DC. Treatment of psychotic disorders. In: Ciraulo DA, Shader RI, editors. *Pharmacotherapy of depression*. 2nd ed. New York: Humana Press; 2011. p. 185–96.
3. Addington D, Addington J, Patten S, Remington G, Moamai J, Labelle A, et al. Double-blind, placebo-controlled comparison of the efficacy of sertraline as treatment for a major depressive episode in patients with remitted schizophrenia. *J Clin Psychopharmacol*. 2002;22:20–5.
4. Zisook S, Kasckow JW, Golshan S, Fellows I, Solorzano E, Lehman D, et al. Citalopram augmentation for subsyndromal symptoms of depression in middle-aged and older outpatients with schizophrenia and schizoaffective disorder: a randomized controlled trial. *J Clin Psychiatry*. 2009;70:562–71.
5. Zisook S, Kasckow JW, Lanouette NM, Golshan S, Fellows I, Vahia I, et al. Augmentation with citalopram for suicidal ideation in middle-aged and older outpatients with schizophrenia and schizoaffective disorder who have subthreshold depressive symptoms: a randomized controlled trial. *J Clin Psychiatry*. 2010;71:915–22.
6. Tiihonen J, Mittendorfer-Rutz E, Torniainen M, Alexanderson K, Tanskanen A. Mortality and cumulative exposure to antipsychotics, antidepressants, and benzodiazepines in patients with schizophrenia: an observational follow-up study. *Am J Psychiatry*. 2016;173:600–6.
7. Rybakowski JK, Vansteelandt K, Szafranski T, Thys E, Jarema M, Wolfgang Fleischhacker W, et al. Treatment of depression in first episode of schizophrenia: results from EUFEST. *Eur Neuropsychopharmacol*. 2012;22:875–82.
8. Goff DC, Freudenreich O, Cather C, Holt D, Bello I, Diminich E, et al. Citalopram in first episode schizophrenia: the DECIFER trial. *Schizophr Res*. 2019;208:331–7.
9. Helper B, Samara MT, Huhn M, Klupp E, Leucht C, Zhu Y, et al. Efficacy and safety of antidepressants added to antipsychotics for schizophrenia: a systematic review and meta-analysis. *Am J Psychiatry*. 2016;173:876–86.
10. Stroup TS, Gerhard T, Crystal S, Huang C, Tan Z, Wall MM, et al. Comparative effectiveness of adjunctive psychotropic medications in patients with schizophrenia. *JAMA Psychiatry*. 2019;76:508–15.

11. Addington D, Addington J, Maticka-Tyndale E. Assessing depression in schizophrenia: the Calgary Depression Scale. *Br J Psychiatry Suppl.* 1993;163:39–44.
12. Poyurovsky M, Bergman J, Pashinian A, Weizman A. Beneficial effect of low-dose mirtazapine in acute aripiprazole-induced akathisia. *Int Clin Psychopharmacol.* 2014;29:296–8.
13. Scotti-Muzzi E, Saide OL. Schizo-obsessive spectrum disorders: an update. *CNS Spectr.* 2017;22:258–72.
14. Woolcott JC, Richardson KJ, Wiens MO, Patel B, Marin J, Khan KM, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med.* 2009;169:1952–60.
15. Fontanella CA, Campo JV, Phillips GS, Hiance-Steelesmith DL, Sweeney HA, Tam K, et al. Benzodiazepine use and risk of mortality among patients with schizophrenia: a retrospective longitudinal study. *J Clin Psychiatry.* 2016;77:661–7.
16. Mancuso CE, Tanzi MG, Gabay M. Paradoxical reactions to benzodiazepines: literature review and treatment options. *Pharmacotherapy.* 2004;24:1177–85.
17. Carpenter WT Jr, Buchanan RW, Kirkpatrick B, Breier AF. Diazepam treatment of early signs of exacerbation in schizophrenia. *Am J Psychiatry.* 1999;156:299–303.
18. Temmingh H, Stein DJ. Anxiety in patients with schizophrenia: epidemiology and management. *CNS Drugs.* 2015;29:819–32.
19. Winkelman JW. Schizophrenia, obesity, and obstructive sleep apnea. *J Clin Psychiatry.* 2001;62:8–11.
20. Stubbs B, Vancampfort D, Veronesi N, Solmi M, Gaughran F, Manu P, et al. The prevalence and predictors of obstructive sleep apnea in major depressive disorder, bipolar disorder and schizophrenia: a systematic review and meta-analysis. *J Affect Disord.* 2016;197:259–67.
21. Poon YPY, Kan CK, Yeung WF, Chung KF. Delayed sleep-wake phase disorder and delayed sleep-wake phase in schizophrenia: clinical and functional correlates. *Schizophr Res.* 2018;202:412–3.
22. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med.* 2017;13:307–49.
23. Leucht S, Helfer B, Dold M, Kissling W, McGrath JJ. Lithium for schizophrenia. *Cochrane Database Syst Rev.* 2015;10:CD003834.
24. Goldman SA. Lithium and neuroleptics in combination: is there enhancement of neurotoxicity leading to permanent sequelae? *J Clin Pharmacol.* 1996;36:951–62.
25. Tiihonen J, Hallikainen T, Ryynanen OP, Repo-Tiihonen E, Kotilainen I, Eronen M, et al. Lamotrigine in treatment-resistant schizophrenia: a randomized placebo-controlled crossover trial. *Biol Psychiatry.* 2003;54:1241–8.
26. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord.* 2018;20:97–170.
27. Calabrese JR, Sullivan JR, Bowden CL, Suppes T, Goldberg JF, Sachs GS, et al. Rash in multicenter trials of lamotrigine in mood disorders: clinical relevance and management. *J Clin Psychiatry.* 2002;63:1012–9.
28. Goff DC, Keefe R, Citrome L, Davy K, Krystal JH, Large C, et al. Lamotrigine as add-on therapy in schizophrenia: results of 2 placebo-controlled trials. *J Clin Psychopharmacol.* 2007;27:582–9.
29. Wang Y, Xia J, Helfer B, Li C, Leucht S. Valproate for schizophrenia. *Cochrane Database Syst Rev.* 2016;11:CD004028.
30. Casey DE, Daniel DG, Wasif AA, Tracy KA, Wozniak P, Sommerville KW. Effect of divalproex combined with olanzapine or risperidone in patients with an acute exacerbation of schizophrenia. *Neuropsychopharmacology.* 2003;28:182–92.
31. Casey DE, Daniel DG, Tamminga C, Kane JM, Tran-Johnson T, Wozniak P, et al. Divalproex ER combined with olanzapine or risperidone for treatment of acute exacerbations of schizophrenia. *Neuropsychopharmacology.* 2009;34:1330–8.

32. Zheng W, Xiang YT, Yang XH, Xiang YQ, de Leon J. Clozapine augmentation with antiepileptic drugs for treatment-resistant schizophrenia: a meta-analysis of randomized controlled trials. *J Clin Psychiatry*. 2017;78:e498–505.
33. Zhang L, Li H, Li S, Zou X. Reproductive and metabolic abnormalities in women taking valproate for bipolar disorder: a meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. 2016;202:26–31.
34. Gotlib D, Ramaswamy R, Kurlander JE, DeRiggi A, Riba M. Valproic acid in women and girls of childbearing age. *Curr Psychiatry Rep*. 2017;19:58.
35. Gotlib D, Perelstein E, Kurlander J, Zivin K, Riba M, Muzik M. Guideline adherence for mentally ill reproductive-aged women on treatment with valproic acid: a retrospective chart review. *J Clin Psychiatry*. 2016;77:527–34.
36. European Medicines Agency. Valproate and related substances. 2018. Available from: <https://www.ema.europa.eu/en/medicines/human/referrals/valproate-related-substances-0>. Accessed on 7/1/2019.
37. Leucht S, Helfer B, Dold M, Kissling W, McGrath J. Carbamazepine for schizophrenia. *Cochrane Database Syst Rev*. 2014;(5):CD001258.
38. Tangamornsuksan W, Chaiyakunapruk N, Somkrua R, Lohitnavy M, Tassaneeyakul W. Relationship between the HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. *JAMA Dermatol*. 2013;149:1025–32.
39. Stefan H, Feuerstein TJ. Novel anticonvulsant drugs. *Pharmacol Ther*. 2007;113:165–83.
40. Berghuis B, van der Palen J, de Haan GJ, Lindhout D, Koeleman BPC, Sander JW, et al. Carbamazepine- and oxcarbazepine-induced hyponatremia in people with epilepsy. *Epilepsia*. 2017;58:1227–33.
41. Correll CU, Maayan L, Kane J, Hert MD, Cohen D. Efficacy for psychopathology and body weight and safety of topiramate-antipsychotic cotreatment in patients with schizophrenia spectrum disorders: results from a meta-analysis of randomized controlled trials. *J Clin Psychiatry*. 2016;77:e746–56.
42. Barkley CM, Hu Z, Fieberg AM, Eberly LE, Birnbaum AK, Leppik IE, et al. Individual differences in working memory capacity predict topiramate-related cognitive deficits. *J Clin Psychopharmacol*. 2018;38:481–8.
43. Minzenberg MJ, Poole JH, Benton C, Vinogradov S. Association of anticholinergic load with impairment of complex attention and memory in schizophrenia. *Am J Psychiatry*. 2004;161:116–24.
44. Torrents R, Ferre JF, Konareff A, Hemery P, Sherwin K, Lassalle C, et al. Misuse of trihexyphenidyl (Artane) on Reunion Island. *J Clin Psychopharmacol*. 2018;38:250–3.
45. Zemishlany Z, Aizenberg D, Weiner Z, Weizman A. Trihexyphenidyl (Artane) abuse in schizophrenic patients. *Int Clin Psychopharmacol*. 1996;11:199–202.
46. Arana GW, Goff DC, Baldessarini RJ, Keepers GA. Efficacy of anticholinergic prophylaxis for neuroleptic-induced acute dystonia. *Am J Psychiatry*. 1988;145:993–6.
47. World Health Organization Heads of Centres Collaborating in WHO Co-ordinated Studies on Biological Aspects of Mental Illness. Prophylactic use of anticholinergics in patients on long-term neuroleptic treatment. A consensus statement. *Br J Psychiatry*. 1990;156:412.
48. Silver H, Geraisy N, Schwartz M. No difference in the effect of biperiden and amantadine on parkinsonian- and tardive dyskinesia-type involuntary movements: a double-blind crossover, placebo-controlled study in medicated chronic schizophrenic patients. *J Clin Psychiatry*. 1995;56:167–70.
49. McEvoy JP, McCue M, Spring B, Mohs RC, Lavori PW, Farr RM. Effects of amantadine and trihexyphenidyl on memory in elderly normal volunteers. *Am J Psychiatry*. 1987;144:573–7.
50. Graham KA, Gu H, Lieberman JA, Harp JB, Perkins DO. Double-blind, placebo-controlled investigation of amantadine for weight loss in subjects who gained weight with olanzapine. *Am J Psychiatry*. 2005;162:1744–6.
51. de Leon J. Benzotropine equivalents for antimuscarinic medication. *Am J Psychiatry*. 2005;162:627.

52. McCreadie RG, Scottish Schizophrenia Lifestyle G. Diet, smoking and cardiovascular risk in people with schizophrenia: descriptive study. *Br J Psychiatry*. 2003;183:534–9.
53. Brown HE, Roffman JL. Vitamin supplementation in the treatment of schizophrenia. *CNS Drugs*. 2014;28:611–22.
54. Brown HE, Roffman JL. Emerging treatments in schizophrenia: highlights from recent supplementation and prevention trials. *Harv Rev Psychiatry*. 2016;24:e1–7.
55. Pawelczyk T, Grancow-Grabka M, Kotlicka-Antczak M, Trafalska E, Pawelczyk A. A randomized controlled study of the efficacy of six-month supplementation with concentrated fish oil rich in omega-3 polyunsaturated fatty acids in first episode schizophrenia. *J Psychiatr Res*. 2016;73:34–44.
56. McGorry PD, Nelson B, Markulev C, Yuen HP, Schafer MR, Mossaheb N, et al. Effect of omega-3 polyunsaturated fatty acids in young people at ultrahigh risk for psychotic disorders: the NEURAPRO randomized clinical trial. *JAMA Psychiatry*. 2017;74:19–27.
57. Sarris J. Herbal medicines in the treatment of psychiatric disorders: 10-year updated review. *Phytother Res*. 2018;32:1147–62.
58. Soares-Weiser K, Rathbone J, Ogawa Y, Shinohara K, Bergman H. Miscellaneous treatments for antipsychotic-induced tardive dyskinesia. *Cochrane Database Syst Rev*. 2018;3:CD000208.
59. Chen X, Hong Y, Zheng P. Efficacy and safety of extract of Ginkgo biloba as an adjunct therapy in chronic schizophrenia: a systematic review of randomized, double-blind, placebo-controlled studies with meta-analysis. *Psychiatry Res*. 2015;228:121–7.

Additional Resources

Website

European Medicines Agency. Valproate and related substances. 2018. Available from: <https://www.ema.europa.eu/en/medicines/human/referrals/valproate-related-substances-0>. Accessed on 7/1/19. – As my contribution to safe prescribing, I discourage the use of valproate in women with childbearing potential unless there is a clear indication for.

Article

Correll CU, Rubio JM, Inczedy-Farkas G, Birnbaum ML, Kane JM, Leucht S. Efficacy of 42 pharmacologic cotreatment strategies added to antipsychotic monotherapy in schizophrenia: systematic overview and quality appraisal of the meta-analytic evidence. *JAMA Psychiatry*. 2017;74:675–84. – An extensive review of the literature on adjunctive approaches, with no clear winner.

Chapter 20

Antipsychotic Drug Interactions



Essential Concepts

- Almost all antipsychotics are metabolized to varying degrees by the hepatic cytochrome P450 (CYP450) isoenzymes 3A4, 2D6, and 1A2. Some have additional non-P450 metabolism, which lowers the risk for drug interactions by providing alternative pathways if major pathways are inhibited.
- Because 3A4 and 2D6 metabolize the bulk of antipsychotics, inducers, inhibitors, or genetic variants of those enzymes are important clinically.
- Smoking increases the metabolism of 1A2-dependent antipsychotics, requiring dose adjustment for olanzapine and clozapine.
- Although antipsychotics are generally safe even with excessive drug serum levels, pimozide, mesoridazine/thioridazine (cardiac toxicity), and clozapine (seizures and hypotension) are exceptions.
- Antipsychotic plasma drug levels are useful in clinical situations in which you want to confirm that a patient has either very low (close to zero) or very high (toxic) drug levels, due to genetic factors or due to nonadherence. Drug levels provide actionable information compared to pharmacogenomic testing which is most helpful to explain unexpectedly high or low drug levels in *adherent* patients.

“I beseech you, in the bowels of Christ, think it possible you may be mistaken.” [1]
—Oliver Cromwell, Lord protector of England, 1599–1658

“I don’t think this is related to my medicine,” you hear yourself telling your patient. Never dismiss a patient’s complaint about a side effect, but consider the possibility that you are wrong and the patient is right, possibly because of a genetic variant affecting drug metabolism or a drug interaction (Cromwell puts the patient’s complaint in more dramatic language).

In this chapter, I focus on *pharmacokinetic* drug interactions related to the all-important hepatic cytochrome P450 (CYP450) enzyme system that does the bulk of metabolism of psychotropics, including antipsychotics, and how it relates to serum drug levels. Renal excretion and plasma binding are generally not a clinical issue with antipsychotics, at least not in routine outpatient care. Important *pharmacodynamic* drug interactions are mentioned for commonly used medication combinations.

Antipsychotic Drug Metabolism

Antipsychotics are mainly metabolized by the hepatic CYP450 enzyme system, but other systems, like the phase II glucuronidation enzyme system (uridine 5'-diphospho-glucuronosyltransferase, or UGT) or P-glycoprotein, contribute to the deactivation and elimination of antipsychotics. For antipsychotic metabolism, the most important cytochrome isoenzymes are 3A4 and 2D6 for almost all antipsychotics, with 1A2 playing a role in a few drugs. Consult Table 20.1 for the main metabolic pathways for commonly used antipsychotics.

Key Point

Note in Table 20.1 that most antipsychotics are metabolized by more than one enzyme or enzyme system. For example, haloperidol, olanzapine, and ziprasidone can be directly deactivated through CYP450-independent pathways. This serves as a built-in safety valve, particularly if enzyme systems cannot be inhibited or induced, as in the case of aldehyde oxygenase.

It is useful to know that antipsychotics do not inhibit P450 enzymes (with the exception of 2D6, which is inhibited by some antipsychotics) and that they do not induce P450 enzymes. In that respect, antipsychotics can generally be safely added to other treatment regimens.

It helps to recall a few general facts about the P450 system to anticipate drug interactions. Some (but not all) isoenzymes can be induced or inhibited, the most important ones being 3A4 and 1A2. Antipsychotic drug levels will be lower in the presence of an inducer and higher in the presence of an inhibitor if either of these isoenzymes metabolizes the antipsychotic. The main inducer for 1A2 is not a medication but smoking (polycyclic aromatic hydrocarbons in tobacco smoke, not nicotine [4]); consequently, smokers predictably require higher doses, compared to nonsmokers, of 1A2-dependent antipsychotics (i.e., olanzapine and clozapine). When smokers quit smoking, olanzapine and clozapine levels will rise, and the dose should be adjusted [5, 6]. The downregulation of 1A2 after smoking cessation occurs rapidly, and dose reductions should be considered already within a few days of stopping [7].

Table 20.1 Antipsychotic metabolic pathways

Antipsychotic	Relevant metabolite	CYP450 metabolism	Alternative metabolism
First-generation antipsychotics			
Haloperidol	HP ^a	3A4, 2D6	Glucuronidation
Fluphenazine	7-OH-FLU ^b	2D6	
Perphenazine		2D6	
Second-generation antipsychotics			
Asenapine		1A2	Glucuronidation
Clozapine	nor-CLZ ^c	1A2, 3A4, 2D6	
Iloperidone		3A4, 2D6	
Lurasidone		3A4	
Olanzapine		1A2	Glucuronidation
Paliperidone			Renal (non-P450)
Quetiapine		3A4	
Risperidone	9-OH-RISP ^d	2D6, 3A4	
Ziprasidone		3A4 (33%)	Aldehyde oxidase (66%)
Third-generation antipsychotics (partial agonists)			
Aripiprazole	One metabolite	2D6, 3A4	
Brexpiprazole		2D6, 3A4	
Cariprazine	Two metabolites	3A4, 2D6	

Based on Refs. [2, 3]

Main metabolizing enzymes in **bold**

^aHP⁺ is likely a neurotoxic metabolite

^b7-Hydroxyfluphenazine

^cNorclozapine or N-desmethylclozapine; only 10% of activity, thus contributing little to the active moiety

^d9-Hydroxyrisperidone = paliperidone; active moiety is risperidone plus 9-hydroxyrisperidone; 9-hydroxyrisperidone is equipotent with risperidone

Pharmacogenomics

Differences between patients in how drugs are metabolized are to a large part determined by genetic factors. Many metabolizing enzymes show genetic polymorphism, the most important ones being the highly polymorphic 2D6 gene [8]. 2D6 genetic polyphorphism results in four clinical phenotypes: so-called extensive (or normal) metabolizers, poor metabolizers (inactive enzyme), intermediate metabolizers (some enzyme activity), and ultrarapid metabolizers (greatly increased enzyme activity) [9]. There is no way of knowing your patient's 2D6 genotype without genotyping, although you can take into account a patient's ethnic background (e.g., some Middle Eastern and African populations have high rates of ultrarapid metabolizers) when considering side effects or nonresponse at usual doses. 2D6 phenotypes matter for risperidone, or older antipsychotics like that have significant 2D6-dependent metabolism [10]: ultrarapid metabolizers might never achieve sufficient plasma levels and be accused of nonadherence; poor metabolizers will appear exquisitely sensitive to standard doses (extrapyramidal symptoms, or EPS) and be

labeled “histrionic.” Genetic 1A2 variants may be important to consider in nonresponsive clozapine patients (see Case below).

With the advent of pharmacogenomics and personalized medicine, genetic testing for enzymes involved in drug metabolism and proteins responsible for drug action has become available [11]. Sometimes, families arrive for their initial visit with a printout of their genetic testing that includes metabolizing enzymes so you need to be able to interpret the results and put them in a clinical context for the family. Importantly, genotyping does not provide you with a full picture unless the complete metabolic pathway is known, including the relative importance of involved isoenzymes. Genetic information merely provides an often incomplete snapshot of somebody’s *potential* for unusual drug metabolism due to genetic factors. Hopefully, we will soon be able to incorporate genetic information to assess the risk for serious side effects (e.g., clozapine-induced agranulocytosis) [12]. At this point, biomarkers other than those involved in drug metabolism are not clinically useful for matching antipsychotics and patients with regard to treatment response [13].

Tip

Undoubtedly, pharmacogenomics and personalized medicine will expand, and possibly one day, we will be in a position to choose the dose and type of antipsychotic based on somebody’s genetic makeup before you start treatment. In the interim, check an antipsychotic drug level if you are unsure about the adequacy of dosing. The information you get from drug levels is immediately actionable as you get distal information about the summative effects of genes and drug interactions (and adherence). Pharmacogenomic testing can then confirm that genetic variants are in fact responsible for unexpectedly high or low drug level (in an *adherent* patient) and guide your subsequent dosing and even drug selection.

Clinical Approach to Drug Interactions

You have two concerns with regard to drug interactions between antipsychotics and the other medicines your patient is taking: loss of antipsychotic efficacy and increased side effects. Usually, you only have to worry about loss of antipsychotic efficacy if a metabolic inducer is present (but realize that this could be an increase in smoking during times of stress, not just another medication for olanzapine and clozapine). Pharmacodynamic interactions that negate antipsychotic efficacy are rare and easy to anticipate (i.e., concomitant treatment with a dopamine agonist). Increased side effects are concerning if they lead to acute tolerability problems (e.g., akathisia or an acute dystonic reaction), if they are life-threatening (e.g., cardiac arrhythmias), or if they increase the long-term morbidity risk (e.g., for tardive dyskinesia or cardiovascular disease). Antipsychotics as a class have a very high margin

of safety, and many patients tolerate even large increases in drug levels. For most antipsychotics, the risk from a higher drug level is EPS and sedation; for clozapine, however, it is seizures and orthostatic hypotension, and pimozide and mesoridazine/thioridazine become cardiotoxic. Keep in mind a risk factor model (i.e., the additive effects of psychotropics and other factors like low potassium or low magnesium determine the risk of torsades rather than one psychotropic being the main culprit) when combining QTc-prolonging medications [14]. Adding ziprasidone to methadone would be an example of additive risk factors increasing the risk for arrhythmias. The risk factor model can similarly be applied to the additive effects of anticholinergic medications. This so-called anticholinergic load impairs complex cognition [15].

Tip

The most important safeguard against drug interaction, other anticipation, is timely clinical follow-up. Ask your patient to call you or follow up with you within a week after you have added a medication or made a dose change. Record motor examination results and side effect complaints prior to your change so that you have a baseline. A baseline ECG to monitor the QTc interval can help you determine if adding a QTc-prolonging medication is safe.

Before you add an antipsychotic (or any psychotropic) to your patient's regimen, consider the following points to avoid some problems related to drug interactions:

- Do not prescribe pimozide or mesoridazine/thioridazine (the latter are no longer widely available since the branded products were withdrawn from the market by the manufacturer) unless under exceptional circumstances. Their cardiac safety profile does not justify the risk. I remain unconvinced that pimozide is particularly effective for delusional disorder which is sometimes used as an argument for its ongoing need, and I do not use it.
- Adjust antipsychotic dose based on smoking status (particularly for olanzapine and clozapine). The prospect of lowering the clozapine dose may add motivation for patients to quit smoking.
- Look at the overall medication regimen, and, to anticipate problems, spot the main inducers or inhibitors from other medical specialties.
- Look at your patient and judge how the patient would tolerate a drug interaction: How sick is the patient medically? Frail patients might tolerate drug interactions very poorly.
- Consider antipsychotic drug levels in certain clinical situations (see next section).
- Appreciate the limited value of pharmacogenomic testing at this point (see previous section). It is most helpful to confirm unusual metabolism after you have obtained a drug level in adherent patients.

Tip

Use electronic drug interaction databases thoughtfully and be aware of their limitations. In many instances, drug interaction warnings are based on theoretical interaction that in fact have never been described clinically or are so rare that they cannot guide your prescribing. Sometimes, they are simply wrong (just because a machine produces a warning does not mean it is accurate). All too often, you find yourself merely clicking through pop-up warnings as the information provided does not help you manage the patient in front of you – an example of alarm fatigue. To make matters worse, once a patient takes more than two or three medications, drug interactions are almost impossible to predict. Last, many drug interactions are only a relative, not absolute, contraindication to combining medications. Refer to Additional Resources for one of the better drug interaction database.

Therapeutic Drug Monitoring (TDM)

TDM has a long history in psychiatry. Most psychiatrists are familiar with it for lithium and tricyclic antidepressants. However, TDM is underused with antipsychotics [16]. Given the lack of dose-response curves for antipsychotics (no “therapeutic window”), many psychiatrists believe that it does not make sense to base dosing on antipsychotic drug levels. This may be a case of throwing the baby out with the bathwater. Antipsychotic drug levels can vary widely between patients for any given dose, and excluding the extremes of drug blood levels (below detectable levels or dangerously high levels) is important information, particularly in complex situations [17]. For many antipsychotics approved in the last two decades, clinical trials have included blood level determinations, and typical plasma level ranges for clinically effective doses are known at the population level. With the development of new assays for antipsychotics, there has been renewed interest in TDM [18]. You could view TDM as a tool for personalized antipsychotic dosing.

TDM offers benefits for these clinical situations [16]:

- Clinicians can make informed decisions regarding the *root* causes of treatment complications, particularly if a poor response to an antipsychotic is due to nonadherence or unusual genetically determined metabolism; the former is more common.
- It similarly allows you to determine if patients who show poor tolerability to an antipsychotic have slow elimination (i.e., toxic blood levels) or if they are highly sensitive to a medication (i.e., side effects despite blood levels that by most patients are well tolerated).
- It identifies patients at higher relapse risk (i.e., those at the low end of typical blood levels), recently shown for the CATIE sample [19]. Such patients may be at increased relapse risk because partial adherence may lead to insufficient blood levels (no margin of error).

- TDM may help you work with patients who want to find the “lowest effective dose.” I would hesitate to lower the antipsychotic dose in patients whose drug level is already on the low end of blood levels reported in clinical efficacy trials.
- It takes the guessing out of complex medication regimens (i.e., more than two drugs), where drug interactions can no longer be meaningfully predicted.
- It helps optimize dosing of long-acting injectable antipsychotics which is more difficult during the initial weeks and months due to the long half-life of the injectable. Check trough level just prior to the next injection to avoid underdosing or overshooting.

You need to avoid overinterpreting blood level results that are in the normal, expected blood level range as there is no tight relationship between blood levels and symptoms. However, this does not mean there is no relationship at all, particularly at the group level. I was involved in a clozapine trial where patients were randomized to low [50–150 n/mL], medium [200–300 ng/mL], and high [350–450 ng/mL] clozapine *serum levels* (not clozapine dose) [20]. While patients assigned to the medium or high serum level groups showed solid clinical improvements, most patients in the low serum level showed no improvement. We also learned in this trial that there were very large clozapine blood level differences *between patients* for a given dose. Moreover, patients assigned to the high serum level group experienced more sedation that correlated with slowing on the electroencephalogram [21]. Together, these results strongly argue for routine clozapine TDM in order to optimize the chances for having a successful clozapine trial (i.e., giving a sufficient clozapine dose but also not an unnecessarily high dose).

In the not so distant future, point-of-care (POC) testing with immediate antipsychotic blood level results may offer psychiatrists information that changes their treatment (e.g., to adjust the dose of a long-acting antipsychotic). Many psychiatrists are familiar with POC testing for diabetes or anticoagulants for which it is well established [22]. The biggest challenge may be to incorporate antipsychotic blood levels into the workflow of psychiatric offices and clinics.

I want to add one last point that relates to TDM: it is very useful to know that the elimination of antipsychotics follows linear pharmacokinetics; you need to measure a drug level only once during steady-state conditions to know the dose-serum level curve for this patient. Linear pharmacokinetics means you double the dose, you double the level; you halve the dose, you halve the level [23].

Clinical Vignette

A man in his 30s with refractory schizophrenia finally agreed to clozapine treatment after many years of chronic psychosis and numerous psychiatric hospitalizations. Following a titration to 100 mg of clozapine per day, his steady-state clozapine level was 30 ng/mL. He was a smoker, and nonadherence seemed unlikely given supervised medication administration in a group home. Clinically, his psychosis had remained unchanged, not surprisingly given the low clozapine blood level. The family had obtained pharmacoge-

nomic testing that showed the 1A2 *1F/*1F enzyme variant (a variant highly inducible by smoking).

This is an example of a systematic approach to a patient with refractory schizophrenia and the value of therapeutic drug monitoring coupled with pharmacogenomic testing. The results have treatment implications: the patient will require higher than usual clozapine doses to reach a target plasma level of 300–400 ng/mL (assuming linear pharmacokinetics and no variability, he would need 1000 mg clozapine daily to reach 300 ng/mL). Some psychiatrists may judiciously use fluvoxamine to “slow down” the very active metabolizing 1A2 enzyme and reduce the need to exceed the FDA-approved clozapine dose of 900 mg/day.

Drug Interactions by Medication Class

Antipsychotics with Antidepressants

The combination of antipsychotics with antidepressants is usually not problematic, but you need to follow your patients clinically as some antidepressants block metabolizing enzymes and lead to higher antipsychotic serum levels. Recall that there are clear differences between selective serotonin reuptake inhibitors (SSRIs) with regard to inhibition P450 enzymes, and in complex situation, you might want to choose an SSRI with few interactions (e.g., citalopram or venlafaxine). Fluoxetine is a strong inhibitor of 2D6, paroxetine of 3A4, and fluvoxamine of 1A2 [2]. Fluvoxamine should be added on judiciously to clozapine and olanzapine as it can more than double serum levels of the antipsychotic [24, 25].

Antipsychotics and Mood Stabilizers

This combination has a good safety record and is usually not problematic. Be careful, however, when you combine lithium with antipsychotics, since severe neurotoxic reactions (resembling a delirium and neuroleptic malignant syndrome) can occur [3]. This combination can also lead to more EPS. Similarly, you often see more EPS, particularly tremor, in patients treated with valproate plus an antipsychotic. Valproate does not significantly interfere with the metabolism of antipsychotics. Older antiepileptic drugs (carbamazepine is a good example) are problematic in any medication regimen as they are pan-inducer of P450 and other drug-metabolizing enzymes [26]. As a rule of thumb, if you double the dose of the antipsychotic, you usually achieve sufficient plasma levels for patients who need to take carbamazepine. I have had patients on carbamazepine where I could not reach satisfactory drug levels (heroic doses add cost and might not be covered by the

insurance company). In such cases, I would switch to oxcarbazepine, which has a lower (but not zero) propensity to induce 3A4 [27]. Lamotrigine can slightly increase some antipsychotic serum levels (via non-P450 mechanism), but the combination is clinically very well tolerated. Antipsychotic TDM may be particularly helpful in treatment regimens that contain antiepileptic drugs [27].

Antipsychotics with Benzodiazepines

The main concern here is pharmacodynamic in the form of additive central nervous system depression. There is a small literature of disastrous consequences (i.e., death) from giving benzodiazepine to clozapine patients. In clinical practice, carefully added benzodiazepines are well tolerated, and benzodiazepines are routinely used in patients on antipsychotics, including clozapine. Be sure to warn patients about drinking alcohol while taking benzodiazepines and antipsychotics, and discuss how taking CNS-active drugs may impair driving. Keep in mind that many a wide variety of medications used in medicine are CNS-active and be mindful of not adding unnecessarily to the “sedative load,” particularly in older patients [28].

References

1. Wikiquote. Oliver Cromwell. Available from: https://en.wikiquote.org/wiki/Oliver_Cromwell. Accessed on 1 July 2019.
2. Schatzberg AF, Nemeroff CB, editors. The American Psychiatric Association publishing textbook of psychopharmacology. 5th ed. Arlington: American Psychiatric Association Publishing; 2017.
3. Freudenberg O, Goff DC. Antipsychotics. In: Ciraulo DA, Shader RI, Greenblatt DJ, Creelman W, editors. Drug interactions in psychiatry. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 177–241.
4. Zevin S, Benowitz NL. Drug interactions with tobacco smoking. An update. Clin Pharmacokinet. 1999;36:425–38.
5. van der Weide J, Steijns LS, van Weelden MJ. The effect of smoking and cytochrome P450 CYP1A2 genetic polymorphism on clozapine clearance and dose requirement. Pharmacogenetics. 2003;13:169–72.
6. Djordjevic N, Radmanovic B, Cukic J, Baskic D, Djukic-Dejanovic S, Milovanovic D, et al. Cigarette smoking and heavy coffee consumption affecting response to olanzapine: the role of genetic polymorphism. World J Biol Psychiatry. 2018;1–53.
7. Anderson GD, Chan LN. Pharmacokinetic drug interactions with tobacco, cannabinoids and smoking cessation products. Clin Pharmacokinet. 2016;55:1353–68.
8. Yang Y, Botton MR, Scott ER, Scott SA. Sequencing the CYP2D6 gene: from variant allele discovery to clinical pharmacogenetic testing. Pharmacogenomics. 2017;18:673–85.
9. Zhou SF. Polymorphism of human cytochrome P450 2D6 and its clinical significance: Part I. Clin Pharmacokinet. 2009;48:689–723.
10. Zhou SF. Polymorphism of human cytochrome P450 2D6 and its clinical significance: part II. Clin Pharmacokinet. 2009;48:761–804.
11. Hoehne MR, Morris-Rosendahl DJ. The role of genetics and genomics in clinical psychiatry. Dialogues Clin Neurosci. 2018;20:169–77.

12. Li KJ, Solomon HV, DeLisi LE. Clozapine pharmacogenomics: a review of efficacy, pharmacokinetics, and agranulocytosis. *Curr Opin Psychiatry*. 2018;31:403–8.
13. Allen JD, Bishop JR. A systematic review of genome-wide association studies of antipsychotic response. *Pharmacogenomics*. 2019;20:291.
14. Beach SR, Celano CM, Sugrue AM, Adams C, Ackerman MJ, Noseworthy PA, et al. QT prolongation, torsades de pointes, and psychotropic medications: a 5-year update. *Psychosomatics*. 2018;59:105–22.
15. Minzenberg MJ, Poole JH, Benton C, Vinogradov S. Association of anticholinergic load with impairment of complex attention and memory in schizophrenia. *Am J Psychiatry*. 2004;161:116–24.
16. Predmore Z, Mattke S, Horvitz-Lennon M. Potential benefits to patients and payers from increased measurement of antipsychotic plasma levels in the management of schizophrenia. *Psychiatr Serv*. 2018;69:12–4.
17. Horvitz-Lennon M, Mattke S, Predmore Z, Howes OD. The role of antipsychotic plasma levels in the treatment of schizophrenia. *Am J Psychiatry*. 2017;174:421–6.
18. Hiemke C, Bergemann N, Clement HW, Conca A, Deckert J, Domschke K, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. *Pharmacopsychiatry*. 2018;51:9–62.
19. Melkote R, Singh A, Vermeulen A, Remmerie B, Savitz A. Relationship between antipsychotic blood levels and treatment failure during the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study. *Schizophr Res*. 2018;201:324–8.
20. VanderZwaag C, McGee M, McEvoy JP, Freudenreich O, Wilson WH, Cooper TB. Response of patients with treatment-refractory schizophrenia to clozapine within three serum level ranges. *Am J Psychiatry*. 1996;153:1579–84.
21. Freudenreich O, Weiner RD, McEvoy JP. Clozapine-induced electroencephalogram changes as a function of clozapine serum levels. *Biol Psychiatry*. 1997;42:132–7.
22. Yip PM, Venner AA, Shea J, Fuezery A, Huang Y, Massicotte L, et al. Point-of-care testing: a position statement from the Canadian Society of Clinical Chemists. *Clin Biochem*. 2018;53:156–9.
23. Freudenreich O. Clozapine drug levels guide dosing [Pearls series]. *Curr Psychiatry*. 2009;8:78.
24. Polciwiartek C, Nielsen J. The clinical potentials of adjunctive fluvoxamine to clozapine treatment: a systematic review. *Psychopharmacology*. 2016;233:741–50.
25. Chiu CC, Lane HY, Huang MC, Liu HC, Jann MW, Hon YY, et al. Dose-dependent alterations in the pharmacokinetics of olanzapine during coadministration of fluvoxamine in patients with schizophrenia. *J Clin Pharmacol*. 2004;44:1385–90.
26. Patsalos PN, Spencer EP, Berry DJ. Therapeutic drug monitoring of antiepileptic drugs in epilepsy: a 2018 update. *Ther Drug Monit*. 2018;40:526–48.
27. Spina E, Pisani F, de Leon J. Clinically significant pharmacokinetic drug interactions of antiepileptic drugs with new antidepressants and new antipsychotics. *Pharmacol Res*. 2016;106:72–86.
28. van der Meer HG, Taxis K, Teichert M, Griens F, Pont LG, Wouters H. Anticholinergic and sedative medication use in older community-dwelling people: a national population study in the Netherlands. *Pharmacoepidemiol Drug Saf*. 2019;28:315–21.

Additional Resources

Websites

<https://reference.medscape.com/drug-interactionchecker> – Medscape's Drug Interaction Checker provides a tiered approach that differentiates between critical (i.e., contraindication or use alternative) and less critical drug-drug interactions. You can enter as many drugs as needed at the same time.

Articles

- Beach SR, Celano CM, Sugrue AM, Adams C, Ackerman MJ, Noseworthy PA, et al. QT prolongation, torsades de pointes, and psychotropic medications: a 5-year update. *Psychosomatics*. 2018;59:105–22. – Clinically useful article about the difficulties with the interpretation and management of the QTc interval.
- Hiemke C, Bergemann N, Clement HW, Conca A, Deckert J, Domschke K, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. *Pharmacopsychiatry*. 2018;51:9–62. – Very German in its encyclopedic nature, this is an excellent guideline for everything you want to know about TDM. Even though developed by a German working group (the AGNP or “Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie”), the article is helpfully in English.

Chapter 21

Polypharmacy



Essential Concepts

- Polypharmacy is a fuzzy concept since, at the molecular level, antipsychotic monotherapy constitutes intrinsic polypharmacy.
- Appropriate reasons for combination treatments are as follows: added efficacy for the primary symptom cluster, supplemental symptom control for comorbid symptoms, and adjunctive to increase tolerability.
- Fixing unnecessary polypharmacy (deprescribing) requires patience and persistence and can run counter to patient expectations. Knowing how to stop a medication is as important as knowing how to start it.
- Time-limited trials and measuring outcomes are safeguards against polypharmacy. A small improvement in a symptom might be neither clinically meaningful nor justification for the long-term risk of the medication.
- Polypharmacy can flag treatment refractoriness.
- The acute treatment requires more and/or different medications than the maintenance phase (cf. oncology and cancer treatment).
- Hippocratic medicine demands that you treat diseases (and not simply symptoms) and that your intervention is effective (and not simply safe). Sometimes this would suggest doing nothing, one of the most difficult things to do in medicine.

“Simplify, simplify.” [1]

—Henry David Thoreau, American transcendentalist, 1817–1862

Today, treatment with more than one medication is the norm, not the exception, for almost any disorder (e.g., hypertension, diabetes), including psychiatric disorders (e.g., bipolar disorder). Unless you have a framework that guides your prescribing practice, patients are at risk for unnecessary and harmful polypharmacy (and you are at risk of being quickly relegated to merely dispensing medications as the

patient's psychopharmacologist [2]). In 2006, up to one third of psychiatric outpatients received three or more psychiatric medications [3]. A decade earlier, this percentage was only 17%. I would argue that this increase represents overtreatment today rather than undertreatment 10 years ago. Overtreatment is clearly a challenge that is now recognized by medical societies. The Choosing Wisely campaign represents one visible effort at the level of professional organizations to reduce unnecessary tests and wasteful prescribing [4], in recognition of a shared professional responsibility to limit risks to patients and to be stewards of scarce resources. The American Psychiatric Association has signed on to this effort; one recommendation relates to polypharmacy and states: "don't routinely prescribe two or more antipsychotics concurrently" [5]. You may want to sign on yourself, asking the Kantian question: would my way of prescribing lead to good, socially acceptable outcomes if followed by all physicians treating similar patients?

Key Point

You must treat schizophrenia spectrum disorders as the syndromes that they are: for most patients, chronic illnesses for which you try to prevent relapse and improve function along the way. With this longitudinal (and overarching) view, any prescribing that is merely symptom-based and cross-sectional will lead to polypharmacy since there is invariably another symptom to target. Sometimes, the most difficult thing to do in medicine is to do nothing.

We have no agreed-upon definition of what constitutes "polypharmacy." In its narrowest sense, polypharmacy refers to the combination of two or more antipsychotics (same-class polypharmacy). In a slightly broader sense, polypharmacy refers to using two or more medications for the same condition. In its broadest sense, it is simple pill counting. Polypharmacy often has a negative connotation and implies the use of (too) many or unnecessary medications. What is rarely talked about is that at the molecular level, the concept might not be very meaningful at all [6]. Monotherapy with clozapine at the pill-counting level is polypharmacy at the molecular level – clozapine targets a multitude of receptors in the brain. With such a fuzzy concept, it is easy to see how one person's rational combination treatment becomes another person's irrational polypharmacy. Still "polypharmacy" has some face validity as a shorthand description for a medication regimen that seems overly complex and that therefore warrants review.

"Just doing something" is a poor long-term strategy, particularly in the management of a lifelong disease with no spontaneous remission. Not every complaint should make you reach for the prescription pad. Apart from cost, clear risks from polypharmacy are the potential for drug interactions, broadening side effects or even limiting effectiveness if medication effects cancel each other out (Table 21.1). The more medications a patient is prescribed, the more opportunities there are for making mistakes taking them or administering them. Psychologically, it can prevent the hard work of acceptance if one focuses on the elusive goal of a cure and result

Table 21.1 Risks of antipsychotic combination treatment

Loss of “atypicality” of antipsychotics (if a first-generation antipsychotic is added to a second-generation antipsychotic)
Added toxicities (short and long term)
Expense
Drug-drug interactions (leading to antipsychotic drug level changes)
Loss of efficacy (if the added medication counteracts the mechanism of action)
Opportunity cost (non-medication solutions are not explored)

in a dependent patient who relies solely on pills, a iatrogenic loss of self-efficacy. Last, even a “safe” medicine can have an idiosyncratic, catastrophic side effect for your patient – a point often overlooked by staff members who pressure you to do something (i.e., prescribe a medicine) for a challenging patient.

Appropriate Use of Polypharmacy

In medicine, “rational” polypharmacy is evidence of a good understanding of pathophysiology. Today, diabetes or hypertension is often treated with medication combinations that target different enzymes in the metabolic pathways or different receptors, acting synergistically. In schizophrenia, it is paradoxically the lack of knowledge of pathophysiology that justifies the empirical use of multiple medications. Polypharmacy is also logical for a complex disease like schizophrenia if you accept that antipsychotics are not “antischizophrenics”: it makes sense to use other drug classes to target symptom clusters not ameliorated by antipsychotics (e.g., depression – see Chap. 19).

These are then three reasonable clinical scenarios (and one more controversial) in which you would use more than one psychotropic:

- For added efficacy – If there is treatment resistance and you need to augment a partial response of core symptoms to your primary treatment.
- For supplemental symptom control – If you need to target specific symptoms, for example, insomnia or agitation not covered by your primary treatment.
- For treatment intolerance – If adjunctive medications are needed to improve tolerability of your primary treatment.
- For psychological support – Engagement of patients with medications in a supportive mode can require the prescribing of medications with marginal or no benefit. This cannot be your principle mode of operation, and it is only justified if done safely and judiciously.

Treating patients who are only partially responsive to antipsychotics remains more an art than a science, and frequently a second antipsychotic is added despite a paucity of data [7]. Risperidone augmentation of clozapine-treated patients is one example of an antipsychotic-antipsychotic combination that became prominent

based on uncontrolled trials. Theoretically, adding dopamine blockade might be useful for some patients who need more dopamine blockade than the fairly loosely bound clozapine provides. Subsequent double-blind trials and meta-analyses have not conclusively resolved the question of added efficacy for this particular combination (or any other combination), leaving the clinician with the need to decide on a case-by-case basis [8, 9].

If you decide you must add a second antipsychotic (even though all schizophrenia guidelines recommend antipsychotic monotherapy), propose a time-limited trial, measure psychopathology, and judge if any change in psychopathology is clinically useful. If the change is not obvious to other people, it probably does not justify the added risks. Which psychotropics to combine is discussed in more detail in the chapters on ancillary medications (Chap. 19), on refractory psychosis (Chap. 12), and on clozapine (Chap. 17).

Tip

Polypharmacy can be a sign of true (i.e., biological) poor treatment response. Make sure you are using the most effective medication for a given diagnosis, including clozapine for refractory schizophrenia; only augment clozapine, not other antipsychotics.

Diagnosing Questionable Polypharmacy

In order to judge a regimen with regard to its appropriateness, ask yourself four questions: What kind of disease are you dealing with? What kind of patient has the disease? What kind of physician is trying to manage the patient and his disease? What kind of society are you practicing in? Answering these questions will help you identify the four main etiological factors (the disease, the patient, the physician, the healthcare system or society) that contribute to polypharmacy [10] (Table 21.2).

Common reasons for complex regimens are due to the following scenarios:

- Schizophrenia is treated according to an acute illness model with an expectation of complete resolution of symptoms and return to previous function (an aspirational and unfortunately often illusory goal): As a result, many regimens are too aggressive.
- The patient is not optimally treated: a refractory patient not receiving clozapine is often managed with polypharmacy.
- The lack of clinically meaningful benefit of the intervention is not recognized: No target symptom was identified or measured; medications are then simply continued at each visit.
- Unrecognized pseudo-refractoriness: For example, partial nonadherence or drug use is responsible for symptoms, not efficacy failure.

Table 21.2 Differential diagnosis of etiological factors leading to polypharmacy

Disease factors (“Biology”): What kind of disease?
Refractory disease
Suboptimal treatment
Side effect management
Misdiagnoses
Missed diagnoses
Patient factors (“Psychology I”): What kind of patient?
Insufficient adherence
Personality style
Consumer choice paradigm
Illness behavior
Physician factors (“Psychology II”): What kind of physician?
Pharmacological hedonism or Calvinism
Early or late adopter
Symptom-based prescribing
Self-image as powerful healer
Fear of patient dissatisfaction
Systems (“Sociology”): What kind of society?
Market-based system with consumer choice
Fragmented healthcare system
Outside pressures (other stakeholders)

Based on Ref. [10]

- Fear of worsening symptoms: The specter of “it would be worse” is raised in refractory patients who are very symptomatic despite maximum treatment, and because of this fear (and not because of proven benefit), no medications are ever discontinued.
- The natural fluctuations of symptoms are not taken into account: If medications were added during an illness flare-up that would have resolved spontaneously, the added medication is falsely credited with having been effective.
- A cross taper was initiated but never completed: There is a risk that your taper will stall when decisions are made on a day-to-day basis.
- The fragmentation in our healthcare system adds many cooks to an imagined team: Rarely are treatment plans coordinated between providers, including between inpatient and outpatient psychiatry and also between medicine and psychiatry.

Maintenance medications and those used during an acute illness phase are not necessarily the same. For example, induction chemotherapy for cancer is usually different from maintenance regimens to prevent cancer recurrence. Similarly, the goals of psychiatric inpatient treatment (rapid stabilization and short-term safety) are different from outpatient treatment (finding the best-tolerated maintenance regimen with the best long-term safety), requiring different pharmacology.

Clinical Vignette

Your patient with schizophrenia had been stable for many years on monotherapy with an antipsychotic while living in a group home, but becomes psychotic a few months after moving into his own apartment. His old antipsychotic is restarted in the hospital since nonadherence is suspected as the main cause of his relapse. Because of the patient's level of agitation, valproate is added, and his diagnosis is changed to schizoaffective disorder. When he does not seem to improve after 1 week, a second antipsychotic is added. Because he also complains about insomnia, an anxiolytic is added during the hospital stay as well. He is discharged on two antipsychotics, valproate, and an anxiolytic.

Unless you recognize that in the case medications were given for acute symptom control, patients like this are at risk for inappropriate long-term pharmacology, particularly if they are seen by different psychiatrists who do not know the longitudinal history (in this case, that the patient with schizophrenia was rather well treated with antipsychotic monotherapy for many years). I have seen patients on ancient legacy regimens that have simply been continued by each new psychiatrist that cared for the patient, in order not to "rock the boat."

Preventing Polypharmacy

At least in your own patients, you have some control over how you practice. While you may lose some patients who perceive you as "stingy" compared to other colleagues, I would view the number of prescriptions as a quality measure. If every patient on your case load receives four prescriptions (antipsychotic, mood stabilizer, antidepressant, and anxiolytic), your approach may be problematic. In your outpatient practice, making a medication change or adjustment at every patient visit may be another sign of problematic prescribing.

Key Point

As a physician, you need to not only know how to start medications but equally importantly, how to stop them. The former is often easy, the latter can be hard. Therefore, think twice before starting or adding a medication. Not starting a medication but seeking non-pharmacological interventions may be the most important thing you can do to actually help a patient. Time-limited trials for most medications are a principle that ought to limit the accruing of medications.

The best protection against becoming a mere psychotropic pill pusher may just be to know yourself and to have a conceptual view of the greater picture, including the society you live in. There are two frameworks that I find useful in looking at my

own medication prescribing in order to prevent polypharmacy. The first framework was most clearly articulated by my colleague (and former neighbor) Nassir Ghaemi: Do you practice Hippocratic medicine or not? Truly Hippocratic medicine is based on two principles which Ghaemi summarizes as the Osler rule and the Holmes rule [11]. Sir William Osler, the great physician, recognized that humans are all too willing to swallow an extra pill with the promise of a cure. There is a reason we have multibillion dollar industries, peddling unproven remedies for countless ailments. Osler was a strong proponent of treating diseases, not symptoms (i.e., the Osler rule). Oliver Wendell Holmes, Sr., an admired physician and writer from New England, challenged the unspoken assumption that drugs are potentially useful unless proven otherwise (in his days, the challenge was homeopathy) and suggested instead to consider drugs ineffective in the absence of evidence. His rule established the primacy of efficacy over safety when prescribing (i.e., the Holmes rule): you should not add a medicine simply because you think it is safe to do. Following these two rules makes you a true practitioner of Hippocratic medicine and makes you less inclined to use inappropriate polypharmacy. To put this philosophical view in stark contrast, you either practice Hippocratic medicine or you practice symptom-based anti-Hippocratic medicine.

In response to the Holmes rule in particular, it is often argued that lack of evidence does not suggest lack of efficacy. True, many clinical questions will never be studied in a clinical trial. (Cynics might say that once they are studied, they are often abandoned according to well-known patterns of medical progress: excitement from a small open-label trial, widespread penetration of a particular clinical practice, until it all ends with the publication of one or several negative double-blind, placebo-controlled trials that throw common practice into question.) However, available evidence for lack of efficacy is often conveniently ignored, and well-established treatments are foregone in favor of those with dubious claims.

A second framework I have found readily applicable was pointed out the late psychiatrist Gerald Klerman. He suggested that most psychiatrists can put themselves in one of two camps: (a) hedonistic, or more willing to prescribe more to reduce suffering, and (b) Calvinistic being more on the stingy side with psychotropics and a view that suffering should be tolerated [12]. Just like you will not be liberal or conservative on all topics, you might find yourself to be more hedonistic with some patients (or some complaints) than with others. Give this distinction some thought the next time you ponder whether to prescribe or not to prescribe for a complaint of insomnia.

The anti-Hippocratic climate and hedonistic approach is of course not at odds with our American cultural identity as a young and vigorous people, each of us in pursuit of their own happiness. If suffering is seen as a disruption of a normal state of bliss, diseases are mere distractions and in need of a (preferably quick, easy, and painless) fix. This becomes problematic if there is none. Without acknowledging this broader, sociocultural context and the expectations that this creates in your patient, you can find yourself fighting windmills when you try to practice Hippocratic medicine.

Tip

You can prevent some polypharmacy by paying attention to your diagnosis. A firm diagnosis is key and increases your chances of evidence-based practice; once you have to resort to soft spectrum diagnoses, you end up with suboptimal treatment. Be particularly careful with maintenance treatments for mere symptom relief. Once you reach three medications for a diagnosis, a fourth one is unlikely to work [13]. Use the most effective treatment for your diagnosis (e.g., clozapine for refractory schizophrenia).

Undoing Polypharmacy

Some patients have learned that any complaint requires a medication. Cultural expectations (a pill for every ailment) and mythological views of medications (“fixing” the problem) are powerful forces. In a patient who expects a medication, you will be perceived as empathic if you prescribe and as punitive and withholding if you do not. Anticipate resistance by patients but also by other team members, group home staff, or family members; they all may hold strong views about the power of a particular medication regimen (and the risks were it to change). It will take time to unlearn such a counterproductive pattern, and you will have to teach your patients your philosophy of prescribing. Importantly, deprescribing as the “process of withdrawal of inappropriate medication supervised by a health care professional with the goal of managing polypharmacy and improving outcomes” is now called [14] is, as noted in the definition, a process and not a one-time effort. Such an approach puts value on time and the healing power of interpersonal connection and commitment. My colleague at MGH, Nicholas Kontos, points out to patients that he is not a coke machine, giving out medications based on patient preference alone; that professionalism demands more from him. Many patients, on the other hand, are interested in reducing medications once educated about the potential downsides of taking so many medications [15].

Key Point

It requires time and persistence to reverse a pattern of (unnecessary) polypharmacy in a patient: deprescribing is a laborious process. Efforts to limit medications run counter to our Western narrative that emphasizes quick and complete fixes by experts, not acceptance of illness and suffering. Note that both the act of giving *and withholding* medications has meaning for patients. Exploring these issues and (re-)educating patient require time.

Deprescribing is a particularly urgent task for our geriatric patients, and a systematic approach to reducing polypharmacy has been proposed [16]. The following is a list of such principles of deprescribing that can be applied to schizophrenia patients:

- Have a patient bring in all his medications (“brown bag examination”): You may be surprised what is in the bag.
- Review your medication regimen at every visit (you are already doing this as part of medication reconciliation): Do you know the indication for each of the medications you prescribe? Does the dose and dosing seem typical? Remove those where the indication is mysterious or no longer valid.
- Review the medication list with emphasis on actual adherence: Which of the medicines are taken as prescribed (see Chap. 31)? Stop medications that are not taken or are taken erratically.
- Give patients control over the process by following their preference [15]: Have him or her identify the one medicine that is seen as “essential” and start removing “non-essential” ones. Identifying duplicate therapy is a good starting point.
- Make deprescribing a collaborative effort: Understand when you need to get buy-in from parties other than the patient (e.g., family, group home) [17].
- Offer non-medication alternatives: Show that you care and not just take something away without offering a better solution.
- “Undiagnosing” problems that are resolved may be a powerful strategy to reduce medications logically [18].

While it may not be possible to reduce antipsychotic polypharmacy in all patients, you need to give it a try. In one randomized trial, for example, two third of patients successfully switched to antipsychotic monotherapy [19].

References

1. Thoreau HD. *Walden; or, life in the woods*. Boston: Ticknor and Fields; 1854.
2. Kontos N, Querques J, Freudenreich O. The problem of the psychopharmacologist. *Acad Psychiatry*. 2006;30:218–26.
3. Mojtabai R, Olfsom M. National trends in psychotropic medication polypharmacy in office-based psychiatry. *Arch Gen Psychiatry*. 2010;67:26–36.
4. ABIM Foundation. Choosing wisely. Available from: <http://www.choosingwisely.org/>. Accessed on 7/1/2019.
5. American Psychiatric Association. Five things physicians and patients should question. 2015. Available from: <http://www.choosingwisely.org/societiesamerican-psychiatric-association/>. Accessed on 7/1/2019.
6. Freudenreich O, Goff DC. Polypharmacy in schizophrenia: a fuzzy concept. *J Clin Psychiatry*. 2003;64:1132; author reply 1132–1133.
7. Freudenreich O, Goff DC. Antipsychotic combination therapy in schizophrenia. A review of efficacy and risks of current combinations. *Acta Psychiatr Scand*. 2002;106:323–30.

8. Correll CU, Rubio JM, Inczedy-Farkas G, Birnbaum ML, Kane JM, Leucht S. Efficacy of 42 pharmacologic cotreatment strategies added to antipsychotic monotherapy in schizophrenia: systematic overview and quality appraisal of the meta-analytic evidence. *JAMA Psychiatr.* 2017;74:675–84.
9. Wagner E, Lohrs L, Siskind D, Honer WG, Falkai P, Hasan A. Clozapine augmentation strategies – a systematic meta-review of available evidence. Treatment options for clozapine resistance. *J Psychopharmacol.* 2019;33:423–35.
10. Freudenberg O, Kontos N, Querques J. Psychiatric polypharmacy: a clinical approach based on etiology and differential diagnosis. *Harv Rev Psychiatry.* 2012;20:79–85.
11. Ghaemi SN. Toward a Hippocratic psychopharmacology. *Can J Psychiatr.* 2008;53:189–96.
12. Klerman GL. Psychotropic hedonism vs. pharmacological Calvinism. *Hast Cent Rep.* 1972;2:1–3.
13. Kontos N, Freudenberg O, Querques J. Reducing polypharmacy: when less is more. *Current Psychiatry [Pearls series].* 2010;9:80.
14. Machado-Alba JE, Gaviria-Mendoza A, Machado-Duque ME, Chica L. Deprescribing: a new goal focused on the patient. *Expert Opin Drug Saf.* 2017;16:111–2.
15. Holmes HM, Todd A. The role of patient preferences in deprescribing. *Clin Geriatr Med.* 2017;33:165–75.
16. Scott IA, Hilmer SN, Reeve E, Potter K, Le Couteur D, Rigby D, et al. Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA Intern Med.* 2015;175:827–34.
17. Gupta S, Cahill JD. A prescription for “deprescribing” in psychiatry. *Psychiatr Serv.* 2016;67:904–7.
18. Page A, Etherton-Beer C. Undiagnosing to prevent overprescribing. *Maturitas.* 2019;123:67–72.
19. Essock SM, Schooler NR, Stroup TS, McEvoy JP, Rojas I, Jackson C, et al. Effectiveness of switching from antipsychotic polypharmacy to monotherapy. *Am J Psychiatry.* 2011;168:702–8.

Additional Resources

Website

<http://www.choosingwisely.org/societies/american-psychiatric-association/> – The American Psychiatric Association has signed on to the choosing Wisely Campaign which represents an effort by the medical profession itself to limit overtreatment. The APA came up with a psychiatry-specific list of 5 reasonable things to avoid.

Articles

- Ghaemi SN. Toward a Hippocratic psychopharmacology. *Can J Psychiatry.* 2008;53:189–96. – An excellent expose on the essence of Hippocratic medicine.
- Freudenberg O, Kontos N, Querques J. Psychiatric polypharmacy: a clinical approach based on etiology and differential diagnosis. *Harv Rev Psychiatry.* 2012;20:79–85. – A more detailed examination of the four etiological categories that can lead to polypharmacy.
- 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2019;67:674–94. – The “Beers criteria” from the American Geriatrics Society are a useful list for “potentially inappropriate” (their terminology) medications in elderly patients. Review this list for your elderly patients with schizophrenia.

Tiihonen J, Taipale H, Mehtala J, Vattulainen P, Correll CU, Tanskanen A. Association of antipsychotic polypharmacy vs monotherapy with psychiatric rehospitalization among adults with schizophrenia. *JAMA Psychiatry*. 2019;76:499–507. – An important contribution that comes to a different conclusion about polypharmacy: we can also err on the side of underprescribing and for some patients antipsychotic polypharmacy may indeed better (something I did not emphasize in this chapter).

Chapter 22

Psychological Treatments: The Patient



Essential Concepts

- Supportive therapy is the pragmatic, real physician trying to help patients in the here and now with encouragement and advice. The foundation of supportive therapy is a good alliance with your patient.
- Supportive therapy has these goals: ameliorate symptoms, reduce anxiety, and increase self-esteem, adaptive skill, and psychological function.
- Cognitive-behavioral therapy (CBT) for psychosis is an evidence-based ancillary treatment that teaches patients to think about their symptoms in ways beyond the broken brain paradigm in order to manage them more effectively through mastery.
- Principles of CBT for psychosis can be easily integrated into treatment to address residual positive and negative symptoms not ameliorated by medications.
- Psychoeducation tries to improve how patients manage their disease on their own by increasing knowledge about the disease. In medicine, this empowering approach is known as chronic disease management. It allows patients to manage disease like diabetes or cancer without relying only on professional help.
- Being resilient is not only a genetic and fixed attribute but something that was also shaped through life experience. We can become more resilient by learning new ways of coping with stress.

“A sense of a wider meaning of one’s existence is what raises a man beyond mere getting and spending. If he lacks this sense, he is lost and miserable.”

– C.G. Jung (Der Mensch und seine Symbole (MS 89)/Man and His Symbols) [1]

Simply dispensing antipsychotics, while treating the brain, does not treat the mind and soul of patients. In this chapter, I discuss supportive therapy, cognitive-behavioral therapy (CBT), psychoeducation, and resilience training as psychological treatment modalities appropriate for most patients with schizophrenia. The choice of therapy hinges more on availability than on research which does not tell us if supportive therapy, for example, is superior to CBT or psychoeducation [2].

Currently, psychological treatment for patients with schizophrenia is typically offered as individual therapy even though group therapy is a powerful modality that is widely used in other contexts. For example, behavioral treatments like social skills training and family psychoeducation have traditionally been provided in group settings in order to harness the power of groups where patients and families learn from and support each other. For the same reasons, smoking cessation groups are preferred over individual smoking cessation counseling [3]. Medicine has started to experience with group visits (e.g., in diabetes care [4]), something that would be interesting to explore further for our population as well.

Psychoanalysis, or insight-oriented psychotherapies, when used alone is an inappropriate and woefully inadequate approach to treat schizophrenia, but you might see the occasional family still ask about psychoanalysis. I was once asked if I was Freudian or Jungian which does not reflect my clinical reality in public and community psychiatry. (I greatly respect both Freud who was a pioneer but particularly Jung who treated patients with serious psychiatric illnesses on his clinic days and whose writings contain much clinical wisdom, particularly as you head into the second half of your career.) That does not mean that the subjective patient experience is unimportant and that in higher-functioning patients, elements from other therapies to address demoralization and existential suffering (the being-thrown-into-this-existence, Heidegger's *Geworfenheit*) could not be used. I have found elements from existential therapies (e.g., Viktor Frankl's logotherapy) very applicable, but you might find other philosophies suit you more (see also Chap. 30, on depression and suicide, and the article on religion and spirituality in schizophrenia, cited in the Additional Resources). Family psychoeducation is covered in the next chapter (Chap. 23), social skills training and cognitive remediation are covered in the chapter on cognition (Chap. 29), and avatar therapy is covered in the chapter on refractory psychosis (Chap. 12).

Supportive Therapy

In some circles, “supportive therapy” has a bad reputation, indicating that since nothing specific can be offered, one resorts to being merely supportive as opposed to attacking “root causes” in dynamic therapies [5]. Apart from the questionable claim about the efficacy of many psychotherapies, at least for more severe disorders, supportive therapy is a useful treatment in its own right; in fact, most physicians in other specialties practice it all the time. Some might even argue that supportive therapy for patients with schizophrenia is one of the more demanding skills because of poor psychological functioning of patients (e.g., those with primitive defense mechanisms).

Supportive therapy contains specific elements that can be taught and fruitfully applied in clinical encounters. Supportive therapy is not merely meeting with a patient and being seemingly supportive by letting him vent – this is a caricature of what supportive therapy entails. Instead, I think of supportive therapy as a pragmatic encounter with the patient, focusing on today's problems ("hic et nunc – here and now") and how to solve them. If you want to get technical about supportive therapy, think of supportive therapy as the kind of therapy in which you benevolently use the good relationship (or positive transference) that you might have with your patients ("Yes, Doc, whatever you think is right for me"). It is rather difficult to be useful in the long run if your patient does not like you (which will happen). In supportive therapy, however, the topic of interest is not the transference or countertransference; be aware of, but do not interpret, transferential issues. You know that you are doing something wrong if your patients leave the office more anxious than when they came in. In supportive therapy you are first and foremost a "real person" for the patient (as opposed to an object of projection). As the expert, you might not have all the answers, but recommendations and suggestions, even some nudging, are helpful, too.

The talk in supportive therapy is conversational and natural. Avoid pauses that become uncomfortable. Talk about what you know: sports and family. To the uninitiated, this seems like chitchatting. In fact, you are doing a mental status examination, and you determine how much life the patient has other than being a professional patient. In patients you follow for many years, focusing only on areas of weakness and psychopathology is counterproductive (see below, in the positive psychology section). Focusing on areas of strength and pride (a patient might not work but have great knowledge about baseball) serves the all-important purpose of fostering a good treatment alliance. A good alliance is the one thing that might save you when you have to make tough choices like a hospitalization.

The use of medications is acceptable (probably the norm) in supportive therapy and an important tool to decrease anxiety and other unpleasant affects. However, learning how to tolerate unpleasant affects that stem from unalterable situations without the use of medications is a long-term goal for all but the most impaired patients.

Goals and Techniques

Supportive therapy has three goals summarized in Table 22.1.

Table 22.1 Goals of supportive therapy

- | |
|--|
| 1. Ameliorate symptoms |
| 2. Decrease anxiety |
| 3. Enhance the triad of self-esteem, adaptive skill, and psychological function (ego function) |

Based on reference [6]

These three goals define the boundaries with more insight-oriented therapies, in which the objective is to gain insight into habitual ways of experiencing people and approaching the world, followed by change. In supportive psychotherapy, psychological insight is not a primary goal and not seen as a prerequisite for change. Because psychological change is not an objective (increased adaptive function with who people are, not what they may become is), shore up healthy defenses and do not challenge defenses.

Supportive techniques are direct and self-explanatory; you will offer praise, encouragement, reassurance, and even advice and instruction [7]. You will find yourself asking for clarification if patients are confusing in their utterances or confused about their experiences. Helping patients to rename experiences can subtly move patients to accept a different view of events (reality testing). Setting limits and encouraging positive behaviors are other elements that are frequently used.

Clinical Vignette

Helga is a 45-year-old woman who has long-standing schizophrenia. She lives alone in an apartment a few houses away from her elderly mother, who was just in the hospital for an acute respiratory illness. You see Helga every other month when she comes for her clozapine clinic visit. Today, she is wearing new glasses.

One of the first things you might comment on is her new glasses. “I have not seen these glasses before, are they new?” The patient proudly affirms this, “Yes, I picked them out myself.” In supportive therapy it would be acceptable to praise the patient, “These look nice on you. You really picked well.” This shows you approval and might enhance the patient’s self-esteem. It would then be very appropriate to talk about the health of the patient’s mother. Saying “I heard your mother was in the hospital. How is she doing?” shows concern and helps with anxieties that the patient might have about her mother’s illness. You could give direct advice: “How about going over to her house and cooking some soup for her?” If the patient describes insomnia related to worrying about her mother, adding a sedative to decrease anxiety and to help with sleep is appropriate (as opposed to focusing on the existential questions that the mother’s illness might have provoked although in patients with better ego function addressing such fears may be appropriate).

Simply being natural and stating the obvious (in this example, new glasses, concerns about mother’s illness) is an essential ingredient in working with patients who suffer from schizophrenia. Some self-disclosure is another ingredient that keeps you real but may not come natural to some clinicians, particularly if they are fearful of boundary violations learned in psychotherapy.

Cognitive-Behavioral Therapy

Cognitive-behavioral therapy (CBT), originally developed as a treatment for depression, is an evidence-based treatment for psychosis that is routinely included in treatment guidelines for schizophrenia. Unfortunately, because the main impetus for developing CBT for psychosis has come from research groups in Great Britain, it can still be very difficult to find practitioners in the United States who can competently use CBT to treat patients with schizophrenia. However, you can easily integrate some principles of CBT into your own routine clinical care, particularly if you limit yourself to addressing a few specific symptoms [8].

CBT has several features that make it an attractive treatment modality. The reductionist and simplistic view of schizophrenia as a “brain disease” is rather pessimistic (and wrong) since it does not take into account the influence of environment and the relative frequency of psychotic symptoms in community samples. Van Os and others have argued strongly for a continuum model of psychosis [9]. CBT tries to help patients develop a view of their disease that goes beyond a “broken brain” model of “madness” and, in doing so, broadens views of how symptoms come about and what can be done about them. For example, normalization of psychotic experiences may reduce stigma.

Key Point

CBT for psychosis makes several assumptions. For one, symptoms are conceptualized as brought on by the combined result of vulnerabilities (which could be biological, social, or psychological) and stressful life experiences. In this view, psychosis is seen as understandable and “normal.” Symptoms are then thought to be maintained by counterproductive appraisals and behaviors which can be identified and changed. The CBT therapist identifies operative reasoning biases and challenges them through such techniques as cognitive restructuring or behavioral experiments. Examples of these biases include selective data gathering, jumping to conclusions, and overconfidence.

CBT is structured in a way that is very different from the usual clinic visit. Individual CBT sessions are usually held weekly, homework is assigned regularly, the CBT therapist adopts a directive (active) role, and sessions follow an agenda that is developed by both the patient and therapist at the beginning of each session. CBT sessions are designed to have a tone of collaborative discovery between the patient and therapist. CBT is also time limited; once patients have completed a course of CBT (e.g., 16–20 sessions), they have learned a set of techniques to use, and it is then up to them to apply these techniques in the face of symptoms or difficult life situations. CBT is educational, and I have had patients tell me that it feels like being in school again.

Let me take delusions as a case in point to show how CBT can work. In a CBT framework, delusions are conceptualized as extreme beliefs that are held with a high level of conviction (but not necessarily always 100% conviction). In this view, delusions are just a belief which opens delusions to Socratic questioning: “What makes you so sure? What is your evidence for this belief? Is it possible you are mistaken?” The CBT therapist aims to identify triggers of dysfunctional thoughts (using the ABC model, antecedent-belief-consequences). After identifying cognitive biases (e.g., “all-or-nothing thinking”; “I am going to be attacked”), you can work on restructuring cognitions and changing maladaptive behaviors (e.g., leaving the subway in response to paranoia). You might set up a behavioral experiment, for example, having patients gradually increase the number of minutes they spend on the subway platform over the course of a week and recode whether they were attacked and what their associated anxiety ratings were. In the subway example, you would help patients identify and challenge automatic thoughts and provide alternative explanations (e.g., a person might be looking at them on the subway platform because they appear nervous, rather than because the person is waiting to attack them).

Overall, the adaptation of CBT to treatment of psychosis is a very positive development. However, it is easy to oversell the benefit of CBT. Surgeons know very well that the most important predictor of outcome is patient selection. CBT for psychosis can be useful for the more motivated patients who have some insight into the pathologic nature of their experiences and who are curious about them. In such patients, ancillary (to antipsychotics) CBT can be rather beneficial. Although CBT does not necessarily lead to symptom remission, patients who benefit are less stressed about their symptoms, because they have learned how to live with their symptoms better which may reduce symptoms in a virtuous cycle. I need to state clearly that for most patients, CBT is no substitute for treatment with antipsychotics (which addresses the biological vulnerability) but an ancillary treatment. One exception is patients who present to a high-risk psychosis clinic but who are not yet psychotic. In those cases, CBT is one of the psychological treatments that should be offered to reduce the risk of developing psychosis [10]. CBT has been further modified to expand to treating negative symptoms and improve social functioning (see Chap. 27).

Psychoeducation

Key Point

Psychoeducation posits that increased knowledge about an illness leads to a better appreciation of the illness and its treatments and thereby ultimately improved illness management. Patients should be experts in their illness and its management. Sometimes targeting the family for becoming experts yields more benefits (see next chapter). Some degree of psychoeducation is the sine qua non of informed consent and shared decision-making.

Being a physician means being a teacher, among other things. Explaining diseases and treatments has always been part of medicine and is an integral part of any patient encounter, at least informally. At its core, psychoeducation is a collaboration that invites patients to become active in their treatment and make informed decisions consistent with their values, rather than simply going along with treatment decided for them. Shared decision-making about a course of treatment is not possible without psychoeducation. In contrast, psychoeducation as a structured, curriculum-based activity with modules to learn about the illness is a fairly new idea in the mental health field. Chronic disease self-management in medicine has always played some role in increasing patient self-efficacy (e.g., patients learning how to manage diabetes on their own). The Health and Recovery Peer (HARP) program [11] or the Wellness Recovery Action Plan (WRAP) [12] are examples of successful adaptations of medical self-management for patients with serious mental illness. Often, such programs are led by peers or with the help of peers. A possible model curriculum for schizophrenia should cover the illness and its treatments (symptoms, treatment, crisis management, recovery, and relapse), as well as wellness education (nutrition, healthy lifestyle, and exercise) [13]. Note that psychoeducation by itself is often insufficient since knowledge alone rarely leads to behavioral change: social support and behavioral nudging are elements that need to complement simply providing information. While self-management might not improve “hard” outcomes (e.g., hospitalization), I have seen patients thrive psychologically from a sense of empowerment and mastery. Have high expectations about your patient’s ability to manage their own affairs, within reason and with appropriate help, as low expectations bear the seeds of a disappointing outcome.

Tip

Many patients use the Internet, which can replace “bibliotherapy” (a fancy term for learning by reading a book), to learn about schizophrenia and medications. I usually do not direct patients to specific websites but only ask them to scan broadly. I want them to also be exposed to unhelpful or extreme views (which they will hear anyways) so we can talk about them and dispel myths and half-truths.

Positive Psychology and Resilience

The last decade has seen a dramatic increase in psychological therapies that have taken the social sciences’ insights about measuring and improving “happiness” into the clinic. More nebulous constructs like defining “the good life,” seeking “eudemonia,” and “flourishing” have become accepted treatment goals of “positive psychology.” This branch of psychology emphasizes mindfulness, value clarification, and action in accordance with those values over the conventional cognitive-behavioral therapy (CBT) approach which is symptom-focused and seeks to fix dysfunctional

thinking. Acceptance and commitment therapy (ACT) is but one example of this therapeutic movement that is sometimes called “the third wave of CBT” [14]. A key element in this therapy is building a repertoire of behavioral skills that, if implemented, may lead to improved well-being. It de-emphasizes the attempt to controlling and changing dysfunctional thinking per se; instead, it asks patients to accept internal experiences via experiential exposure and then take it from there. Fighting internal windmills may not be the best use of our time, particularly if it comes at the expense of living in the world. In the end, traditional CBT and more current CBT approaches have much in common, at least at the level of actual practice, despite theoretical differences.

Enhancing resilience through therapy as an outgrowth of positive psychology has gained traction in the past decade. A term from material sciences, resilience captures the ability to bounce back undamaged after being put under stress. Resilience makes the difference between people who strive despite stress and those who crumble. Resilience is not merely a fixed and inborn temperament (although some people seem to be indestructible) but contains elements that are learned growing up or that can be acquired when faced with adversity. Building resilience comes easier for some people than others but is something that many patients can at least try. Like with Viktor Frankl’s logotherapy, there is a critical choice to be made: to embrace resilience and refuse to only be the victim of circumstance (“fate”). Resilient people have learned to be optimistic (realistic yet hopeful), do not avoid things they fear, and reach out for help, for example. They take responsibility for those things they can control, flexibly drawing from a repertoire of cognitive and emotional coping mechanisms, including acceptance. Ten resilience-enhancing coping mechanisms (resilience factors) that help patients overcome adversity are listed in Table 22.2.

Improving “coping” can easily be integrated into clinical care as even impaired patients have an intuitive understanding that they have problems related to coping with people and life’s circumstances, including the slings and arrows of outrageous medical fortune, to paraphrase Shakespeare. A move away from the pure problem-solving coping of the 1990s to self-compassion puts a modern spin on coping that is consistent with the principles of positive psychology and resilience. If your patient

Table 22.2 Ten coping strategies that build resilience

Maintain a <i>realistic</i> optimistic outlook
Confront your fears
Rely on your moral compass
Practice religion and spirituality
Seek out and accept social support
Learn from sturdy role models
Stay physically fit
Stay mentally sharp
Acquire a repertoire of emotional and cognitive coping skills
Find meaning, purpose, and growth, <i>despite everything</i>

Adapted from [15]

Table 22.3 Coping styles**Emotion-based coping**

Are painful psychological experiences such as anxiety or despair interfering with your patient's ability to cope?

The source of the painful psychological experiences is not addressed but the triggered emotions are instead directly managed, to avert psychological paralysis. Tools are medications, CBT, or relaxation (or humor, if patients can use it). Pay attention to complications like alcoholism

Problem-based coping

How well is your patient dealing with the practical aspects of treatment such as keeping doctors' appointments or going to work when fatigued from chemotherapy?

The ability to effectively problem-solve hinges on cognitive resources (memory, attention, executive function). Your patient may need help to identify “the next step” and resources. Assist with concrete things (child care, transportation, financial assistance, support groups, information)

Attitudinal-based coping

Can your patient embrace an attitude of accepting unavoidable circumstances – which is not the same as passivity? Can your patient find meaning in the illness: “Has this illness taught you anything or changed you?”

Engage your patient in a discussion of his or her *Weltanschauung* (philosophy of life): they all have one. Understand his or her views of fairness and ultimate concerns. Some patients can relate to insights from secular or spiritual thinkers, if presented judiciously and with great sensitivity to a patient’s background

Adapted from [16]

seems to be coping poorly, you can help by first identifying the patient’s main coping style (emotion-based, problem-based, attitudinal-based) and then increasing his or her ability to flexibly shift between them (see Table 22.3). A focus on the process, coping well does not assume that all of life’s problems can be solved. It also recognizes that emotional growth takes time.

Patients who successfully adapt to medical and psychiatric adversity usually have access to a broad range of coping strategies that they shift flexibly between. While the three coping styles are not necessarily hierarchical, I nudge patients who only try to manage their emotions toward problem-solving and ultimately toward an attitude of acceptance.

When engaging in “positive psychology,” we need to guard against defining “the good life” for somebody else or, worse, talking away deficits and resorting to wishful thinking at the expense of providing meaningful support. Resilience building only goes so far, particularly in patients with cognitive impairment. A strong argument can also be made that we should offer evidence-based treatment (conventional CBT, targeting dysfunctional thoughts) before jumping on the bandwagon of mindfulness-based treatments that have less of an evidence base [17]. However, I would like to be clear: I see the emphasis on a person’s potential, respect for patient values and patient empowerment that underlies the positive psychology movement as a fundamentally positive development in clinical psychiatry. It speaks volumes that the American Psychiatric Association’s publishing outfit has published a book titled *Positive Psychiatry* [18].

References

1. Jung CG. *Man and his symbols*. New York: Doubleday; 1964.
2. Buckley LA, Maayan N, Soares-Weiser K, Adams CE. Supportive therapy for schizophrenia. *Cochrane Database Syst Rev*. 2015;14:CD004716.
3. Cather C, Pachas GN, Cieslak KM, Evins AE. Achieving smoking cessation in individuals with schizophrenia: special considerations. *CNS Drugs*. 2017;31:471–81.
4. Eisenstat SA, Ulman K, Siegel AL, Carlson K. Diabetes group visits: integrated medical care and behavioral support to improve diabetes care and outcomes from a primary care perspective. *Curr Diab Rep*. 2013;13:177–87.
5. Buckley P. Supportive psychotherapy. A neglected treatment. *Psychiatr Ann*. 1986;16:515–21.
6. Pinsker H. *A primer of supportive psychotherapy*. Hillsdale: The Analytic Press, Inc.; 1997.
7. Conte HR, Plutchik R. Supportive psychotherapy. Controlled research in supportive psychotherapy. *Psychiatr Ann*. 1986;16:530–3.
8. Lincoln TM, Peters E. A systematic review and discussion of symptom specific cognitive behavioural approaches to delusions and hallucinations. *Schizophr Res*. 2019;203:66–79.
9. Verdoux H, van Os J. Psychotic symptoms in non-clinical populations and the continuum of psychosis. *Schizophr Res*. 2002;54:59–65.
10. Devoe DJ, Farris MS, Townes P, Addington J. Attenuated psychotic symptom interventions in youth at risk of psychosis: a systematic review and meta-analysis. *Early Interv Psychiatry*. 2019;13:3–17.
11. Druss BG, Zhao L, von Esenwein SA, Bona JR, Fricks L, Jenkins-Tucker S, et al. The Health and Recovery Peer (HARP) program: a peer-led intervention to improve medical self-management for persons with serious mental illness. *Schizophr Res*. 2010;118:264–70.
12. Pratt R, MacGregor A, Reid S, Given L. Wellness Recovery Action Planning (WRAP) in self-help and mutual support groups. *Psychiatr Rehabil J*. 2012;35:403–5.
13. Bisbee CC, Vickar GM. A review of psychoeducation for patients with schizophrenia. *Psychiatr Ann*. 2012;42:205–10.
14. Hayes SC. Acceptance and commitment therapy, relational frame theory, and the third wave of behavioral and cognitive therapies. *Behav Ther*. 2004;35:638–65.
15. Southwick SM, Charney DS. *Resilience : the science of mastering life's greatest challenges*. New York: Cambridge University Press; 2012.
16. Freudreich O, Kontos N, Querques J. Support patients coping with medical illness [Pearls series]. *Curr Psychiatry*. 2008;7:76.
17. Hofmann SG, Sawyer AT, Fang A. The empirical status of the “new wave” of cognitive behavioral therapy. *Psychiatr Clin North Am*. 2010;33:701–10.
18. Jeste DV, Palmer BW, editors. *Positive psychiatry : a clinical handbook*. Arlington: American Psychiatric Publishing; 2015.

Additional Resources

Websites

<https://www.thenationalcouncil.org/store/products/team-solutions-solutions-wellness/> – This collaboration between a university and a drug company offers free materials for a model psychoeducation curriculum covering illness (“Team Solutions”) and wellness (“Solutions for Wellness”).

Books

- Jeste DV, Palmer BW, editors. Positive psychiatry : a clinical handbook. Arlington: American Psychiatric Publishing; 2015. – Psychiatry's pendant to positive psychology.
- Pinsker H. A primer of supportive psychotherapy. Hillsdale: The Analytic Press, Inc; 1997. – First and still best book to explain supportive therapy. If you cannot get it anymore, there are later version based on the original book with co-authors in the “Core Competencies in Psychotherapy Series” (Introduction to Supportive Psychotherapy) [19, 20].
- Southwick SM, Charney DS. Resilience : the science of mastering life’s greatest challenges. New York: Cambridge University Press; 2012. – While not specifically written for patients with serious mental illness, this book provides a good overview of the resilience construct, in clear language and with real-world examples of 10 resilience factors.

Article

- Mohr S, Brandt PY, Borras L, Gillieron C, Huguelet P. Toward an integration of spirituality and religiosity into the psychosocial dimension of schizophrenia. Am J Psychiatry. 2006;163:1952–9. – As I did not discuss the role of spirituality and religion for people with psychotic disorders in more detail beyond listing it as a resilience factor, read this article as a good starting point.

Suggested Reading

- Winston A, Rosenthal RN, Pinsker H. In: Gabbard GO, editor. Introduction to supportive psychotherapy. Washington, DC: American Psychiatric Publishing, Inc; 2004.
- Winston A, Rosenthal RN, Pinsker H. In: Gabbard GO, editor. Learning supportive psychotherapy : an illustrated guide. Washington, DC: American Psychiatric Publishing; 2012.

Chapter 23

Psychological Treatments: The Family



Essential Concepts

- Family members (often parents or siblings) can be the greatest resource your patient has. Help family members understand the illness, and let them help you take care of their child or sibling.
- Families need more help when there is violence or the police are involved, when there is frequent relapse, or when the need for reassurance is high.
- Use the stress-diathesis model to explain the role of stressful environments (which can be the family environment) on the patient *without assigning blame*.
- The expressed emotion model captures the reality that some family environments are more stressful than others *for vulnerable patients*, leading to relapse. Critical comments may be particularly difficult to manage for those patients sensitive to interpersonal interactions.
- Refer families to the National Alliance on Mental Illness (NAMI) which provides family education and support. Their 12-week family-taught family-to-family education program improves coping and family function.
- Open dialogue is an intervention that engages a patient's larger social network at a time of crisis such as a psychotic episode, emphasizing open and honest discussion between all parties affected by the patient's illness and seeking a mutually agreed upon solution.

“Never tell people how to do things. Tell them what to do and they will surprise you with their ingenuity.”

— George S. Patton, US Army General, 1885–1945 [1]

Schizophrenia affects everybody in the family. A narrow, dyadic view of patient and therapist is unhelpful at best and at times dangerous; you need eyes and ears in the community, and the family is your natural ally. Today, family work is more pragmatic and less theory driven than decades ago. In this chapter, I provide some suggestions on how to work with the family of your patient with schizophrenia, for everybody's benefit.

Reasons for Family Involvement

Families often play a crucial role in aiding treatment and recovery simply because many patients are still living with their families or have returned to the family home after a crisis or a hospitalization. Having a child or sibling with any illness is stressful for parents and siblings; having a child or sibling with psychosis is even more stressful. Family homeostasis is disrupted, and families struggle to regain a sense of normal family life. In other areas of medicine, the burden on caregivers is openly acknowledged and addressed. Family members who take care of patients with Alzheimer's disease, for example are supported, whereas families who have a member with schizophrenia all too often still suffer alone [2]. Psychologically problematic is the fact that a child with schizophrenia might be lost without being dead, leading to protracted grief that does not resolve [3].

Think of these as the goals of family involvement and interventions:

- Prevent family burnout to avoid abandonment of patients in the long run. All homeless patients had parents and a home at some point.
- Decrease isolation of families because of the stigma of mental illness.
- Alleviate guilt about having caused the illness.
- Provide a realistic assessment of the illness and its prognosis, not too positive, not too negative. Always give hope that a good life is still possible.
- Teach families how to supervise medication adherence gently, without power struggles. Give the parent permission to be in charge of the medicine if the patient lives at home.
- Teach skills on how to avoid and handle crises. Do this without being patronizing but do it in a spirit of collaboration. Acknowledge the strengths that families have shown. Assume that solutions are in the family.
- Help reconnect patients with family members from whom they have been estranged, if this is desired.
- Reduce relapse rates by reducing stressful interactions among family members (see below, under Expressed Emotions).

Make it clear that you not only understand that families have concerns but that you *value* their involvement. Families often complain that they are viewed as obstacles to treatment rather than assets. A good working relationship with families goes a long way, as Tom Sawyer (and General Patton) recognized.

Tip

Tom Sawyer understood how to motivate people to get a job done. Apply the Tom Sawyer approach to problem-solving: Identify what needs to be done, and then delegate appropriately (i.e., know the limits of family responsibilities). There is no reason that a family member cannot try to get a discharge summary from a hospitalization that happened in Alaska (assuming you practice in Boston, like me). (I found the Tom Sawyer approach mentioned in Kanter [4].)

As important as it is to help families help their sick relative, you also need to help patients deal with their families (the idea of “managing up,” from the business world). While I always talk with family members who have accompanied the patient to the appointment, I also always talk to the patient alone as well to address concerns that the patient has about his or her family. As a rule of thumb, I always include the patient when speaking with the family to model an open approach that cuts through the collusion and the real patient concern that “things are done behind my back.” If families want to use email to communicate with me, I insist that patients are included in order to foster patient-centered care. Most patients readily accept some family involvement if you explain your reasons for it. Make family involvement an official part of treatment by having your patient sign the required paperwork related to patient privacy. Do not forget that families can always let you know if there are concerns (even if a patient has not signed the proverbial “release”).

Selection of Families

All families that want to be involved in the treatment of their child or sibling should be involved in it, but the degree and type of involvement vary. For many families, simply being available for questions by phone or the occasional email is sufficient. Even in those “low-maintenance cases,” I ask all my patients to bring one family member to one of the appointments “to touch base” at least once a year and at the beginning of treatment. Having had family contact at the beginning of treatment goes a long way in managing a crisis later in treatment. Do not forget to include siblings of patients. Eventually, they may be the ones who have to take over for aging parents. Siblings may also have a less conflicted relationship with the patient compared to parents, particularly if patients resist the often-needed resumption of parental supervision.

Tip

Know who is in the patient’s family. I have found that it works best if you set aside a visit during which you literally draw a family tree with the patient. I do this even with patients I have known for years: “Let me go over your family today in a little more detail.” Figure out, “Who lives where? When was the last time you saw your brother? What is your father doing?” For some patients, staff members in group homes or day programs are their family. Find out who is important and trusted.

Table 23.1 Red flags for need for intensive family involvement

Frequent arguments that lead to violence
Families who call 911
Adherent patients who relapse more than once per year
Relatives with frequent staff contact for reassurance
Based on reference [6]

There are two situations in which it is mandatory to work more extensively with families: first-episode patients and problematic families. Family work may be especially important during the first episode, as relatives tend to experience the greatest amount of distress during the first 2–5 years of illness. Modern first-episode treatment programs all include a family component [5]. The eminent British cross-cultural psychiatrist Julian Leff has identified several red flags for families who need more help than just basic education (Table 23.1) [6].

Working with Families

The first step is to help family members understand what schizophrenia is (and what it is not). You cannot expect the average person to know the difference between schizophrenia, “split personalities,” or sociopathy. Without education, grossly distorted “personalized lay views” result.

Most family members want to know how they can best help, including what not to do. A useful model to discuss the interaction between genes and environment is the stress-diathesis model, which I prefer over the expressed emotion model (see Expressed Emotions). The stress-diathesis model holds that we all have different abilities to buffer against stress, and if overstressed, symptoms may arise [7]. Most patients and families find this view (which is probably close to some biological truth) intuitive, resonating with their own experience, and more hopeful than the “broken brain” view.

Key Point

It helps to explain schizophrenia as a disorder that leaves the sufferer very sensitive to the environment, including the family situation (stress-diathesis model). Medications buffer against social stress to some extent, but sometimes the environment (i.e., the family atmosphere) needs to be changed as well. In that way, families can positively affect how well somebody is doing. This does not mean that families are to blame if patients are not doing well; there can be many reasons for this.

Here is a list of very concrete steps to help the family of somebody with schizophrenia:

- Direct families to the National Alliance on Mental Illness (NAMI) for support in their communities (see Additional Resources). NAMI is the largest and oldest

grassroots organization dedicated to helping families who have a relative with mental illness, particularly schizophrenia. There are chapters in all 50 states. Families should start with their local chapter.

- Many NAMI chapters offer psychoeducation for families via a family-taught program, “family-to-family” [8]. This 12-week course has been shown to enhance carer coping, a sense of empowerment, and also their self-care [9].
- Provide reading suggestions to learn about schizophrenia (see Additional Resources).
- Help develop skills for crisis intervention (and how to avoid crises) and an explicit crisis plan. Patients want to be involved in this manner [10]. Prescribe new solutions for recurrent problems.
- Be available. Do not hide behind regulatory barriers. Involve families from the get-go and keep them involved.
- Be transparent. Psychiatry is not a sect; explain what you are doing and why.
- Set a tone that makes families allies. Never blame (i.e., think twice before making a statement that contains “should” or “should not”).
- Practice “cultural humility” [11]. We live in a multicultural society, and your idea of what a family ought to do is just one among many competing visions of human life.

If available, so-called multiple family groups in which several families are seen together can offer advantages; this group format might provide some corrective: “Some families are worse off. My problems are not unique.” Do not forget that while you have seen hundreds of cases of schizophrenia and their families, families have seen one. Families might give each other helpful suggestions about local resources and strategies as well.

Tip

At some point, let the family identify one family member who will communicate with you and whom you can contact with urgent matters. Ask other members of the family to funnel concerns thought that “family spokesperson.”

Expressed Emotions

No section on family treatment would be complete without mentioning the concept of expressed emotions (EE). The EE construct was based on the clinical observation (in Great Britain) that some patients relapsed more rapidly than others following hospital discharge, depending on the environment they returned to. Those who returned to their families had higher relapse rates than those with different dispositions. Subsequent studies in many cultures have confirmed that some families, so-called high-EE families, create a stressful family atmosphere that doubles the relapse rate compared to low-EE families. High-EE families are characterized by three key factors: frequent criticism, hostility, and overinvolvement [12].

High EE in and of itself is not pathological; many families have a high-EE style. Some families might be naturally more laid back when it comes to psychotic behavior. Conversely, I would not underestimate the toll on any healthy family that has to cope with an ill relative who might not only not get substantially better but who in addition seems to be sabotaging treatment – by not taking medication, for example. In such families, a high EE may be viewed as reactive.

Although families cannot be blamed for being high EE, the atmosphere in such families can be very stressful for somebody with schizophrenia (or other disorders like depression). Not all family members contribute equally to high EE; often, you can identify a particularly critical family member even in a brief office visit. The ideas behind EE are not restricted to families but can usefully be applied to group homes. Emergency room visits in chronic patients who live in group homes can sometimes be traced back to a particular staff member that is problematic from an EE perspective. Creating a milieu conducive to healing may be a constructive way of explaining EE to families.

Key Point

For some patients with schizophrenia, family atmosphere matters and can contribute to a psychotic relapse. Critical relatives who hold patients responsible for their illness seem to have the most impact on potential relapse. Find out from the patient, “On a scale from 1 to 10, how critical is your family of you?,” and gently address this with the family.

The overinvolvement seen in some families is often entrenched and the result of severe disability on the part of the patient. I have seen patients who are shepherded around every minute of the day. Do not be harsh but consider that the amount of involvement was at some point possibly necessary and represents a solution that the family has come up with but that now has become problematic. While counterintuitive, prescribing reduced contact with the ill family member (paradoxical intervention) is sometimes necessary since patients need time to themselves to grow up and develop some degree of independence. This could be as simple as letting the patient go to the movies alone. Some families need to learn to tolerate failure if their ill child or sibling does not succeed with an endeavor; it is a normal part of growing up and life. However, I do not believe psychiatrists have particular expertise in judging where the line between too much and just right involvement is and how much risk families ought to assume.

Clinical Vignette

After developing psychosis in this second year of college and following a psychiatric hospitalization, Alexander finds himself living at home again with his parents. He has responded well to the antipsychotic and is waiting for a

community college class to start. He sleeps in and stays up late (but sleeps only 8 hours total). He denies feeling fatigued from the medications. His mother is constantly berating him for not getting up and “doing something.” She wants his medications to be changed, “so he is more motivated.” Alexander feels his mother is highly critical of almost anything he does or does not do.

This is an example of a fairly common scenario that creates stress for everybody and that can be reduced with some gentle education: a delayed sleep-wake cycle (also known as “sleeping in”) is physiologically normal for younger people, getting up at 7 A.M. bright-eyed and bushy-tailed is unusual, particularly if there is no reason to do so. I explain to patients and families that “it is twice as difficult for somebody with a mental illness to look half as normal,” to teach them the importance of not pathologizing every observation. Even if getting up late were a sign of negative symptoms, creating stress for the patient is counterproductive. You could prescribe no contact before noon.

One problem with EE is not always acknowledged: its focus on the family ignores the larger society and its values. Living in a culture that believes in individual liberty and responsibility (to the point of atomistic hyperindividualism) may be inherently more stressful than more collectivist societies, beyond mere resources. Targeting families to lower EE, while broadly helpful, may not be able to overcome some intrinsic stressfulness of our Western philosophy of life (*Weltanschauung*) about the mind (how it breaks and how to fix it – those images are already typical for our rational-technical approach) that we have all internalized. Local solutions may not be transferrable as customs (including help seeking) are intimately tied to culture and cannot abstractly be taken and repackaged. Applying solutions taken from other cultures may not work for psychiatric disorders where local considerations as opposed to universalist assumptions about the mind are critical (an argument elegantly summarized by Ethan Watters in *Crazy Like Us* [13]). How different cultures contribute to different patient outcomes is discussed more in the chapter on natural history (Chap. 7).

Open Dialogue

Open dialogue (OD) is a particular clinical approach that originated in Finland and relies heavily on engaging a person’s social network like their family to solve psychiatric crises, including a first episode of psychosis [14]. OD relies on “network meetings” to mobilize a person’s natural supports in order to seek a solution that is collectively developed and agreed upon [15]. An interdisciplinary mobile outreach team meets patients and their families at home to de-emphasize the medical aspect of the problem. As the name OD implies, shared decision-making is made openly and not behind the back of a patient (or the person in crisis, as patients are referred to).

OD also acknowledges the reality that a psychotic illness affects not just the patient but his or her entire social network and community. OD emphasizes those elements of good psychiatric care that ought to be standard and not optional. Unfortunately, most clinics are not offering OD-like services which are personnel- and time-intensive and hence costly.

References

1. Wikiquote: George S. Patton. Available from https://en.wikiquote.org/wiki/George_S._Patton. Accessed on 7/1/2019.
2. Jones K. Addressing the needs of carers during early psychosis. *Early Interv Psychiatry*. 2009;3:S22–6.
3. Miller FE. Grief therapy for relatives of persons with serious mental illness. *Psychiatr Serv*. 1996;47:633–7.
4. Kanter J. Engaging significant others: the Tom Sawyer approach to case management. *Psychiatr Serv*. 1996;47:799–801.
5. Mueser KT, Penn DL, Addington J, Brunette MF, Gingerich S, Glynn SM, et al. The NAVIGATE program for first-episode psychosis: rationale, overview, and description of psychosocial components. *Psychiatr Serv*. 2015;66:680–90.
6. Leff J. Working with the families of schizophrenic patients. *Br J Psychiatry Suppl*. 1994;164:71–6.
7. Nuechterlein KH, Dawson ME. A heuristic vulnerability/stress model of schizophrenic episodes. *Schizophr Bull*. 1984;10:300–12.
8. Dixon L, Lucksted A, Stewart B, Burland J, Brown CH, Postrado L, et al. Outcomes of the peer-taught 12-week family-to-family education program for severe mental illness. *Acta Psychiatr Scand*. 2004;109:207–15.
9. Mercado M, Fuss AA, Sawano N, Gensemer A, Brennan W, McManus K, et al. Generalizability of the NAMI family-to-family education program: evidence from an efficacy study. *Psychiatr Serv*. 2016;67:591–3.
10. Farrelly S, Brown G, Rose D, Doherty E, Henderson RC, Birchwood M, et al. What service users with psychotic disorders want in a mental health crisis or relapse: thematic analysis of joint crisis plans. *Soc Psychiatry Psychiatr Epidemiol*. 2014;49:1609–17.
11. Foronda C, Baptiste DL, Reinholdt MM, Ousman K. Cultural humility: a concept analysis. *J Transcult Nurs*. 2061;27:210–07.
12. Heru AM. Family psychiatry: from research to practice. *Am J Psychiatry*. 2006;163:962–8.
13. Watters E. The shifting mask of schizophrenia in Zanzibar. In: *Crazy like us: the globalization of the American psyche*. New York: Free Press; 2011.
14. Seikkula J, Alakare B, Aaltonen J. Open dialogue in first-episode psychosis I: an introduction and case illustration. *J Constr Psychol*. 2001;14:247–66.
15. Gordon C, Gidugu V, Rogers ES, DeRonck J, Ziedonis D. Adapting open dialogue for early-onset psychosis into the U.S. health care environment: a feasibility study. *Psychiatr Serv*. 2016;67:1166–8.

Additional Resources

Websites

<https://www.nami.org> – The website of the National Alliance on Mental Illness (NAMI) which has chapters in all 50 states. The group started around a kitchen table in 1979 as a grass-roots movement of several families who cared for somebody with serious mental illness. NAMI is primarily a resource for family members (education and support) and advocacy. As part of your treatment plan, refer families to their local NAMI chapter.

Books

Amador XF. I'm not sick, I don't need help. 10th ed. Peconic: Vida Press; 2010. – The first book (first published in 2000) that tried to provide guidance about how to tackle the vexing issue of treatment refusal as a result of impaired insight (Amador suggested the anosognosia analogy for lack of insight in schizophrenia).

Karp DA. The burden of sympathy: how families cope with mental illness. New York: Oxford University Press; 2001. – A sociologist brings to life the vicissitudes of caring for a mentally ill family member in postmodern America. A required reading for families *and psychiatrists*.

Komrad MS. You need help!: A step-by-step plan to convince a loved one to get counseling. Center City: Hazelden Foundation; 2012. – Another book that provides pragmatic advice about how to engage and nudge help-rejecting patients towards psychiatric treatment.

Mueser KT, Gingerich S. The complete family guide to schizophrenia: helping your loved one get the most out of life. New York: The Guilford Press; 2006. – An eminently practical guide for families about how best to help their relative with schizophrenia. While dated, its basic ideas remain valid.

Torrey EF. Surviving schizophrenia: a family manual. 7th ed. New York: Harper Perennial; 2019. – The standard guide for families (and patients) by one of the outspoken and engaged leaders in public psychiatry; now in its 7th edition which speaks for itself.

Chapter 24

Psychiatric Rehabilitation and Recovery



Essential Concepts

- Psychiatric rehabilitation and psychiatric treatment are separate, yet equally important, complementary components of schizophrenia care.
- Psychiatric rehabilitation focuses on function and role outcomes, not on symptoms. Good programs build new skills that can be used toward achieving rehabilitation goals.
- A rehabilitation assessment clarifies the patient's goals and then assesses skills and supports needed to attain these goals, taking into account strengths and weaknesses. Rehabilitation goals are personal goals that can only be developed in collaboration with a patient, not for him or her.
- Work adds so much to ourselves that vocational rehabilitation (particularly supported employment) should be given utmost attention, even though the odds for competitive employment for patients with schizophrenia are less than 1 in 5.
- Assertive community treatment (ACT) is a service delivery model that brings care that previously required institutionalization to seriously ill patient in the community, increasing their freedom.
- A functioning welfare state providing sufficient support for its citizens is a necessary basis for rehabilitation and reintegration in society.
- Peer support can play a large role in fostering a hopeful attitude toward recovery as a mindset in patients and their families, regardless of clinical status.
- Recovery means different things to different people. Recovery can be viewed as a mindset and psychological process that allows people to recover a sense of personhood that is not merely defined by having schizophrenia. It does not mean that no help is needed, including medications.

“There can be no transforming of darkness into light and of apathy into movement without emotion.” (cited in [1])

– C.G. Jung 1875–1961, Swiss psychiatrist

It requires more than medicines to treat most illnesses. Rehabilitation medicine is an unquestioned and obligatory part of care for many medical conditions: for optimal *functional* results, orthopedic surgery is followed by rehabilitation in the form of physical therapy (PT). Similarly, psychiatric care (i.e., pharmacological and psychological treatments) for schizophrenia needs to be accompanied by psychiatric or psychosocial rehabilitation in order to achieve the best possible functional outcomes. Unfortunately, all too often only medications are provided, with expectable poor result. Clinical training needs to occur in the real world of community settings in order for young psychiatrists to appreciate the limitations of a “meds only” symptom-based focus and instead make them champions for rehabilitation and its focus on function and societal reintegration. Psychiatric rehabilitation is complicated by a sociocultural context of stigma, exclusion, and discrimination. Changing societal attitudes and discriminatory laws are part of rehabilitation in the larger sense of societal reintegration.

Terminology

I will follow the tradition in the mental health field and juxtapose psychiatric *treatment* with psychiatric *rehabilitation* even though you could consider rehabilitation to be one of the tools of treatment at your disposal. Psychiatric treatment and psychiatric rehabilitation are not mutually exclusive but rather complement each other. Consistent with my professional role and medical training, I will refer to patients rather than clients or consumers. The very nature of rehabilitation is person-centered as the patient is critical in defining rehabilitation goals.

To avoid the inflation of the term rehabilitation to include any program that the patient attends, a pioneer of rehabilitation in the United States, William Anthony, has suggested considering skill building to be the critical element of narrowly defined rehabilitation. If an activity does not involve skill building, it is better called enrichment. Going bowling with peers is enrichment, not rehabilitation in the narrow sense (unless the goal is to build the skill of becoming a proficient bowler). In a broader sense, however, even bowling can be rehabilitation if a stated goal is teaching social skills and not merely killing time. Good programs focus on acquiring one specific skill at a time and provide ongoing support down the road, as needed. Successful rehabilitation decreases social isolation, improves skills and confidence, enlarges social networks, and increases the chances of returning to work or school. Successful rehabilitation should allow the patient to be a member of society and contribute to the greatest extent possible.

Rehabilitation starts as early as possible and is not contingent on symptom resolution, which can be elusive. First-episode programs therefore need to have a strong

Key Point

One useful definition of “psychosocial rehabilitation” is the following by Bachrach: “A therapeutic approach that encourages a mentally ill person to develop his or her fullest capacity through learning and environmental supports” [2]. This patient-centered definition acknowledges the need for patient participation as well as the need for adjustments by family and community. It also puts the patient in the middle of the rehabilitation effort.

rehabilitation component (e.g., modeled after the RAISE initiative, see in the first-episode Chap. 11). However, it is difficult to fully participate in rehabilitation programs if you are too ill. This is similar to pain and PT: your ability to participate in PT is limited if you are in too much pain but very possible with some modicum of pain control.

Rehabilitation Goals and Assessment

Psychiatric rehabilitation does not focus on symptoms but on function and role outcomes [3]. It will come as no surprise that most patients have dreams and aspirations similar to the rest of us: to live a life with security, friends, and a sense of belonging; with a few things they can call their own; and with something meaningful to do. The World Health Organization recommends assessing health and disability in six domains: cognition, mobility, self-care, getting along, life activities, and community participation (see Chap. 8 for a longer discussion about how to measure function) [4]. These six generic domains need to be made concrete in dialogue with a patient whose specific goals will vary based on illness stage and interests. A rehabilitation assessment clarifies the patient’s goals and then assesses internal and external resources available and skills and supports needed to attain these goals. (Almost) all patients bring some internal strengths to the table (e.g., humor), and most also have weaknesses that need to be addressed (e.g., negative symptoms), either by building skills or by directly compensating for them. Some patients can rely on family support or entitlements due to previous work. Difficult cases for rehabilitation have serious interpersonal deficits and seemingly endless social needs, with few internal or external resources to draw from.

Tip

A good rehabilitation question to ask: “Where would you like to be one year from now?” Based on the answer (e.g., get my GED), you need to figure out which new skills are needed to get there (e.g., take GED classes) and the supports needed (e.g., where to enroll the patient, financial supports, individual tutors).

For adult patients, competitive employment in some capacity would be a crucial rehabilitation achievement that unfortunately is rarely achieved in our society if you have schizophrenia. Work defines our role in society and can give us meaning, beyond the mundane consideration of allowing us to buy things. In the United States, less than 15% of patients with schizophrenia in the representative Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) cohort worked competitively [5]. True, not everybody wants to work, not everybody can work, and working does not make sense for everybody economically. However, the reasons for this poor functional outcome might go deeper and can leave us with some pessimism. The sociologist Sennet has used the term “specter of uselessness” to indicate a dilemma in a society built on modern meritocracy in which new values are no longer skills but adaptability and employees are judged by potential and not by actual skills and achievements [6]. These larger, socioeconomic factors that lead to lack of opportunity are huge impediments to successfully finding work for persons with disabilities like schizophrenia. All societies to some extent or another are confronting this specter of uselessness in postcapitalist societies, with highly specialized service industries and their need for knowledge workers instead of unskilled laborers [7].

While it ultimately is the patient who needs to decide about his or her rehabilitation goals [8], it would be foolish to focus merely on strengths and desires and lose sight of real-world impairment and deficits (for the assessment of negative symptoms and cognition, see Chaps. 28 and 29, respectively). Psychiatrists can be very useful in delineating cognitive impairment (e.g., by ordering neuropsychological testing) and help pace and prioritize rehabilitation efforts. While I am not opposed to adopting the more positive language of rehabilitation and the recovery movement when appropriate (see last section of this chapter), I suggest a healthy sense of realism and frank discussion of impairments and impediments to rehabilitation as well. Motivational impairment is one of the biggest obstacles to successful psychiatric rehabilitation that is often not acknowledged honestly enough.

Clinical Vignette

Andreas is a 45-year-old man with deficit schizophrenia. He lives in a group home with other patients who also have schizophrenia. Every morning the “program van” comes and picks up the patient and the other group home members to go to the “recovery-oriented” (from the program brochure) psychosocial day program where he spends 5 hours every workday either in groups or in a common area. Staff members have signed him up for the groups that he must sit through. In the offered groups, he sits and waits until time is up. Sometimes he protests that he would rather stay in the group home; this is usually ignored.

This patient represents a not so rare but rarely talked about problem: you cannot rehabilitate to people, only with them. While rehabilitation goals will be determined by motivated persons, what about those who are content sitting

at home doing nothing? After all, we allow citizens to make this decision, unless you have a mental illness. Does family opinion or staff opinion matter, or are rehabilitation goals solely determined by patients? I am not proposing that there is an easy answer, but simply pointing out that forcing program participation is closer to social control than rehabilitation engaged in freely. At a minimum, for any program that you send your patient to, ask yourself what the goals of the programs are and if you would send a family member to the program.

“Wellness” is a fairly recent focus of rehabilitation, as the “wellness” movement has swept the country. While the goal staying well is a difficult one to be against, I will caution against overlooking the need for taking care of real patients clinically: patients who have symptoms and difficulties functioning. They may not be able to jump on the wellness bandwagon easily. Not everybody can pick himself up by his or her bootstraps. Good rehabilitation specialists work with patients while acknowledging the real world (e.g., cognitive deficits, lack of interpersonal skills, limited education, poverty), providing adequate support and fostering a hopeful attitude that change for the better is possible, *despite everything and in the long run*.

Providing false hope by setting unrealistic and unattainable goals with resulting failure is a poor prescription. High expectations can be too much, and some patients crumble under the stress of a new goal. However, low expectations can become self-fulfilling prophecies, and some need to be challenged in order to move. Show flexibility in setting goals and humility about your ability to predict the future; I have been proved wrong both ways. Some patients will surprise you with talents and accomplishments that seemed impossible; others where you had no concerns proved less resilient. In all cases, I remain hopeful for small improvements with time.

Tip

Moving toward more “independence” comes up regularly in discussions about rehabilitation goals. The Peter Principle applies to rehabilitation: patients are “promoted” toward more and more independence until they reach their own level of “incompetence” with regard to independent living; the group home was too restrictive, the own apartment with daily visiting nursing visits worked well, and the own apartment without support proved insufficient.

Not all patient goals are psychiatric rehabilitation goals in its narrow sense as described earlier (skill building). Instead, patients often have a host of social needs that are non-disease issues, for example, poverty or homelessness that often must be dealt with before educational or vocational rehabilitation attempts. It is difficult to learn a skill if you are hungry and have no place to sleep. Note that “housing” per se is not a goal of narrowly defined, *psychiatric* rehabilitation, even though stable and

secure housing is obviously personally desired and a societal goal. There is an advantage of restricting rehabilitation to skill building as you can design programs that address needed skills and provide support: maintaining housing can be easily conceptualized as a rehabilitation goal if loss of housing is the result of poor budgeting skills resulting in eviction because of not paying rent. What rehabilitation can do is provide supported housing and teach budgeting skills.

Rehabilitation Tools

Psychosocial rehabilitation requires a wide range of services (Table 24.1). The best services also serve real-world patients, not the ideal patient. For example, integrated substance use programs accept patients who have schizophrenia and a substance use disorder instead of splitting services between two different programs with different program philosophies. Ideally, psychosocial rehabilitation programs are a step toward independence, and program attendance is not an end in itself. Social skills training has been a core component of many rehabilitation programs. As it addresses deficits in social cognition, I included it in the chapter on cognition (see Chap. 29).

One well-known and successful rehabilitation program is the clubhouse model that was started in the 1950s by patients themselves after they were discharged from state hospitals as part of deinstitutionalization. There are now clubhouses in many major cities in the United States and other countries although funding restrictions limit their potential reach (see under Additional Resources). Clubhouses engage patients by simply allowing them to be part of something normal. Once members are ready, they participate in running the program and learn new skills (e.g., cooking, budgeting, or answering the clubhouse central phone line). The clubhouse model takes its strengths from the power of peer support and offers companionship that is not contingent on some professional therapeutic (and paid) relationship. Clubhouses are not psychiatry's extended arm to supervise medications, so do not look to them for help with this aspect of care. Clubhouses may have unique names.

Table 24.1 Psychiatric rehabilitation tools

Modality	Goals
Social skills training	Improve social adjustment and independent living skills
Supported vocational rehabilitation	Return to competitive, paid employment
Supported employment	Enhance work tenure
Supported housing	Enhance community tenure and prevent homelessness
Supported exercise	Improve physical fitness
Assertive community treatment (ACT)	Reduce psychiatric hospitalizations and risk to community
Case management	Coordinate rehabilitation and treatment services
Entitlement programs	Satisfy basic needs to enable patients to participate in rehabilitation

The original one in NYC, for example, is called “Fountain House,” going back to 1948. In my home state, a clubhouse across from the community mental health center where I work is called “Center Club.” Some clubhouses offer additional services such as helping their members with housing or vocational rehabilitation.

Many so-called rehabilitation programs are not rehabilitation programs in the skill-building sense. Many are mostly social programs with recreational activities. I do not want to minimize the importance of such programs for individual patients, as they might provide them with the only socially meaningful opportunity they have. Some patients are in fact not ready for rehabilitation, and such programs (also known as drop-in centers) provide the basis for engagement as a limited yet necessary first goal. I have also come to conclude since the last edition of this book that for many patients with serious psychiatric disorders, a clubhouse-like facility or drop-in center is one of the few sanctuaries left in a society that mostly values performance and function. Nevertheless, from a larger perspective, creating psychiatric ghettos where patients live in parallel to “real” life because we do not offer high-quality psychiatric rehabilitation is problematic.

Providing an appropriate level of support is a critical element for successful rehabilitation. As you can see from Table 24.1, many rehabilitation tools include “supported” in their names to indicate that patients are not left to their own devices at work, at home, or in the gym but get help in order to succeed at work, living independently, or exercise, respectively. A supported employment program, for example, might communicate with employers about special accommodations and be available for collaborative problem-solving if a worker struggles rather than simply terminating employment. Supported employment is one evidence-based treatment that leads to about 50% employment rates compared to 25% for standard vocational programs [9]. A main rule of supported employment is a zero exclusion: only wanting to work is needed. Patients are then placed rapidly in competitive jobs, along with support throughout the employment; there is no lengthy prevocational training required to create the “perfect worker.” Unfortunately, supported employment is often unavailable or if available only used for short periods of time, partially explaining the low employment numbers for patients with schizophrenia [10].

The way services are delivered is as important as the nature of the services themselves as patients have to be able to access the services in order to use them. Office-based case management is sufficient for patients who can attend office appointments and who can work with a case manager. The patient with schizophrenia who never comes to his outpatient appointments, however, needs a different, more active approach like outreach where the program comes to the patient instead of the patient to the program. Developed in Madison, Wisconsin, in the 1970s by Marx, Test, and Stein [11], assertive community treatment (ACT) is one example of such a proactive treatment delivery model that was specifically designed to provide comprehensive treatment to patients with schizophrenia in their communities instead of needing to chronically institutionalizing them. ACT has also been called a “hospital without walls” because it offers in the community all those services that previously only a state hospital could provide. ACT programs are an evidence-based practice [12] that are particularly well suited to bring services to difficult to reach populations, not

just patients with schizophrenia (e.g., forensic patients, homeless patients, young patients, patients with substance use disorders). ACT teams are multidisciplinary teams that are available 24/7 and provide assistance with psychosocial needs in addition to psychiatric, substance use, and medical care. One critique of ACT has been the nonvoluntary aspect of engagement with a service (the team will “reach out”). We should not ignore, however, that most patients value community living and gain more freedoms than they lose from ACT involvement, particularly when compared to living in a “total institution,” to use Goffman’s term for a state hospital. ACT-like programs are acronym heaven, with names like PACT (Program for Assertive Community Treatment), CSP (Community Support Program), or MTT (Mobile Treatment Teams).

All modern societies have some form of welfare and entitlement programs to assist people who need help for reasons outside their control such as illness. In the United States, welfare programs that are based on needs alone (not on previous contributions) include Supplemental Security Income (SSI), Medicaid, and special vouchers for housing, transportation, or food stamps (now known officially as Supplemental Nutrition Assistance Program or SNAP) (Table 24.2). While sounding similar to SSI, Social Security Disability Insurance (SSDI) is different in that it entitles people who have worked and paid Social Security taxes before becoming disabled to some income. Medicare similarly is an entitlement based on previous contributions. Note that payments from any of these programs are tools for rehabilitation, and “getting SSI” does not constitute “rehabilitation.” It is often worthwhile to apply for SSI or SSDI since eligibility might qualify patients for other assistance programs (e.g., Medicaid or state rehabilitation programs). Unfortunately, the term welfare has a bad connotation to American ears, conjuring up images of undeserving social parasites (the “welfare queen”), and providing welfare to its citizens as a function of government is easily demonized [13]. As a result, welfare services are poorly funded, or patients will not access them because of the stigma associated with using them.

Tip

Make a list of services and organizations involved in the patient’s rehabilitation. Consider yourself as the (at least informal) leader of an invisible team; your leadership role stems from your legal-rational authority (training and position) but also perhaps from charismatic (“the experienced doctor with gray hair”) and traditional (customary hierarchy) sources of authority, to use terms from Weber’s classic tripartite model. Delegate, but avoid wishful thinking: the night-shift person in the group home you are dealing with might have little understanding of schizophrenia and should not be burdened with tasks beyond his or her expertise.

Table 24.2 Entitlement and welfare programs

SSI	Federal assistance for the aged, blind, or disabled, based on financial need alone
SSDI	Federal insurance benefit based on previous work and payment of Social Security taxes
Medicaid	Federal health insurance program for low-income people administered by the state (with different rules for eligibility in different states); known by different names in some states; for example, in Massachusetts, the program is known as MassHealth
Medicare	Federal health insurance program for people over 65 and other groups

SSI Supplemental Security Income

SSDI Social Security Disability Income

Recovery

Psychiatric rehabilitation has a strong tradition of de-emphasizing professional involvement, probably rooted in the times when many patients were simply warehoused in “rehabilitation units.” When you read the rehabilitation literature, you will note that patients are often called “clients” or “consumers” in an effort to empower patients by de-emphasizing the traditional power differential between physicians and patients. You will further notice that rehabilitation services usually embrace a “recovery-oriented philosophy,” with hope being a fundamental ingredient in rehabilitation and an emphasis on function and strengths, not dysfunction and weakness. I would argue that traditional psychiatric care if practiced well has much in common today with recovery-oriented rehabilitation, particularly in the ultimate goal of actually helping patients improve their lives. Good psychiatrists have always understood that giving hope is critical for the human condition, particularly if fate has been cruel. The recovery movement continues to remind psychiatry that the power to use coercion is an aspect of psychiatry’s history and current tools that require eternal vigilance to prevent misuse.

With a medical mindset, recovery can be narrowly viewed as functional recovery and measured using specific criteria (see Chap. 10). In this sense, a full *restitutio ad integrum* (which is often implied when people speak about recovery) is not achievable for most patients with schizophrenia. Pretending that everybody can fully recover from schizophrenia and live independently is at best unhelpful and often cruel. For the group of severely ill patients, the time-honored rehabilitation goal of preventing clinical worsening needs to still be an accepted goal on a treatment plan. Even modest goals, such as reducing distress and reducing hospitalizations over the next 6 months, are valid rehabilitation goals that can be conveyed with a sense of optimism and hope that further improvement is always possible. However, some would call this view too medical and pessimistic and offer a view of recovery in which recovery is seen as a mindset and process, not an end point. Recovery (or recovering) describes the process through which patients shed the patient label and develop identities (again) by which they are not defined through their illness or dis-

ability, at least not exclusively. Recovery means there is more to life than visiting the doctor or the day program. In the broadest sense, recovery means being welcome in society and partaking in it (e.g., by voting), not being marginalized or hidden away. Your answer to your patient who asks if he can recover from schizophrenia will depend on your own definition of recovery. My best answer blends realistic medical knowledge with hope for the future that things can improve, particularly if a patient can accept help and if he can develop an attitude toward his illness that favors agency and responsibility over passivity and victimhood.

Tip

Make sure you understand how your patient understands recovery and “being recovered” as it may inform your approach to the patient and your treatment plan. What does successful recovery look like? Do they see recovery as categorical (all-or-nothing) or as a process? Do they believe they have an acute condition that will resolve or a chronic illness that dooms them? Do they emphasize clinical symptoms, or do they pay more attention to psychological or physical health? Do they use role function like being in school, having friends, or working as markers of recovery?

A more recent, major development in schizophrenia care has been the growth of the peer movement in the United States [14]. Increasingly, peers or “people with lived experience” (e.g., with a psychotic disorder) provide support or even more direct care for patients with schizophrenia. Peer support has always played a large role in substance use treatment and rehabilitation, so the concept itself is not new. Peer involvement in schizophrenia care can take many forms. Peer counselors, for example, are people with lived experience who are trained (and paid) to directly provide mental health services (e.g., on an inpatient unit to provide psychoeducation). Peer-run wellness initiatives or family-led groups (e.g., NAMI’s family-to-family program; see Chap. 23) have become important resources for my patients and their families as the Department of Mental Health in Massachusetts has been an early champion for this progressive approach to care. I see the peer movement as a fundamentally positive development unless peers are used to avoid hiring experts where expert knowledge is needed and we end up with a deskilled mental health workforce as a result.

Key Point

The nature of rehabilitation requires that you work as part of an interdisciplinary team of which many team members might have philosophical views different from yours – something that can create tension and power struggles. Team-based care in the community is particularly difficult since you may never meet all people involved in your patient’s care. You need to figure out who can do what for you and your patient: some team members will have great titles but accomplish very little for your patients. The most effective team member may be a nonprofessional outreach worker.

Modern healthcare systems and today's psychiatrists are rightly expected to provide recovery-oriented services that foster patient independence and minimize intrusion into people's lives. Respecting personal recovery goals is one tenet of recovery-oriented care [8]. Tolerating patient decisions and goals even if they seem wrong can be hard for treatment teams. However, we ourselves take for granted the right to try and fail at something. Should we not afford our patient this same right? While we want to spare people the pain of failure, it may be a necessary step toward growing up. However, clinicians (and the state) do not need to unconditionally support unrealistic recovery goals. In some instances, we also have fiduciary and moral responsibilities to offer more help, even if less is demanded, particularly to avoid catastrophic outcomes. If taken seriously, recovery-oriented care will create moral dilemmas and distress as we struggle to balance our own values with competing patient, professional, and societal values (e.g., patient autonomy including the right to be let alone, protection of a vulnerable person, community safety, resource stewardship). Moral distress can be a limbic warning to not misuse the power we as physicians ultimately have over people's lives and instead to be as open to true person-centered care as we possibly can.

References

1. Thomas EF, McGarty C, Mavor KI. Transforming "apathy into movement:" the role of prosocial emotions in motivating action for social change. *Personal Soc Psychol Rev.* 2009;13: 310–33.
2. Bachrach LL. Psychosocial rehabilitation and psychiatry in the care of long-term patients. *Am J Psychiatry.* 1992;149:1455–63.
3. Rossler W. Psychiatric rehabilitation today: an overview. *World Psychiatry.* 2006;5:151–7.
4. World Health Organization. International classification of functioning, disability and health (ICF). Available at: <https://www.who.int/classifications/icf/en/>. Accessed on 7/1/19.
5. Rosenheck R, Leslie D, Keefe R, McEvoy J, Swartz M, Perkins D, et al. Barriers to employment for people with schizophrenia. *Am J Psychiatry.* 2006;163:411–7.
6. Sennett R. The culture of the new capitalism. New Haven, London: Yale University Press; 2006.
7. Drucker PF. Post-capitalist society. New York: Harper Collins Publishers; 1993.
8. Windell D, Norman R, Malla AK. The personal meaning of recovery among individuals treated for a first episode of psychosis. *Psychiatr Serv.* 2012;63:548–53.
9. Drake RE, Bond GR, Goldman HH, Hogan MF, Karakus M. Individual placement and support services boost employment for people with serious mental illnesses, but funding is lacking. *Health Aff (Millwood).* 2016;35:1098–105.
10. McGurk SR, Mueser KT. Sustaining the long-term effects of supported employment for persons with psychiatric disabilities. *Am J Psychiatry.* 2016;173:953–5.
11. Marx AJ, Test MA, Stein LI. Extrahospital management of severe mental illness. Feasibility and effects of social functioning. *Arch Gen Psychiatry.* 1973;29:505–11.
12. Mueser KT, Deavers F, Penn DL, Cassisi JE. Psychosocial treatments for schizophrenia. *Annu Rev Clin Psychol.* 2013;9:465–97.
13. Garland D. The welfare state. A very short introduction. New York: Oxford University Press; 2016.
14. Duckworth K, Halpern L. Peer support and peer-led family support for persons living with schizophrenia. *Curr Opin Psychiatry.* 2014;27:216–21.

Additional Resources

Website

<http://www.iccd.org> – The International Center for Clubhouse Development; provides information and listings by state of certified clubhouses modeled after the first one, Fountain House in New York City.

<https://www.who.int/classifications/icf/en/> – The WHO's International Classification of Functioning, Disability and Health (ICF) is a good starting point to understand how diseases impact function and how to assess it comprehensively.

Book

Garland D. The welfare state. Very short introduction. New York: Oxford University Press; 2016. – A concise introduction to welfare, including a defense of its importance for modern societies, from Oxford University's Very Short Introduction series.

Article

Rössler W. Psychiatric rehabilitation today: an overview. World Psychiatry. 2006;5:151–7. – A good conceptual introduction to psychiatric rehabilitation.

Chapter 25

Medical Morbidity and Mortality



Essential Concepts

- Physical health and wellness matter as much as mental health to patients with schizophrenia. Reducing premature deaths from cardiac disease and cancer is an important long-term treatment goal.
- Psychiatrists need a medical prevention mind-set if we want to succeed in reducing the mortality gap between patients with schizophrenia and the general population.
- Providing safe and effective psychiatric treatment is the basis for good medical care: there is no health without mental health.
- Routine health monitoring in conjunction with primary care to prevent medical morbidity and mortality should be implemented. This includes preventive healthcare (e.g., eye examinations, colonoscopy, cancer screening), vaccinations (e.g., influenza), and screening for infectious diseases (e.g., human immunodeficiency virus [HIV], hepatitis).
- On average, at least four out of ten patients with schizophrenia have the metabolic syndrome. Preventing weight gain and the metabolic syndrome are important to reduce cardiac mortality. Sustained weight control requires lifestyle modification.
- In young patients, chose wisely which antipsychotic you start, and consider adding metformin prophylactically for patients who need metabolically high-risk antipsychotics (olanzapine and clozapine).
- Switching antipsychotics for metabolic reasons is a decision that must take into account the risk of psychiatric instability.
- Guideline-concordant metabolic monitoring is the basis for population-based management that helps identify patients who need to receive more aggressive interventions to prevent diabetes and cardiovascular disease.

- Improvements at the systems level to reduce care fragmentation are needed so patients with schizophrenia can routinely receive timely and standard care for medical conditions.
- Psychiatrists can play a key role in reverse integrated care for patients with serious mental illness.

“Mens sana in corpora sano.” [1]
 (“A sound mind in a sound body.”)

Juvenal, Roman poet, late 1st and early 2nd century

Patients with schizophrenia die much younger than their peers without schizophrenia, a sad truth known as “mortality gap.” It has been estimated that having schizophrenia shortens the average life expectancy by more than a decade [2]. Although some of the excess mortality stems from suicides and accidents (40%), medical illness, particularly cardiovascular disease, is responsible for the majority of the excess deaths (60%) [3]. Despite a greater awareness of the importance of medical illness in patients with schizophrenia and some gains in improving longevity, this health disparity has not been rectified [4]. While it is easy to blame a patient’s “lifestyle” (smoking, no exercise, poor diet) and the disease (negative symptoms), this ignores the powerful influence of social circumstances on health (see Chap. 32 for more on the social determinants of health). The health impact pyramid [5] is a sobering reminder that broad-based measures directed at the whole population (the bottom of the pyramid) are the most impactful if we want to prevent diseases. Reducing poverty and changing cultural values about smoking are examples. Once we encounter patients in the clinic (the top of the pyramid), our power to prevent illnesses is limited compared to community efforts.

It would be equally wrong to look only at the metabolic side effects from antipsychotics, a clear risk factor for diabetes and cardiovascular disease. Sometimes patients believe not taking antipsychotics would be the medically safest approach to take. Population-based data do not support this view: providing no psychiatric treatment is associated with the highest risk of death, including death from cardiovascular mortality [6]. This has face validity: a psychotic patient who is untreated does not experience antipsychotic-associated weight gain, but he will be unable to take care of himself medically (e.g., taking antihypertensive medications regularly). As Brock Chisholm, first Director-General of the World Health Organization noted, “without mental health there can be no true physical health” (or *mens sano in corpora sano and vice versa*, if you prefer a Latin phrase from an older source) [7]. Providing optimal psychiatric care which includes safe prescribing may in fact be your biggest contribution to reducing medical mortality. In this chapter, I provide concrete examples what a psychiatrist can do to help reduce the mortality gap for our patients with schizophrenia, with emphasis on metabolic monitoring and care coordination.

Table 25.1 Medical causes of mortality in schizophrenia

Cardiovascular disease	Heart attack
Cancer	Lung cancer
Pulmonary disease	COPD Influenza and pneumonia

Based on Ref. [8]

Causes of Medical Mortality

We should focus our energies on those diseases that are responsible for the largest number of premature deaths: cardiovascular disease and cancer, particularly lung cancer [8]. Lung diseases (pneumonia, COPD) are another disease category that contributes to the health disparity (see Table 25.1). Smoking is one of the most important modifiable risk factors that contributes to all three conditions. See smoking as the threat to your patients, both in terms of health risk and as a potential financial hardship (i.e., patients can spend more than one third of their income on cigarettes). Psychiatrists, given their expertise in addictions and their frequent visits with patients relative to primary care, are ideally positioned to take the lead in smoking cessation. Given its importance, I dedicate a whole chapter to smoking (see Chap. 27). The increased risk of dying from pulmonary infection for patients with schizophrenia is underappreciated. These deaths are probably the result from seeking care late. Cancer mortality including death from lung cancer is similarly often due to a delayed diagnosis at a later disease stage [9]. Even when patients with schizophrenia receive cancer care, there is always the risk of an interruption of care if psychiatric issues are allowed to intrude [10]. The issue of care coordination with medicine including specialty care like oncology is discussed at the end of this chapter, in a section on reverse care integration.

All the major cardiac risk factors (smoking, diabetes, hypertension, dyslipidemia) are highly prevalent in patients with schizophrenia [11]. In a typical sample of chronic schizophrenia patients, between 40 and 60% of patients are diagnosed with the metabolic syndrome. In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), the increased prevalence of risk factors translated into a fourfold increased 10-year cardiac risk over the general population [12]. It is particularly concerning that cardiac risk factors are already present in young, first-episode patients. In the RAISE sample, for example, 13% of patients who were on average 24 years old already had the metabolic syndrome; half the patients smoked, and half were obese [13]. Focusing on physical health early, when patients start taking medications, might prevent some of the morbidity and mortality that we see in today's cohort of middle-aged and older patients.

Tip

Calculate each patient's 10-year Framingham cardiac risk in order to provide your patient with a concrete about their risk of dying from heart disease. An increased risk might motivate some patients to quit smoking and change their lifestyle.

For an easy-to-use calculator, see <https://www.framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-year-risk/>.

Medical Prevention Mind-Set

Concern yourself with the physical health of your patients. As a psychiatrist, you often have much more contact with a psychiatric patient than does the primary care physician (PCP), and you might be in a much better position to monitor physical health and to advise behavioral changes. The extent of your involvement in medical aspects of your patient's care is going to be determined by your training, the local resources, a patient's preference, and ultimately how you define your role. The American Psychiatric Association's position is clear: some medical aspects of care are essential components of psychiatric practice (APA) [14]. Without psychiatric leadership, the gap in life expectancy will not be reduced.

The American Psychiatric Association has developed a grid that delineates the role of the psychiatrist vis-à-vis medical care, centered around the acuity of the medical problem and medical resources available [15]. For most medical problems (e.g., dyslipidemia or diabetes), your role will usually be small unless you happen to be trained in both psychiatry and medicine; most psychiatrists will not manage acute medical issues or take on chronic care tasks. However, awareness of medical issues and intervening if needed may well fall into your scope of responsibilities. Simply linking a patient to primary care is often all that is needed. Sometimes, you may need to go the proverbial extra mile: not receiving standard medical care for diagnosed conditions (e.g., cardioprotective medications after a heart attack) is one factor that contributes to the increased mortality in patients with schizophrenia [16]. Advocating for your patients to receive optimal medical care may be needed if we want to close the aforementioned mortality gap [17].

If you detect a medical problem incidentally or because of metabolic screening, you can decide to treat what you are comfortable with or defer to a PCP. Even if your patient has a PCP, there is no harm in reinforcing the need for preventive screening (e.g., eye examinations or cancer screenings like a colonoscopy or mammography), reviewing vaccination requirements (e.g., influenza vaccine in the fall), or suggesting testing for infectious diseases when indicated (e.g., tuberculosis, hepatitis C virus, HIV) [18]. Your patients might trust your advice more than you realize, and your verbal intervention might actually lead to their accessing some preventive healthcare. Many chronic patients have community-based case workers who could be engaged to make PCP appointments or cancer screening tests happen.

For blood-borne infections (hepatitis C and HIV), the identification of infected patients via screening is a critical first step in the so-called cascade of care (identifying patients, linking them to care, starting treatment, persisting with treatment to achieving desired health outcome) [19]. Routine screening for HIV (regardless of risk factors) and HCV screening (based on risk factors and cohort screening) as recommended by the CDC can easily be incorporated into clinic workflows for new patients. Both HIV and hepatitis C care have been revolutionized when highly effective antiviral treatments became available. In the case of hepatitis C, a short course with well-tolerated direct-acting antivirals can now eradicate the virus from a patient's blood stream [20]. Screening is particularly rewarding for medical conditions where treatment makes a real difference, as is the case for those two blood-borne infections (see case at the end of the chapter). Moreover, identifying infected patients who are unaware reduces secondary infections which is an important infection control goal for public health authorities.

Tip

PCP offices are a resource to you, not a burden: work with them. Make a phone call, email, or write a note to introduce yourself (the latter probably uncommon today). PCPs are often pleasantly surprised if a psychiatrist takes an interest in the physical health of their patient. Difficult care coordination with psychiatry ranks perennially high on the list of complaints primary care has about psychiatry.

I suggest that you assume primary responsibility for at least two aspects of physical health: smoking cessation and monitoring the side effects of the medications that you prescribe, especially antipsychotic-associated weight gain and metabolic problems (i.e., metabolic screening). In a survey at our hospital, the primary care doctors very strongly believed that managing smoking cessation falls under psychiatry's purview [21].

Record the following medical information in every patient chart:

- Smoking status as a “vital sign” (packs per day, number of pack years); note tobacco use disorder on the problem list, if present.
- Calculate the body mass index (BMI), not just weight; note on the problem list if overweight or obese.
- Dyslipidemia, diabetes, or hypertension, if present.
- Presence of the metabolic syndrome.
- Activity level (e.g., inactive, walks, exercises three times a week) and diet.

Metabolic Disease Prevention

Helping patients maintain a normal weight or lose excess weight is probably the most vexing and maddening medical problem that you will be trying to address. The importance of preventing weight gain or promoting weight loss lies in avoiding the

downstream medical consequences of being overweight or obese, particularly the metabolic syndrome. Obesity causes a host of other complications beyond the metabolic syndrome that adversely affect quality of life (e.g., daytime sedation from obstructive sleep apnea).

Tip

Calculate each patient's BMI and put it in your note. You will be surprised how many patients for whom you did not suspect a weight problem are overweight or obese according to their BMI. Also determine for each patient if they meet criteria for the metabolic syndrome.

There are many BMI calculators on the web (e.g., https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/english_bmi_calculator/bmi_calculator.html).

A cynic might say that we have no tool to prevent weight gain – the rates of obesity in the United States keep increasing every year in every state, despite billions spent on “healthier” food and weight loss drugs. You are trying to prevent weight gain against this background of an ever-increasing BMI in the general population; and you are attempting this in a population that might be less equipped to do so, on account of disease-intrinsic motivational deficits or poverty. It is an uphill battle.

To add insult to injury, our medications clearly exacerbate any such weight gain that might occur naturally. Almost all antipsychotics show weight gain after extended use [22]. In a meta-analysis, only ziprasidone did not cause weight gain [23]. The weight gain is more pronounced in younger and antipsychotic-naïve patients [24]. Antipsychotic-induced weight gain is not clearly dose-dependent: lowering the dose is therefore usually not a successful management strategy. I find it useful to view psychotropics as one more risk factor toward weight gain that patients must take into account (as opposed to attributing all and any weight gain to medications alone). For more details about antipsychotic-associated weight gain, see Chap. 13.

With a metabolic prevention mind-set, you prefer antipsychotics with the least liability toward weight gain to prevent added iatrogenic morbidity; you screen and monitor to detect, and you prevent/blunt weight gain in order to mitigate by intervening early and proactively.

Preventing Metabolic Problems (Primary Prevention)

Choose your antipsychotic wisely: select an antipsychotic with a lower liability for weight gain. The partial agonist antipsychotics (brexpiprazole [25], cariprazine [26], and aripiprazole [24]), lurasidone [27], and ziprasidone [23] appear to be safest in this regard. Suffice it to say that this is not always possible: our most

effective antipsychotics, olanzapine and clozapine, are also the most problematic ones with regard to weight gain [28].

I listed the addition of metformin below, under secondary prevention although it can be added from the get-go, before weight gain or metabolic abnormalities have occurred. The distinction between primary and secondary prevention is not clear-cut since when a disease begins is only categorical in the minds of people who develop disease classifications.

Introduce ancillary nonmedical prevention efforts (diet and exercise) early, and make illness self-management part of your treatment plan. Exercise should be supported (a sibling will do) exercise. It cannot simply left up to the patient's motivation. Without your patient making some therapeutic lifestyle changes (TLC), the new term for "diet and exercise," it will be very difficult to treat obesity successfully. While you want to be an advocate for healthy living, guard against becoming a crusader for better-than-well [29]. Patients should not lose weight to please you. You cannot give them the impression that failure to lose weight is a personal insult to you and causes you to be disappointed in them. Weight loss in and of itself is also not the goal; healthier living and increasing fitness are. Thus, do not focus on simply how much weight was lost but how the efforts of better eating and of more walking are beneficial, including for a sense of mastery. It is very encouraging that behavioral interventions to manage weight gain can be successful in patients with serious mental disorders [30]. Core interventions used in a behavioral intervention trial known as STRIDE that helped patients succeed in losing weight included increasing awareness through monitoring, creating personalized diet and exercise plans, reducing calories, improving diets, increasing physical activity, and graphing progress [31]. Personalizing interventions appears to be critical for long-term success [32].

However, much more work remains to be done. The health results of a multicomponent workplace wellness program have been disappointing [33]. A well-conducted trial in obese patients with schizophrenia termed CHANGE similarly failed to show cardiovascular benefits from individual lifestyle coaching over treatment as usual [34]. Last, the role of digital medicine to track behaviors (e.g., counting steps) in order to encourage behavioral change may have been oversold [35]. Together, these results that run counter to our intuition to recommend "lifestyle modifications" should give us pause before uncritically rolling out "wellness programs" for our population.

In the interim, I would encourage the following six behavioral changes that would have a positive effect in the long term, if implemented and sustained.

- Have patients weigh themselves every week to catch small but steady weight gain.
- Normal portions for whatever is eaten. Teach patients about portion size so they appreciate how much they consume. Do not micromanage what they eat.
- Stimulus control. It might be simpler to ban some food items from entering the house than trying to control the amount eaten.
- No deserts. (As a compromise for New England, limit donuts to once a week for breakfast).

- No soft drinks but water instead.
- Alcohol only in moderation. Teach patients about the additional calories from drinking alcohol regularly.

Tip

Get your patient to be more active. Stress the benefits of an active lifestyle to the patient (including for cognition) [36]. Regular exercise *even in the absence of weight loss* can improve the metabolic syndrome [37]. Always be reasonable: How likely is it that a person who never ran a mile in his life will start jogging regularly? Perhaps the person used to swim and can join the local YMCA again. Perhaps taking the stairs instead of the elevator can literally be the first step. Wearing a device that counts steps can concretely offer feedback about actual activity levels.

Metabolic Screening (Secondary Prevention)

Metabolic monitoring guidelines have existed for over a decade. The American Psychiatric Association's consensus statement on antipsychotics drugs and diabetes, for example, was published in 2004 [38]. The consensus statement which was developed together with the American Diabetes Association, among others, described the metabolic risks associated with SGA drugs and recommended baseline and ongoing assessment of metabolic parameters. Despite clear guidance, many healthcare systems have failed to develop systems to implement these recommendations, leading to low rates of guideline-concordant screening [39]. If made a priority, however, screening rates can be substantially improved. In one state mental health system, glucose screening, for example, approached 80% after a series of performance improvement initiatives were implemented [40]. Insulin resistance appears to be genetically linked to schizophrenia itself, adding further urgency to metabolic screening regardless of treatment [41].

You may decide to practice some population-based management and set up your own metabolic monitoring program for your clinic or a cohort of patients treated with antipsychotics. We know from quality improvement research that the best way to do it is by choosing a simple measure that you do for every patient, *without variation*. HbA1c for diabetes screening is one such example of a good variable for population-based management. If you set up metabolic screening by “bundling” certain variables, you avoid missing data by performing tasks together as opposed to viewing them as single tasks. In our psychiatric resident clinic, we found substantially increase screening rates for BMI, glucose, and lipids after the introduction of a “metabolic screening bundle” [42] consisting of four components: body mass index [BMI]; blood pressure; fasting glucose; and fasting lipid panel (total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides). Consult available guidelines regarding physical health monitoring for your patients in order to select which variables to monitor [43, 44]. Choose wisely which test you add to

Table 25.2 Metabolic monitoring

As antipsychotic-induced weight gain and metabolic problems often come together, monitor them together when you start an antipsychotic:

Before starting an antipsychotic

Get baseline weight, height, and waist circumference*

Get baseline fasting glucose, HbA1c, and fasting lipid profile*

Get baseline blood pressure*

While being treated with an antipsychotic**

Check weight every visit

Repeat the metabolic bundle at least annually, depending on risk

Based on the 2004 Consensus Conference recommendations [38, 43] and the 2014 NICE Schizophrenia Guideline [44]

*Consider collecting those variables together as a “metabolic bundle”

**More stringent monitoring can be clinically necessary. However, perfect is the enemy of good: start monitoring now and do your best to implement some longitudinal monitoring. Most importantly, recognize early weight gain and intervene early (consider a 5% weight gain significant)

Consider bundling other tests that are part of your routine health monitoring with the metabolic bundle (e.g., electrocardiogram to check for QTc interval abnormalities and the Abnormal Involuntary Movement Scale to screen for tardive dyskinesia)

your screening battery as screening can cause harm, including false-positive results or squandering healthcare resources [45]. Table 25.2 summarizes metabolic monitoring recommendations.

The prevention or reversal of antipsychotic-induced weight gain and metabolic problems using medications is an active area of research. Most interventions are unlikely to be offered by psychiatrists but left to primary care or specialty care (e.g., liraglutide) [46]. Olanzapine co-formulated with the opiate antagonist samidorphan which blunts olanzapine-associated weight gain is under development [47]. However, some medications are easy to use and should not exceed a psychiatrist’s comfort level (e.g., metformin) [48].

Tip

Consider the prophylactic use of metformin to prevent diabetes in patients on metabolically high-risk antipsychotics (olanzapine, clozapine). This strategy is effective in the short run and safe [49]. Metformin does not cause hypoglycemia. Taking metformin with food avoids gastrointestinal side effects (nausea, diarrhea). The optimal dose for the full effect is 1000 mg twice daily.

Mitigating Metabolic Complications (Tertiary Prevention)

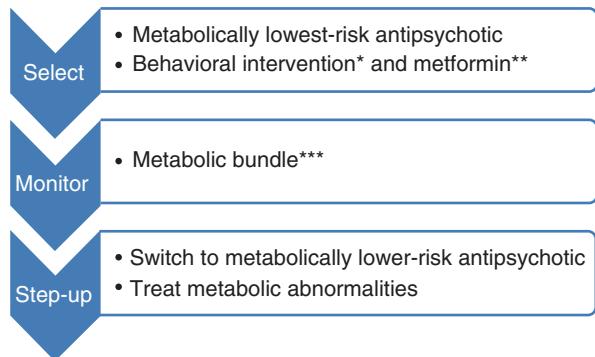
If as a result of your screening you detect problems, you need to step up care. The most powerful intervention can be switching to a less metabolically problematic antipsychotic. In the Comparison of Antipsychotics for Metabolic Problems

(CAMP) study, a switch to aripiprazole was an effective strategy that improved metabolic parameters [50]. However, this is not always clinically possible, particularly in patients who receive clozapine. In many cases you will have to weigh the risks and benefits of switching from a stable antipsychotic regimen to a generally less weight-inducing antipsychotic such as ziprasidone or aripiprazole. This is an important clinical decision that you have to make with the patient (and family member). Do not sacrifice psychiatric stability on the altar of weight loss.

Selected patients might benefit from time-limited trials of available FDA-approved weight loss medications (e.g., lorcaserin, liraglutide, or the phentermine/topiramate combination, of which the latter two are particularly effective [51]). Alternatively, other medications like amantadine [52] or topiramate [53] that psychiatrists may be more comfortable using have been found in meta-analyses to be at least somewhat effective. If weight loss is insignificant after 6 months or so on one of those medications, you can always stop the trial. Even seemingly small decreases in body weight might have beneficial effects, however, on metabolic parameters. Suffice it to say that in an ideal world, weight loss medications are to be combined with behavioral interventions, although desperate situations require desperate measures.

All too often, a metabolically high-risk antipsychotic is used chronically without trying to switch to a metabolically safer one or any other attempt at intervention. Particularly in first-episode patients, you need to be the “man in the arena,” to paraphrase President Teddy Roosevelt, emphasizing that sometimes action is needed, even at some risk of getting blood, sweat, and dust in your face [54]. The adage well captures a modern psychiatrist who actively manages metabolic risks through sequential antipsychotic trials, metabolic screening, and ancillary measures where needed. Figure 25.1 depicts such an active medical prevention-focused psychiatric treatment stance.

Fig. 25.1 Metabolic risk management for patients treated with antipsychotics



*Prescribe (supported) exercise, if possible

**Add metformin for high-risk antipsychotics (olanzapine, clozapine)

***Minimum bundle: BMI, HbA1c, lipid profile

Preferred bundle: Add waist circumference and blood pressure

Reverse Integrated Care

No intervention can be sustained if it depends on your effort and memory. While population-based management for metabolic monitoring can start with a spreadsheet, at some point it needs to be incorporated into the electronic medical record in order to have a real patient registry that assures that nobody falls through the cracks [55]. Without a support system that supports your efforts to provide integrated medical and psychiatric care, you are fighting an uphill battle. Working harder in a poorly designed system will not do. Ultimately, meaningful integration between medicine and psychiatry needs to occur at the level of systems.

The term “reverse” integrated care highlights the need to bring medical care to the psychiatric setting, just like psychiatry has been successful in bringing psychiatric care into the primary care setting [56]. You may realize that we are reinventing the wheel: patients in state hospitals used to receive integrated care. When I started out my career in a state hospital, we had internists and neurologists who had clinics in the state hospital. Different models of care delivery that bring resources to patients are needed today. While sometimes there are no resources, the challenge is often to identify and coordinate available resources for patients to benefit from them. Table 25.3 provides three examples from our own program’s efforts to improve the medical care for patients with schizophrenia cared for in our community. CHAMPS which stands for Coordinated Health And Medical Prevention Service is the acronym for our metabolic monitoring program that we implemented in high-risk patients (clozapine clinic) [57]. For our homeless shelter population, our psychiatric nurse provides counseling and screening using elements of the STIRR (screen, test, immunize, reduce risk, refer) model [58]. One of my colleagues has developed a service that helps bridge care between community psychiatry and our hospital’s academic cancer center in order to provide timely and standard care, including lung cancer screening to schizophrenia patients [59]. In your community, different solutions to the fragmentation problem may be needed.

Table 25.3 Examples of reverse care integration for schizophrenia patients

Program	Elements
CHAMPS	Annual metabolic bundle
	Monthly review of all lab results by internist in order to step up care
	Routine care coordination with primary care doctor
Infectious disease screening	Risk identification and counseling
	HIV and hepatitis C screening
	Linkage to primary care for screen-positive patients
Cancer care	Service to link community providers with cancer center resources
	Lung cancer screening

CHAMPS Coordinated Health And Medical Prevention Service [57]

Our patients, unfortunately, fall into a group that is both physically and behaviorally complex. Much work needs to be done to overcome the obstacles toward better care integration: a fee-for-service structure that limits what psychiatrists can do medically, a safety net structure that puts CMHCs and FQHCs on parallel tracks, a tradition of “I only do therapy,” or the tension between a dyadic treatment model and team-based and population-based care.

Case

In a screening effort in our clozapine clinic many years ago, we discovered that one of our patients, Maurice, had chronic hepatitis C. Because of severe disorganization from schizophrenia, the hepatologist did not want to provide interferon-based treatment which was the standard at the time [60]. We revisited treatment with Maurice, now in his 60s, when direct-acting antiviral medications became available and successfully treated him with a 12-week course of ledipasvir-sofosbuvir (i.e., sustained non-detectable HCV RNA serum levels) [61]. In order to assure adherence to this expensive medical treatment, medication dispensation was tied to his clozapine regimen (supervised by a visiting nurse), and hepatitis C-related blood work was done in the clozapine clinic where the patient had been reliably attending for two decades.

Ultimately, collaboration is an attitude: you can first choose to address medical issues and then figure out how to go about it. Know your prevention priorities, smoking cessation and diabetes prevention, but look for other opportunities. Consider, for example, implementing hepatitis C screening in your clinic [62]. Screening for blood-borne infection (HIV, HCV) is necessary to identify patients who do not know that they are infected in order to prevent secondary infections.

Donald Berwick who was in charge of the Centers for Medicare and Medicaid Services (CMS) during the Clinton Administration noted that “All organizations are perfectly designed to get the results they get” (he used this phrase when he gave Grand Rounds at our hospital a few years ago). Given the lack of resources (e.g., no access to behavioral interventions for weight management or smoking cessation for patients with serious mental illness) and the fragmentation in our care system, we ought not to be shocked about the increased mortality in our patients. Not receiving standard care for diagnosed diseases or receiving care late are two major factors in the increased mortality seen in patients with schizophrenia. It is encouraging that providing optimal (which often simply means standard) medical care appears to reduce the mortality gap, as observed in a cohort study that examined the efficacy of secondary prevention on mortality after myocardial infarction [16]. Only better coordinated and ultimately fully integrated care that brings timely and standard care to all patients with schizophrenia will lead to better health outcomes.

Key Point

While important, physical health monitoring (screening) alone does not improve morbidity and mortality. Psychiatry needs to be at the forefront of improving hard health outcomes (death) for patients with serious mental illness. In collaboration with primary care and specialty care, we need to assure that patients with schizophrenia receive active interventions (timely and standard medical care) when indicated [63].

References

1. Wikipedia. Mens sano in corpore sano. Available from: https://en.wikipedia.org/wiki/Mens_sano_in_corpore_sano. Accessed on 7/1/2019.
2. Crump C, Winkleby MA, Sundquist K, Sundquist J. Comorbidities and mortality in persons with schizophrenia: a Swedish national cohort study. *Am J Psychiatry*. 2013;170:324–33.
3. Ringen PA, Engh JA, Birkenaes AB, Dieset I, Andreassen OA. Increased mortality in schizophrenia due to cardiovascular disease – a non-systematic review of epidemiology, possible causes, and interventions. *Front Psych*. 2014;5:137.
4. Tanskanen A, Tiihonen J, Taipale H. Mortality in schizophrenia: 30-year nationwide follow-up study. *Acta Psychiatr Scand*. 2018;138:492–9.
5. Frieden TR. Shattuck lecture: the future of public health. *N Engl J Med*. 2015;373:1748–54.
6. Torniainen M, Mittendorfer-Rutz E, Tanskanen A, Bjorkenstam C, Suvisaari J, Alexanderson K, et al. Antipsychotic treatment and mortality in schizophrenia. *Schizophr Bull*. 2015;41:656–63.
7. Kolappa K, Henderson DC, Kishore SP. No physical health without mental health: lessons unlearned? *Bull World Health Organ*. 2013;91:3–3A.
8. Olfson M, Gerhard T, Huang C, Crystal S, Stroup TS. Premature mortality among adults with schizophrenia in the United States. *JAMA Psychiatry*. 2015;72:1172–81.
9. Irwin KE, Henderson DC, Knight HP, Pirl WF. Cancer care for individuals with schizophrenia. *Cancer*. 2014;120:323–34.
10. Irwin KE, Park ER, Shin JA, Fields LE, Jacobs JM, Greer JA, et al. Predictors of disruptions in breast cancer care for individuals with schizophrenia. *Oncologist*. 2017;22:1374–82.
11. de Hert M, Schreurs V, Vancampfort D, van Winkel R. Metabolic syndrome in people with schizophrenia: a review. *World Psychiatry*. 2009;8:15–22.
12. Goff DC, Sullivan LM, McEvoy JP, Meyer JM, Nasrallah HA, Daumit GL, et al. A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. *Schizophr Res*. 2005;80:45–53.
13. Correll CU, Robinson DG, Schooler NR, Brunette MF, Mueser KT, Rosenheck RA, et al. Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders: baseline results from the RAISE-ETP study. *JAMA Psychiatry*. 2014;71:1350–63.
14. American Psychiatric Association. Position statement on the role of psychiatrists in reducing physical health disparities in patients with mental illness. 2015. Available from: <https://www.psychiatry.org/File%20Library/About-APA/Organization-Documents-Policies/Policies/Position-2015-Role-of-Psychiatrists-in-Reducing-Physical-Health-Disparities-in-Patients-with-Mental-Illness.pdf>. Accessed on 7/1/2019.
15. Vanderlip ER, Raney LE, Druss BG. A framework for extending psychiatrists' roles in treating general health conditions. *Am J Psychiatry*. 2016;173:658–63.

16. Kugathasan P, Horsdal HT, Aagaard J, Jensen SE, Laursen TM, Nielsen RE. Association of secondary preventive cardiovascular treatment after myocardial infarction with mortality among patients with schizophrenia. *JAMA Psychiatry*. 2018;75:1234–40.
17. Druss BG. Can better cardiovascular care close the mortality gap for people with schizophrenia? *JAMA Psychiatry*. 2018;75:1215–6.
18. Goff DC, Cather C, Evins AE, Henderson DC, Freudenreich O, Copeland PM, et al. Medical morbidity and mortality in schizophrenia: guidelines for psychiatrists. *J Clin Psychiatry*. 2005;66:183–94.
19. Gardner EM, McLees MP, Steiner JF, Del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. *Clin Infect Dis*. 2011;52:793–800.
20. Chasser Y, Kim AY, Freudenreich O. Hepatitis C treatment: clinical issues for psychiatrists in the post-interferon era. *Psychosomatics*. 2017;58:1–10.
21. MacLaurin SA, Henderson DC, Freudenreich O. Delineating responsibility: primary care provider perspective. *Psychiatr Serv*. 2015;66:333.
22. Musil R, Obermeier M, Russ P, Hamerle M. Weight gain and antipsychotics: a drug safety review. *Expert Opin Drug Saf*. 2015;14:73–96.
23. Tek C, Kucukgoncu S, Guloksuz S, Woods SW, Srihari VH, Annamalai A. Antipsychotic-induced weight gain in first-episode psychosis patients: a meta-analysis of differential effects of antipsychotic medications. *Early Interv Psychiatry*. 2016;10:193–202.
24. Bak M, Fransen A, Janssen J, van Os J, Drukker M. Almost all antipsychotics result in weight gain: a meta-analysis. *PLoS One*. 2014;9:e94112.
25. Kane JM, Skuban A, Hobart M, Ouyang J, Weiller E, Weiss C, et al. Overview of short- and long-term tolerability and safety of brexpiprazole in patients with schizophrenia. *Schizophr Res*. 2016;174:93–8.
26. Durgam S, Greenberg WM, Li D, Lu K, Laszlovszky I, Nemeth G, et al. Safety and tolerability of cariprazine in the long-term treatment of schizophrenia: results from a 48-week, single-arm, open-label extension study. *Psychopharmacology*. 2017;234:199–209.
27. Meyer JM, Mao Y, Pikalov A, Cucchiaro J, Loebel A. Weight change during long-term treatment with lurasidone: pooled analysis of studies in patients with schizophrenia. *Int Clin Psychopharmacol*. 2015;30:342–50.
28. Buchanan RW, Kreyenbuhl J, Kelly DL, Noel JM, Boggs DL, Fischer BA, et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr Bull*. 2010;36:71–93.
29. Fitzgerald FT. The tyranny of health. *N Engl J Med*. 1994;331:196–8.
30. Bartels SJ. Can behavioral health organizations change health behaviors? The STRIDE study and lifestyle interventions for obesity in serious mental illness. *Am J Psychiatry*. 2015;172:9–11.
31. Green CA, Yarborough BJ, Leo MC, Yarborough MT, Stumbo SP, Janoff SL, et al. The STRIDE weight loss and lifestyle intervention for individuals taking antipsychotic medications: a randomized trial. *Am J Psychiatry*. 2015;172:71–81.
32. Ward MC, White DT, Druss BG. A meta-review of lifestyle interventions for cardiovascular risk factors in the general medical population: lessons for individuals with serious mental illness. *J Clin Psychiatry*. 2015;76:e477–86.
33. Song Z, Baicker K. Effect of a workplace wellness program on employee health and economic outcomes: a randomized clinical trial. *JAMA*. 2019;321:1491–501.
34. Speyer H, Christian Brix Norgaard H, Birk M, Karlsen M, Storch Jakobsen A, Pedersen K, et al. The CHANGE trial: no superiority of lifestyle coaching plus care coordination plus treatment as usual compared to treatment as usual alone in reducing risk of cardiovascular disease in adults with schizophrenia spectrum disorders and abdominal obesity. *World Psychiatry*. 2016;15:155–65.
35. Tufekci Z. Quantified self. *Sci Am*. 2019;320:85.

36. Firth J, Stubbs B, Rosenbaum S, Vancampfort D, Malchow B, Schuch F, et al. Aerobic exercise improves cognitive functioning in people with schizophrenia: a systematic review and meta-analysis. *Schizophr Bull.* 2017;43:546–56.
37. Firth J, Cotter J, Elliott R, French P, Yung AR. A systematic review and meta-analysis of exercise interventions in schizophrenia patients. *Psychol Med.* 2015;45:1343–61.
38. American Diabetes Association. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care.* 2004;27:596–601.
39. Morrato EH, Newcomer JW, Kamat S, Baser O, Harnett J, Cuffel B. Metabolic screening after the American Diabetes Association's consensus statement on antipsychotic drugs and diabetes. *Diabetes Care.* 2009;32:1037–42.
40. Morrato EH, Campagna EJ, Brewer SE, Dickinson LM, Thomas DS, Miller BF, et al. Metabolic testing for adults in a state Medicaid program receiving antipsychotics: remaining barriers to achieving population health prevention goals. *JAMA Psychiatry.* 2016;73:721–30.
41. Tomaszik J, Lago SG, Vazquez-Bourgon J, Papiol S, Suarez-Pinilla P, Crespo-Facorro B, et al. Association of insulin resistance with schizophrenia polygenic risk score and response to antipsychotic treatment. *JAMA Psychiatry.* 2019 (in press).
42. Wiechers IR, Viron M, Stoklosa J, Freudenreich O, Henderson DC, Weiss A. Impact of a metabolic screening bundle on rates of screening for metabolic syndrome in a psychiatry resident outpatient clinic. *Acad Psychiatry.* 2012;36:118–21.
43. Marder SR, Essock SM, Miller AL, Buchanan RW, Casey DE, Davis JM, et al. Physical health monitoring of patients with schizophrenia. *Am J Psychiatry.* 2004;161:1334–49.
44. NICE. *Psychosis and schizophrenia in adults: prevention and management.* 2014. Available from: <https://www.nice.org.uk/guidance/cg178>. Accessed on 7/1/2019.
45. Grimes DA, Schulz KF. Uses and abuses of screening tests. *Lancet.* 2002;359:881–4.
46. Larsen JR, Vedtofte L, Jakobsen MSL, Jespersen HR, Jakobsen MI, Svensson CK, et al. Effect of liraglutide treatment on prediabetes and overweight or obesity in clozapine- or olanzapine-treated patients with schizophrenia spectrum disorder: a randomized clinical trial. *JAMA Psychiatry.* 2017;74:719–28.
47. Martin WF, Correll CU, Weiden PJ, Jiang Y, Pathak S, DiPetrillo L, et al. Mitigation of olanzapine-induced weight gain with samidorphan, an opioid antagonist: a randomized double-blind phase 2 study in patients with schizophrenia. *Am J Psychiatry.* 2019;176:457–67.
48. Gerken AT, Baggett TP, Freudenreich O. Consider Rx metformin to prevent metabolic syndrome [Pearls series]. *Curr Psychiatr Ther.* 2016;15:e1–2.
49. Zheng W, Li XB, Tang YL, Xiang YQ, Wang CY, de Leon J. Metformin for weight gain and metabolic abnormalities associated with antipsychotic treatment: meta-analysis of randomized placebo-controlled trials. *J Clin Psychopharmacol.* 2015;35:499–509.
50. Stroup TS, McEvoy JP, Ring KD, Hamer RH, LaVange LM, Swartz MS, et al. A randomized trial examining the effectiveness of switching from olanzapine, quetiapine, or risperidone to aripiprazole to reduce metabolic risk: comparison of antipsychotics for metabolic problems (CAMP). *Am J Psychiatry.* 2011;168:947–56.
51. Khera R, Murad MH, Chandar AK, Dulai PS, Wang Z, Prokop LJ, et al. Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis. *JAMA.* 2016;315:2424–34.
52. Zheng W, Wang S, Ungvari GS, Ng CH, Yang XH, Gu YH, et al. Amantadine for antipsychotic-related weight gain: meta-analysis of randomized placebo-controlled trials. *J Clin Psychopharmacol.* 2017;37:341–6.
53. Correll CU, Maayan L, Kane J, Hert MD, Cohen D. Efficacy for psychopathology and body weight and safety of topiramate-antipsychotic cotreatment in patients with schizophrenia spectrum disorders: results from a meta-analysis of randomized controlled trials. *J Clin Psychiatry.* 2016;77:e746–56.
54. Wikipedia. Citizenship in a Republic. Available from: https://en.wikipedia.org/wiki/Citizenship_in_a_Republic. Accessed on 7/1/2019.

55. Nasrallah HA, Harvey PD, Casey D, Csoboth CT, Hudson JI, Julian L, et al. The Management of Schizophrenia in Clinical Practice (MOSAIC) Registry: a focus on patients, caregivers, illness severity, functional status, disease burden and healthcare utilization. *Schizophr Res.* 2015;166:69–79.
56. Esswein SA, Druss B. Chapter 8: Integrating care in the public sector. In: Summergrad P, Kathol RG, editors. *Integrated care in psychiatry: redefining the role of mental health professionals in the medical setting*. Heidelberg: Springer; 2014. p. 127–41.
57. MacLaurin SA, Vincenzi B, Donahue L, Marcri B, Namey LB, Brent B, et al. CHAMPioning guideline concordant care in a clozapine clinic: applying prevention principles to a high risk cohort. Poster presented at Institute on Psychiatric Services; Washington, DC. October 6–9, 2016.
58. Rosenberg S, Brunette M, Oxman T, Marsh B, Dietrich A, Mueser K, et al. The STIRR model of best practices for blood-borne diseases among clients with serious mental illness. *Psychiatr Serv.* 2004;55:660–4.
59. Irwin KE, Park ER, Fields LE, Corveley AE, Greer JA, Perez GK, et al. Bridge: person-centered collaborative care for patients with serious mental illness and cancer. *Oncologist.* 2019; (in press).
60. Silverman BC, Kim AY, Freudenreich O. Interferon-induced psychosis as a “psychiatric contraindication” to hepatitis C treatment: a review and case-based discussion. *Psychosomatics.* 2010;51:1–7.
61. Herold S, Freudenreich O. Hepatitis C virus and schizophrenia: expanding the role of the community psychiatrist. *Psychosomatics.* 2016;57:634–7.
62. Freudenreich O, Gandhi RT, Walsh JP, Henderson DC, Goff DC. Hepatitis C in schizophrenia: screening experience in a community-dwelling clozapine cohort. *Psychosomatics.* 2007;48:405–11.
63. Ilyas A, Chesney E, Patel R. Improving life expectancy in people with serious mental illness: should we place more emphasis on primary prevention? *Br J Psychiatry.* 2017;211:194–7.

Additional Resources

Web Sites

<https://www.integration.samhsa.gov/integrated-care-models> – The website for the SAMHSA-HRSA Center for Integrated Health Solutions (CIHS) contains a lot of information and tools about integrated care. Spend some time to look around.

Articles

Fitzgerald FT. The tyranny of health. *N Engl J Med.* 1994;331:196–8. – Mandatory reading so you do not become a health zealot.

Marder SR, Essock SM, Miller AL, Buchanan RW, Casey DE, Davis JM, et al. Physical health monitoring of patients with schizophrenia. *Am J Psychiatry.* 2004;161:1334–49. – Important consensus guidelines on health monitoring. While over a decade old, people still refer to them as the fundamental principles are as current as they were in 2004.

Irwin KE, Freudenreich O, Peppercorn J, Taghian AG, Freer PE, Gudewicz TM. Case records of the Massachusetts General Hospital. Case 30–2016. A 63-Year-old woman with bipolar disorder, cancer, and worsening depression. *N Engl J Med.* 2016;375:1270–81. – A case discussion that illustrate the complexity of providing optimal cancer care (breast cancer in this case) if there is poorly controlled psychiatric illness.

Chapter 26

Dual Diagnosis



Essential Concepts

- “Dual-diagnosis” patients, as used in this chapter, are patients with schizophrenia who also suffer from a drug or alcohol use disorder. Half of the patients with schizophrenia have a current or past problem with drugs or alcohol.
- Alcohol and cannabis use disorders are the most common comorbidities after nicotine.
- Given the scope of the problem, screen all patients with schizophrenia for substance use, including for “low-grade” use that is nevertheless impairing.
- Treatment is most successful if concurrent and integrated, that is, the patient receives treatment in one system.
- Evidence-based pharmacotherapy for alcohol use disorders, particularly naltrexone, should be routinely considered for schizophrenia patients whose drinking is problematic. It is most effective if combined with other psychosocial treatments for substance use disorders.

“Bacchus hath drowned more men than Neptune.” [1]

—Thomas Fuller, British physician and adage collector, 1654–1734

“Dual diagnosis” denotes the co-occurrence of a psychiatric condition, in our case schizophrenia, and a drug or alcohol use disorder. The term is neither precise (other dual diagnoses exist, e.g., mental illness with developmental disorders) nor does it delineate a homogeneous class of patients (different mental disorders ranging from anxiety disorders to psychosis combined with any use to dependence), but the term has stuck. It came into being when, in the 1980s, a new cohort of “young adult chronic patients” who had never been institutionalized overwhelmed a treatment system that was ill-prepared to treat poorly compliant, drug-misusing patients with schizophrenia in the community, leading to the phenomenon of revolving-door psychiatric admissions.

Key Point

Although the term “dual diagnosis” captures the problem of rather significant comorbidity, the term is not a diagnosis with specific interventions. Each of the disorders present in “dual” contributes to the outcome independently and needs to be diagnosed and treated optimally and specifically in its own right. The two disorders, however, do interact: the presence of one makes the treatment of the other more difficult.

In this chapter, I am discussing substance use in patients with diagnosed schizophrenia; the diagnostic difficulties that arise regarding drug-induced psychosis versus schizophrenia are dealt with in a separate chapter (Chap. 4). Smoking is so common and its consequences so devastating that I devote the whole next chapter (Chap. 27) to tobacco (nicotine) dependence.

Caffeine, another common comorbidity, deserves a brief mention. In moderation, caffeine can be useful to counteract drug-induced sedation. However, excessive caffeine use can cause caffeine intoxication (“caffeinism”). Consider caffeinism in your restless patient with sleep problems. Some patients are genetically predisposed to caffeine sensitivity; one cup of coffee lasts them all day [2].

Scope of the Problem

Substance use and a mental illness, alone or in combination, put people at high-risk for getting entangled in the legal system [3]. Already in their first episode of schizophrenia, 30% of patients have a substance use disorders (the exact percentage will vary with region and definition of substance use). Substance-misusing first-episode patients are typically young men, and they often have better premorbid social but poorer academic adjustment compared to their non-using counterparts [4]. In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) cohort, which is more representative of chronic patients, almost four in ten patients had a current substance use problem [5]. Lifetime rates of any substance use problem are even higher.

Tip

Epidemiology counts, literally and figuratively: as a rule of thumb, remember that at least half of your patients with schizophrenia have a lifetime problem with substance use and about one quarter will have an active substance use disorder.

In the United States, alcohol and cannabis are the most common problems among patients with schizophrenia. Cocaine use, and, interestingly, hallucinogen use, occurs with some frequency as well, whereas, curiously, opiate misuse seems to be infrequent to almost nonexistent in typical community mental health centers. Know your particular epidemiologic situation (e.g., is methamphetamine or phencyclohexylpiperidine [PCP] use common in your community?) and the drug use patterns in your patient population (e.g., college students misusing prescription stimulants or party drugs, including ketamine).

Those with alcohol problems seem to have a worse prognosis because alcohol is quite simply a rather toxic substance if used excessively. It is interesting that despite the adverse consequences of drug use, patients with schizophrenia and drug use problems (other than alcohol) tend to look better with regard to negative symptoms, even though positive symptoms are exacerbated. This suggests some drugs either remedy a deficit (the “self-medication hypothesis”) or that drug use flags those patients who have a better prognosis because they are less biologically impaired; you have to be more “with it” to be able to obtain drugs. Many epidemiologic studies suggest that cannabis use is especially problematic as it may represent a risk factor for schizophrenia. Frequent premorbid cannabis use (i.e., more than 50 times) increases the risk for the development of schizophrenia by sixfold, for example [6]. This is seen as evidence that – in susceptible patients – cannabis can trigger psychosis (see Chap. 4 for a longer discussion of this important public health concern).

Drug use can have devastating effects on patients, families, and society. Other than the obvious social (e.g., homelessness, drug-related crimes), legal (i.e., arrests), financial (i.e., compounding poverty), and medical (e.g., human immunodeficiency virus [HIV] which can lead to patients being “triple diagnosed” with HIV, a drug problem, and a psychiatric disorder) problems from drug use, drugs can maintain or cause psychiatric symptoms, and drug use is an important factor in psychotic relapse. One consequence of drug use is poorer compliance with medical and psychiatric treatment of all its sequelae from poorly treated diseases. Violence is much more likely if there is drug use. Substance use is a potentially avoidable contributor to premature mortality in schizophrenia patients. Unfortunately, substance use starts early, around or often before a first-episode psychosis, and is a significant problem in young, first-episode patients (see Chap. 11).

Assessment

Given the prevalence of substance use in schizophrenia, screening all patients to detect substance use problems is important. All too often, significant substance use is either not recognized at all or its severity not acknowledged. Your interview needs to include careful probing for use of substances of all classes, past and current.

Make sure you get collateral information and do not rely on self-report alone. In addition, a structured screening tool for substance use problems that is part of an initial patient evaluation facilitates its detection and treatment planning. I use the abbreviated Alcohol Use Disorders Identification Test for Consumption (AUDIT-C), for example, to screen all new patients for problems with alcohol use even though the tool was not specifically developed for use in schizophrenia populations; cutoffs in particular may not apply (even low-grade drinking can be problematic for some patients) [7]. I would argue that it does not matter so much which specific tool you use: using one tool consistently for all your patients is what matters most. Laboratory screening to help diagnose unrecognized problems is essential. Urine drug testing is one tool that can provide valuable information if its limitations (false-positive and false-negative results) and ramifications (legal difficulties) are also taken into account and openly discussed with a patient. Saliva drug testing for point-of-care use in the office and hair testing for drugs ingested in the previous 3 months are options to consider. Hair testing poses its own problems – depending on the hair style in fashion (you need a sufficient amount). For our profession, drug testing is never a tool to “catch patients” but ought to be seen as clinical information that can inform your treatment plan.

Diagnostically, you have two problems. First, it can be next to impossible to disentangle the contributions to psychopathology from the primary disorder and from substances. In many cases, however, the longitudinal history will eventually clarify the diagnoses (see Chap. 4 for a longer discussion). Second, patients with schizophrenia lead different lives, and the usual screening questions and diagnostic categories do not necessarily work well: if you never worked or if you never married, you cannot lose your job or your marriage over drinking.

Tip

Classify as “use with impairment” or “misuse” to indicate problematic use that does not reach the level of severity required for a drug use disorder. Even low-grade use can be devastating for vulnerable brains in vulnerable populations. Neither of those terms is used in DSM-5. Some social drinking that is unproblematic and allows patients to enjoy life and feel “normal” should not be pathologized.

Try to figure out where your patients fit in a four-stage dual-diagnosis treatment model put forth by the pioneers in dual-diagnosis research, Drs. Robert Drake and Kim Mueser:

1. Engagement – Patients have no working relationship with a clinician.
2. Persuasion – Patients are in contact with clinicians, discussing substance use.
3. Active treatment – Patients are working to reduce or cease substance use.
4. Relapse prevention – Patients have not had problems related to substances for several months.

Using the “transtheoretical model of behavioral change model” (also known as stages of change model) [8], you can assign your patient to a particular stage (pre-contemplation, contemplation, preparation, action, maintenance) as this will determine the most helpful next steps (you may need to first read a book on Motivational Interviewing to do this well, see under Additional Resources).

Finally, pay attention to the language you use when discussing addictions with your patient but also with your colleagues [9]. Patients are not “drug abusers,” for example, but patients with a substance use disorder (the DSM-5 term); they are not “clean” (as opposed to dirty?) but in recovery. Respectful and professional language is one small contribution to reducing the stigma that surrounds substance use disorders.

Treatment

Probably the most important conceptual insight gained over the past decades has been that both the addiction and the psychiatric disorder need to be treated simultaneously, not sequentially, and preferably in an integrated setting. If provided in this way, the long-term outcomes are often quite positive, as shown by my colleagues up North, in the Dartmouth Psychiatric Research Center [10]. Unfortunately, old habits die hard and systems change slowly, leaving many patients struggling to find optimal treatment in our fragmented healthcare system. This means that your patients are probably better off if you are comfortable providing all their psychopharmacology and if your own clinic also offers the psychosocial services necessary to address substance use (e.g., assertive outreach, case management, supported housing). Many psychosocial substance use programs need to be modified to take into account the cognitive problems that often accompany schizophrenia. However, higher-functioning patients can successfully take advantage of community support programs like Alcoholics Anonymous or other similar 12-step facilitation programs [11]. I see it as a hopeful sign if a patient attends AA meetings as he is basically acknowledging that there is a problem. Routinely encourage patients to look into this free resource.

Tip

For patients who participate in AA, show your interest by asking them, “What step are you working on?” The answer may lead to a helpful discussion of their substance use journey, their hopes for recovery, and also their concerns about failing.

Meet your patients where they are: if abstinence is unrealistic, work on harm reduction. Contingency management (e.g., payeeship) can work well to motivate patients to learn skills to change substance use behaviors. Expect that treatment

needs to be provided (and closely monitored) for many years for incremental learning to occur. Motivational interviewing is a key skill to engage patients in a way that encourages change (see Additional Resources).

Pharmacologic treatment of the addiction is ancillary to the psychosocial treatments, never the only treatment. At the same time, pharmacologic treatments that are evidence-based should be offered. So-called medication-assisted treatment (MAT) for alcohol dependence, for example, remains woefully underused, particularly in patients with serious mental illness [12]. Three medications are FDA-approved for the treatment of alcoholism. The antidipsomanic medication naltrexone (brand name ReVia) at a dose of 50 mg per day can safely be used in alcoholic patients with schizophrenia. Naltrexone is also available as a once-a-month injectable form (brand name Vivitrol), which eliminates the need to take (and remember) pills. I stay away from disulfiram (brand name Antabuse) because of some reports of psychosis [13] and its potential dangerousness if alcohol is consumed despite taking disulfiram, not uncommon in patients with serious mental illness [14]. Only in highly motivated and very reliable patients, it could be considered. I am unsure which patient can reliably take the third available antidipsomanic, acamprosate (brand name Campral), which has to be taken three times daily (two 333 mg pills three times daily).

With regard to antipsychotics in dually diagnosed patients, consider the following points:

- Often, patients will not take medications when they take drugs for fear of an interaction. While not completely unfounded, patients can be told to continue their oral antipsychotic even when using drugs, unless there is a specific interaction that would be dangerous.
- Long-acting antipsychotics can help avoid treatment interruption during times of drug use and should be the preferred mode of administration.
- Clozapine might have unique efficacy to reduce substance use in schizophrenia [15].
- Cocaine increases a patient's risk for dystonias [16], neuroleptic malignant syndrome, and priapism; cocaine might be particularly dangerous with clozapine.
- Avoid QTc-prolonging antipsychotics for patients on methadone [17] to reduce the risk for the development of torsade de pointes.

Clinical Vignette

You have known Emilian for 10 years after he moved to Boston from the West Coast “because of the weather.” In his 50s now, he is reliable in his clinic visits and takes an antipsychotic for schizophrenia. He lives in an apartment and does some volunteer work. One day, he does not show up for his monthly appointment. To your surprise, you learn that he was found drunk in an alley and admitted to a hospital, acutely psychotic. After his discharge, he tells you for the first time that he had a severe alcohol problem in his 30s but thought “I

have it under control.” He started drinking again a few months ago and had stopped his antipsychotic for fear of “an interaction.”

The moral of this vignette is that epidemiology counts, literally and figuratively: The odds for a lifetime substance use history are 50:50. Unfortunately, relapse remains a lifelong possibility for any substance use disorder, and preventing alcohol relapse became an important focus of treatment in Emilian’s case. Naltrexone and a referral to Alcoholics Anonymous (AA) helped him to re-establish sobriety.

A small group of patients has such a severe substance use disorder that they seem to be beyond reach, despite maximum outreach efforts and the use of coercion (e.g., court-ordered admissions for severe substance use that has spiraled out of control, which my state allows). Such end-stage cases with an infaust prognosis often create tension in treatment teams, as team members try to come to term with their own helplessness. On the other hand, it can be very gratifying to see patients who seemed beyond help recovery once they address their substance use disorder. Progress and recovery seem to coincide when they *completely* stop using all substances, including alcohol and particularly also cannabis. Always remember, as George Vaillant, a Harvard psychiatrist who studied adult development, including recovery from alcoholism, showed in his long-term outcome cohort studies of alcoholism that getting a life (back) together requires more than not using a substance [18]. The therapeutic work of rebuilding relationships, creating meaningful activities, and coming to terms with the life lived now begins in earnest once drinking stops.

References

1. Wikiquote. Thomas Fuller. Available from: [https://en.wikiquote.org/wiki/Thomas_Fuller_\(writer\)](https://en.wikiquote.org/wiki/Thomas_Fuller_(writer)). Accessed on 7/1/2019.
2. Meredith SE, Juliano LM, Hughes JR, Griffiths RR. Caffeine use disorder: a comprehensive review and research agenda. *J Caffeine Res.* 2013;3:114–30.
3. Moore KE, Oberleitner LMS, Zonana HV, Buchanan AW, Pittman BP, Verplaetse TL, et al. Psychiatric disorders and crime in the US population: results from the National Epidemiologic Survey on Alcohol and Related Conditions Wave III. *J Clin Psychiatry.* 2019;80(2). pii: 18m12317.
4. Swartz MS, Wagner HR, Swanson JW, Stroup TS, McEvoy JP, McGee M, et al. Substance use and psychosocial functioning in schizophrenia among new enrollees in the NIMH CATIE study. *Psychiatr Serv.* 2006;57:1110–6.
5. Swartz MS, Wagner HR, Swanson JW, Stroup TS, McEvoy JP, Canive JM, et al. Substance use in persons with schizophrenia: baseline prevalence and correlates from the NIMH CATIE study. *J Nerv Ment Dis.* 2006;194:164–72.
6. Andreasson S, Allebeck P, Engstrom A, Rydberg U. Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. *Lancet.* 1987;2:1483–6.

7. Higgins-Biddle JC, Babor TF. A review of the Alcohol Use Disorders Identification Test (AUDIT), AUDIT-C, and USAUDIT for screening in the United States: past issues and future directions. *Am J Drug Alcohol Abuse.* 2018;44:578–86.
8. Prochaska JO, Velicer WF. The transtheoretical model of health behavior change. *Am J Health Promot.* 1997;12:38–48.
9. Botticelli MP, Koh HK. Changing the language of addiction. *JAMA.* 2016;316:1361–2.
10. Drake RE, Luciano AE, Mueser KT, Covell NH, Essock SM, Xie H, et al. Longitudinal course of clients with co-occurring schizophrenia-spectrum and substance use disorders in urban mental health centers: a 7-year prospective study. *Schizophr Bull.* 2016;42:202–11.
11. Ferri M, Amato L, Davoli M. Alcoholics Anonymous and other 12-step programmes for alcohol dependence. *Cochrane Database Syst Rev.* 2006;(3):CD005032.
12. Robertson AG, Easter MM, Lin H, Frisman LK, Swanson JW, Swartz MS. Medication-assisted treatment for alcohol-dependent adults with serious mental illness and criminal justice involvement: effects on treatment utilization and outcomes. *Am J Psychiatry.* 2018;175:665–73.
13. Williams JB. Use of disulfiram for treatment of alcohol addiction in patients with psychotic illness (letter). *Am J Psychiatry.* 2019;176:80–1.
14. Mueser KT, Noordsy DL, Fox L, Wolfe R. Disulfiram treatment for alcoholism in severe mental illness. *Am J Addict.* 2003;12:242–52.
15. Arranz B, Garriga M, Garcia-Rizo C, San L. Clozapine use in patients with schizophrenia and a comorbid substance use disorder: a systematic review. *Eur Neuropsychopharmacol.* 2018;28:227–42.
16. van Harten PN, van Trier JC, Horwitz EH, Matroos GE, Hoek HW. Cocaine as a risk factor for neuroleptic-induced acute dystonia. *J Clin Psychiatry.* 1998;59:128–30.
17. Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MC. QTc interval screening in methadone treatment. *Ann Intern Med.* 2009;150:387–95.
18. Vaillant GE. The natural history of alcoholism revisited. Cambridge: Harvard University Press; 1995.

Additional Resources

Website

<https://www.recoveryanswers.org/> – The Recovery Research Institute is a nonprofit research institute, founded in 2012 by a colleague of mine from the MGH Center for Addiction Medicine, Dr. John Kelly. The website provides a host of materials regarding addiction treatment and recovery. Consider signing up for their bulletin that summarizes progress in addiction medicine.

Book

Miller WR, Rollnick S. Motivational interviewing: helping people change. 3rd ed. New York: The Guilford Press; 2013. – Every psychiatrist should have read one book about motivational interviewing (MI) – the “Miller-Rollnick” is written by the two pioneers in the field of MI. The first edition of this standard text was published in 1991.

Chapter 27

Tobacco Use Disorder



Essential Concepts

- The majority of patients with schizophrenia smoke cigarettes, around six to eight out of ten patients. Many smokers with schizophrenia are severely addicted to nicotine.
- Psychiatrists are well qualified and positioned to take a leadership role in smoking cessation efforts for patients with serious mental illness.
- All patients in your clinic need to have their smoking status assessed and documented. View it as a quality measure.
- Assist smoking patients with schizophrenia with smoking cessation to reduce cardiovascular mortality and lung disease. Make smoking cessation an explicit treatment goal and offer help to all patients, regardless of motivation to quit.
- Opt-out care and making treatment the default option may be necessary if we want to nudge more people toward smoking cessation. Waiting until patients opt in is not as effective as behavioral economics has clearly shown when it comes to nudging somebody toward a behavior.
- Motivational interviewing is a useful technique to help those smokers who opt out of care to resolve ambivalence about making a change (from smoking to quitting), allowing them to decide *for themselves* that a change is not only possible but desirable.
- Most patients with schizophrenia will need maximum treatment to successfully quit, including pharmacotherapy.
- Varenicline is the most effective medication to initiate and sustain smoking cessation; it is well tolerated and does not cause more neuropsychiatric side effects than bupropion or nicotine replacement therapy. NRT alone may be mostly ineffective in long-term smokers with serious mental illness.

- After a successful quit attempt, many patients with schizophrenia require long-term maintenance pharmacological treatment compared to more time-limited approaches for the general population.
- Since the social environment has a large impact on smoking, assess who in the patient's environment smokes.
- Smoking reduces antipsychotic drug levels, particularly for olanzapine and clozapine, via induction of the 1A2 P450 enzyme.
- The role and safety of e-cigarettes vis-à-vis established smoking cessation pharmacotherapy is unclear and requires further study. E-cigarettes may represent a harm reduction approach for patients seriously addicted to cigarettes. Patients who switch to e-cigarettes should switch over completely and not also smoke cigarettes.

“It’s easy to quit smoking. I have done it hundreds of times.”[1]

Usually attributed to Mark Twain, 1835–1919

The majority of patients with schizophrenia smoke cigarettes, often prior to onset of psychosis. Until the 1990s, in a typical community mental health center or inpatient setting, it was not unusual to have 80–90% of patients who smoke. While smoking rates may no longer be as dramatic, a recent survey found that 62% of schizophrenia patients were current smokers [2] although in some settings this rate may be as high as 80%. In our clozapine clinic, 40% are current smokers, 30% ex-smokers, and only 30% never smoked [3]. By means of comparison, the population rate of smoking in my home state of Massachusetts is now at a historic low of 14% (number for the year 2015) [4], very much in line with overall US numbers [5]. This difference in smoking between patients with schizophrenia and the general population represents a clear health disparity. Patients with schizophrenia are often heavy smokers (more than 20 cigarettes/day, including 2 or 3 packs/day), suggesting that many patients are severely addicted to nicotine.

Smoking is not only one of the Framingham risk factors for heart disease but also causes a host of smoking-related lung diseases that can lead to early death or reduced quality of life (lung cancer and chronic obstructive pulmonary disease) [6]. Smoking cessation greatly reduces the mortality risk for many of the smoking-related diseases: the average life expectancy of patients with schizophrenia would be transformed if they did not smoke. First-episode patients are at high-risk of becoming the next cohort of long-term smokers with schizophrenia, unless smoking cessation is pursued as aggressively as other treatment goals during a critical period for cardiovascular risk prevention [7].

Key Point

Smoking cessation is a core physician task, and psychiatrists in particular must be able to competently nudge patients toward a quit attempt (using motivational interviewing) and then help them quit and remain quit (using medications). Moreover, all members of the treatment team need to be on board with making smoking cessation a treatment priority in order to convey a coherent message to the patient [8].

Promoting smoking cessation represents a paradigm shift for psychiatry. Traditionally, smoking was seen to be part of the mental health culture; the smoke break continues to be part of some treatment settings to combat boredom. Mental health counselors who smoked themselves saw smoking with patients as an opportunity for engagement rather than as a problem. The tobacco industry played its own, nefarious role in slowing down the decline in smoking among psychiatric patients [9]. Today, some remain confused about the potential benefits of smoking in this population, such as calming patients or treating presumed nicotinic deficits. I have always been struck by the power of the self-medication hypothesis given the discrepancy between lack of convincing benefits of nicotine on cognition, for example [10] (if anything, smoking may impact cognition negatively), and obvious medical harm. As a result of powerful myths and ideas, however, nicotine use disorder has not been addressed as vigorously in this patient population as in the rest of society. These attitudes are changing, and most psychiatric treatment settings are today smoke-free, for example. Concerns about units becoming unmanageable due to violence once smoking bans went into effect turned out to be unfounded. If anything, the level of physical assaults has decreased, at least in units where bans were thoughtfully implemented with staff support and training [11]. It is encouraging that fewer younger patients with schizophrenia smoke compared to their older peers [2] which suggests a cohort effect. Only in the past several years, a not yet understood association between smoking and psychosis risk was noted in population-based samples that merits further study [12].

Key Point

See smoking as the threat it is for your patients, both in terms of health risk but also as a financial disaster when patients spend more than one third of their income on cigarettes. Psychiatrists, with their expertise in addictions and their frequent visits with patients, are ideally positioned to take the lead in smoking cessation. Moreover, our colleagues in medicine believe smoking cessation in “our patients” is our responsibility [13].

I cannot overemphasize the pernicious effects of low expectations. From social science research, we know that nothing is more effective in creating poor outcomes than having low expectations. I have been taught by many patients with schizophrenia that smoking cessation is possible, even in cases that seemed beyond hope. As Mark Twain recognized, sustained abstinence requires more than one attempt – on average, five attempts in ex-smokers from the general population. It is, however, incorrect to claim that severely addicted patients with schizophrenia do as well with smoking cessation as normal control-population cohorts. In some patients, harm reduction (smoking less) might be all that can be accomplished in a given quit attempt. Unfortunately, smoking less can lead to compensatory smoking with higher exposure to carbon monoxide (CO) and carcinogens. The literature is also pointing toward higher relapse rates in patients with schizophrenia once pharmacologic smoking cessation treatment is withdrawn, indicating that maintenance treatment might have to be provided for

at least 1 year [14], perhaps even longer. For some patients, smoking remains a way of life, and they point to it as one of the few enjoyable activities they have left.

The next sections about assessment and treatment view smoking as a chronic relapsing substance use disorder caused by addiction to nicotine [15]. Viewed in this way, patients who smoke are successfully treated within the framework of chronic disease management (i.e., offered care that is continuous and coordinated on the professional side while also empowering patients to effectively manage their condition) [16]. At the systems level in your clinic, consider organizing your smoking cessation efforts around the treatment cascade framework (taken from HIV care): identify smoking status, link to smoking-specific care which may include you, treat with pharmacotherapy, and quit and remain quit as the main outcome [3]. The framework recognizes the need for population-based management (registry, identification of smokers, tracking of treatments and results) if we want to reduce smoking in serious mental illness. The desired outcome for all patients is to not smoke cigarettes, not even occasionally.

Assessment of Smoking Status

Obtain Smoking History

To help, you must first identify smokers. At the initial visit, obtain a good smoking history (age of first smoking, amount of current smoking, previous quit attempts, longest duration of previous abstinence, smoking-related health problems). For all practical purposes, regular smokers are addicted to nicotine and qualify for a diagnosis of nicotine use disorder. Get a good understanding of the patient's life and who smokes in his environment. Smoking is a good example of the power of social networks: it is quite difficult to quit smoking if all your friends or household members smoke [17]. As part of every follow-up office visit, assess the patient's amount of smoking and offer treatment. Although this might seem excessive, it is nevertheless useful for patients to know that you, as their psychiatrist, take smoking seriously and have smoking cessation as a treatment goal because you care for them. Do not forget that by now, many patients are aware of the downsides from smoking and want to quit, so the question of motivation may not be as critical or predictive of success as is often assumed. I admit that there is a small group of patients who get annoyed if you ask them about their smoking (the "anti-contemplation" group, as Dr. Ronald Diamond, a community psychiatrist from the University of Wisconsin referred to [personal communication]); I still do ask, with an apologetic smile.

Tip

You might want to consider smoking status as a “vital sign;” it is that important and a measure of the quality of care a patient receives. Add smoking status to a patient’s problem list. Is your patient a current, former, or never smoker? For current smokers, record the amount of smoking (e.g., one pack per day). Young patients who smoke occasionally may not consider themselves smokers, so ask broad-based: “Do you ever smoke cigarettes?” Don’t forget to inquire about other tobacco products and e-cigarettes.

If you only had two questions to ask your smoker, you can assess the degree of biological nicotine dependence by asking the following questions taken from the “Fagerstrom,” a widely used questionnaire in smoking research [18]:

- “How soon after you wake up do you smoke your first cigarette?” (waiting 1 hour or more suggests low dependence)
- “How many cigarettes do you smoke per day?” (Ten or less suggests low dependence).

The degree of biological dependence matters, as more severe addiction results in withdrawal and greater difficulties in quitting. Biological dependence is considered severe if more than 20 cigarettes are smoked and if smoking is one of the first things done after waking up (within 30 minutes). Note that this might not be valid if smoking is not ad lib (e.g., group home). The more severely addicted, the more intensive treatment may be necessary.

Motivate to Quit

Motivational interviewing is a helpful technique to help smokers resolve ambivalence they have about making a change (from smoking to not smoking). One important principle of motivational interviewing is that you never argue for change, but let the patient come to the conclusion that change is not only possible but desirable. For this to occur, the benefits of quitting must outweigh the benefits of continuing to smoke; have a patient list the positive things about smoking, not just the negative things, to clarify this for patients.

One concrete thing you can do is calculate a patient’s 10-year risk for a major cardiac event using Framingham risk scoring (see Additional Resources in Chap. 21 on how to do this). This might increase motivation to eliminate one major risk factor, smoking.

A note of caution: while we made some gains in treating tobacco dependence in patients with serious mental illness, prevalence of smoking remains high. Collectively, we may need to adopt an approach to tobacco that makes treatment the default option if we want to make further progress [19]. A default is the option that will occur if no action is taken. In this case, the default starts patients on treatment, unless a patient opts out (of the default). Opt-out care contrasts with our current approach of no treatment as the default where we wait until patients declare that they are ready for a quit attempt (i.e., until they opt in), at which point we offer treatment. You know from your own experience with behavioral economics that opt-out defaults are more powerful as no action is required [20] (e.g., if the opt-out default for your employer is to automatically put away some money for your retirement, you will end up with savings as you will simply go along with the default).

Key Point

Emphasizing motivation to quit as a precondition for treatment is a recipe for inaction. The default option should be that we offer treatment (opt-out care). Continue to engage those patients who opt out using motivational interviewing.

Help to Quit

The “five As” developed by the US Public Health Service are a useful framework for help with smoking cessation [21]:

- Ask (about smoking) – “Do you smoke?” “Do you want to quit?”
- Advise (against smoking and recommend quitting).
- Assess (readiness to quit) – “Are you interested in quitting within the next month?” Note the Key Point on the previous page regarding the problem of the current opt-in approach. You may consider de-emphasizing motivation to quit and go straight to assist and not insist on making readiness to quit a precondition for treatment.
- Assist (with smoking cessation) – Offer and start pharmacotherapy and refer to smoking cessation program.
- Arrange (for follow-up) – See or call patient 1 week after quitting.

“Ask” corresponds to identifying your smokers in clinic (the vital sign sticker on the chart, paper, or electronic) and a quick check about their level of motivation to quit, as discussed above. “Advise and assess” are your core clinical responsibility in identified smokers, using motivational interviewing. At this stage, you might be more proactive and already offer treatment, particularly if you believe that our current opt-in approach to smoking cessation is limiting and motivation to quit overemphasized (see Key Point above about opt-out care) [19]. “Assist” requires you to be comfortable prescribing smoking cessation pharmacotherapy. Routine referrals to general smoking cessation programs can be difficult for patients with schizophre-

nia, so you might have to provide counseling yourself. (Although groups are probably more effective than 1:1 counseling.) For higher functioning patients who use the Internet, refer them to an internet website (see under Additional Resources below) or to 1-800-QUIT-NOW.

For long-term smokers, quitting can seem impossible, particularly if smoking is also a “habit” that fills loneliness and boredom. Intermediate, achievable goals, like temporary abstinence or a reduced number of cigarettes per day (or even simply delaying every cigarette by 20 minutes), not complete smoking cessation, are necessary and acceptable stepping-stones to eventual commitment to quitting for good.

Tip

Use motivational interviewing techniques to guide patients toward quitting if they opt out of treatment (e.g., have patients make a list of benefits from smoking, benefits from quitting, and barriers to quitting – feared weight gain could be a formidable obstacle). We used to assign patient to one of Prochaska and DiClemente’s five stages of change (i.e., pre-contemplation, contemplation, preparation, action, and maintenance/relapse); this may encourage inactivity on the part of the physician if somebody is labeled “pre-contemplation” [22]. You may want to drop this reference frame.

Pharmacotherapy for Smoking Cessation

Initiating Smoking Cessation Treatment

All patients who are attempting to quit should be offered drug therapy to eliminate nicotine withdrawal and block the reinforcing properties of nicotine. Three medications are FDA-approved for smoking cessation: nicotine replacement therapy (NRT), bupropion, and varenicline. In the general population, NRT and bupropion given alone roughly double quit rates compared to placebo [15]. Varenicline (a selective alpha-4 beta-2 nicotinic acetylcholine receptor partial agonist) is most effective, tripling your chances of quitting [23]. Tolerability of the available smoking cessation aids is generally good. The most frequent side effects are insomnia for bupropion (make sure to take second dose not at bedtime), abnormal dreams for the nicotine patch (make sure to take patch off before going to bed), and nausea for varenicline, in about 1/4 of patients (take with food and full glass of water). I would avoid bupropion in patients with an increased seizure risk [24, 25]. Combining varenicline with NRT represents an evidence-based approach that ought to be offered to those with severe addiction. In clinical trials, smoking cessation is usually accompanied by some form of counseling.

Offering smoking cessation pharmacotherapy may be essential, particularly in long-term smokers with schizophrenia [26]. It may even be necessary to use maximum pharmacological combination pharmacotherapy (bupropion or varenicline

plus patch, which act synergistically plus high-dose nicotine replacement therapy (NRT; patch plus gum/inhaler/spray)) in order to be successful. On the other hand, combining varenicline with bupropion may not be an effective strategy [27].

The most effective agent, varenicline, had a somewhat difficult time as the FDA added a black box warning in 2009, warning about suicide which frightened many patients (contributing to 17,000 annual premature deaths that would have been avoided had varenicline prescriptions not dropped off as a result [28] – an example of the law of unintended consequences). This warning was removed in 2016 after a large (over 8000 subjects) clinical trial (known as the Evaluating Adverse Events in a Global Smoking Cessation Study or EAGLES trial) that evaluated the neuropsychiatric safety of varenicline and bupropion in comparison to nicotine and placebo showed increased rates of neuropsychiatric symptoms (aggression, depression, suicidal ideation, agitation) in all treatment groups, *including the placebo group*. While patients with psychiatric illnesses had more neuropsychiatric symptoms compared to their non-ill peers (the trial comprised about 50% of patients with a stable psychiatric diagnosis), there were no meaningful differences between the various treatments including placebo. The increased side effect rate during quit attempts is a marker of the difficult patient population, not an effect of the medications used to assist in quitting. The EAGLES results confirmed an earlier meta-analysis of bupropion for smoking cessation in schizophrenia that found no increase in positive symptoms [29]; this was a concern because of bupropion's dopaminergic action. Given its superior efficacy and the severity of addiction in many patients with serious mental illness, varenicline should be a first-line choice unless there are specific concerns about its use. Close clinical monitoring during a quit attempt is important regardless of the medication used (i.e., regimen with or without varenicline) as some patients will experience neuropsychiatric side effects (around 10% in EAGLES across all treatments including placebo) that may require a change in the treatment plan.

The basic outline of an 8-week to 12-week drug treatment plan for *initiating* smoking cessation is simple, and you should be able to routinely help a patient set up an individualized plan using these *general* steps:

1. Set quit date, *if possible*.
2. Start bupropion or varenicline up to 1 month prior to quit date.
3. Quit.
4. Add patch for 12 weeks, plus gum/lozenges/spray/inhaler as needed for craving throughout.
5. Continue bupropion or varenicline for several months.
6. After successful quit attempt, determine relapse prevention regimen.

The exact timing of those general steps depends on the medication used, the patients severity of addiction and comorbid psychiatric and medical disorders, and a patient's preference (see exemplary protocols for bupropion and varenicline in Tables 27.1 and 27.2, respectively). A typical plan for uncomplicated cases (e.g., no severe addiction, no serious psychiatric illness) should be last at least 3 months, with the possibility of simply extending for another 3 months.

Table 27.1 Exemplary 12-week smoking cessation treatment protocol for bupropion SR

	Week –2 or –1	Start bupropion SR 150 mg qam for 3 days then 150 mg bid
	Week 0	Quit date
	Week 0–6	Start nicotine replacement therapy (NRT) Transdermal patch 21 mg ^a every 24 hours Plus PRN NRT (gum/lozenge/inhaler/spray) ^b
	Week 6 and 8	Transdermal patch 14 mg every 24 hours
	Week 8 and 12	Transdermal patch 7 mg every 24 hours
	Week 12	Stop transdermal patch or extend for 3 months Stop bupropion SR (no need to taper) or extend for 3 months
	Week 24	Assess need for maintenance treatment
Don't use bupropion in patients at increased seizure risk (e.g., seizure disorder or binge drinking)		
Tell patients that they can smoke while using the patch to avoid treatment discontinuation		
^a If smoking <10 cigarettes per day, start with 14 mg patch		
^b Dual NRT (combination NRT = patch plus gum/lozenge/inhaler/spray) unless smoking <10 cigarettes per day		

Table 27.2 Exemplary 12-week smoking cessation treatment protocol for varenicline

Week –1 to –4 ^a	Titrate varenicline 0.5 mg for 3 days, then 0.5 mg for 4 days, then 1 mg twice daily ^b
Week 0	Quit date, <i>if possible</i> ^c
Week 0–12	Continue varenicline for 3 months
Week 12+	Determine need for maintenance treatment ^d

^aIf patient picks quit date, start varenicline at least 1 week before quit date; alternatively, start varenicline and give patient 1 month to set quit date while taking varenicline 1 mg bid

^bTake with food and water to minimize nausea. Can titrate more slowly if patient worried about side effects or give 0.5 mg per day if patient worried about starting

^cIf no quit date, reduce smoking by 50% in the first month, then 50% in the second month, and then keep reducing to zero

^dGiven high relapse risk for those with SMI, recommend continuation of varenicline following quit attempt (up to 1 year has been studied)

Tip

While nicotine replacement therapy (NRT) may be a good choice for the average smoker, NRT may be the least effective treatment approach for patients with SMI who are severely addicted. Consider *adding* NRT during quit attempts with bupropion or varenicline, but do not use NRT as the main approach. Freely combine available nicotine products. Gums or lozenges (4 mg for heavy smokers, otherwise 2 mg; can use every hour) and nicotine patches (apply daily) are available over the counter; “inhalers” (not really inhalers, despite the name) or nasal sprays require prescriptions (both are irritating). Provide patient with information about how to use NRT correctly!

Using varenicline in patients willing to take the medication in order to smoke less but unwilling to commit to smoking cessation per se may benefit from a “reduce-to-quit” approach or pre-loading pharmacotherapy [30]. This strategy is not yet fully incorporated into guidelines but may reduce the level of smoking and eventually increase smoking rates in some [31]. Particularly for patients with schizophrenia, setting a quit date may be more stressful than helpful. One last point, remind patients that they can always quit or reduce smoking without using medications (probably the most common mode of quitting among ex-smokers) [32]. While you want to offer professional help, you might also want to support a patient’s self-efficacy. As noted earlier, however, patients with severe addiction may not be able to quit without pharmacological help.

Among high school and college students, so-called vaping using e-cigarettes and other vaporizers (“ENDS” for electronic delivery systems) has largely replaced regular cigarette smoking. The Monitoring the Future survey showed that almost 30% of 12 graders had vaped nicotine in 2018 [33]. The public health ramifications are unclear. To those who fear that e-cigarette use are merely one step to the inevitable progression toward traditional cigarette smoking [34] and a renormalization of smoking after decades of progress [35], this trend is alarming [36]; others are more hopeful that vaping will lower the overall rate of smoking initiation [37]. Not surprisingly, some patients with schizophrenia have also started to experiment with e-cigarettes [38]. To what extent e-cigarettes can play a role in helping heavy smokers including smokers with schizophrenia quit or avoid smoking cigarettes (assuming e-cigarettes are overall less toxic) remains to be studied [39]. In one well-designed, randomized trial, e-cigarettes were twice as effective than well-established NRT in helping motivated smokers quit (18% abstinence after 1 year compared to 10%) albeit at the cost of ongoing e-cigarette use (80% of participants continued to use e-cigarettes compared to just under 10% in the NRT group) [40]. For some patients, e-cigarettes may be more of a hindrance than help to successful quitting [41]. The next decade will show if e-cigarettes are a “disruptive technology” that has the potential to make conventional cigarettes obsolete [42]. Today I would say that if I had to choose between e-cigarettes and regular cigarettes for my heavy smoker, I would prefer they use e-cigarettes despite concerns about vaping-related lung injury.

Maintenance Treatment

In many smoking cessation programs for the general population, smoking cessation treatment is usually tapered and discontinued after a successful quit attempt. This approach might work for some patients but not for the group of patients in whom tobacco is more helpfully conceptualized as a chronic disease, with fluctuating disease intensity and treatment needs. For patients with schizophrenia, long-term engagement in treatment might be needed as the relapse rates are rather high once pharmacotherapy is discontinued [14]. Moreover, NRT alone may not be an effective long-term maintenance strategy, and I do not recommend it to patients [43]. If

you can, monitor for abstinence to help prevent relapse or intervene early (e.g., monitor expired CO or cotinine levels in plasma, urine, or saliva). Most patients in the community mental health center where I work require several attempts and prolonged treatment with pharmacotherapy (1 year or more) to successfully quit and stay quit. In ideal circumstances, you would be able to refer patients to group treatment to support the individual. At the risk of simplifying the interaction between biology and psychology, addressing the “habit” aspect of smoking requires counseling in order to acquire new, healthier habits.

Clinical Problems

Drug Interactions

Smoking influences the metabolism of antipsychotics. Most affected are those antipsychotics that are substrates of the CYP1A2 enzyme, specifically clozapine and olanzapine. As a rule of thumb, some patients are able to decrease by one third to one half their respective antipsychotic plasma level when they smoke, as certain ingredients in tobacco smoke, specifically polycyclic aromatic hydrocarbons (but not nicotine itself), induce CYP1A2 [44]. There is great interindividual variability, however. One would expect that smoking cannabis (similar to smoking cigarettes) has some potential for drug-drug interactions although this effect should only be relevant in very heavy smokers [45]. NRT, which is merely nicotine, has no effect on 1A2. First-generation antipsychotic levels are also significantly reduced in smokers, possibly because smoking effects UGT which plays some role in antipsychotic metabolism. To complicate things, caffeine (many smokers drink a lot of coffee) has the opposite effect on 1A2; it blocks it (Table 27.3).

Enzyme induction can be important if patients are adjusted on an antipsychotic in a (smoke-free) hospital where they might have been receiving the patch. Clozapine poses the greatest risk for toxicity (seizures) or subtherapeutic blood levels (relapse), and therapeutic drug monitoring can help adjust the clozapine dose [46]. If patients successfully quit smoking (or are forced to not smoke in a hospital), their regular clozapine dose may need to be lowered within a couple of days. While the full effect

Table 27.3 Nicotine facts

Half-life	2 hours
Primary metabolite	Cotinine, half-life 24 hours ^a
Metabolism	Major 2A6
	Minor 2B6, glucuronidation

Smoking^b induces 1A2 (and probably other enzyme systems, including UGT)

^aCotinine is a useful marker of tobacco smoking. Cotinine can be measured in plasma, urine, and saliva

^bNote that it is not nicotine itself but polycyclic aromatic hydrocarbons in cigarette smoke

of smoking cessation will only be apparent after 2–3 weeks, increased clozapine blood levels can be measured after only a few days due to rapid downregulation of CYP1A2 [47]. Conversely, the antipsychotic dose has to be adjusted upward (by as much as 50%) after discharge once patients resume smoking at home. In this case, however, the enzyme induction takes several weeks as new enzymes have to be synthesized, so adjust the dose gradually.

Nicotine Withdrawal

Smokers who are admitted to a hospital for medical or psychiatric reasons and are not allowed to smoke can experience nicotine withdrawal. Clearly, this must be addressed with NRT, lest you want more severely addicted patients to sign out against medical advice. The signs and symptoms of nicotine withdrawal include the above-noted anxiety but also irritability, difficulties concentrating, insomnia, and restlessness, all of which make an accurate assessment of a patient's mental state more difficult. Its symptoms overlap with common reasons for an admission (psychosis, mania, depression).

Patient Concerns

Anticipate concerns, for example, weight gain and anxiety that patients who are considering quitting will have and try to alleviate those. Weight gain is a key concern for some patients and a major driver of relapse. On average, patients who quit will gain up to 10 lbs (compare, however, this risk with 10 years of smoking 1 pack per day). Importantly, the post-cessation weight gain does not offset the reduction in cardiovascular risk that was achieved from not smoking anymore, at least not during the first year [48]. This calculus, however, may shift for those patients who continue to gain weight after they quit smoking and develop diabetes as a result [49]. Managing post-cessation weight gain in already overweight or obese smokers may thus require additional pharmacotherapy (e.g., combining varenicline with lorcaserin [50]).

Many patients with schizophrenia (and perhaps their clinicians) hold the mistaken belief that nicotine is calming [51], whereas in reality it is anxiogenic (just ask any nonsmoker who tries a cigarette). Smoking simply alleviates the anxiety that stems from nicotine withdrawal. Consistent with the anxiogenic properties of smoking, ex-smokers who successfully quit were found to have lower anxiety levels compared to the time when they smoked [52]. Quitting may also improve depressive symptoms [53]. Nicotine withdrawal is limited to about 2 weeks, and it can be easily treated with NRT.

Patients are often concerned about smoking while using the patch or other nicotine products. While not necessarily recommended (patients may be overstimulated

from too much nicotine), most longitudinal studies have not found an increased risk of serious problems (e.g., heart attack) in patients with no or stable heart disease [54]. Patients can also be reassured that the aforementioned EAGLES trial found no increased cardiovascular risk from taking any of the smoking cessation medications [55].

References

1. Quote Investigator. It's easy to quit smoking. I have done it a thousand times. Available at: <https://quoteinvestigator.com/2012/09/19/easy-quit-smoking/>. Accessed 1 July 2019.
2. Dickerson F, Schroeder J, Katsafanas E, Khushalani S, Origni AE, Savage C, et al. Cigarette smoking by patients with serious mental illness, 1999–2016: an increasing disparity. *Psychiatr Serv.* 2018;69:147–53.
3. Freudenreich O, MacLaurin SA, Irwin KI, Cather C, Schnitzer KM, Paude S, et al. Smoking cessation in serious mental illness: a multi-pronged approach using the treatment cascade framework. 27th European Congress of Psychiatry, Warsaw, Poland, April 6–9, 2019.
4. Massachusetts Department of Public Health. Massachusetts Tobacco Cessation and Prevention Program (MTCP). Available from: <https://www.mass.gov/massachusetts-tobacco-cessation-and-prevention-program-mtcp>. Accessed 1 July 2019.
5. Wang TW, Asman K, Gentzke AS, Cullen KA, Holder-Hayes E, Reyes-Guzman C, et al. Tobacco product use among adults – United States, 2017. *MMWR Morb Mortal Wkly Rep.* 2018;67:1225–32.
6. Thun MJ, Carter BD, Feskanich D, Freedman ND, Prentice R, Lopez AD, et al. 50-Year trends in smoking-related mortality in the United States. *N Engl J Med.* 2013;368: 351–64.
7. Srihari VH, Phutane VH, Ozkan B, Chwastiak L, Ratliff JC, Woods SW, et al. Cardiovascular mortality in schizophrenia: defining a critical period for prevention. *Schizophr Res.* 2013;146:64–8.
8. Stubbs B, Vancampfort D, Bobes J, De Hert M, Mitchell AJ. How can we promote smoking cessation in people with schizophrenia in practice? A clinical overview. *Acta Psychiatr Scand.* 2015;132:122–30.
9. Prochaska JJ, Hall SM, Bero LA. Tobacco use among individuals with schizophrenia: what role has the tobacco industry played? *Schizophr Bull.* 2008;34:555–67.
10. Quisenjaerts C, Morren M, Hulstijn W, de Brujin E, Timmers M, Streffer J, et al. The nicotinic receptor as a target for cognitive enhancement in schizophrenia: barking up the wrong tree? *Psychopharmacology.* 2014;231:543–50.
11. Robson D, Spaducci G, McNeill A, Stewart D, Craig TJK, Yates M, et al. Effect of implementation of a smoke-free policy on physical violence in a psychiatric inpatient setting: an interrupted time series analysis. *Lancet Psychiatry.* 2017;4:540–6.
12. Gurillo P, Jauhar S, Murray RM, MacCabe JH. Does tobacco use cause psychosis? Systematic review and meta-analysis. *Lancet Psychiatry.* 2015;2:718–25.
13. MacLaurin SA, Henderson DC, Freudenreich O. Delineating responsibility: primary care provider perspective. *Psychiatr Serv.* 2015;66:333.
14. Evans AE, Cather C, Pratt SA, Pachas GN, Hoepfner SS, Goff DC, et al. Maintenance treatment with varenicline for smoking cessation in patients with schizophrenia and bipolar disorder: a randomized clinical trial. *JAMA.* 2014;311:145–54.
15. Barua RS, Rigotti NA, Benowitz NL, Cummings KM, Jazayeri MA, Morris PB, et al. 2018 ACC expert consensus decision pathway on tobacco cessation treatment: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol.* 2018;72:3332–65.

16. Wagner EH. Chronic disease management: what will it take to improve care for chronic illness? *Eff Clin Pract.* 1998;1:2–4.
17. Blok DJ, de Vlas SJ, van Empelen P, van Lenthe FJ. The role of smoking in social networks on smoking cessation and relapse among adults: a longitudinal study. *Prev Med.* 2017;99:105–10.
18. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom test for nicotine dependence: a revision of the Fagerstrom tolerance questionnaire. *Br J Addict.* 1991;86:1119–27.
19. Richter KP, Ellerbeck EF. It's time to change the default for tobacco treatment. *Addiction.* 2015;110:381–6.
20. Johnson EJ, Medicine GD. Do defaults save lives? *Science.* 2003;302:1338–9.
21. AHRQ. 5 major steps to intervention. Available from: <https://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/5steps.html>. Accessed 1 July 2019.
22. Prochaska JO, Velicer WF. The transtheoretical model of health behavior change. *Am J Health Promot.* 1997;12:38–48.
23. Anthenelli RM, Benowitz NL, West R, St Aubin L, McRae T, Lawrence D, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet.* 2016;387:2507–20.
24. Beyens MN, Guy C, Mounier G, Laporte S, Ollagnier M. Serious adverse reactions of bupropion for smoking cessation: analysis of the French Pharmacovigilance Database from 2001 to 2004. *Drug Saf.* 2008;31:1017–26.
25. Macaluso M, Zackula R, D'Empaire I, Baker B, Liow K, Preskorn SH. Twenty percent of a representative sample of patients taking bupropion have abnormal, asymptomatic electroencephalographic findings. *J Clin Psychopharmacol.* 2010;30:312–7.
26. Cather C, Pachas GN, Cieslak KM, Evins AE. Achieving smoking cessation in individuals with schizophrenia: special considerations. *CNS Drugs.* 2017;31:471–81.
27. Ebbert JO, Hatsukami DK, Croghan IT, Schroeder DR, Allen SS, Hays JT, et al. Combination varenicline and bupropion SR for tobacco-dependence treatment in cigarette smokers: a randomized trial. *JAMA.* 2014;311:155–63.
28. Gaballa D, Drowos J, Hennekens CH. Smoking cessation: the urgent need for increased utilization of varenicline. *Am J Med.* 2017;130:389–91.
29. Tsoi DT, Porwal M, Webster AC. Efficacy and safety of bupropion for smoking cessation and reduction in schizophrenia: systematic review and meta-analysis. *Br J Psychiatry.* 2010;196:346–53.
30. Rennard S, Hughes J, Cinciripini PM, Kralikova E, Raupach T, Arteaga C, et al. A randomized placebo-controlled trial of varenicline for smoking cessation allowing flexible quit dates. *Nicotine Tob Res.* 2012;14:343–50.
31. Ebbert JO, Hughes JR, West RJ, Rennard SI, Russ C, McRae TD, et al. Effect of varenicline on smoking cessation through smoking reduction: a randomized clinical trial. *JAMA.* 2015;313:687–94.
32. Chapman S, MacKenzie R. The global research neglect of unassisted smoking cessation: causes and consequences. *PLoS Med.* 2010;7:e1000216.
33. Monitoring the Future. Available at: <http://www.monitoringthefuture.org/pressreleases/18drugpr.pdf>. Accessed 1 July 2019.
34. Leventhal AM, Strong DR, Kirkpatrick MG, Unger JB, Sussman S, Riggs NR, et al. Association of electronic cigarette use with initiation of combustible tobacco product smoking in early adolescence. *JAMA.* 2015;314:700–7.
35. Fairchild AL, Bayer R, Colgrove J. The renormalization of smoking? E-cigarettes and the tobacco "endgame". *N Engl J Med.* 2014;370:293–5.
36. Primack BA, Soneji S, Stoolmiller M, Fine MJ, Sargent JD. Progression to traditional cigarette smoking after electronic cigarette use among US adolescents and young adults. *JAMA Pediatr.* 2015;169:1018–23.
37. Levy DT, Warner KE, Cummings KM, Hammond D, Kuo C, Fong GT, et al. Examining the relationship of vaping to smoking initiation among US youth and young adults: a reality check. *Tob Control.* 2018. <https://doi.org/10.1136/tobaccocontrol-2018-054446>.

38. Miller BJ, Wang A, Wong J, Paletta N, Buckley PF. Electronic cigarette use in patients with schizophrenia: prevalence and attitudes. *Ann Clin Psychiatry*. 2017;29:4–10.
39. Malas M, van der Tempel J, Schwartz R, Minichiello A, Lightfoot C, Noormohamed A, et al. Electronic cigarettes for smoking cessation: a systematic review. *Nicotine Tob Res*. 2016;18:1926–36.
40. Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. *N Engl J Med*. 2019;380:629–37.
41. Kalkhoran S, Glantz SA. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. *Lancet Respir Med*. 2016;4:116–28.
42. Abrams DB. Promise and peril of e-cigarettes: can disruptive technology make cigarettes obsolete? *JAMA*. 2014;311:135–6.
43. Prochaska JJ. Nicotine replacement therapy as a maintenance treatment. *JAMA*. 2015;314:718–9.
44. Tsuda Y, Saruwatari J, Yasui-Furukori N. Meta-analysis: the effects of smoking on the disposition of two commonly used antipsychotic agents, olanzapine and clozapine. *BMJ Open*. 2014;4:e004216.
45. Anderson GD, Chan LN. Pharmacokinetic drug interactions with tobacco, cannabinoids and smoking cessation products. *Clin Pharmacokinet*. 2016;55:1353–68.
46. Lowe EJ, Ackman ML. Impact of tobacco smoking cessation on stable clozapine or olanzapine treatment. *Ann Pharmacother*. 2010;44:727–32.
47. Faber MS, Fuhr U. Time response of cytochrome P450 1A2 activity on cessation of heavy smoking. *Clin Pharmacol Ther*. 2004;76:178–84.
48. Thorndike AN, Achtyes ED, Cather C, Pratt S, Pachas GN, Hoeppner SS, et al. Weight gain and 10-year cardiovascular risk with sustained tobacco abstinence in smokers with serious mental illness: a subgroup analysis of a randomized trial. *J Clin Psychiatry*. 2016;77: e320–6.
49. McElroy SL. The dual epidemic of tobacco dependence and obesity among those with severe mental illness. *J Clin Psychiatry*. 2016;77:e327–8.
50. Hurt RT, Croghan IT, Schroeder DR, Hays JT, Choi DS, Ebbert JO. Combination varenicline and lorcaserin for tobacco dependence treatment and weight gain prevention in overweight and obese smokers: a pilot study. *Nicotine Tob Res*. 2017;19:994–8.
51. Esterberg ML, Compton MT. Smoking behavior in persons with a schizophrenia-spectrum disorder: a qualitative investigation of the transtheoretical model. *Soc Sci Med*. 2005;61:293–303.
52. McDermott MS, Marteau TM, Hollands GJ, Hankins M, Aveyard P. Change in anxiety following successful and unsuccessful attempts at smoking cessation: cohort study. *Br J Psychiatry*. 2013;202:62–7.
53. Cather C, Hoeppner S, Pachas G, Pratt S, Achtyes E, Cieslak KM, et al. Improved depressive symptoms in adults with schizophrenia during a smoking cessation attempt with varenicline and behavioral therapy. *J Dual Diagn*. 2017;13:168–78.
54. Ford CL, Zlabek JA. Nicotine replacement therapy and cardiovascular disease. *Mayo Clin Proc*. 2005;80:652–6.
55. Benowitz NL, Pipe A, West R, Hays JT, Tonstad S, McRae T, et al. Cardiovascular safety of varenicline, bupropion, and nicotine patch in smokers: a randomized clinical trial. *JAMA Intern Med*. 2018;178:622–31.

Additional Resources

Web Sites

<https://www.cdc.gov/tobacco> – The smoking and tobacco use site put out by the Centers for Disease Control and Prevention.

<https://smokefree.gov/> – Refer all patients, assuming they use computers or smart phones, to this US Government website from the National Cancer Institute.

<https://www.becomeanex.org/> – A web-based support program by the non-profit Truth Initiative that has set out to create a smoke-free culture in America, targeting our youth and young adults so they do not become the next generation of smokers.

Articles

Barua RS, Rigotti NA, Benowitz NL, Cummings KM, Jazayeri MA, Morris PB, et al. 2018 ACC expert consensus decision pathway on tobacco cessation treatment: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol.* 2018;72:3332–65. – Very well organized document by the American College of Cardiology about how everything you need to know about smoking cessation, including assessment and pharmacology.

Cather C, Pachas GN, Cieslak KM, Evins AE. Achieving smoking cessation in individuals with schizophrenia: special considerations. *CNS Drugs.* 2017;31:471–81. – An excellent review of smoking cessation with special consideration for patients with schizophrenia; from my hospital's own smoking cessation program.

Chapman S. E-cigarettes: the best and the worst case scenarios for public health. *BMJ.* 2014;349:g5512. – A very readable essay about e-cigarettes from a public health perspective.

Siegel DA, Jatlaoui TC, Koumans EH, Kiernan EA, Layer M, Cates JE, et al. Update: interim guidance for health care providers evaluating and caring for patients with suspected e-cigarette, or vaping, product use associated lung injury – United States, October 2019. *MMWR Morb Mortal Wkly Rep.* 2019;68:919–927. – Concerns about lung injuries (including deaths) related to vaping have emerged as vaping has become more widespread, tempering my enthusiasm for vaping as a tool to help patients quit or switching to e-cigarettes.

Chapter 28

Negative Symptoms



Essential Concepts

- Negative symptoms are a core feature of schizophrenia; they have diagnostic and prognostic significance.
- Negative symptoms comprise two main clusters: diminished emotional expression and diminished motivation.
- Among the five consensus negative symptom domains (alogia, blunted affect, anhedonia, avolition, asociality), “failure of the will” (avolition) might be particularly pernicious with regard to function.
- Avoid and treat secondary negative symptoms, particularly depression.
- Educate family members about negative symptoms to reduce undue pressure on the patient.

“Dementia praecox consists of a series of clinical states which have as their common characteristic a peculiar destruction of the internal connections of the psychic personality with the most marked damage of the emotional life and volition.”

– Emil Kraepelin, from the 8th edition of his textbook (1913) [1]

In this chapter, we look at a nonpsychotic symptom cluster: negative symptoms. Negative symptoms are characterized by a loss or diminution of function: something is missing that you expect to be there. Missing is the independent drive, the curiosity about the world, and the boundless energy that we expect from young people. Older psychiatrists used the idea of a failure of the will to describe these deficiencies. Missing are also the facial expressions and body language that we take for granted when we engage with somebody in dialogue. Patients themselves can perceive the lackluster quality of their inner experiences which can be a painful insight.

Both Emil Kraepelin (see epigraph) and Eugen Bleuler recognized the centrality of these symptoms to the experience of schizophrenia. In English-speaking coun-

tries, Bleuler's contribution to psychiatry is often pragmatically summarized in the four As mnemonic for the core disturbances (he called them basic) in schizophrenia: disturbance of *affect*, loosening of *associations*, *ambivalence*, and *autism* [2]. (Bleuler himself never created such a list which also does not work with the German words which do not all start with As.) Nevertheless, two out of his four As are what we call negative symptoms today. In 1980, the British psychiatrist Timothy Crow made a very influential distinction between type I (mainly positive symptoms) and type II (mainly negative symptoms, with poor response to antipsychotics) schizophrenia [3]. A modern conceptualization of negative symptoms based on expert consensus includes five broad symptom domains [4], listed in Table 28.1. This five-factor structure has held up well in the decade since the consensus conference in 2005; a possible sixth dimension (lack of normal negative emotions or distress) is being discussed [5].

As a less modifiable aspect of the schizophrenia syndrome, negative symptoms are more the essence of schizophrenia than positive symptoms, which can be seen as accessory (albeit key in defining psychotic disorders!). It is rather obvious to any clinician that negative symptoms, unless mild, are profoundly impairing. Among the negative symptoms, amotivation (i.e., avolition or lack of will) might be primus inter pares, particularly with regard to outcome [6]. "Will" is what keeps us going, and there is simply no substitute for it if it is missing. A concept related to amotivation is apathy [7]. Depending on the clinical sample, most patients will have some degree of negative symptoms.

The centrality of negative symptoms is acknowledged and officially recognized in the current DSM-5 as an explicit diagnostic criterion of schizophrenia (this was not the case as late as DSM-III). Two clinical subtypes of schizophrenia in which negative symptoms are the predominant feature have been described (Table 28.2).

Negative symptoms can be a major factor in poor community functioning: imagine a person devoid of drive or capacity to experience reward and the clinical problems this poses with regard to rehabilitation, interpersonal functioning, or work. Clinically, the negative symptom domain, rather than the cognitive domain, often seems to be the critical factor that determines community outcomes. I will add, however, that the distinction between negative and cognitive symptoms is less clear-cut than consensus definitions of the terms imply. Saying little in the interview (i.e., showing poverty of speech or alogia on mental status exam) and a poor

Table 28.1 Five consensus negative symptom domains^a

Alogia	Lack of words (poverty of speech or poverty of content to speech)
Blunted affect ^b	Lack of affectivity (expression of emotions)
Anhedonia	Lack of capacity for pleasure
Avolition ^c	Lack of volition ("will") and motivation
Asociality	Lack of social drive

^aTerms based on a National Institute of Mental Health-supported consensus conference [4]

^bBlunted affect is preferred over flat affect which is merely the most extreme form of blunting

^cConfusingly often used interchangeably with amotivation and apathy

Table 28.2 Schizophrenia subtypes with prominent negative symptoms

Deficit schizophrenia ^a	Patients with prominent negative symptoms that are enduring and primary. Might be a separate disease within the schizophrenias (with different risk factors suggesting different etiology). Depending on the chronicity of the patient sample, up to 30% will have the deficit syndrome
Simple schizophrenia ^b	Patients who never experience clear-cut positive symptoms but drift slowly into a withdrawn, empty mental state of essentially negative symptoms

^aBased on Refs. [8, 9]

^bBased on Ref. [10]. Officially recognized in ICD-10; called “simple deteriorative disorder” in the DSM-IV research section; removed in DSM-5

performance on the verbal fluency test correlate; the former is considered a negative symptom, the latter a cognitive impairment [11]. Even motivated people will fail and eventually give up on pursuing their goals if they lack executive function. Social stress due to poor processing speed can lead young people to withdraw from social life in order to avoid stressful situations and their own perceived ineptitude. As these examples show, negative symptoms can sometimes be understood as a reaction to cognitive deficits and even have a psychologically protective effect. A closer look at a core negative symptom domain, anhedonia (inability to experience pleasure), offers another example of the complexity of the negative symptom constructs and the interplay with cognition. Many patients with anhedonia appear to have deficits in *anticipatory* pleasure (i.e., they do not derive pleasure from imagining and planning pleasurable activities like visiting the new burger place on the weekend – a cognitive task) but not in *consummatory* pleasure (i.e., they enjoy a burger in front of them just like you and me) [12]. Anticipatory pleasure is a critical component for a life lived fully. Think about the good feelings that planning for a vacation engenders in you (often more than the trip itself, with its stressful plane rides and the vagaries of travel, including returning with diarrhea). Current work attempts to further delineate anhedonia biotypes, moving away from a monolithic anhedonia concept [13].

Clinical Assessment

Subtle negative symptoms might not be obvious to the observer, but patients who can express their inner experiences will note that they have changed: things are harder; more mental effort is necessary to achieve the same results; previously enjoyable things are no longer exciting; and they do not feel close to other people. In more severe cases, negative symptoms can be observed, and patients will appear blunted, disengaged from the world, and unable to participate in life beyond a very narrow area of their immediate concern (Bleuler's observation of autism). Little is said either literally because patients are monosyllabic or because not much information is conveyed (alogia). Nonverbal communication is impaired as well. The patient uses gestures sparingly; he speaks with a monotone voice, and he does not empha-

size speech with his hands; and he does not look at you and shows little facial expression (blunted affect). Goal setting is reduced (including, e.g., the simple goal of getting up and taking a shower); patients fail projects because they do not persist (avolition). They stop doing things they used to enjoy (anhedonia), and they no longer derive pleasure from social contacts which become infrequent (asociality). Parents can often identify these personality changes in their sons or daughters. A child that used to be outgoing, laugh easily, and be socially active has become homebound, quiet, and disinterested in the future.

Key Point

Factor analysis suggests that the negative symptoms can be combined into two clusters or dimensions: blunted affect and alogia form a diminished emotional expressivity cluster; avolition, anhedonia, and asociality form a diminished motivation cluster [14]. This distinction is somewhat helpful clinically (you can assess the emotional expressivity cluster in the office visit whereas the motivation cluster requires collateral information) but not for treatment planning; there you need to look at individual domains to identify the best treatment target [15].

These are some useful questions for assessing negative symptoms:

- “Have you noticed a change in your emotions?” (blunted affect)
- “What are your plans for this week?” (avolition)
- “What gets you excited?” (anhedonia)
- “When is the last time you did something with a friend?” (avolition)

Once you have identified the presence of negative symptoms, you are not quite done: negative symptoms (just like a headache) are not a diagnosis. You now need to figure out why it is that you see negative symptoms: you need a differential diagnosis (Fig. 28.1).

For pedagogical purposes, a framework that differentiates between secondary negative symptoms (i.e., symptoms that are the result of an identifiable cause like depression) and primary ones (i.e., what is left after secondary causes have been ruled out) is helpful. As further explained in the treatment section, while the primary/secondary distinction is not without its problems, I find it useful to organize my approach toward a patient with negative symptoms.

Tip

A helpful distinction can sometimes be drawn between depression and negative symptoms, despite some conceptual overlap (e.g., anhedonia characterizes both conditions). Although family members frame any withdrawal as “depression,” some patients can clearly distinguish between the anguished state of depression as a state of “suffering” and negative symptoms as a state of “emptiness.” This distinction is not always clear, however.

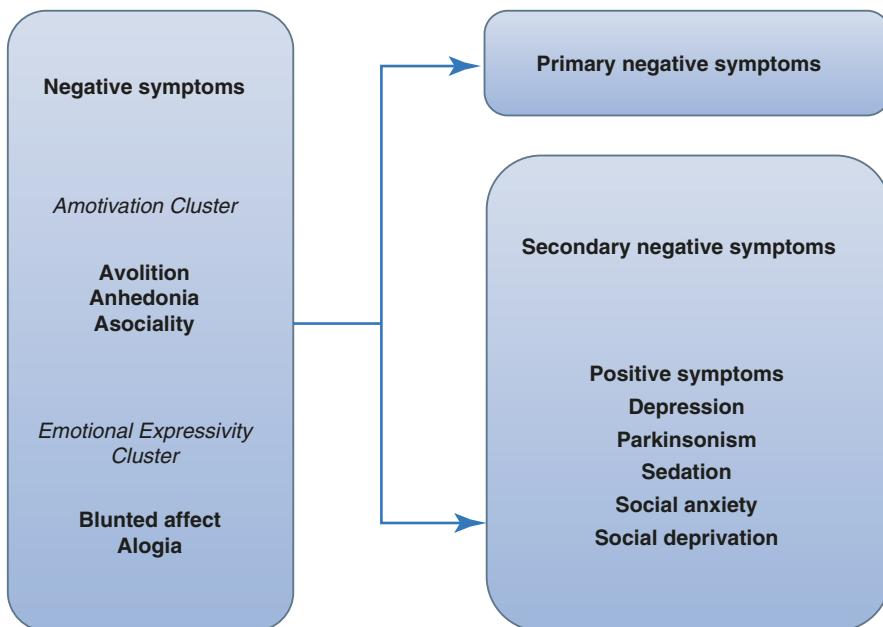


Fig. 28.1 Differential diagnosis of negative symptoms

Last, I want to note that although psychiatry owns the term “negative symptoms,” negative symptoms are not specific to schizophrenia [16]. Other specialties observing the same phenomenon might simply have different words for it (e.g., apathy [7] and abulia [17] are terms used in neurology). Ratings scales for negative symptoms like the Scale for the Assessment of Negative Symptoms (SANS) [18] can be applied to other patient groups, for example, to patients with Alzheimer’s disease [19] or to apathetic patients after a traumatic brain injury [20]. Consider using a more recent scale like the Brief Negative Symptom Scale (BNSS) or the Clinical Assessment Interview for Negative Symptoms (CAINS) if you decide to go the route of measurement-based care [21]. The clinical assessment of negative symptoms using a scale, however, remains challenging and is not routinely done in clinical practice due to time constraints and the need for an informant (e.g., patients will often paint a rosier picture of the richness of their social lives than family members).

Treatment

The honest assessment is that we have no great specific treatment for primary negative symptoms [22]. While pharmacological treatments often have disappointingly little clinical impact on primary negative symptoms, we as clinicians will often try an add-on strategy given the urgent clinical need. Which medications added to ongoing antipsychotic treatment have at least some support? Adding 15 mg of

L-methylfolate may help some patients [23]. L-Methylfolate is the bioactive form of the B vitamin folate; giving the active form of folate circumvents genetically determined reduced bioavailability. Consider checking a vitamin B12 level prior to giving folate in order to exclude pernicious anemia. Standard folic acid supplementation (2 mg of folate together with 400 µg of B12 was used in a trial [24]) can be used if L-methylfolate is not an option because of its cost. In some analyses, antidepressants show benefit [25], and adding an SSRI is worth a try, particularly given the conceptual fuzziness of negative symptoms vis-à-vis depression (see also the Clinical Vignette below). Mirtazapine is an antidepressant that could be tried, based on several positive studies [26]; however, mirtazapine is sedating and causes weight gain, neither side effect being ideal for a patient already struggling with negative symptoms. Similar to the failure to develop drugs to improve cognition in schizophrenia, no drug has made it through the necessary positive phase III trials to gain FDA approval for negative symptoms. It has been particularly disappointing that inhibitors of the glycine transporter, like bitopertin (which reverses a proposed cause of negative symptoms, a hypofunctioning NMDA receptor), have not yet survived the vagaries of clinical trials beyond proof-of-concept studies [27]. Neurostimulation like transcranial magnetic stimulation (TMS) for negative symptoms is an area of active research with some encouraging results [28].

Antipsychotics clearly improve negative symptoms (poor engagement, psychotic withdrawal) in acutely ill patients, as any inpatient clinician will attest to. In patients who participate in clinical drug trials, the improvement in negative symptoms is measurable (effect size 0.39) but occurs together with an improvement in overall psychopathology [29]; most will consider the negative symptoms to be secondary to the acute illness state. I remain unconvinced that antipsychotics can fundamentally treat primary negative symptoms in stable patients given the detrimental effect of dopamine blockade on motivational brain systems. However, not all antipsychotics might be equal when it comes to negative symptoms. In a clinical trial designed to specifically treat negative symptoms, the partial dopamine agonist, cariprazine, was better than a full dopamine antagonist comparator antipsychotic (risperidone) [30]. Should we dismiss such a response difference as merely being due to differences in the propensity to cause secondary negative symptoms or is one antipsychotic more effective for primary symptoms? This example shows the difficulties we have with separating primary from secondary negative symptoms – how does a clinician know what is primary and what is secondary? At some point, the argument becomes rather academic and even circular (what is treatable is secondary even if it was originally viewed as primary). Certainly from the patient's perspective, it does not matter if a symptom is “primary” or “secondary.” As a way out, the term “persistent” negative symptoms has been proposed to move away from a definition of negative symptoms that more or less implies treatment nonresponsiveness, like the primary symptoms of the deficit syndrome [31]. Persistent negative symptoms simply describe those residual negative symptoms that endure once common causes for negative symptoms (psychosis, depression, extrapyramidal side effects) are excluded.

Social skills training or cognitive-behavioral therapy for negative symptoms are potentially quite helpful, if available. CBT in particular attempts to reverse the secondary social withdrawal from repeated unpleasant social experiences and role fail-

ure; patients can feel quite defeated and inadequate [32]. One obvious problem is that negative symptoms make engagement in treatment difficult: a catch-22. Left to their own devices, many patients will pay lip service to treatment efforts but not initiate or participate (e.g., physical activation). Family, friends, or peers are critical in order to make progress.

Aggressively Treat Secondary Causes of Negative Symptoms

Given the lack of good treatments for primary negative symptoms, identifying causes of possible secondary negative symptoms is all the more critical as improving those may make a real difference. First, review all medications and avoid those that cause or make negative symptoms worse. Offenders are all sedating medications and antipsychotics that cause Parkinsonism (bradyphrenia and bradykinesia). It is rather difficult to get motivated if you are fighting daytime sleepiness, particularly if you already have problems with motivation to begin with. If you suspect Parkinsonism, switch to another antipsychotic if you can (rather than adding an anticholinergic, which impairs cognition; see Chap. 29). Next, make sure that positive symptoms are optimally treated. Sometimes, unrecognized positive symptoms (e.g., paranoia) can lead you to falsely conclude that primary negative symptoms are present. Importantly, aggressively identify treatable psychiatric comorbidities such as social anxiety and depression, even if subsyndromal [33].

Clinical Vignette

I saw a young man in consultations 2 years after his first episode of psychosis had forced him to put his college education on hold. Although his psychosis had resolved with a low-dose second-generation antipsychotic, he appeared rather blunted, and he had been unable to return to college. He eloquently described a sense of loss of volition and a lack of emotional vividness. His Beck Depression Inventory II (BDI-II) depression score was only slightly elevated (total score of 15), but he considered himself somewhat depressed and unable to get motivated. I recommended a trial of an antidepressant for his residual affective and/or negative symptoms. When he returned for a follow-up visit 6 months later, I noted no change in his blunted appearance. However, his BDI-II total score was 2, and he considered himself recovered; he had taken up some classes at a local college.

Always consider the possibility of secondary negative symptoms, in this case, impairing subsyndromal depression [33]. A self-rating scale for depression (e.g., the BDI-II) is useful (necessary) to identify and track subsyndromal symptoms. Another way of conceptualizing the clinical problem in the young man is to say that his anhedonia (a shared, core feature of both depression and negative symptoms) was antidepressant-responsive, thus avoiding any academic discussion about what I was “really” treating.

Also address social withdrawal that stems from an attitude of social defeat and demoralization. Patients socialized to institutional living often have lost any initiative and can appear quite defeated or demoralized, particularly if they did not choose to live in the institution. Note, however, that patients can be neglected or “institutionalized” in the community as well [34]. Group homes, for example, can create the same psychological chains of control that discourage patient initiative, adding to negative symptoms. The squeaky wheel in a group home may be the one still dreaming and making staff demands to get there; he should be listened to, not medicated until he gives up.

Pace Yourself and the Family in Treating Negative Symptoms

As alluded to earlier, lack of environmental stimulation leads to a withering of social interest and competence (think about the deleterious effects of psychosocial neglect in the Romanian orphanages as an extreme form of social deprivation). Intuitively, families and group home staff recognize that “doing nothing” is probably not conducive to regaining social competence. However, some families and the treatment team push too hard and too early for patients to “get better.” For some patients, negative symptoms appear to have a protective function (e.g., from over-stimulation), and improvement follows its own trajectory and time course unless it is interfered with. There is a fine line between pushing too hard and doing too little.

Tip

Spend time explaining negative symptoms and their impact on functioning to family members. Explain that negative symptoms are not simply willful refusal to participate in life. Otherwise, patients are labeled as “lazy” and unrealistically pushed and criticized (see “high EE” in Chap. 23). Protect the patient from overly aggressive expectations; instead, be a proponent of “slow medicine” [35], and stress the importance of giving patients time to heal. But do not have expectations that are unduly low as low expectations can lead to low achievements.

References

1. de Oliveira-Souza R, Marrosos RP, Moll J. The dementias of schizophrenia. *Dement Neuropsychol*. 2007;1:124–30.
2. McNally K. Eugene Bleuler's four As. *Hist Psychol*. 2009;12:43–59.
3. Crow TJ. Molecular pathology of schizophrenia: more than one disease process? *Br Med J*. 1980;280:66–8.
4. Kirkpatrick B, Fenton WS, Carpenter WT Jr, Marder SR. The NIMH-MATRICS consensus statement on negative symptoms. *Schizophr Bull*. 2006;32:214–9.

5. Strauss GP, Esfahlani FZ, Galderisi S, Mucci A, Rossi A, Bucci P, et al. Network analysis reveals the latent structure of negative symptoms in schizophrenia. *Schizophr Bull.* 2018; <https://doi.org/10.1093/schbul/sby133>.
6. Foussias G, Remington G. Negative symptoms in schizophrenia: avolition and Occam's razor. *Schizophr Bull.* 2010;36:359–69.
7. Marin RS. Apathy: concept, syndrome, neural mechanisms, and treatment. *Semin Clin Neuropsychiatry.* 1996;1:304–14.
8. Kirkpatrick B, Buchanan RW, Ross DE, Carpenter WT Jr. A separate disease within the syndrome of schizophrenia. *Arch Gen Psychiatry.* 2001;58:165–71.
9. Kirkpatrick B, Mucci A, Galderisi S. Primary, enduring negative symptoms: an update on research. *Schizophr Bull.* 2017;43:730–6.
10. Black DW, Boffeli TJ. Simple schizophrenia: past, present, and future. *Am J Psychiatry.* 1989;146:1267–73.
11. Fervaha G, Takeuchi H, Foussias G, Agid O, Remington G. Using poverty of speech as a case study to explore the overlap between negative symptoms and cognitive dysfunction. *Schizophr Res.* 2016;176:411–6.
12. Gard DE, Kring AM, Gard MG, Horan WP, Green MF. Anhedonia in schizophrenia: distinctions between anticipatory and consummatory pleasure. *Schizophr Res.* 2007;93:253–60.
13. Auerbach RP, Pagliaccio D, Pizzagalli DA. Toward an improved understanding of anhedonia. *JAMA Psychiatry.* 2019;76(6):571–3.
14. Kimhy D, Yale S, Goetz RR, McMarr LM, Malaspina D. The factorial structure of the schedule for the deficit syndrome in schizophrenia. *Schizophr Bull.* 2006;32:274–8.
15. Strauss GP, Nunez A, Ahmed AO, Barchard KA, Granholm E, Kirkpatrick B, et al. The latent structure of negative symptoms in schizophrenia. *JAMA Psychiatry.* 2018;75:1271–9.
16. Foussias G, Agid O, Fervaha G, Remington G. Negative symptoms of schizophrenia: clinical features, relevance to real world functioning and specificity versus other CNS disorders. *Eur Neuropsychopharmacol.* 2014;24:693–709.
17. Barrett K. Treating organic abulia with bromocriptine and lisuride: four case studies. *J Neurol Neurosurg Psychiatry.* 1991;54:718–21.
18. Andreasen NC. Negative symptoms in schizophrenia. Definition and reliability. *Arch Gen Psychiatry.* 1982;39:784–8.
19. Gulyaner II, Dutta E, Vilkas N, Ongseng F, Finestone H, Gallagher R, et al. Hypofrontality and negative symptoms in patients with dementia of Alzheimer type. *Neuropsychiatry Neuropsychol Behav Neurol.* 2000;13:53–9.
20. Rao V, Spiro JR, Schretlen DJ, Cascella NG. Apathy syndrome after traumatic brain injury compared with deficits in schizophrenia. *Psychosomatics.* 2007;48:217–22.
21. Carpenter WT, Blanchard JJ, Kirkpatrick B. New standards for negative symptom assessment. *Schizophr Bull.* 2016;42:1–3.
22. Remington G, Foussias G, Fervaha G, Agid O, Takeuchi H, Lee J, et al. Treating negative symptoms in schizophrenia: an update. *Curr Treat Options Psychiatry.* 2016;3:133–50.
23. Roffman JL, Petruzzli LJ, Tanner AS, Brown HE, Eryilmaz H, Ho NF, et al. Biochemical, physiological and clinical effects of l-methylfolate in schizophrenia: a randomized controlled trial. *Mol Psychiatry.* 2018;23:316–22.
24. Roffman JL, Lamberti JS, Achtyes E, Macklin EA, Galendez GC, Raeke LH, et al. Randomized multicenter investigation of folate plus vitamin B12 supplementation in schizophrenia. *JAMA Psychiatry.* 2013;70:481–9.
25. Singh SP, Singh V, Kar N, Chan K. Efficacy of antidepressants in treating the negative symptoms of chronic schizophrenia: meta-analysis. *Br J Psychiatry.* 2010;197:174–9.
26. Vidal C, Reese C, Fischer BA, Chiapelli J, Himelhoch S. Meta-analysis of efficacy of mirtazapine as an adjunctive treatment of negative symptoms in schizophrenia. *Clin Schizophr Relat Psychoses.* 2015;9:88–95.
27. Bugarski-Kirola D, Blaettler T, Arango C, Fleischhacker WW, Garibaldi G, Wang A, et al. Bitopertin in negative symptoms of schizophrenia-results from the phase III FlashLyte and DayLyte studies. *Biol Psychiatry.* 2017;82:8–16.

28. Aleman A, Enriquez-Geppert S, Knegtering H, Dlabac-de Lange JJ. Moderate effects of non-invasive brain stimulation of the frontal cortex for improving negative symptoms in schizophrenia: meta-analysis of controlled trials. *Neurosci Biobehav Rev.* 2018;89:111–8.
29. Leucht S, Arbter D, Engel RR, Kissling W, Davis JM. How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. *Mol Psychiatry.* 2009;14:429–47.
30. Nemeth G, Laszlovszky I, Czobor P, Szalai E, Szatmari B, Harsanyi J, et al. Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial. *Lancet.* 2017;389:1103–13.
31. Mucci A, Merlotti E, Ucok A, Aleman A, Galderisi S. Primary and persistent negative symptoms: concepts, assessments and neurobiological bases. *Schizophr Res.* 2017;186:19–28.
32. Perivoliotis D, Cather C. Cognitive behavioral therapy of negative symptoms. *J Clin Psychol.* 2009;65:815–30.
33. Zisook S, Kasckow JW, Golshan S, Fellows I, Solorzano E, Lehman D, et al. Citalopram augmentation for subsyndromal symptoms of depression in middle-aged and older outpatients with schizophrenia and schizoaffective disorder: a randomized controlled trial. *J Clin Psychiatry.* 2009;70:562–71.
34. Kontos N, Freudenreich O, Querques J. Outpatient institutionalization – 100 words. *Br J Psychiatry.* 2014;205:339.
35. Sweet V. Slow medicine: the way to healing. New York: Riverhead Books; 2017.

Additional Resources

Book

Baumeister RT, Tierney J. *Willpower: rediscovering the greatest human strength.* New York, NY: The Penguin Press; 2011. – A revisiting of the idea of the will that applies to patients with negative symptoms.

Articles

- Marder SR, Galderisi S. The current conceptualization of negative symptoms in schizophrenia. *World Psychiatry.* 2017;16:14–24. – A recent summary and update that provides more detail about the five negative symptoms domains and how these five constructs are actually measured (provides helpful examples from the established negative symptom rating scales).
- McNally K. Eugene Bleuler's four As. *Hist Psychol.* 2009;12:43–59. – As noted in the chapter, Bleuler never articulated his four As. Using Bleuler's four As as an example, the author argues that progressive research agendas ignore historical context at their own peril. The article is a passionate plea to avoid intellectual laziness and read the primary literature.

Chapter 29

Cognition in Schizophrenia



Essential Features

- Cognitive deficits are a core feature of schizophrenia. How well patients with schizophrenia will do in life is not determined by positive symptoms but in part by the degree of cognitive impairment.
- 75% of patients with schizophrenia are globally impaired across a broad range of neuropsychological tests. Several areas are more affected than others, specifically attention, verbal memory, and executive function.
- The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative identified seven cognitive domains to assess in treatment trials: processing speed, attention/vigilance, working memory (verbal and nonverbal), verbal learning, visual learning, reasoning and problem-solving, and social cognition.
- Social cognition (e.g., face recognition, emotional processing, and theory of mind) is often impaired, leading to difficulties reading social clues and navigating ambiguous and complex social environments. Social skills training attempts to improve social competence.
- Cognitive impairments are already present prior to the onset of psychosis and remain stable during the chronic illness phase. Schizophrenia is not a classic neurodegenerative disorder with progressive worsening of cognition.
- Comprehensive assessment of cognition requires time. For bedside testing and initial screening, complete the Montreal Cognitive Assessment (MoCA).
- The clock-drawing test is a good screening test for executive dysfunction which is invariably impaired in more severely ill patients.
- Antipsychotics are not pro-cognitive agents. If anything, their use has a cognitive cost. Minimize any medications that can impair cognition (in particular, anticholinergic medications and benzodiazepines).
- Non-medication treatments (social skills training and cognitive remediation) should be routinely included in rehabilitation.

“Tell me and I’ll forget; show me and I may remember; involve me and I’ll understand.”
— Author unknown

Cognitive deficits are a core feature of schizophrenia. Kraepelin’s term for schizophrenia, “dementia praecox,” speaks to his early recognition that intellect and functional decline are important aspects of this disorder. Kraepelin also described patients with mental retardation who developed schizophrenia and for whom he used the term *Pfropfschizophrenie* (from the German *pflanzen*, “to graft on”) to denote that the psychosis seems to have been grafted upon a brain with developmental intellectual disability [1]. Kraepelin’s thinking is reminiscent of today’s neurodevelopmental model of schizophrenia that views certain cognitive deficits as part of the vulnerability for schizophrenia.

The effects of cognitive impairment can be devastating when it comes to function. Cognition predicts the ability to work, to participate in rehabilitation, or to function in the community. Real-life performance is complex, however, and while cognitive competence matters, significant negative symptoms (see previous chapter) are a second impediment to good community outcomes [2]. In many cases, a host of external factors (lack of opportunity for work, lack of access to high-quality rehabilitation, structural work disincentives) ultimately determines if a person with schizophrenia works or not, regardless of the degree of cognitive difficulties.

The heterogeneity of cognitive deficits and the lack of an easy assessment tool suitable for routine clinical practice led to the decision to not list cognitive impairment as an explicit diagnostic criterion in DSM-5 despite its clinical relevance [3]. This omission does not argue against the central importance of cognition in schizophrenia. Lack of insight into illness (anosognosia) can be viewed as a neurocognitive deficit and could therefore have been included in this chapter. Given its importance, however, I moved it to its own chapter (see Chap. 31 on illness insight and medication adherence).

Cognitive Impairments in Schizophrenia

Cognition in schizophrenia is not fixed, and describing its time course requires a developmental or life-span perspective [4]. Importantly, cognitive impairment associated with schizophrenia (CIAS) is present before the onset of psychosis, possibly starting during puberty [5] and clearly detectable in prodromal patients and in young people at high-risk for psychosis [6]. Although there might be some worsening around the time of the first episode of psychosis, the deficits plateau after the initial episode and remain stable throughout life until the effects of aging worsen cognition. In other words, the cognitive damage is done once patients present with psychosis. There is no progressive worsening of cognition in established schizophrenia, and in that sense, schizophrenia is not a classic neurodegenerative disorder [7]. Current research efforts attempt to better characterize the varied trajectories and etiologies of abnormal brain development (including putative “toxic” effects of

untreated psychosis and medication effects) with the hope to intervene early enough to get abnormally developing brains “back on track” and perhaps prevent the development of schizophrenia, among other neurodevelopmental disorders completely [8].

Key Point

Although it is possible to be cognitively intact if you have schizophrenia, about 75% of patients would nevertheless be classified as impaired on standard, comprehensive neuropsychological batteries [9], sometimes reaching the level of dementia if the deficits encompass several cognitive domains and are severe enough.

Even those patients who are unimpaired on testing around the time of their first episode of psychosis probably have an illness-related decrement in their cognitive function, including a decrease in their premorbid IQ [10]. In one study, declining scholastic test scores between the 8th and 11th grade were seen in those adolescent students who later developed schizophrenia [11], consistent with major illness-related brain changes during adolescence. On neuropsychological testing in established schizophrenia, the pattern of impairment is described as both generalized (performance is impaired on a wide variety of tests) and specific (there is a typical pattern of impairment, with some areas more impaired than others) [12]. The biggest impairments are seen in the areas of attention (such as sustained attention or vigilance), verbal learning and memory, and executive function. In these key areas of cognition, patients show impairments between 1 and 1½ and 2 standard deviations below healthy controls. Reasoning, problem-solving, and speed of information processing are other cognitive domains that are usually impaired. Social cognition which encompasses face recognition, emotional processing, and theory of mind, among others [13], is increasingly recognized as an area of functionally highly relevant deficit [14]. Reading social clues like other people’s emotions and intentions and navigating ambiguous and complex social environments are key functions of our social brain that patients with schizophrenia have great difficulties with [15].

A simplified neuroanatomical model of cognition in schizophrenia suggests that almost all patients have some problems with basic memory and learning (temporal-hippocampal system), coupled with executive dysfunction (prefrontal systems). The prefrontal dysfunction, in particular, prevents the use of organizational strategies to learn new material, which is necessary for effective learning. In Alzheimer’s disease, the memory problem is rather basic (the memory stores themselves are degraded); in schizophrenia, some aspects of the memory problem are at a higher level (where strategies and flexibility are needed for better access of memory stores). The cognitive problems of schizophrenia are unlike those of Alzheimer’s dementia or of typical “brain damage” in that the disease is neither progressive nor can the dysfunction be easily localized to one particular brain area, respectively. It is there-

fore better think of impaired function (e.g., executive dysfunction) as opposed to impaired regions (e.g. frontal lobe dysfunction).

Behavioral disinhibition is another example of a failure of the complex interplay between different brain regions, in this case of a failure of top-down cognitive control. Usually, the prefrontal cortex functions as a break “from above” on other, “lower” brain systems [16] and prevents automatic responses to irrelevant stimuli. This function can be impressively impaired in a subgroup of patients; such patients might have a low frustration tolerance, are impulsive, and act without foresight or regard for social convention. They can display stimulus-bound responses, including broadly inappropriate reactions to the interviewer. They can be quite endearing in their honesty (“Doc, you need a haircut”) and immediacy (“Hey Doc, going home to your wife,” shouted across the subway platform after spotting me) because they lack the brakes (and social wisdom) that prevent most of us from saying what comes to mind without some censorship.

The manifold, widespread, and varied cognitive difficulties seen in schizophrenia patients seem to be the result of a failure of the coordinated activity between distributed brain regions (brain networks) and not the result of a nonfunctioning brain modules with a specific function (e.g., a stroke taking out Broca’s area). (This is not to say that a failure in a critical brain region like the thalamus could not result in widespread network disruptions [17].) In such a network model, the exact clinical expression of connectivity abnormalities would depend on which networks are affected, how severely out-of-sync the circuits are, and how much the impaired brain can compensate. Often, the cognitive impairment in schizophrenia only becomes apparent when the brain is sufficiently challenged (cognitively overtaxed) as compensatory mechanisms cover up what can be viewed as reduced brain efficiency as opposed to frank deficits. Sometimes, superimposed traditional “brain damage” (e.g., a head injury) further complicates the clinical picture.

Key Point

Although schizophrenia is clearly not a mere frontal lobe dementia, many patients have executive problems, and a minority have deficits akin to fronto-temporal dementia with regard to severity and neuropsychological profile (albeit not neuroanatomically) [18].

Clinical Assessment

It should have become clear that any examination of a patient with schizophrenia is incomplete if you assess only positive and negative symptoms: you must also assess cognition. I stress this because, as noted earlier, cognition (despite being a core feature of the illness) is not included in current diagnostic criteria as a specific and explicit diagnostic criterion and might be overlooked, particularly because the deficits can be rather subtle and overshadowed by more obvious positive or negative symptoms.

You should also know that the relationship between symptoms and cognition is not strong. Although there is some connection between negative symptoms and cognition (those with significant negative symptoms tend to have worse cognition), the correlation is rather weak ($r = 0.13\text{--}0.27$ in the Clinical Antipsychotic Trials of Intervention Effectiveness [CATIE] baseline data) [19]. Positive symptoms have essentially no correlation with cognition. In other words, you cannot really judge the severity of cognitive problems from the severity of clinical symptoms.

There is consensus regarding the optimal battery of neurocognitive tests to characterize cognition in schizophrenia. A decade ago, the National Institute of Mental Health (NIMH) convened an expert group for their so-called Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative that standardized the cognitive assessment of patients in schizophrenia trials to improve cognition [20]. The group selected and bundled ten cognitive tests to assess seven cognitive domains into a standard cognitive battery for use in clinical trials: the MATRICS Consensus Cognitive Battery (MCCB) [21] (see Table 29.1 for the seven cognitive domains).

Unfortunately, such a standardized and comprehensive assessment of cognition is time-consuming and not easy as some areas of cognition require a computer or other equipment (and many tests are copyrighted). For some key domains (e.g., social cognition), no easy-to-use bedside tests are clinically available. Even shorter assessment batteries like the Brief Assessment of Cognition in Schizophrenia (BACS) [22] take too long (the BACS takes 30 minutes) to be incorporated in routine clinical visits. (Do not forget, however, that you could always spread out your cognitive assessment: there is no need to complete everything in one visit.) Performance-based measures of functional capacity to better explain a patient's disability add additional assessment complexity [23], including who to obtain reliable information from.

I suggest that you get your hands on some of the tests used in the various cognitive batteries to look at the principle behind them and then create your own poor man's versions of them. For example, look at the Hopkins Verbal learning Test (HVLT) and then create your own word list – you will need 12 words from 3 taxonomic categories – give a patient 3 trials to learn the list, and see how the patient organizes learning.

Table 29.1 Seven consensus cognitive domains in schizophrenia

Processing speed
Attention/vigilance
Working memory (verbal and nonverbal)
Verbal learning
Visual learning
Reasoning and problem-solving
Social cognition

Based on [20]

Tip

The most useful information might not come from the test results themselves but how a patient approaches a test, so it does not matter so much what exact test you use. What matters is that you administer the screening test yourself to get an appreciation of the patient's cognitive struggles. Pay particular attention to the effort spent on the cognitive task (motivation); suboptimal effort will result in worse test scores [24].

For a bedside assessment of cognition, I suggest you examine the following key areas of cognition:

- Assess sustained attention/vigilance – Hard to test without a computer but a fundamental problem in schizophrenia; I use the digit span forward to make sure basic attention is okay.
- Assess working memory – Digit span backward and Trails B.
- Assess verbal learning and memory – Have patient learn a word list (e.g., based on HVLT, as mentioned above); look for poor memorization strategies that ignore semantic relationships, not absolute performance.
- Assess frontal lobe functions – This is a very important area to examine. At a minimum, have patient draw a clock [25]. Table 29.2 presents other screening tests that you could use.
- Estimate processing speed – Trails A.
- The digit symbol substitution test (DSST) is an excellent screening test for cognitive difficulties that stem from deficits in multiple domains which is typical for schizophrenia [26] – The DSST is a highly sensitive but not specific measure for the efficiency of brain function (processing speed) that relies on the intactness of several related systems, including working memory [27].
- Complete the Mini-Mental State Examination (MMSE) – Note that the MMSE is not sufficient to assess cognition in patients with schizophrenia per se. A normal MMSE is useful information, as are the items on the MMSE that pose problems for the patient.
- If you have the time, substitute the Montreal Cognitive Assessment (MoCA) for the MMSE – The MoCA is more involved than the MMSE but covers more areas, including some tests of frontal lobe function, and correlates well with specific tests that assess cognition in schizophrenia [28]. Drawing a clock is included in the MoCA.

Table 29.2 Bedside assessment of executive function

Clock-drawing test ^a
Luria's hand maneuvers
Cognitive estimates
Verbal fluency – category fluency (supermarket items) and letter fluency (FAS)
Trails B

^aIf you only could do one test to check executive function do this one

During the course of the interview, you should be able to form an opinion about the patient's IQ and ability to think in abstract terms. One of the best estimates of intelligence is a person's vocabulary (estimates of premorbid IQ use simple lists of words that have to be read aloud by patients are scored based on correct pronunciation, e.g., "terpsichorean"). Asking about similarities and the meaning of a proverb or sayings are good screening questions to determine ability to abstract. I prefer to ask proverbs or sayings that the patient does not know to see how the patient approaches the interpretation. If you speak another language, translate one from your language (e.g., from the German: "The dumbest farmer harvests the biggest potatoes."). Another way of gauging intelligence and practical thinking is the use of cognitive estimates: How high does an airplane fly? How tall is the Prudential (a tower in Boston – you obviously might want to choose a more local example)?

Remember that concrete thinkers do not benefit from abstract explanations. Do not be surprised if a concrete thinker resists a medication switch because the other medication requires a higher dose (e.g., 100 mg of quetiapine instead of 1 mg of risperidone).

Do not forget to ask about difficulties with reading, writing, spelling, and mathematics. A significant minority of patients is functionally illiterate but would never call themselves illiterate. Many patients struggle with reading for a different reason: what they read does not register, and they have to go over the same paragraph over and over again. This is a receptive language problem (one of the basic symptoms, see Chap. 7) that gets in the way of comprehending what is read. Patients describe this experience as if reading a text in Latin: they can read it aloud but it means nothing. A history of school problems could lead to a diagnosis of a specific learning disability that can accompany neurodevelopmental disorders. If a learning disorder is present, consider testing for velo-cardio-facial syndrome (VCFS) [29].

Tip

Routinely order comprehensive neuropsychological testing (with emphasis on attention, memory, and executive functions) of your patient with schizophrenia to document areas of strength and weakness. I suggest doing testing once a patient is clinically stable and has reached a plateau, not during an acute illness phase. The results will help you understand the specific difficulties your patient is going to have with family, group homes, or jobs. If you could only do one test, do the digit symbol coding task which seems to tap quite well the inefficiencies of the schizophrenia brain quite well [27, 30]. Try also to have a baseline MoCA on every patient.

Structural brain imaging is only helpful to exclude other causes of cognitive deficits (e.g., stroke). While a clinical brain CT or MRI can confirm findings typical for schizophrenia (enlarged ventricles and cortical thinning [31]), those are neither specific nor helpful for further treatment planning. Functional neuroimaging like PET, MEG, or fMRI is widely used in research but has not yet found its way into the clinic.

Treatment

Currently, no medications are available that can specifically treat the cognitive impairment of schizophrenia. The development of pro-cognitive medications for neurocognitive disorders like schizophrenia remains an unfulfilled need despite many attempts to target receptor systems associated with cognition (e.g., cholinergic, nicotinic, or glutamate systems). One example of a failed compound that ought to work but fails in the clinic includes a partial agonist at the alpha-7 nicotinic acetylcholine receptor [32, 33] even though nicotinic receptors clearly play a major role in memory and learning. One obstacle in drug development for cognition is the need for some practice in order for learning to occur; the mere administration of a putatively pro-cognitive agent without cognitive remediation (that in addition needs to be specific for the cognitive domain treated) might simply not work. To complicate matters, for drugs to be clinically useful, they need to show improvement in real-world function and not merely better cognitive test scores [34].

There was hope that the second-generation antipsychotics would have cognitive benefits over the first-generation antipsychotics, a hope that was not borne out in trials of chronic [35] and first-episode patients [36]. The sobering conclusion of decades of research is that antipsychotics have no pro-cognitive effects per se but instead carry some liability toward further impairing cognition related to receptor profile and dose. In one well-done study of antipsychotic-naïve, first-episode patients, risperidone was clinically effective but worsened already impaired spatial working memory, likely an unintended (and unavoidable) consequence of the effect of dopamine-blocking antipsychotics on frontal dopamine systems [37]. The development of non-dopaminergic antipsychotics is therefore an urgent need.

Social Skills Training and Cognitive Remediation

“Social skills groups” used to be a staple of state hospital rehabilitation programs and are often offered in day programs today. Social skills including interpersonal skills are abilities that allow us to be successful as members of our social communities (family, friends, work). We need to be socially competent in order to negotiate with others and achieve personal goals. Traditional social skills training is usually offered in a group setting, combining didactic instruction with role-play (learning by doing). Patients learn to be more aware of how they get across to other people and adjust their interactions accordingly (e.g., making eye contact when speaking with somebody). Rehearsing a job interview may be one specific task that is learned via role-play. Budgeting or using public transportation are other typical modules that target instrumental role skills needed for independent living. One of the best known such program was developed by Dr. Robert Liberman at the West Los Angeles VA (see Additional Resources). One caveat: merely socializing in a day program is not social skills training. Social skills training uses principles from behavioral learning to build a skill and is a highly structured, methodical approach.

A variant of social skills training is cognitive remediation. Cognitive remediation (cognitive rehabilitation, “cog rem”) encompasses a wide variety of non-pharmacological treatments that attempt to improve cognition and patient functioning. Approaches are quite varied [38], and the best cognitive training approach remains to be fully elucidated [39]. Cognitive remediation can target specific, very basic perceptual skills, high-level executive processes, or more general cognitive abilities. Programs can have patients work alone with computers or involve therapists. Modern computer programs often use game-like features to engage patients. Still: I remain skeptical that simply putting your average patient in front of a computer will lead to the acquisition of skills that transfer to the real world and lead to better community function. (A recent, large trial that used computerized training was negative [40].) The best results are probably obtained when cognitive remediation is combined with more traditional rehabilitation [41], particularly social skills training.

Tip

State hospitals used to offer comprehensive cognitive assessments and rehabilitation, services that fell by the wayside when inpatient stays were reduced to rapid symptom stabilization. In my hospital, I often use resources intended for other disorders (e.g., speech and language pathology offers help for patients with executive dysfunction). Your patient may have access to services developed for traumatic brain injury patients or for patients with ADHD.

Bedside Clinical Approach

Individual clinicians can help their patients’ cognition by paying attention to the following points:

Educate Family Members

Help family members understand that schizophrenia is also a neurocognitive (brain) disorder and not merely a psychological affliction that would resolve with “talk therapy.” This insight is painful but necessary as the cognitive difficulties are not necessarily apparent to a layperson who might instead insist that a family member is willfully difficult or unmotivated. Make concrete what executive dysfunction in particular looks like in real-world situations. Executive dysfunction becomes obvious when patients are left to their own devices (e.g., patients who had lived with their parents might be unable to function alone in college). If there is executive dysfunction, patients need somebody else’s executive function to substitute for them in those areas in which they have difficulties: planning ahead, implementing plans, and flexibility in solving problems that invariably arise. Enlist the help of the family or friends (or the rehabilitation team) to get things done, using their executive capabilities to compensate for the patient’s lack thereof.

Rely on Routines, Not on Memory

Recall one fundamental problem that many patients with schizophrenia have: verbal memory. If patients have problems with verbal memory, talking is not the best approach, and verbal repetition is not the best strategy for memory consolidation. Patients should not rely on their memory but write things down and use lists. Write down your medication instructions for your patients too (but also remember that many patients with schizophrenia have reading impairment that leaves them functionally illiterate). However, the best way of learning for patients with schizophrenia is by doing, through creating routines (using implicit memory) as grasped by the writer of the proverb at the beginning of this chapter.

Do Not Rush Patients

Processing speed as summative marker of brain efficiency can be markedly impaired in patients. This is one factor why social interactions are stressful for patients: they simply cannot keep up with small talk and the quick back-and-forth required during banter. Avoid machine gun-like medical questioning but allow patients to think about your question and listen to their answers. If given enough time, many patients will be able to answer your questions. Think how you slow down with geriatric patients; do the same with your patient with schizophrenia.

Do Not Add Insults to Injury

It is imperative to avoid further compromising an already compromised brain with medications that impair cognition [42]. Anticholinergics, in particular, can worsen complex attention and memory in schizophrenia by 1 standard deviation [43]. I think it is rarely, if ever, justified to use a maintenance antipsychotic that requires the long-term addition of an anticholinergic. In those cases in which you have to start an anticholinergic, review the ongoing need for it a month after you start it (and try to lower the antipsychotic dose). Discourage diphenhydramine (Benadryl) for insomnia. Review your use of benzodiazepines, which also worsen memory function (but keep in mind the Yerkes-Dodson law and its inverted U-curve that posits an optimal amount of anxiety for performance, beyond which performance worsens; treating anxiety can thus improve performance).

Keep the Brain Healthy

I am ending this chapter with the most powerful intervention we have to increase cognition: physical exercise [44]. Unfortunately, exercise regimens are notoriously difficult to implement, particularly for patients with negative symptoms.

Behavioral scheduling (e.g., going to the gym every Tuesday at 11 am) is one technique that can work, particularly if family members are involved. Counsel patients to limit substances toxic to the brain (alcohol) and ensure treatment of diabetes and hypertension.

References

1. Catinari S, Vass A, Ermilov M, Heresco-Levy U. Pffropfschizophrenia in the age of deinstitutionalization: whose problem? *Compr Psychiatry*. 2005;46:200–5.
2. Fervaha G, Foussias G, Agid O, Remington G. Motivational and neurocognitive deficits are central to the prediction of longitudinal functional outcome in schizophrenia. *Acta Psychiatr Scand*. 2014;130:290–9.
3. Keefe RS, Fenton WS. How should DSM-V criteria for schizophrenia include cognitive impairment? *Schizophr Bull*. 2007;33:912–20.
4. Sheffield JM, Karcher NR, Barch DM. Cognitive deficits in psychotic disorders: a lifespan perspective. *Neuropsychol Rev*. 2018;28:509–33.
5. Davies N, Russell A, Jones P, Murray RM. Which characteristics of schizophrenia predate psychosis? *J Psychiatr Res*. 1998;32:121–31.
6. Seidman LJ, Shapiro DI, Stone WS, Woodberry KA, Ronzio A, Cornblatt BA, et al. Association of neurocognition with transition to psychosis: baseline functioning in the second phase of the North American Prodrome Longitudinal Study. *JAMA Psychiatry*. 2016;73:1239–48.
7. Rund BR, Barder HE, Evensen J, Haahr U, ten Velden Hegelstad W, Joa I, et al. Neurocognition and duration of psychosis: a 10-year follow-up of first-episode patients. *Schizophr Bull*. 2016;42:87–95.
8. Insel TR. Rethinking schizophrenia. *Nature*. 2010;468:187–93.
9. Palmer BW, Heaton RK, Paulsen JS, Kuck J, Braff D, Harris MJ, et al. Is it possible to be schizophrenic yet neuropsychologically normal? *Neuropsychology*. 1997;11:437–46.
10. Meier MH, Caspi A, Reichenberg A, Keefe RS, Fisher HL, Harrington H, et al. Neuropsychological decline in schizophrenia from the premorbid to the postonset period: evidence from a population-representative longitudinal study. *Am J Psychiatry*. 2014;171: 91–101.
11. Fuller R, Nopoulos P, Arndt S, O’Leary D, Ho BC, Andreasen NC. Longitudinal assessment of premorbid cognitive functioning in patients with schizophrenia through examination of standardized scholastic test performance. *Am J Psychiatry*. 2002;159:1183–9.
12. Bilder RM, Goldman RS, Robinson D, Reiter G, Bell L, Bates JA, et al. Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. *Am J Psychiatry*. 2000;157:549–59.
13. Green MF, Horan WP, Lee J. Social cognition in schizophrenia. *Nat Rev Neurosci*. 2015;16:620–31.
14. Mier D, Kirsch P. Social-cognitive deficits in schizophrenia. *Curr Top Behav Neurosci*. 2017;30:397–409.
15. Burns J. The social brain hypothesis of schizophrenia. *World Psychiatry*. 2006;5:77–81.
16. Knutson KM, Dal Monte O, Schintu S, Wassermann EM, Raymont V, Grafman J, et al. Areas of brain damage underlying increased reports of behavioral disinhibition. *J Neuropsychiatry Clin Neurosci*. 2015;27:193–8.
17. Woodward ND, Heckers S. Mapping thalamocortical functional connectivity in chronic and early stages of psychotic disorders. *Biol Psychiatry*. 2016;79:1016–25.
18. de Vries PJ, Honer WG, Kemp PM, McKenna PJ. Dementia as a complication of schizophrenia. *J Neurol Neurosurg Psychiatry*. 2001;70:588–96.

19. Keefe RS, Bilder RM, Harvey PD, Davis SM, Palmer BW, Gold JM, et al. Baseline neurocognitive deficits in the CATIE schizophrenia trial. *Neuropsychopharmacology*. 2006;31:2033–46.
20. Green MF, Nuechterlein KH, Gold JM, Barch DM, Cohen J, Essock S, et al. Approaching a consensus cognitive battery for clinical trials in schizophrenia: the NIMH-MATRICS conference to select cognitive domains and test criteria. *Biol Psychiatry*. 2004;56:301–7.
21. Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, Cohen JD, et al. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. *Am J Psychiatry*. 2008;165:203–13.
22. Velligan DI, DiCocco M, Bow-Thomas CC, Cadle C, Glahn DC, Miller AL, et al. A brief cognitive assessment for use with schizophrenia patients in community clinics. *Schizophr Res*. 2004;71:273–83.
23. Harvey PD, Velligan DI, Bellack AS. Performance-based measures of functional skills: usefulness in clinical treatment studies. *Schizophr Bull*. 2007;33:1138–48.
24. Fervaha G, Zakzanis KK, Foussias G, Graff-Guerrero A, Agid O, Remington G. Motivational deficits and cognitive test performance in schizophrenia. *JAMA Psychiatry*. 2014;71:1058–65.
25. Bozikas VP, Kosmidis MH, Gamvroula K, Hatzigeorgiadou M, Kourtis A, Karavatos A. Clock Drawing Test in patients with schizophrenia. *Psychiatry Res*. 2004;121:229–38.
26. Jaeger J. Digit symbol substitution test: the case for sensitivity over specificity in neuropsychological testing. *J Clin Psychopharmacol*. 2018;38:513–9.
27. Dickinson D, Ramsey ME, Gold JM. Overlooking the obvious: a meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. *Arch Gen Psychiatry*. 2007;64:532–42.
28. Yang Z, Abdul Rashid NA, Quek YF, Lam M, See YM, Maniam Y, et al. Montreal Cognitive Assessment as a screening instrument for cognitive impairments in schizophrenia. *Schizophr Res*. 2018;199:58–63.
29. Murphy KC, Jones RG, Griffiths E, Thompson PW, Owen MJ. Chromosome 22qII deletions. An under-recognised cause of idiopathic learning disability. *Br J Psychiatry*. 1998;172:180–3.
30. Knowles EE, Weiser M, David AS, Glahn DC, Davidson M, Reichenberg A. The puzzle of processing speed, memory, and executive function impairments in schizophrenia: fitting the pieces together. *Biol Psychiatry*. 2015;78:786–93.
31. Hajima SV, Van Haren N, Cahn W, Koolschijn PC, Hulshoff Pol HE, Kahn RS. Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. *Schizophr Bull*. 2013;39:1129–38.
32. Haig G, Wang D, Othman AA, Zhao J. The alpha7 nicotinic agonist ABT-126 in the treatment of cognitive impairment associated with schizophrenia in nonsmokers: results from a randomized controlled phase 2b study. *Neuropsychopharmacology*. 2016;41:2893–902.
33. Haig GM, Bain EE, Robieson WZ, Baker JD, Othman AA. A randomized trial to assess the efficacy and safety of ABT-126, a selective alpha7 nicotinic acetylcholine receptor agonist, in the treatment of cognitive impairment in schizophrenia. *Am J Psychiatry*. 2016;173:827–35.
34. Stover EL, Brady L, Marder SR. New paradigms for treatment development. *Schizophr Bull*. 2007;33:1093–9.
35. Keefe RS, Bilder RM, Davis SM, Harvey PD, Palmer BW, Gold JM, et al. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. *Arch Gen Psychiatry*. 2007;64:633–47.
36. Davidson M, Galderisi S, Weiser M, Werbeloff N, Fleischhacker WW, Keefe RS, et al. Cognitive effects of antipsychotic drugs in first-episode schizophrenia and schizoaffective disorder: a randomized, open-label clinical trial (EUFEST). *Am J Psychiatry*. 2009;166:675–82.
37. Reilly JL, Harris MS, Keshavan MS, Sweeney JA. Adverse effects of risperidone on spatial working memory in first-episode schizophrenia. *Arch Gen Psychiatry*. 2006;63:1189–97.
38. Best MW, Bowie CR. A review of cognitive remediation approaches for schizophrenia: from top-down to bottom-up, brain training to psychotherapy. *Expert Rev Neurother*. 2017;17:713–23.
39. Keshavan MS, Vinogradov S, Rumsey J, Sherrill J, Wagner A. Cognitive training in mental disorders: update and future directions. *Am J Psychiatry*. 2014;171:510–22.

40. Mahncke HW, Kim SJ, Rose A, Stasio C, Buckley P, Caroff S, et al. Evaluation of a plasticity-based cognitive training program in schizophrenia: results from the eCaesar trial. *Schizophr Res.* 2019;208:182–9.
41. Wykes T, Huddy V, Cellard C, McGurk SR, Czobor P. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *Am J Psychiatry.* 2011;168:472–85.
42. Eum S, Hill SK, Rubin LH, Carnahan RM, Reilly JL, Ivleva EI, et al. Cognitive burden of anticholinergic medications in psychotic disorders. *Schizophr Res.* 2017;190:129–35.
43. Minzenberg MJ, Poole JH, Benton C, Vinogradov S. Association of anticholinergic load with impairment of complex attention and memory in schizophrenia. *Am J Psychiatry.* 2004;161:116–24.
44. Stubbs B, Vancampfort D, Hallgren M, Firth J, Veronese N, Solmi M, et al. EPA guidance on physical activity as a treatment for severe mental illness: a meta-review of the evidence and Position Statement from the European Psychiatric Association (EPA), supported by the International Organization of Physical Therapists in Mental Health (IOPTMH). *Eur Psychiatry.* 2018;54:124–44.

Additional Resources

Book

Liberman RP. Recovery from disability: manual of psychiatric rehabilitation. Arlington: American Psychiatric Publishing, Inc.; 2008. – Written by a pioneer in psychiatric rehabilitation, this practical book includes a chapter on social skills training.

Article

Best MW, Bowie CR. A review of cognitive remediation approaches for schizophrenia: from top-down to bottom-up, brain training to psychotherapy. *Expert Rev. Neurother.* 2017;17:713–23. – A helpful review to organize conceptually the confusing world of the many treatments that all get subsumed under the broad category of “cognitive remediation.”

Chapter 30

Depression and Suicide



Essential Concepts

- Schizophrenia is a disease with premature mortality in about 5% of patients: you can die *from* it young, not merely *with* it in old age. The cause of death is suicide.
- Most suicides by patients with schizophrenia occur in the first few years after diagnosis.
- Risk factors for suicide in schizophrenia are the known risk factors for suicide in other conditions: particularly drug use, depression, or demoralization but also psychosis itself.
- Use behavioral dissection (a step-by-step account of the suicide attempt), and try to understand the nature of the crisis, including the patient's intolerable mind state ("psychache").
- Depression is common in schizophrenia particularly in the early years of the illness.
- Demoralization can occur early in the course of illness as well if the illness does not get better and its ramifications on a patient's life become obvious to the patient.
- Clozapine reduces suicidality in schizophrenia.
- Schizophrenia brings many elements of caring for patients with chronic illness into sharp focus, particularly that some patients can become demoralized when their symptoms do not improve. The treatment of demoralization is giving hope. This requires time and commitment, including by the patient's community.

“There is but one truly serious philosophical problem, and that is suicide. Judging whether life is or is not worth living amounts to answering the fundamental question of philosophy.”

— Albert Camus (“The Myth of Sisyphus”), 1942 [1]

“The most serious of schizophrenic symptoms is the suicidal drive.”

— Eugen Bleuler, 1911 [2]

The early prognosis in schizophrenia quo ad vitam (“with regard to life”) is largely determined by suicide. Suicide is, in fact, the number one cause of premature death in schizophrenia patients in the age group from 15 to 24 years [3]. Suicide is closely followed by accidents until natural causes of death take over the statistic in midlife and beyond. Increasingly, unnatural deaths from drug use have become a major concern in first-episode cohorts [4]. Taken together, young patients with schizophrenia face a high premature mortality that is comparable to the mortality risk of patients in their 70s [5].

The great Swiss psychiatrist Eugen Bleuler recognized suicide as a key clinical concern at a time when psychiatrists were just beginning to study schizophrenia. Today, we can only imagine how much some patients must have suffered in Bleuler’s time when incessant, unrelenting auditory hallucinations drove them to suicide to silence the voices, as no treatment was available to quell them. Incessant voices are one instance where the self-medication hypothesis has some face validity, in patients who drink excessively to literally drown the voices.

Most modern studies suggest that around 5% of patients diagnosed with schizophrenia die from suicide [6]. Of note, the 5% figure represents the case fatality rate from suicide which is lower than the often-quoted proportionate mortality rate of 10–15% [7]; the former reflects better a patient’s individual lifetime risk. Although most practitioners recognize that schizophrenia is disabling, it is often not considered to be potentially lethal, so we need to focus on this important statistic: schizophrenia is a disease with 5% mortality. You can die *from* schizophrenia as opposed to merely dying *with* it in old age. This risk of death from suicide is comparable to that of patients with primarily depressive disorders and many potentially lethal medical disorders.

Suicide attempts are even more common than completed suicides. As many as half of the patients with schizophrenia that you encounter will have attempted suicide. This suicide risk is not stable over a patient’s life. The risk is greatest in the first few years of the illness, including the prodromal period [8]. Accordingly, most suicides occur in the first several years following diagnosis. However, suicides occur at any age [9]. In long-standing schizophrenia, another risk factor for suicide is relapse and hospitalization. The risk of suicide increases shortly before going to the hospital (while acutely ill), while the patient is in the hospital, and shortly after discharge, particularly if the patient is socially isolated.

Risk Factors for Suicide

What mediates suicidality in schizophrenia? Importantly, most risk factors are the same as the risk factors in other patient populations, namely, substance use, a prior history of a suicide attempt and depression [10]. Psychosis itself is a risk factor unique

to this population. Importantly, no one risk factor supersedes another risk factor in importance; the key to understanding individual risk lies in appreciating the interplay between the various risk factors present in a patient (see below for an example) [11].

The first risk factor you should evaluate is substance use because of its effect on impulse control and mood. While not always possible, clinicians should also determine if a patient accidentally overdosed on drugs or if it was a suicide attempt.

The next risk factor you should consider is depression, which occurs often in the course of schizophrenia. Depressive symptoms are very common in early course schizophrenia to the point of being part and parcel of the early illness course. Usually, depressive symptoms resolve in parallel with the resolution of positive symptoms. However, a period of depression can follow the resolution of positive symptoms, when patients are getting better. Such depressive symptoms and syndromes in the setting of improving or residual schizophrenia following an acute psychotic episode are sometimes called “post-psychotic depression,” an admittedly poorly defined entity without clear time boundaries or severity definitions [12]. In addition to this purported connection to resolving or resolved psychosis, patients can develop a depressive episode at any point in their lives. Schizophrenia does not render one immune from depression.

The third key risk factor you should focus on is psychosis itself. Although probably less common today compared to the days of Bleuler, uncontrolled psychotic symptoms can still be responsible for unbearable psychologic pain (or psychache, as the father of American suicidology, Edwin Shneidman, calls it [13]), leading to suicide attempts. Though you might think that the so-called command hallucinations should be responsible for suicides, clinical studies suggest that this is true for a small minority of patients (about 10%), but not for most [14]. Some psychotic patients die by accident in response to hallucinations or delusions. I treated a patient who jumped off a bridge not because he wanted to die, but in response to God’s voice asking him, as a test of faith, to jump to prove his worthiness.

Tip

Make sure you understand a patient’s acute mental suffering: his or her “psychache.” This psychache might come from acute psychosis; from clinical depression with its distorted self-loathing and gloomy views; or from hopelessness. The psychache can be made worse by anxiety, which could stem from your treatment, in the form of akathisia. Relieve acute suffering acutely by treating aggressively with medications (and by hospitalizing somebody, if necessary).

The patient’s emotional and cognitive response to receiving a diagnosis of schizophrenia is also important. Receiving a (stigmatizing) diagnosis of schizophrenia is traumatic. The diagnosis brings fear and leads to a severe feeling of loss: the loss of one’s future and standing in society. The way people see themselves and their role in society matters greatly. Imagined or real social exclusion can lead to a state of alienation and lack of purpose in life, which can result in what sociologists call

anomic suicide. This seems to be particularly relevant for those patients who develop a good understanding of their predicament and its consequences, particularly if they had good academic achievements before the onset of schizophrenia. They are often the most intact patients who, in theory, have the best chances of substantial recovery and good long-term outcome. Having “insight into illness” turns out to be a double-edged sword: insight is generally helpful in active disease management, but it might increase the suicide risk [15]. Conversely, patients who are unaware of their symptoms, who are not bothered by their disability, and who have little understanding of their predicament are probably at lower risk for suicide.

Key Point

Demoralization is the loss of hope and loss of meaning and purpose in life. Demoralized people feel isolated from people and society. Demoralization is not the same as depression, although they can come together and there is some obvious overlap. One of the hallmarks of demoralization is a complaint of suicidality. The treatment for demoralization is giving hope and decreasing isolation.

Good questions for you to ask to tap into demoralization are as follows:

What do you want to accomplish over the next year?

What are your hopes for the future?

You have your whole life in front of you; what do you want to do with the time?

Keep in mind that patients with negative symptoms might have little to say to these questions.

A helpful model to put together various risk factors, including biology, life circumstances, life experience, and psychological reactions, is Mann's stress-diathesis model of suicide [16]. In this model, no one single factor leads to a suicide. Instead, it is the confluence of factors, some biological, some characterological, and some external that determine a person's proneness to suicide. In this scheme, an adolescent patient with schizophrenia, for example, might become acutely distressed with hallucinations (a state-dependent stressor) and attempt suicide because of a biological predisposition toward impulsive action (neurocognitive impairment associated with schizophrenia) but also because of a lack of resilience (problem-based coping ability that he never acquired as he became sick at a young age); the latter two factors represent trait-dependent susceptibilities. Treatment can target each of those risk factors to reduce suicide risk.

Assessment of Suicidality

First, language matters, and I recommend using the CDC definition for self-injurious behaviors like a suicide attempt. The CDC defines a suicide attempt as “a non-fatal, self-directed, potentially injurious behavior with an intent to die as

a result of the behavior; might not result in injury” [17]. This definition clearly links ideation (the wish to be dead) with the act. It avoids the inflationary extension of the term suicide attempt to include risk-taking activities that could result in death (excessive speeding, substance use, smoking). I would not use terms like “passive suicidality” and similarly imprecise constructs (suicide gesture, parasuicide).

It is important to routinely assess suicidal ideation and monitor depression and demoralization when you treat patients with schizophrenia. Your assessment of suicidality should follow general clinical guidelines; the process is not different for schizophrenia except that you take into account schizophrenia-specific risks (e.g., psychosis itself). I use “the ABCs of suicide” to comprehensively review important clinical data that go into my suicide risk assessment (see Table 30.1) [18]. The ABCs are based on Mann’s aforementioned stress-diathesis model to understand suicidality and help you collect the facts about a suicide attempt or suicidal ideation, the proximate events leading to a suicidal crisis, and the distal diathesis that might put somebody at higher suicide risk to being with.

Table 30.1 Suicide assessment: the ABCs of suicide

A	Acute assessment (acute medical concerns)
B	Behavioral dissection (facts and chronology)
C	Crisis
D	Diagnostic 4 Ds (depressed, deranged, disturbed, delirious/diseased)
E	Ethanol and drugs
F	Family (and personal) history of suicide
G	Gun availability
H	Homicide risk
I	Infanticide risk

Brief instructions for use:

Make sure you address acute medical concerns after a suicide attempt (e.g., cardiac monitoring). Behavioral dissection is an interview technique that will help you get down to the facts and chronology, instead of relying on vagueness and opinion, to determine exactly what happened. You basically keep asking: “And the, what exactly did you do?” And you press for details: “Did you put the gun in your mouth or just hold it in your lap?”

Understand the crisis that pushed the patient over the edge. A crisis is often a loss, which can be the loss of an idea or the patient’s future.

Rule out four treatable diagnoses that increase suicide risk. Of the diagnostic 4 Ds (depressed; deranged, as in a psychotic state; disturbed, as in personality disordered; and delirious/diseased, as in suffering from a medial illness), depression and psychosis are the two most important state-dependent psychiatric conditions that need to be diagnosed and optimally treated.

The remaining elements of the ABCs are self-explanatory and can serve as a checklist to make sure that you do not overlook other important considerations.

Adapted from [18]

In addition to a good clinical assessment, the severity of suicidal ideation should be assessed with a rating scale. A group at Columbia University was instrumental in introducing concise terminology to the field of suicidology that was subsequently adopted by the CDC, and their “Columbia Scale” (short for Columbia-Suicide Severity Rating Scale or C-SSRS) is an excellent scale to assess both aspects of a suicide attempt: the suicidal ideation and the behavior itself. The scale is a concise, semi-structured interview with helpful probing questions that you can easily go over with your suicidal patient [19].

Tip

Keep track of depressive symptoms and suicidality with a rating scale. A well-validated rating scale for depression in schizophrenia is the Calgary Depression Scale for Schizophrenia (CDSS; see under Additional Resources). This scale is constructed in a way that avoids mistakenly rating negative symptoms as evidence for depression. Items that overlap in both conditions (e.g., anhedonia) are not included. Alternatively, a self-rating scale, such as the widely used Beck Depression Inventory or the nine-item Patient Health Questionnaire depression scale (PHQ-9) (which both contain an item on suicidality), can easily be integrated into routine clinical care. If patients endorse suicidality, you can then follow-up with questions from the Columbia Scale (C-SSRS). Although I strongly advocate using rating scales, no rating scale score can substitute for clinical judgment.

Treatment of Suicidality

Psychopharmacologic treatment with the goal of symptom control is often helpful, although this can, of course, only be true for those patients who accept your treatment. Suicides seem to occur more frequently in those with schizophrenia who remain untreated or who are insufficiently treated. This makes nonadherence and partial adherence risk factors for suicide. Psychiatric treatment can thus be viewed as suicide prevention.

In patients who present for treatment, maximum treatment of positive symptoms and active psychosis is the mandatory first step. While doing this, avoiding side effects that compound a patient’s psychache, particularly akathisia, is important. Consider a clozapine trial if patients remain symptomatic. Clozapine is not only the most effective antipsychotic for positive symptoms but also has the lowest liability for drug-induced dysphoric states like akathisia. In addition, it turns out that clozapine reduces suicidality. An international landmark trial, InterSePT (which stands for “International Suicide Prevention Trial”) showed (using a randomized design) that clozapine can reduce suicidal behavior and suicide attempts in schizophrenia by about one quarter when compared to olanzapine [20]. Due to the low number of suicide deaths, the trial was not able to show if clozapine reduces actual suicide deaths.

Because of the strength of this finding and the clinical relevance of suicidality, clozapine was subsequently approved by the Food and Drug Administration for recurrent suicidal behavior in schizophrenia, the only drug that carries this indication. The suicide-protective mechanism might be severalfold, not mutually exclusive, including better symptom control, fewer extrapyramidal side effects, and less impulsivity; the anti-aggressive efficacy of clozapine is likely not solely related to dopamine blockade. I would add, though, that about half the patients in the trial received antidepressants in addition to their assigned antipsychotic. Clozapine alone might therefore not be sufficient to treat depression and suicidality in schizophrenia. The choice of olanzapine as the comparator drug might have watered down clozapine's true efficacy compared to most antipsychotics, as olanzapine has some properties similar to clozapine. As noted earlier, there was no difference in *completed* suicides between the olanzapine and clozapine arm in the InterSePT trial.

One problem with administering clozapine for suicidality is that those patients at the highest risk for suicide are early in the course of their illness and infrequently receive clozapine in a timely manner because other antipsychotics are tried first. By the time clozapine is considered, it might be too late. I wonder sometimes if I should be more aggressive and move to clozapine earlier, rather than later, despite the risks of clozapine treatment. This is one of the truly difficult clinical decisions.

Tip

Consider a trial of clozapine earlier, rather than later, for suicidal patients with schizophrenia. Clozapine might have a direct effect on the neurobiology of the "suicidal drive." It also works better for positive symptoms and causes less distressing neuroleptic-induced dysphoria or akathisia.

If depressive symptoms are present in the florid, acute phase of first-episode psychosis, antidepressants are probably not necessary. As nicely shown in the seminal EUFEST, depressive symptoms resolve as psychosis recedes with antipsychotic treatment and no depression-specific interventions are needed [21]. An older piece of literature even suggests that antidepressants given during this phase might hinder a therapeutic response. Although a common clinical problem, the pharmacologic management of depressive symptoms in the post-acute phase of psychosis is surprisingly poorly studied. There seems to be a rather high placebo response rate to antidepressants in this phase. Nevertheless, I would clearly treat syndromal presentations of major depression and chronic, subsyndromal forms of depression with an added antidepressant, once the acute phase is over and positive symptoms are well controlled. Citalopram has been shown in a placebo-controlled trial to reduce *subsyndromal* depressive symptoms in an older (age 40 or above) schizophrenia cohort [22]. In addition, citalopram also reduced suicidal ideation in those patients who experienced it at baseline [23]. Before adding an antidepressant, however, rule out nonadherence to the antipsychotic medication, drug use, and extrapyramidal side effects that can look like depression.

One last thought on reducing suicidality with psychotropics: giving lithium to a patient with bipolar disorder can be lifesaving. Unfortunately, there is no good evidence that lithium is effective for the core symptoms of schizophrenia [24]. Nevertheless, in more episodic forms of psychosis with significant mood components, it is reasonable to try lithium as an add-on therapy.

Key Point

Although a cure is not always possible, treatment that alleviates suffering is. Accepting suicide for philosophical reasons (i.e., my life as a schizophrenic is not worth living; a “Bilanzsuizid” or “balance sheet suicide”) is unacceptable and negligent. As a clinician, you must remove any such moral reasoning and first search for treatable mental states that can drive suicidality, such as depression and demoralization, and you must try to modify a diathesis that makes people suicide-prone. From your professional point of view as a physician, suicide is not the logical consequence of schizophrenia but the ultimate sad and tragic outcome.

I started this chapter with a quote by Albert Camus. He would surely argue that suicidal thinking cannot be reduced to the clinical concept of “depression” but that a broader frame of reference is required that includes a person’s philosophy of life. You will hear this view echoed when patients ask you: “Wouldn’t you be depressed and suicidal if you had been told you had schizophrenia?” In this question, you recognize the experience of sadness and loss and being at a loss. In essence, however, your patient is asking, “Is this life still worth living?” “What value does my life have in this society?” Such questions carry the unspoken assumption that nobody can help, particularly not with medicine. Suicide is seen as logical for philosophical reasons; more factors seem to speak for suicide than against it. Several societies where physician-assisted suicide is legal have basically accepted this line of reasoning: that suicide can be rational and getting help to commit suicide is closer to a right and not something to be prevented at all cost. The debates about euthanasia and physician-assisted suicide are not academic but require reflection about your own philosophy of life, including the value of life itself.

I agree with Camus that existential questions matter and that they matter fundamentally, including for physicians. After all, medicine is in the business of the human condition, with its plights of disease and death. Psychiatric illnesses in particular may be the single most important source of misery that exceeds poverty or unemployment, something mental health practitioners may not appreciate [25]. However, we should not accept as the final word the philosophical “balance sheet” thinking of a patient with schizophrenia who has given up. Instead, we should move toward clinical reasoning and employing clinical tools. Our therapeutic goal when faced with such demoralized patients is to give back to the patient a vision of his or

her future: to re-moralize them. In Victor Frankl's words, while we often cannot change a situation, we can always choose our attitude toward a situation. As a clinician, this is our professional responsibility toward suicidal patients: to alleviate suffering that stems from diagnosable, clinical mental states that can lead to suicide. Sometimes medication can alleviate suffering directly by treating positive symptoms or clinical depression or the neurobiology of the suicidal drive. At other times we guide patients psychotherapeutically, and we treat demoralization with hope. Suffice it to say, providing longitudinal care and support and accompanying patients through their illness, thereby imbuing patients with a sense of therapeutic optimism, constitute a necessary first step. While not all diseases are curable, all diseases are treatable. Remember Camus' stance toward the absurdity of our existence: he did not give up but chose to embrace the struggle itself.

Clinical Vignette

Heinz was a 19-year-old young man who had excelled in high school and had gained acceptance into a prestigious college in Cambridge, Massachusetts. A few months into his first semester, he was seen at the student mental health clinic for depression, when he had become withdrawn and stopped going to classes. A few weeks later, he was admitted to a private hospital in the outskirts of Boston with florid psychosis in the form of paranoia, hallucinations, and disorganized thinking, suggesting that this diagnosis was first-episode schizophrenia. His positive symptoms remitted completely, but his improvement plateaued otherwise, and he was unable to return to his school because of subtle cognitive problems and negative symptoms. Three months after his psychotic episode, he took an overdose of over-the-counter sleeping pills.

This patient was at high-risk for suicide when he came to understand that schizophrenia might prevent him from pursuing the career he had envisioned. He was probably psychologically ill-prepared for "failure," given his life before schizophrenia. He represents a typical face behind the statistic of 50% lifetime suicide attempts in schizophrenia: he was young, diagnosed with schizophrenia, and he had excellent academic prospects.

The loss of a patient to suicide is usually a devastating event for the family but also for the clinic and the clinicians who were directly involved. After a suicide, it is important to pause and not just move on to business as usual. Reviewing deaths administratively in a clinic and also informally with colleagues is critical to allow to eventually come to terms with this difficult aspect of our job. I always reach out to the family, express my own and the clinic's sadness about the death, and offer help (e.g., referral to support groups or grief counseling) [26].

References

1. Camus A. *Le mythe de Sisyphe*. Paris: Gallimard; 1942.
2. Bleuler E. *Dementia praecox. The group of schizophrenia*. New York: International Universities Press; 1911/1950.
3. Lin JJ, Liang FW, Li CY, Lu TH. Leading causes of death among decedents with mention of schizophrenia on the death certificates in the United States. *Schizophr Res*. 2018;197:116–23.
4. Reininghaus U, Dutta R, Dazzan P, Doody GA, Fearon P, Lappin J, et al. Mortality in schizophrenia and other psychoses: a 10-year follow-up of the SOP first-episode cohort. *Schizophr Bull*. 2015;41:664–73.
5. Schoenbaum M, Sutherland JM, Chappel A, Azrin S, Goldstein AB, Rupp A, et al. Twelve-month health care use and mortality in commercially insured young people with incident psychosis in the United States. *Schizophr Bull*. 2017;43:1262–72.
6. Palmer BA, Pankratz VS, Bostwick JM. The lifetime risk of suicide in schizophrenia: a reexamination. *Arch Gen Psychiatry*. 2005;62:247–53.
7. Dutta R, Murray RM, Hotopf M, Allardyce J, Jones PB, Boydell J. Reassessing the long-term risk of suicide after a first episode of psychosis. *Arch Gen Psychiatry*. 2010;67:1230–7.
8. Nordentoft M, Madsen T, Fedyszyn I. Suicidal behavior and mortality in first-episode psychosis. *J Nerv Ment Dis*. 2015;203:387–92.
9. Talaslahti T, Alanen HM, Hakko H, Isohanni M, Hakkinen U, Leinonen E. Mortality and causes of death in older patients with schizophrenia. *Int J Geriatr Psychiatry*. 2012;27:1131–7.
10. Popovic D, Benabarre A, Crespo JM, Goikolea JM, Gonzalez-Pinto A, Gutierrez-Rojas L, et al. Risk factors for suicide in schizophrenia: systematic review and clinical recommendations. *Acta Psychiatr Scand*. 2014;130:418–26.
11. Franklin JC, Ribeiro JD, Fox KR, Bentley KH, Kleiman EM, Huang X, et al. Risk factors for suicidal thoughts and behaviors: a meta-analysis of 50 years of research. *Psychol Bull*. 2017;143:187–232.
12. Donde C, Vignaud P, Poulet E, Brunelin J, Haesebaert F. Management of depression in patients with schizophrenia spectrum disorders: a critical review of international guidelines. *Acta Psychiatr Scand*. 2018;138:289–99.
13. Shneidman ES. *The suicidal mind*. Oxford: Oxford University Press; 1996.
14. Zisook S, Byrd D, Kuck J, Jeste DV. Command hallucinations in outpatients with schizophrenia. *J Clin Psychiatry*. 1995;56:462–5.
15. Crumlish N, Whitty P, Kamali M, Clarke M, Browne S, McTigue O, et al. Early insight predicts depression and attempted suicide after 4 years in first-episode schizophrenia and schizoaffective disorder. *Acta Psychiatr Scand*. 2005;112:449–55.
16. van Heeringen K, Mann JJ. The neurobiology of suicide. *Lancet Psychiatry*. 2014;1:63–72.
17. Centers for Disease Control. Available from: <https://www.cdc.gov/violenceprevention/suicide/definitions.html>. Accessed 1 July 2019.
18. Freudreich O. The ABCs of suicide. *J Clin Psychiatry*. 2005;66:1194–5.
19. Project TL. Available from: <http://cssrs.columbia.edu/>. Accessed 1 July 2019.
20. Meltzer HY, Alphs L, Green AI, Altamura AC, Anand R, Bertoldi A, et al. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry*. 2003;60:82–91.
21. Rybakowski JK, Vansteelandt K, Szafranski T, Thys E, Jarema M, Wolfgang Fleischhacker W, et al. Treatment of depression in first episode of schizophrenia: results from EUFEST. *Eur Neuropsychopharmacol*. 2012;22:875–82.
22. Zisook S, Kasckow JW, Golshan S, Fellows I, Solorzano E, Lehman D, et al. Citalopram augmentation for subsyndromal symptoms of depression in middle-aged and older outpatients with schizophrenia and schizoaffective disorder: a randomized controlled trial. *J Clin Psychiatry*. 2009;70:562–71.
23. Zisook S, Kasckow JW, Lanouette NM, Golshan S, Fellows I, Vahia I, et al. Augmentation with citalopram for suicidal ideation in middle-aged and older outpatients with schizophrenia

- and schizoaffective disorder who have subthreshold depressive symptoms: a randomized controlled trial. *J Clin Psychiatry*. 2010;71:915–22.
24. Leucht S, Helfer B, Dold M, Kissling W, McGrath JJ. Lithium for schizophrenia. *Cochrane Database Syst Rev*. 2015;(10):CD003834.
 25. Fleche S, Layard R. Do more of those in misery suffer from poverty, unemployment or mental illness? *Kyklos (Oxford)*. 2017;70:27–41.
 26. Gutin NJ. Helping survivors in the aftermath of suicide loss. *Curr Psychiatr Ther*. 2018;17:27–33.

Additional Resources

Websites

- <http://www.ucalgary.ca/cdss> – The CDSS is available at this website. The University of Calgary has a very active schizophrenia research program, and the CDSS comes out of its Department of Psychiatry.
- <http://www.suicidology.org> – The website of the American Association of Suicidology. A good starting point for more information. This site has a large number of links to other organizations and resources related to suicide.
- <https://www.cdc.gov/injury/index.html> – The Centers for Disease Control's website that contains up-to-date statistics about suicide and terminology (e.g., what should be called a suicide attempt).
- <http://cssrs.columbia.edu/> – Extensive materials about the Columbia Scale.

Chapter 31

Illness Insight and Antipsychotic Medication Adherence



Essential Concepts

- Insight into illness is neither necessary nor sufficient for adherence to medications.
- Illness insight is not a simple, all-or-nothing concept but is multidimensional: awareness of symptoms, acknowledgment of illness, and acceptance of need for treatment.
- Some patients have an anosognosia-like neurological deficit in recognizing that they are psychiatrically ill and could benefit from psychiatric treatment.
- The health belief model posits that patients who judge themselves at risk for a disease weigh the risks, benefits, and costs of intervening medically. Importantly, this calculation is made *from the patient's point of view*, not yours.
- Effectiveness of medicine is driven by its efficacy; nobody likes to take ineffective or marginally effective medications, particularly if there are many side effects.
- To assess antipsychotic medication adherence, you need to assess both (drug) attitude and (compliance) behavior. Drug attitude sums up a patient's subjective risk-benefit assessment of a medication. A good drug attitude predicts adherence unless there are barriers like cost.
- Both patients and their physicians confidently overestimate the degree of antipsychotic adherence; be aware of this bias and use collateral and objective information about actual adherence.
- Adherence-enhancing interventions can be grouped into universal (applied to all patients, regardless of risk), selective (applied to those at risk of non-adherence), and indicated (applied to those not taking antipsychotics). The choice of your interventions is also determined if nonadherence is intentional or inadvertent.

“The desire to take medicine is perhaps the greatest feature which distinguishes man from animals.” [1]

– Sir William Osler, father of modern medicine, 1849–1919

Poor adherence to potentially quite effective medications is not a specific problem for psychiatry but a challenge for all of medicine, particular for chronic conditions [2]. Apparently, the great Osler had it wrong. Nonadherence to antipsychotics is a clinical problem in at least 50% of all patients with schizophrenia [3]. In one study that followed patients after hospital discharge, only about 20% of patients had persisted with taking medications after 6 months [4]. First-episode patients who have much to lose from poor adherence often stop medications as early as immediately after hospital discharge [5]. Nonadherence is not limited to antipsychotics but extends to medications to manage chronic medical conditions such as antihypertensive medications [6]. In schizophrenia, adherence to antipsychotics is one of the most important determinants of prognosis. Recognizing medication adherence problems and identifying reasons for nonadherence are therefore important considerations in the treatment of patients with schizophrenia. Note that “adherence” is now generally preferred over the older, more paternalistic term “compliance.”

Families frequently ask for “more therapy” for a nonadherent family member, revealing two incorrect assumptions about the connection between insight and adherence: (1) that insight is necessary and sufficient for adherence and (2) that insight is a function of the amount of treatment provided (and hence can increase if only enough treatment is given). Unfortunately, insight does not necessarily translate into adherence; and lack of insight sides comfortably with excellent adherence. I will discuss insight and adherence in two separate sections in order to not conflate them, like families often do.

Key Point

“Lack of insight” poses one of the biggest obstacles to the treatment of schizophrenia. However, the reverse is not correct: a good understanding of one’s illness and the proposed treatment is neither necessary nor sufficient for anyone to take medications.

Insight into Illness

Clinicians who treat patients with schizophrenia are well aware of the vexing clinical problem of “lack of insight” in schizophrenia. “Lack of insight” has many clinical facets. Patients insist on delusional ideas despite evidence to the contrary; they may be unaware of abnormal movements like tardive dyskinesia [7]; and they can show a striking unawareness how they get across in social situations (deficits in comportment). In a seminal World Health Organization (WHO) study of schizophrenia, a key finding was that “lack of insight” was the most useful clinical feature

in distinguishing schizophrenia from other mental disorders [8]. Consequently, much work has been dedicated to better understand the nature of this lack of insight. Clearly, insight into illness is not the simple shorthand “patient has no insight” that psychiatrists sometimes use to describe patients, particularly patients who disagree with treatment recommendations, which usually means not wanting to take an antipsychotic. Some patients might very well agree with you that they suffer from a mental illness and that they have symptoms, but they do not see medications as the solution. The acceptance of need for treatment and type of treatment, in particular, is shaped by cultural expectations and a person’s Weltanschauung (German for world view).

The most eloquent, clinical definition of “insight” comes from Sir Aubrey Lewis. He defined insight as “a correct attitude toward a morbid change in oneself” [9]. Lewis’ definition is, however, epistemologically problematic as it treats lack of insight as an objective phenomenon (i.e., there is a “correct” attitude). A different view of insight emphasizes the subjective aspect of insight and the psychological process of creating a narrative in exchange with an audience [10]. Another approach breaks down insight into several dimensions [11]:

- *Awareness of symptoms* – ability to recognize inner experiences or observations as abnormal
- *Acknowledgment of illness* – ability to see oneself as suffering from an illness
- *Acceptance of need for treatment* – ability to acknowledge that treatment could be useful, particularly to prevent relapse

The multidimensional approach has the advantage that it is practical and can be applied to patient care, without getting bogged down in concerns about ontology and epistemology.

Tip

To assess insight as it relates to taking antipsychotics, I focus on acknowledgment of illness and need for treatment: “Do you have any mental health problems? Do you need any treatment for mental health problems? Do your medications do you any good?” (Adapted from the Insight into Treatment Attitude Questionnaire, or ITAQ, developed by Dr. Joseph McEvoy [12].)

An important question is whether you can improve insight into illness. Some would say that psychosis (particularly delusions) by definition has an element of lack of insight built into the definition. However, patients who are just relapsing or patients in the prodrome of schizophrenia are often able to recognize that something is wrong (abnormal perceptions or attenuated psychosis) and seem have at least partial insight. Some patients are aware that “they are losing it.” Allowing for doubt into the veracity of one’s experiences and observations is also the basis for cognitive-behavioral therapy for psychosis. Unfortunately, this capacity to self-observe and

reflect gets lost once patients develop full-blown psychosis or mania. Unpleasant affect like depression adds to the ability to have insight, akin to pain as a warning that something is wrong [13]. That said, clinicians are familiar with a group of patients who seem fundamentally unable to critically examine their experiences. This inability to recognize themselves as somebody with symptoms (suggesting an illness) has been compared to the anosognosia of neurology [14]. Such a neurological deficit would be akin to neglect syndromes or the unawareness about their illness that Alzheimer's patients in later disease phases show. Some studies suggest that lack of insight is not just a metaphor but a true neuropsychiatric deficit [15] that you would not expect to be remedied by talking. However, in some patients, “denial” as a psychological mechanism is probably operative [16], where ongoing conversation can lead to improved insight. The trick of course is to not confuse one with the other, and accept that both (and other views about what insight is and how we create it) are not mutually exclusive.

I find it helpful to view insight into having a serious psychiatric disorder as something that has to be learned (“constructed”), often painfully, through trial and error (and often not entirely voluntary [17]), a view consistent with the narrative view of insight. Psychologically, some “Leidensdruck” (a German word describing the sense of being compelled to act to alleviate suffering) may be necessary for initiating the process of trying a medicine to learn how it may help [13]. Leidensdruck may be overwhelming affects or a more cognitive appraisal that things are not going well. Manic patients lack insight into the need to change anything or take medications because there is no Leidensdruck, quite the contrary.

Medication Adherence

It is the rare patient who in fact “nonadherent” to all aspects of treatment. I treat patients who see me regularly for their appointments but just do not want to take antipsychotics. Others miss their appointments regularly but always call on time to have their medications refilled by the pharmacy. Thus, be clear what you mean if you describe somebody as “nonadherent.” For this chapter, the emphasis will be on antipsychotic medication adherence.

Reasons for Poor Medication Adherence

There is only one way to adhere 100% to medications but 100 reasons for not adhering well. Table 31.1 lists common risk factors for poor antipsychotic adherence.

Often, you will be able to identify one main obstacle to better adherence. I suggest you look at three key determinants of nonadherence: healthcare access problems, neuropsychiatric and cognitive deficits, and health belief models [18].

Table 31.1 Factors that contribute to poor antipsychotic adherence

Poor symptom control ^a
Medication side effects
Complicated medication regimen
Impaired judgment and insight
Substance use
Real-life, pragmatic problems (money, transportation)
Stigma associated with schizophrenia
Poor therapeutic alliance
Wishful thinking

^aPoor medication efficacy is a major obstacle to adherence. Patients who perceive benefit from medication are more willing to take them

Healthcare Access Problems

Start with the obvious: an important group of patients takes less medication than prescribed not because of ill will but because the patients have no money or because they could not get transportation or for a host of other real-life reasons. Healthcare is simply not the most important of their many pressing needs. It makes no sense to give patients a prescription they cannot afford. Simply ask, “Can you get this prescription filled today?” Inpatient teams bear some responsibility to assure that a medication started in the hospital will be covered on the outpatient side.

Neuropsychiatric and Cognitive Deficits

Cognitive psychologists differentiate between competence and performance: competence is the potential ability to do something; performance refers to the actual behaviors. Competence is the prerequisite for good performance. Hence, make sure that your patient is not too impaired (i.e., has the competence) to actually implement your recommendations. You need to take into account education and ability to think in abstract terms when you explain your plan. Anticipate problems and recognize that your patient might not be able to problem-solve flexibly. An example would be to receive a different looking medication than what he is used to because of a change in medication supplier. Problems in the cognitive realm should become obvious when you ask the patient to repeat your medication plan: “Tell me again, how are you going to take the medications?”

Health Belief Model

Key Point

According to the health belief model, patients weigh the perceived benefits of treatment with the perceived risks and costs of treatment, taking into account perceived vulnerability for the condition in question [19]. Not that it is risks, costs, and benefits *from the patient's point of view*, not yours.

One prediction from the health belief model is that patients will discontinue medications that they perceive as not working, that seem to have too many side effects compared to the benefits, or that are not deemed necessary to begin with. Note that it is the balance of efficacy and side effects not simply lack of side effects that determines adherence in this model: patients with cancer risk dying from their treatment because of the possible benefit. Quality of life concerns are often in opposition to efficacy considerations, particularly during maintenance treatment when patients have to decide if the present side effect burden is worth the theoretical relapse risk [20]. A second prediction from the health belief model is that a patient's viewpoint can run counter to society's views: a psychotic patient rejects treatment for fear of side effects, even though society can feel compelled to involuntarily treat or confine the patient for reasons of safety. Some patients are better viewed as holding "dysfunctional health beliefs" than having "no insight" [21]. You can address dysfunctional health beliefs by providing information and education in order to have patients reconsider their stance.

Assessment of Medication Adherence

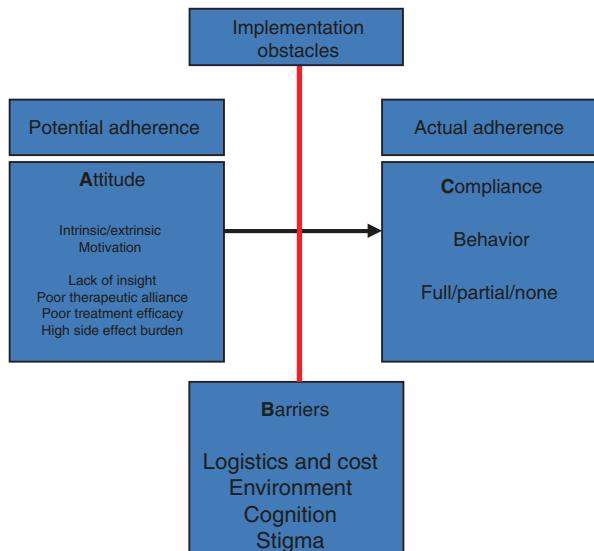
In order to use medications optimally, you need to understand which medications are taken and if they are taken as prescribed (and the reasons for any deviation from the treatment plan). A careful assessment of medication adherence is a critically important task for any patient you are prescribing medications for [22]. Medication reconciliation often stops at a mere listing of the prescribed medications, without trying to gauge how much is actually taken. Studies have shown that psychiatrists routinely overestimate how much of their medications patients are taking (a typical case of "we are all above average") [23]. Interestingly, patients similarly confidently overestimate their degree of adherence; I think this an honest overestimation, not an attempt to deceive. Be aware of this bias.

Medication adherence is both an attitude and a behavior, and you need to assess both [22]. Without some modicum of motivation to take medications (i.e., a positive drug attitude), adherence is very unlikely. On the other hand, motivation alone does not guarantee that medications are actually taken; barrier can interfere in linking the attitude with the desired behavior. Figure 31.1 depicts this relationship graphically.

To arrive at a good clinical estimate of medication adherence, use the ABCs to assess three variables: A for attitude, B for barriers, and C for compliance by asking three questions:

1. What is my patient's *attitude* toward antipsychotics?
2. Are there *barriers* for a motivated patient to implement optimal adherence?
3. What is my best quantitative estimate of actual *compliance* behavior?

Fig. 31.1 The ABCs of estimating adherence to antipsychotics: attitude, barriers, and compliance behavior. (Based on reference [24])



The A: Professed Drug Attitude

A drug attitude is positive if a medication is perceived as warranted, effective, and tolerable. Drug attitude is powerful in its ability to predict antipsychotic effectiveness [25]. Find out about patients motivations for considering medications and past experiences, both positive and negative. Is the motivation intrinsic or extrinsic (the court, a nagging mother)? A positive drug attitude does not mean that patients are taking medications for the “right” reasons (e.g., a maintenance antipsychotic for insomnia). Since having a good drug attitude (which in turn is influenced by a world view and health beliefs regarding psychiatric illness and treatment) is a critical basis for potentially taking medications, you can make an educated guess about potential threats to adherence using a prototype approach (see Table 31.2) [26]. The “true believer,” for example, is a patient who takes antipsychotics because he agrees with your biomedical explanation for his problems (a diagnosis of schizophrenia) and the treatment (the taking of an antipsychotic). The “clinic trooper” is a patient who never missed his clinic appointment; he does not question his illness and treatment for which he has some understanding although not as sophisticated as the true believer and often more concrete (e.g., taking medications for sleep). On the other end of the spectrum, there is the psychotic “constitutional combatant” with “no insight” into his predicament, who is unable to reason other than about his right to refuse treatment which he pursues relentlessly. A more pleasant variant (once admitted to the hospital and after some initial treatment) is the “coffee guy” whose chief complaint for yet another state hospital admission is “I just came for coffee.” Such

Table 31.2 Adherence prototypes

	Drug attitude	World view	Possible adherence threats
True believer	Good	Biomedical	Lack of efficacy “Pill fatigue”
Clinic trooper	Good	Idiosyncratic	Complacency Mistakes
Reluctant recruit	Ambivalent	Unformed/ambivalent	Poor efficacy Unacceptable side effects
“The coffee guy” ^a	Indifferent/lip service	Not verbalized/uninterested	Lack of supervision
Constitutional combatant	Negative to hostile	Incompatible with biomedical model	No alliance

Based on [26]

^aNamed in honor of a patient I knew with repeat state hospital admission, always committed and brought in by police and causing a ruckus, having as his chief complaint the next morning, “I just came for coffee”

patients have no good explanation why police were called to bring them in. Many patients are in the “reluctant recruit” group; they are still learning about their illness and its treatments. They did not choose to be recruited to patienthood. This is the natural starting point for patients at the beginning of their illness.

The B: Barriers to Adherence

Even motivated patients may have poor adherence if there are barriers (financial, family members who are against medications, chaotic life) that prevent the implementation of taking pills regularly. Get a comprehensive understanding of the obstacles to better adherence. Note that there is not a necessarily overlap between what physicians and what patients view as important factors regarding poor adherence [27].

The C: Actual Compliance Behavior

There is no gold standard for assessing actual medication adherence; each method can be subverted, if so desired. I use a combination of the following more or less objective measures to estimate adherence in my patients [28]:

- Directly ask patients to estimate their degree of compliance, for example, “Of the last 5 days, how many days have you missed your pills?” Find out details about how medications are taken (when, where, are there routines to help them remember).
- Call the pharmacy and see if there are obvious gaps in refilling medications (technically called the medication possession ratio), reflecting the number of

days that a patient even has pills [18] available to be taken (based on the number of pills picked up from the pharmacy and the time interval they are supposed to cover [29]).

- Check antipsychotic serum levels (see Chap. 20, Therapeutic Drug Monitoring).
- Have patients keep a medication log and bring in pills for direct count.
- Estimate a patient's cognitive competence regarding a regular behavior such as taking medications daily. Are there routines?
- Ask other people about their views of the patient's compliance.

Using the above methods you should be able to estimate a patient's level of adherence (e.g. almost 100%, partial 20%–80%, less than 20%). For clinical purposes, 80% adherence is probably sufficient for many patients although the best minimally sufficient level of adherence is not known and hinges on individual factors. In a study that used pharmacy and medical claims data, rehospitalization was predicted in a dose-dependent manner by the degree of partial nonadherence [30]. Some individuals may require close to 100% adherence to avoid relapse (e.g., the lower a maintenance dose, the more magnified partial adherence becomes). In first-episode patients, even brief periods of nonadherence are associated with more symptoms and an increased relapse risk [31]. As noted earlier, patients might be taking only some of their medications and honestly think they are doing a good job. This can have unintended consequences since both you and the patient operate under the assumptions that the medication is taken but not working. Typical results of partial adherence are unnecessarily high medication doses and polypharmacy ("advanced psychopharmacology").

Tip

Do not overlook partial adherence. Consider partial adherence in any patient whose symptoms are poorly controlled. Each visit, estimate adherence by asking: "In the last 5 days, how many pills have you missed?" This question makes it concrete and opens the door for further discussion if the answer is anything but "none."

Optimizing Medication Adherence

The exact intervention to increase medication adherence hinges on the problem: the most effective solution hinges on the reason for nonadherence. A public health prevention model for adherence-enhancing interventions that I find conceptually useful distinguishes between universal (applied to all patients, regardless of risk), selective (applied to those at risk of nonadherence), and indicated (applied to those not taking antipsychotics) interventions [32].

Below are some general (universal) principles to promote medication adherence:

- Most importantly, focus on patient goals; the medication needs to represent something of value to the patient. For concrete thinkers, the benefit can be con-

crete, such as staying out of the hospital. If patients are unable to identify a reason they should take their medications, they are unlikely to take them.

- Give patients a positive drug experience, if possible – put differently, avoid aversive conditioning, for example, an acute dystonic reaction, and do not ignore distressing nonpsychotic symptoms. You have probably more success in improving a patient's drug attitude via a good clinical experience than his global “insight” [33].
- Simple regimens are almost always better. Find once-a-day regimens. Avoid confusing dose regimens (e.g., different doses of the same medicine). Work under the assumption that complexity increases the likelihood of error.
- Use psychoeducation to provide one explanatory model (i.e., your model which is usually the biomedical model, to the extent that it makes sense). Allow a parallel patient model (stress model) that might be equally valid. Psychoeducation has to be tailored to the patient's education.
- Offer long-acting injectable antipsychotics unless not indicated (see Chap. 20). While not a panacea, LAIs provide information about real adherence and take the guessing out of the game.

Environmental supports (e.g., pill box, automatic refills, digital medicine) work best if there is some cognitive impairment and nonadherence is unintentional [34]. If nonadherence is intentional, direct supervision is necessary. In addition, various forms of leverage (e.g., representative payee, housing) are used to improve adherence for this group of patients [35], often without much reflection about the coercive nature of the interventions [36]. Finally, do not prescribe surreptitiously to patients with schizophrenia. Some families will ask you. You misuse your powers and risk irreparable breach of trust not just in you but in any form of psychiatric treatment [37].

Specific corrective actions to mitigate nonadherence, making a distinction between intended and unintended nonadherence, are summarized in Table 31.3 [38].

Table 31.3 Remedies for nonadherence to antipsychotic medications in schizophrenia patients

Risk factors ^a	Intervention ^b
<i>For intended nonadherence</i>	
Poor therapeutic alliance	Optimize overall care experience Minimize perceived coercion
Negative drug attitude	Persist in trying to achieve good efficacy Increase “subjective well-being under neuroleptics
Poor insight ^c	Consider long-acting antipsychotics (LAIs) Consider directly observed therapy (DOT) ^d Incentivize taking antipsychotics (e.g., financial) Use motivation interviewing principles
<i>For unintended nonadherence</i>	
Cognitive difficulties	Consider long-acting antipsychotics (LAIs) Enlist support (e.g., visiting nurses, family members)

Table based on Ref. [38]

^aRisk factors are not mutually exclusive

^bThe interventions are not specific for just one risk factor

^cIn some patients, insight per se may not be amenable to change

^dDOT is used in medicine for HIV care or tuberculosis treatment. Consider enlisting the help of visiting nurses for DOT

Last, never give up. I follow patients even if they do not take antipsychotics. Some patients need time and your support over many years. Eventually, some come around and will try an antipsychotic. Following them even when nonadherent gives them a sense of regaining some control over their lives and can strengthen the alliance. However, acknowledge when voluntary treatment is not working, when insight in some form is not forthcoming, and when involuntary treatment becomes necessary (see next chapter). This group of patients that rejects antipsychotics in situations where most would consider them critical is challenging for clinicians and particularly families. Consult the two books in the Additional Resources section for more help with this group.

References

1. Wikiquote. William Osler. Available from: https://en.wikiquote.org/wiki/William_Osler. Accessed on 7/1/2019.
2. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med.* 2005;353:487–97.
3. Lacro JP, Dunn LB, Dolder CR, Leckband SG, Jeste DV. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. *J Clin Psychiatry.* 2002;63:892–909.
4. Misdrahi D, Tessier A, Husky M, Lange AC, Vrijens B, Llorca PM, et al. Evaluation of adherence patterns in schizophrenia using electronic monitoring (MEMS(R)): a six-month post-discharge prospective study. *Schizophr Res.* 2018;193:114–8.
5. Tiihonen J, Haukka J, Taylor M, Haddad PM, Patel MX, Korhonen P. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. *Am J Psychiatry.* 2011;168:603–9.
6. Dolder CR, Furtek K, Lacro JP, Jeste DV. Antihypertensive medication adherence and blood pressure control in patients with psychotic disorders compared to persons without psychiatric illness. *Psychosomatics.* 2005;46:135–41.
7. Emsley R, Niehaus DJ, Oosthuizen PP, Koen L, Chiliza B, Fincham D. Subjective awareness of tardive dyskinesia and insight in schizophrenia. *Eur Psychiatry.* 2011;26:293–6.
8. World Health Organization. Report of the international pilot study of schizophrenia. Geneva: WHO; 1973.
9. Lewis AJ. The psychopathology of insight. *Br J Med Psychol.* 1934;14:332–48.
10. Tranulis CS, Freudenreich O, Park L. Narrative insight: rethinking insight in psychosis. *Int J Cult Ment Health.* 2009;2:16–28.
11. David AS. Insight and psychosis. *Br J Psychiatry.* 1990;156:798–808.
12. McEvoy JP, Apperson LJ, Appelbaum PS, Ortlip P, Brecosky J, Hammill K, et al. Insight in schizophrenia. Its relationship to acute psychopathology. *J Nerv Ment Dis.* 1989;177:43–7.
13. Freudenreich O, Deckersbach T, Goff DC. Insight into current symptoms of schizophrenia. Association with frontal cortical function and affect. *Acta Psychiatr Scand.* 2004;110:14–20.
14. Arango C, Amador X. Lessons learned about poor insight. *Schizophr Bull.* 2011;37:27–8.
15. Nair A, Palmer EC, Aleman A, David AS. Relationship between cognition, clinical and cognitive insight in psychotic disorders: a review and meta-analysis. *Schizophr Res.* 2014;152:191–200.
16. Cooke MA, Peters ER, Kuipers E, Kumari V. Disease, deficit or denial? Models of poor insight in psychosis. *Acta Psychiatr Scand.* 2005;112:4–17.
17. Tranulis C, Goff D, Henderson DC, Freudenreich O. Becoming adherent to antipsychotics: a qualitative study of treatment-experienced schizophrenia patients. *Psychiatr Serv.* 2011;62:888–92.

18. Perkins DO. Predictors of noncompliance in patients with schizophrenia. *J Clin Psychiatry*. 2002;63:1121–8.
19. Jones CJ, Smith H, Llewellyn C. Evaluating the effectiveness of health belief model interventions in improving adherence: a systematic review. *Health Psychol Rev*. 2014;8:253–69.
20. Staring AB, Mulder CL, Duivenvoorden HJ, De Haan L, Van der Gaag M. Fewer symptoms vs. more side-effects in schizophrenia? Opposing pathways between antipsychotic medication compliance and quality of life. *Schizophr Res*. 2009;113:27–33.
21. Linden M, Godemann F. The differentiation between ‘lack of insight’ and ‘dysfunctional health beliefs’ in schizophrenia. *Psychopathology*. 2007;40:236–41.
22. Velligan DI, Weiden PJ, Sajatovic M, Scott J, Carpenter D, Ross R, et al. The expert consensus guideline series: adherence problems in patients with serious and persistent mental illness. *J Clin Psychiatry*. 2009;70(Suppl 4):1–46.
23. Byerly M, Fisher R, Whatley K, Holland R, Varghese F, Carmody T, et al. A comparison of electronic monitoring vs. clinician rating of antipsychotic adherence in outpatients with schizophrenia. *Psychiatry Res*. 2005;133:129–33.
24. Freudenberg O, Kontos N, Querques J. The ABCs of estimating adherence to antipsychotics [Pearls series]. *Curr Psychiatr Ther*. 2011;10:90.
25. Gaebel W, Riesbeck M, von Wilmsdorff M, Burns T, Derk EM, Kahn RS, et al. Drug attitude as predictor for effectiveness in first-episode schizophrenia: results of an open randomized trial (EUFEST). *Eur Neuropsychopharmacol*. 2010;20:310–6.
26. Freudenberg O, Tranulis C. A prototype approach toward antipsychotic medication adherence in schizophrenia. *Harv Rev Psychiatry*. 2009;17:35–40.
27. Pyne JM, McSweeney J, Kane HS, Harvey S, Bragg L, Fischer E. Agreement between patients with schizophrenia and providers on factors of antipsychotic medication adherence. *Psychiatr Serv*. 2006;57:1170–8.
28. Sajatovic M, Velligan DI, Weiden PJ, Valenstein MA, Ogedegbe G. Measurement of psychiatric treatment adherence. *J Psychosom Res*. 2010;69:591–9.
29. Sperber CM, Samarasinghe SR, Lomax GP. An upper and lower bound of the medication possession ratio. *Patient Prefer Adherence*. 2017;11:1469–78.
30. Weiden PJ, Kozma C, Grogg A, Locklear J. Partial compliance and risk of rehospitalization among California Medicaid patients with schizophrenia. *Psychiatr Serv*. 2004;55:886–91.
31. Subotnik KL, Nuechterlein KH, Ventura J, Gitlin MJ, Marder S, Mintz J, et al. Risperidone nonadherence and return of positive symptoms in the early course of schizophrenia. *Am J Psychiatry*. 2011;168:286–92.
32. Velligan D, Sajatovic M, Valenstein M, Riley WT, Safren SA, Lewis-Fernandez R, et al. Methodological challenges in psychiatric treatment adherence research. *Clin Schizophr Relat Psychoses*. 2010;4:74–91.
33. Beck EM, Cavelti M, Kvrgic S, Kleim B, Vauth R. Are we addressing the ‘right stuff’ to enhance adherence in schizophrenia? Understanding the role of insight and attitudes towards medication. *Schizophr Res*. 2011;132:42–9.
34. Velligan DI, Diamond P, Mueller J, Li X, Maples N, Wang M, et al. The short-term impact of generic versus individualized environmental supports on functional outcomes and target behaviors in schizophrenia. *Psychiatry Res*. 2009;168:94–101.
35. Monahan J, Redlich AD, Swanson J, Robbins PC, Appelbaum PS, Petrilia J, et al. Use of leverage to improve adherence to psychiatric treatment in the community. *Psychiatr Serv*. 2005;56:37–44.
36. Zigmund T. Pressures to adhere to treatment: observations on ‘leverage’ in English mental healthcare. *Br J Psychiatry*. 2011;199:90–1.
37. Whitty P, Devitt P. Surreptitious prescribing in psychiatric practice. *Psychiatr Serv*. 2005;56:481–3.
38. Freudenberg O, Cather C. Antipsychotic medication nonadherence: risk factors and remedies. *Focus*. 2012;10:124–9.

Additional Resources

Books

Amador XF. I'm not sick, I don't need help. 10th ed. Peconic: Vida Press; 2010. – The first book (first published in 2000) that tried to provide guidance about how to tackle the vexing issue of treatment refusal as a result of impaired insight. (Amador suggested the anosognosia analogy for lack of insight in schizophrenia).

Komrad MS. You need help!: a step-by-step plan to convince a loved one to get counseling. Center City: Hazelden Foundation; 2012. – Another book that provides pragmatic advice about how to engage and nudge help-rejecting patients towards psychiatric treatment.

Article

Freudenreich O, Tranulis C. A prototype approach toward antipsychotic medication adherence in schizophrenia. Harv Rev Psychiatry. 2009;17:35–40. – If you are interested in more details about the prototype approach towards understanding medication adherence.

Velligan DI, Weiden PJ, Sajatovic M, Scott J, Carpenter D, Ross R, et al. The expert consensus guideline series: adherence problems in patients with serious and persistent mental illness. J Clin Psychiatry. 2009;70(Suppl 4):1–46. A good summary of adherence, its assessment, and its remedies, from the Consensus Guideline series.

Chapter 32

Social Aspects of Schizophrenia Care



Essential Concepts

- You cannot practice medicine without considering the impact of social adversity like poverty or homelessness on illness. Social determinants of health (SDOH) matter for all aspects of disease (causation, propagation, recovery).
- Some health outcomes of schizophrenia are explained by social factors and are not due to schizophrenia per se.
- A significant minority (25%) of the homeless population in the United States have schizophrenia.
- Social institutions and structures including laws (written and unwritten) can be set up in a way that they cause “structural violence” to some groups. Drug laws that preferentially target one group are an example.
- A psychosocial history needs to inquire about social adversity, trauma, legal problems, education and work history, immigration history, and available resources (financial, social support). The experience of racism represents chronic social stress, with biological (allosteric load) and psychological (identity formation) ramifications.
- Professionalism requires some form of advocacy for equitable care and social justice.
- Patients with a stigmatizing illness like schizophrenia suffer from both the illness and *the reaction that people have to the illness*.
- Various attempts to destigmatize schizophrenia have not had the hoped for benefit (name change) and at times even backfired (emphasizing biogenetic causation that depicts schizophrenia as a brain disease).
- Many patients with schizophrenia are profoundly lonely due to illness (negative symptoms) but also because of social exclusion (stigma).

“Une manière commode de faire la connaissance d’une ville est de chercher comment on y traînalee, comment on y aime et comment on y meurt.”

(Perhaps the easiest way of making a town’s acquaintance is to ascertain how the people in it work, how they love, and how they die.)

– Albert Camus (1913–1960), *The Plague*.

A useful distinction can be made between the sociology *in* psychiatry and the sociology *of* psychiatry. The sociology *in* psychiatry concerns itself with the impact (either causative or modifying) of social factors on disease (e.g., the role of anomie in suicide, the role of immigration on schizophrenia risk, the role of family stress on relapse risk, the effects of class and race on health). The sociology *of* psychiatry examines psychiatry’s role in societies, particularly with regard to social control of “deviance” (e.g., the effects of getting a stigmatizing disease label; the parameters for involuntary treatment; the function of the state hospital as a “total institution,” a term coined by Erving Goffman [1]). Many sociologic aspects of care are discussed already throughout this book. In this chapter, I focus on social adversity and stigma.

Social Adversity

According to the World Health Organization, the social determinants of health (SDOH) are “the circumstances in which people are born, grow up, live, work and age, and the systems put in place to deal with illness.” And further, “these circumstances are in turn shaped by a wider set of forces: economics, social policies, and politics.” In other words, the social determinants of health are shaped by how a society organizes itself, reflecting power and values in a society. Those are large forces that impinge on all of us, including our patients.

The social consequences of *having* schizophrenia are rather significant and lead to much social adversity. Schizophrenia puts you at an economic disadvantage, and many patients experience a downward social drift into unemployment and poverty (social selection theory) [2]. A significant minority of the homeless population has schizophrenia, perhaps as many as 25% [3]. While substance use and nonadherence are contributing factors, the lack of affordable housing plays a large role [4]. Simply providing housing, with no preconditions (housing first), is a successful intervention to house patients with serious mental illness [5]. Some level of support *enhances* autonomy if it prevents a patient from becoming homeless again (e.g., helping a patient with executive dysfunction pay the rent; arranging for a visiting nurse to assist with medications).

While “schizophrenia” may independently work against patients, poverty and minority status (e.g., being a person of color) alone correlate with many observations in patients with schizophrenia (e.g., increased cancer mortality [6] or smoking [7]). Surviving breast cancer, for example, is tightly connected to ethnicity and income [8]. In a just society, surviving cancer ought not to depend on your cultural background or your “net worth.”

Tip

Bad economic conditions (in other words, poverty) are real for many of your patients. Try to understand the barriers that poverty or living in a shelter puts up for each patient, particularly with regard to practical issues that relate to your treatment efforts, like adherence.

One caveat: even though poverty or unemployment are a significant source of discontent related to social determinants of health, much misery stems from having a serious mental illness [9]. Symptoms of anxiety and depression are distressing, and an awareness of the real cost of having schizophrenia is demoralizing. Not all mental suffering is explained by the social determinants of health.

Structural Violence

It is impossible to practice medicine without acknowledging the social realities of patients. Paul Farmer, an infectious disease specialist who has spent most of his career traveling between Harvard and Haiti to bring modern medicine to rural Haiti, has stressed the importance of biosocial causation of illness [10]. It is not possible to isolate an illness and study its “natural course” without considering how people ended up in harm’s way, their access to care, and their adherence to treatment. The natural illness course is an abstraction. Farmer uses the term “structural violence” (a term coined by Johan Galtung and by liberation theologians in the 1960s to denote social structures that impede humans from reaching their potential) to emphasize the pernicious effects of adverse social conditions on clinical outcomes [11]. The “natural” history of tuberculosis varies greatly, depending on where and how you contract the bacterium and what kind of treatment you get. Similarly, the “natural” history of schizophrenia will be difficult to understand if social and sociocultural factors (e.g., society’s view of autonomy) are ignored.

Tip

Develop some “structural competence:” begin to appreciate and spot how some patients are hemmed in and systematically disadvantaged by the structures (e.g., clinic rules, eligibility for treatment) that we have set up [12].

A blatant example of structural violence would be a system of care that shifts people either to psychiatric care or to the correctional setting, depending on your ability to pay. A more subtle example of invisible structures is the ward rules that govern (punish) behaviors on inpatient units.

Social Advocacy

The social needs for our patients can sometimes be overwhelming and instill a sense of powerlessness. Advocacy is an activity that is empowering and can take different forms. True, improving “the system” so access to care is equitable and resources are allocated fairly would have the biggest impact for the most number of people. However, small acts of advocacy directed at the patient in front of you (writing a letter of support for an agency, prolonging a hospitalization to set up a realistic treatment plan) can go a long way for *that* patient. While not every physician went into medicine to become a social justice crusader, professionalism requires some engagement for equitable care and social justice [13].

Key Point

A problem without a solution is not a need for psychiatry¹. However, many intractable social problems like poverty and homelessness are exactly the problems that your patients struggle with and that have an impact on management and prognosis. Advocacy to improve health disparities falls within a physician’s professional obligation.

Assessment

In addition to obvious social determinants of health (poverty or homeless), understanding your patient’s social background (upbringing, educational achievements, work history, social standings) is a necessary part of your psychiatric assessment as your treatment recommendations will need to be socioculturally appropriate and practically feasible. Many patients seen in medical settings have experienced trauma in their lives. For many, growing up was a never-ending series of traumatic events; they never had an “average expectable upbringing.” Childhood trauma in its many variations (including sexual trauma) is increasingly recognized as an environmental risk factor for schizophrenia [14], so inquire about it, in a sensitive way. Some patients with schizophrenia may have the so-called syndemic conditions (e.g., trauma and HIV) that lead to poor clinical outcomes unless both are recognized and addressed [15].

Depending on where you practice, you will have a significant number of patients whose parents immigrated to the United States or who themselves are immigrants. Cultural humility (which is a better term than “cultural competence”) is a needed curious and non-judgmental attitude to engage patients from different cultural backgrounds successfully [16]. First-generation immigrants are at higher risk for schizophrenia, probably related to social stress from the experience of prejudice and discrimination [17].

¹Norman Sartorius during Grand Rounds at Cambridge Hospital, Cambridge, Massachusetts, in 2006.

Table 32.1 Assessment of psychosocial history

History of social adversity (minority experience, homelessness, poverty)
Trauma history
Legal history
Education and work history (social status)
Immigration history
Resources (financial, social support)

You do not have to be an immigrant to experience exclusion and racism. African Americans continue to be treated as second-class citizens, often regardless of social status achieved [18]. Racism is chronically stressful and goes under the skin: it has biological effects on inflammatory markers, for example [19], which may account for some racial disparities seen in health care (e.g., lower birth weight risk or higher diabetes risk in minority populations). But chronic social stress related to your position in an invisible hierarchy also has psychological ramifications. Do not underestimate the cumulative effects on the development of identity and a worldview from repeated assaults on your worth from microaggressions (a term coined by the Massachusetts General Hospital psychiatrist Chester M. Pierce) – the daily indignities, not always on purpose, when you are permanently reminded that you are different and not as worthy [20]. Be sensitive about the long shadow of history (see the Tuskegee syphilis experiment) [21] when black minority patients appear suspicious, and help rejection, even if you believe you are doing nothing wrong and consider yourself squarely in the enlightenment camp. Table 32.1 lists components of the psychosocial history

Stigma

It is a myth that “schizophrenia is an illness like any other.” If it were, patients would not have to decide whom they are going to tell about it. Schizophrenia remains a highly stigmatizing condition; being afflicted with it leaves the sufferer with a “mark or token of infamy, disgrace, or reproach.” Stigma is a powerful psychological force and societal reality for patients with mental disorders, including schizophrenia. The pervasive emotion attached to stigma is shame leading patients to deny illness, hide symptoms from others, and refuse to seek care. Shame can be pervasive in families themselves; you can see this in families in which a positive family history of psychotic illness might never be acknowledged.

Key Point

Schizophrenia is not “an illness like any other” as anti-stigma campaigns may claim. This slogan is propaganda. In contrast to other illness, patients with stigmatizing illnesses like schizophrenia have to face the disease itself and in addition their own and society’s reactions to having the disease. Reactions include shame on the inside with reluctance to seek help and prejudice and rejection coming from outside leading to social exclusion.

Stigma leads to social exclusion from full community participation and loss of opportunity. Unemployment is but one form of social exclusion, and patient often do not vote, do not go to church anymore, etc. A vicious cycle is set into motion since unemployment leads to poverty, which limits opportunities many of us take for granted (e.g., taking a vacation). Subtle forms of exclusion can be seen in discriminating practices and legislation, e.g., lack of real-world parity between medical and psychiatric care, despite legislation declaring parity (see Weissman's essay under Addition Resources). Patients themselves may accept and internalize societal stereotypes about schizophrenia via a psychological process called self-stigmatization [22]. This attitude is disastrous since patients will give up even trying to build a new life. The resulting social isolation is a form of psychological death (and can precipitate suicide). Increasingly, loneliness is recognized as a risk factor for important health outcomes including physical and mental health [23]. Addressing loneliness should therefore become an important part of treatment for patients with schizophrenia, particularly as they are getting older which will only increase their already large social isolation [24].

Key Points

Many patients with schizophrenia have small social networks due to illness (negative symptoms) but also because of social exclusion (stigma). Reducing loneliness is an important treatment goal in schizophrenia.

Psychiatry, while well intentioned, inadvertently contributed to stigma through anti-stigma campaigns that emphasized a “broken brain” model of mental illness, placing less emphasis on psychosocial determinants [25]. In hindsight, it was a mistake to simplistically insist that “schizophrenia is a brain disease.” Patients and the public clearly prefer psychosocial explanations over biogenetic ones as a more hopeful model since it allows for (self-) control. Particularly in first-episode patients, a more sophisticated view of psychosis that allows for societal factors to cause or modify disease seems to be more useful (and ultimately more accurate!).

Another area in which psychiatry contributed to stigma was by propagating that “patients with mental illness are not more dangerous than the general population.” This is too simplistic a narrative and cannot counter the affect (fear) that stories of crimes committed by somebody with schizophrenia engender. Nothing stigmatizes more patients with mental illness than the one, highly publicized case in which a patient who was allowed to go untreated pushed somebody in front of a subway. Some patients with psychosis are dangerous because of their psychiatric illness, even if the vast majority is not. Pointing out that patients with schizophrenia are at higher risk of becoming victims themselves cannot counter the fear that exists in society about schizophrenia. How to effectively reduce stigma in a society and, as important, discrimination rooted in stigma remains challenging. Advocating for the resources to providing effective psychiatric treatment for

patients with serious mental illness is one small contribution that psychiatry can make to reduce stigma toward our patients.

When patients first get ill, they and their families know as much about schizophrenia as the general public: very little. Most would be hard-pressed to explain the difference between multiple personalities, psychopathy, and schizophrenia or to identify hallucinations as a core feature. Many would probably equate schizophrenia with unpredictable violence. Many assume that a patient with schizophrenia cannot report facts or internal states accurately. One result of such stereotypes results in “epistemic injustice:” [26] a patient’s account of events or experiences is doubted which can be summarized in the adage, “It is twice as difficult to look half as normal if you have a psychiatric illness.” Psychoeducation of patients and families and referral to reputable sources are important ways to help patients and their families overcome stereotypes of schizophrenia (see Chaps. 22 and 23).

Tip

It is important to recall the images that “schizophrenia” conjures up in the lay public, and accordingly be very cautious about how you introduce the idea of schizophrenia and how you talk about it. Do not avoid the term, but be cognizant of its associations, and be flexible in working with how patients see causation.

Community efforts to increase knowledge about psychosis (similar to knowing the signs of a heart attack) can bring people with psychosis earlier into treatment [27]. Such public education campaigns are effective while ongoing, but the benefit does not persist once campaigns end [28].

As a way of decreasing stigma, some have suggested changing the name of schizophrenia to, say, Kraepelin’s disease or salience syndrome [29]. In Japan, in 2005, schizophrenia was renamed “Togo Shitcho Sho” (“disintegration disorder”) [30]. While there may be a measurable benefit from a name change on some aspects of stigma, it remains to be seen if actual discrimination can be reduced as well [31]. I find Susan Sontag’s argument persuasive that schizophrenia will only truly cease to be stigmatizing once it ceases to be a metaphor (in this case, for unpredictability and lack of control) [32]. In the interim, the best hope for reducing stigma is better treatment that allows patients to live normal lives and be integrated into society. Equally important, however, are nondiscriminatory policies and laws that prevent people from acting on their stigma.

The consequences of stigma for patients are real, and many patients struggle with these questions at some point during their illness or even their whole lives:

- The issue of disclosure: Who, what, and when should I tell about my mental illness? How do I explain a gap in my résumé caused by being hospitalized?
- How are my friends going to view me? Am I still worthy?
- The issue of self-blame: What did I do wrong?

- Is it true, I have a mental illness? How should I conceptualize schizophrenia? Which model of causation of mental illness should I adopt (biogenetic versus psychosocial)?
- How much can I get integrated into a society that values work so much, even if I do not work? (See Chap. 25, Sennett's specter of uselessness [33]).
- Is my life worth living?

Key Point

Receiving any diagnosis is a social act that comes with meaning for a person. It changes a person's status in a society from health to ill or from normal to "crazy." It changes how people think about themselves and how other people think about the patient, requiring psychological adjustments.

References

1. Goffman E. *Asylums. Essays on the social situation of mental patients and other inmates.* Garden City: Anchor Books; 1961.
2. Cooper B. Schizophrenia, social class and immigrant status: the epidemiological evidence. *Epidemiol Psychiatr Soc.* 2005;14:137–44.
3. Dickey B. Review of programs for persons who are homeless and mentally ill. *Harv Rev Psychiatry.* 2000;8:242–50.
4. Foster A, Gable J, Buckley J. Homelessness in schizophrenia. *Psychiatr Clin North Am.* 2012;35:717–34.
5. Aubry T, Nelson G, Tsemberis S. Housing first for people with severe mental illness who are homeless: a review of the research and findings from the at home-chez soi demonstration project. *Can J Psychiatr.* 2015;60:467–74.
6. Zhuo C, Tao R, Jiang R, Lin X, Shao M. Cancer mortality in patients with schizophrenia: systematic review and meta-analysis. *Br J Psychiatry.* 2017;211:7–13.
7. Dickerson F, Schroeder J, Katsafanas E, Khushalani S, Origoni AE, Savage C, et al. Cigarette smoking by patients with serious mental illness, 1999–2016: an increasing disparity. *Psychiatr Serv.* 2018;69:147–53.
8. Martinez ME, Gomez SL, Tao L, Cress R, Rodriguez D, Unkart J, et al. Contribution of clinical and socioeconomic factors to differences in breast cancer subtype and mortality between Hispanic and non-Hispanic white women. *Breast Cancer Res Treat.* 2017;166: 185–93.
9. Fleche S, Layard R. Do more of those in misery suffer from poverty, unemployment or mental illness? *Kyklos (Oxford).* 2017;70:27–41.
10. Farmer PE, Nizelye B, Stulac S, Keshavjee S. Structural violence and clinical medicine. *PLoS Med.* 2006;3:e449.
11. Griffin M, Weiss Block J, editors. *In the company of the poor: conversations between Dr. Paul Farmer and Fr. Gustavo Gutierrez.* Maryknoll, New York: Orbis Books; 2013.
12. Metzl JM, Hansen H. Structural competency: theorizing a new medical engagement with stigma and inequality. *Soc Sci Med.* 2014;103:126–33.
13. ABIM Foundation, American College of Physicians-American Society of Internal Medicine, European Federation of Internal Medicine. Medical professionalism in the new millennium: a physician charter. *Ann Intern Med.* 2002;136:243–6.
14. Popovic D, Schmitt A, Kaurani L, Senner F, Papiol S, Malchow B, et al. Childhood trauma in schizophrenia: current findings and research perspectives. *Front Neurosci.* 2019;13:274.

15. Brezing C, Ferrara M, Freudenreich O. The syndemic illness of HIV and trauma: implications for a trauma-informed model of care. *Psychosomatics*. 2015;56:107–18.
16. Tervalon M, Murray-Garcia J. Cultural humility versus cultural competence: a critical distinction in defining physician training outcomes in multicultural education. *J Health Care Poor Underserved*. 1998;9:117–25.
17. Morgan C, Charalambides M, Hutchinson G, Murray RM. Migration, ethnicity, and psychosis: toward a sociodevelopmental model. *Schizophr Bull*. 2010;36:655–64.
18. Montenegro RE. My name is not “interpreter” [A piece of my mind]. *JAMA*. 2016;315:2071–2.
19. Allen AM, Thomas MD, Michaels EK, Reeves AN, Okoye U, Price MM, et al. Racial discrimination, educational attainment, and biological dysregulation among midlife African American women. *Psychoneuroendocrinology*. 2019;99:225–35.
20. Sue DW, Capodilupo CM, Torino GC, Bucceri JM, Holder AM, Nadal KL, et al. Racial microaggressions in everyday life: implications for clinical practice. *Am Psychol*. 2007;62:271–86.
21. Gamble VN. Under the shadow of Tuskegee: African Americans and health care. *Am J Public Health*. 1997;87:1773–8.
22. Bathje GJ, Marston HN. Self-stigmatization. In: Teo T, editor. *Encyclopedia of critical psychology*. New York: Springer New York; 2014. p. 1713–6.
23. Lee EE, Depp C, Palmer BW, Glorioso D, Daly R, Liu J, et al. High prevalence and adverse health effects of loneliness in community-dwelling adults across the lifespan: role of wisdom as a protective factor. *Int Psychogeriatr*. 2019;31:1447–62.
24. Egli GML, Palmer BW, Martin AS, Tu X, Jeste DV. Loneliness in schizophrenia: construct clarification, measurement, and clinical relevance. *PLoS One*. 2018;13:e0194021.
25. Wiesjahn M, Jung E, Kremser JD, Rief W, Lincoln TM. The potential of continuum versus biogenetic beliefs in reducing stigmatization against persons with schizophrenia: an experimental study. *J Behav Ther Exp Psychiatry*. 2016;50:231–7.
26. Crichton P, Carel H, Kidd IJ. Epistemic injustice in psychiatry. *BJPsych Bull*. 2017;41:65–70.
27. Melle I, Larsen TK, Haahr U, Friis S, Johannessen JO, Opjordsmoen S, et al. Prevention of negative symptom psychopathologies in first-episode schizophrenia: two-year effects of reducing the duration of untreated psychosis. *Arch Gen Psychiatry*. 2008;65:634–40.
28. Joa I, Johannessen JO, Auestad B, Friis S, McGlashan T, Melle I, et al. The key to reducing duration of untreated first psychosis: information campaigns. *Schizophr Bull*. 2008;34:466–72.
29. Tranulis C, Lecomte T, El-Khoury B, Lavarenne A, Brodeur-Cote D. Changing the name of schizophrenia: patient perspectives and implications for DSM-V. *PLoS One*. 2013;8:e55998.
30. Maruta T, Matsumoto C. Renaming schizophrenia. *Epidemiol Psychiatr Sci*. 2019;28:262–4.
31. Yamaguchi S, Mizuno M, Ojio Y, Sawada U, Matsunaga A, Ando S, et al. Associations between renaming schizophrenia and stigma-related outcomes: a systematic review. *Psychiatry Clin Neurosci*. 2017;71:347–62.
32. Sontag S. *Illness as metaphor, and, AIDS and its metaphors*. New York: Picador USA; 2001.
33. Sennett R. *The culture of the new capitalism*. New Haven & London: Yale University Press; 2006.

Additional Resources

Book

Griffin M, Weiss Block J, editors. *In the company of the poor : conversations between Dr. Paul Farmer and Fr. Gustavo Gutierrez*. Maryknoll, New York: Orbis Books; 2013. – If you are interested in accompaniment, solidarity, or structural violence, then this book is for you. Gustavo Gutierrez from Lima, Peru is one of the father's of liberation theology. While you may not like it's theoretical foundations (theology and Marxism), there is value in its ethical stance towards improving the social lives of the poor.

Article

Montenegro RE. My name is not “interpreter” [A piece of mind]. JAMA. 2016;315:2071–2. – Mandatory reading if you believe the American experience is the same for everybody in our “post-racial” world. The author who is an accomplished physician and sociologist and who happens to be Latino provides a striking example of microaggression when he was mistaken for the valet.

Weissman MM. Stigma [A piece of my mind]. JAMA. 2001;285:261–2. – If you believe there is parity between medical care and mental health care, read this essay about one patient and his mother who encounter both treatment systems. While written in 2001, this powerful essay is as current as ever.

Chapter 33

Forensic Aspects of Schizophrenia Care



Essential Concepts

- Physicians have moral obligations not only toward the welfare of their patients but also toward the commonwealth of the citizens in their community. Protecting the public from harm from psychotic patients is such a professional duty for which society has given us great powers. We owe it to our patients and society to use them judiciously.
- A violence risk assessment is part of every psychiatric evaluation as *some* patients with schizophrenia are potentially violent when untreated.
- The standard of care is the so-called structured clinical judgment, a systematic assessment of risk factors to estimate risk, followed by clinical management that matches the estimated risk.
- Prevention of violence due to psychiatric illness is a crucial treatment goal as patients may not only harm other people but ultimately themselves. Providing effective treatment with antipsychotics is the best clinical tool to reduce violence in those patients.
- Involuntary hospitalization and treatment may be necessary and in most countries are allowed for patients with psychosis who are dangerous to others and to themselves or who are incapacitated to the point that they can no longer take care of themselves.
- Assisted outpatient treatment (AOT) is but one tool along a spectrum of tools for assisted treatment (coerced care).
- The ethical use of power in the service of treatment (coercion) is a key concern for psychiatry. Our profession's history is a stark reminder that each of us has the moral obligation to work on reducing the amount of coercion used in psychiatry and speaking up when there is misuse of power.

- Evaluations for capacity to consent to or refuse medical treatment follow the same principles for patients with schizophrenia as for any other patient. You need to assess a patient's ability to choose a course of action, to retain facts about the possible treatment options, to appreciate the likely consequences for each option (including foregoing treatment), and to reach a reasoned conclusion consistent with professed values.
- The four-quadrant approach offers a framework for ethical decision-making that assures a broad inquiry into all facets of a case: the medical facts, the patient's values and wishes, the patient's quality of life, and other stakeholders' concerns.
- Lack of appropriate paternalism in healthcare can result in patient abandonment.

“... nor shall any state deprive any person of life, liberty, or property, without due process of law; ...”

— Fourteenth Amendment to the United States Constitution

A fundamental right in our society is that citizens have the “right to be let alone,” in Supreme Court Louis Brandeis’s words [1]. In the medical arena, this means that (competent) patients can refuse even lifesaving treatments. However, the public also has the right to be protected, and physicians have obligations toward the welfare of the general public as well. In diseases that potentially affect a community, the personal perspective on liberty is important but not sufficient to ignore community interests. Just as patients might not have the right to go untreated and spread tuberculosis, they might not have the right to endanger other people while psychotic. Forensic psychiatry sits uncomfortably between systems of care (the medical system) and systems of punishment (the criminal justice system) [2]. Patients caught up in both systems bring to the forefront your own views about moral responsibility, the limits of an open society, and how to balance conflicting dual roles as a physician and as an agent of the state.

In this chapter, I examine forensic issues that all psychiatrists deal with on a daily basis: violence and its relationship to psychiatric illness, including the task to assess violence and prevent violence; involuntary treatment; and capacity assessments. Narrow forensic issues such as an assessment for competency to stand trial are outside the scope of this chapter. Correctional psychiatry that emphasizes the setting of care is dealt with in the last chapter (Chap. 34).

Tip

Be a good clinician, not a bad lawyer: provide good clinical care not only based on respect of patient autonomy but also based on the values of nonmaleficence (doing no harm) and beneficence (doing good). Do not give bad legal advice, but consult a lawyer for legal questions. Obviously, know and follow the laws of the land as they pertain to your practice. Above all, know your Weltanschauung with regard to your own responsibilities toward society.

Violence

The link between psychosis and violence has been much debated and at times even discounted, probably because of efforts to decrease stigma [3]. I think it defies common sense that psychosis would not in certain instances and in certain people increase the risk for violence: it certainly does, unless you have never worked in a psychiatric hospital or emergency room. Hospitals, particular psychiatric settings, are a high-risk workplace, and violence against healthcare workers should not be ignored but openly discussed [4]. While the risk for violence is difficult to predict and impossible to avoid completely, we can nevertheless manage it. A systematic risk assessment combined with clinical interventions flowing from the identified risk factors to estimate risk (structured professional judgment model) is our tool as clinicians to play our part in preventing violence and its pernicious consequences for the victims.

Violence Risk Assessment

“Violence” is clearly etiologically heterogeneous [5], and in only a small subgroup of people is violence directly linked to psychosis. A host of static and dynamic risk factors have been identified. Alcohol and drug use are particularly important triggering factors of violence across all disorders [6]. A second path toward violence is paved by criminogenic risk factors [7]. The “Big Four risk factors” are a history of antisocial behavior, antisocial personality patterns, antisocial cognitions, and having antisocial associates or peers. Premorbid delinquency manifesting in childhood is an ominous sign that contributes to violence independent from psychosis [8]. The most dangerous patients I have encountered come from a small subgroup of persons with schizophrenia: young, substance-using male patient who are antisocial and suffer from paranoid schizophrenia. When decompensated, these patients are extremely volatile and paranoid, with no impulse control or moral barriers, which makes them dangerous. Traumatic brain injury can compound the problem of poor impulse control [9].

Unfortunately, several cultural scripts (e.g., school shooting, mass shooting) are available that give psychotic patients who are alienated from society a form of recognition by means of hitherto unthinkable acts of violence against members of their community. Not all school shootings or other mass shootings are perpetrated by psychotic individuals [10]; a correct diagnosis that also takes into account psychological motivations (anger, revenge fantasies, degree of alienation) is critical if we want to intervene effectively, including not expediently and simplistically blaming all mass shootings on untreated serious mental illness [11]. Identifying psychotic patients in order to treat them and prevent violence is a critical public health task. While early and consistent treatment for psychotic patients who are prone to violence will not address all (or even a large part of) violence in our society, it will address those acts of violence attributable to psychosis. An offender typology brings some conceptual order to violence: is violence the result of psychosis, of being disadvantaged, reactive, and instrumental, or gang/drug related [12]?

Tip

The most useful predictors of violence are any past history of violence and substance use. Therefore, get a good legal history, previous arrests, prison time, probations, and exact legal charges. Go back to middle school, and look for conduct disorder as a sign of beginning sociopathy and early substance use [13]. Look for bullying as a sign of alienation from peers and harboring grudges and resentments against society. Manic symptoms are another clinical indicator of potential violence as patients are disinhibited.

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) evaluated the propensity for violence in a sample of almost 1500 patients. The 6-month prevalence for any act of violence was close to 20% [14]. You should note, however, that serious violence (in this study defined as assault resulting in injury, lethal weapon threat or use, or sexual assault) was much less common, 3.6%. Serious violence was associated with positive symptoms, whereas other forms of violence were better predicted by environmental variables. Not surprisingly, negative symptoms had a protective effect. In a different analysis of serious, injurious violence (i.e., actually inflicting physical injury) in the CATIE sample, baseline injurious violence, recent violent victimization, and poor medication adherence were the best predictors of harming somebody physically during the 18 month trial, occurring in 5% of patients [15]. This risk may be an underestimate as the assessments were based on self-report.

Tip

It is not psychosis per se that determines the risk of violence but the nature of the delusions (particularly thoughts of persecution) and hallucinations (i.e., command type) [16]. Find out exactly what patients are thinking and planning, and engage them in a discussion of violence, for example, how likely they think it is that they will take preventive or retaliatory action. Is your patient embittered [17]?

You must know your legal responsibilities with regard to warning identified victims and protecting them and the public (the so-called duty to warn and protect). To safeguard the public, all states have provisions for committing a patient with schizophrenia who is violent.

Here are some key points to remember to stay safe in your line of work as a psychiatrist treating schizophrenia:

- When you work with psychotic patients, remain alert to the possibility of harm from your patient. There is no glory in being stoic and accepting being assaulted as part of your job. Always trust your limbic warning system if it signals “danger.”

Table 33.1 Clinical assessment of aggression^a

Excitement	Is the patient motorically accelerated and pressured in his or her speech (this looks hypomanic)?
Tension	Is the patient showing overt signs of anxiety or fear? Is he tense and sweating?
Hostility	Is the patient angry and irritable? Sarcastic? Resentful? Making threats?
Uncooperativeness	Does the patient refuse to comply with tasks asked of him or her?
Poor impulse control	How well is the patient able to tolerate frustration? Does the patient fly off the handle regardless of consequences?

^aThese five items are taken from the Positive and Negative Syndrome Scale (PANSS) in which they comprise the Excited Cluster (PANSS-EC) [21]

- Just like you assess the potential for suicide in all patients, you must estimate the risk for immediate violence and the potential for violence in the future. You do this by combining an actuarial approach (past history) with your cross-sectional data on exam (Table 33.1).
- Simply ask a patient about his self-perception of future violence. It correlates with other methods of risk assessment and is an easy way to augment your assessment [18]. A positive response in insightful patients is more helpful than in patients who not only deny any possibility of future violence but who (inaccurately) deny any history of past violence [19].
- Record any history of violence during acute psychosis in your lifetime problem list, so the information does not get lost.
- Have a plan in place in your treatment setting how to respond to violence. Debriefing after an incident of violence and an administrative review are important steps to prevent future acts of violence and support affected staff member [20].

The currently best model to estimate risk and devise a risk management plan that matches the risk estimate is called “structured professional judgment model.” In this approach, risk factors are systematically evaluated, including past behaviors but also current clinical markers and factors impacting risk management. Thus the obtained actuarial information is then used to inform clinical judgment. Clinical judgment alone tends to overestimate risk. The most commonly used instrument to assess and manage violence risk is the Historical Clinical Risk Management-20, Version 3 [22].

Violence Risk Reduction

Preventing violence is important not just to protect yourself and society but also to combat stigma. Allowing a small subset of violent persons with schizophrenia to go untreated is a disservice to all patients with schizophrenia who are trying to live peaceful lives. In addition to healthcare workers and innocent bystanders, there are two other groups who suffer if psychotic violence is not prevented. The most com-

mon targets of violence are family members since patients often live with them. Discuss the possibility of violence with the family who (just like clinicians) may have a tendency to minimize this aspect of the illness. Last, patients themselves become victims if they commit a crime while psychotic, a potentially preventable socio-toxic consequence from being psychotic. In one chart review study, clozapine was found to reduce recidivism in patients with criminal histories [23]. Preventing the “criminalization” of being psychiatrically ill is a legitimate treatment goal. Unfortunately, the reduction in psychiatric treatment beds since the 1950s had two unintended consequences: (1) it has shifted treatment into jails and prisons or to no treatment in the streets, and (2) I suspect it effectively prevents treatment prior to an act of violence has occurred, when patients are less ill, as psychiatric beds are now reserved for the most ill.

The most effective *clinical* interventions to *prevent* more violence from high-risk patients target these areas:

- Nonadherence – Consider long-acting antipsychotics. Refer to ACT teams (Table 33.2), if available. Consider outpatient commitments, if available. While there are efficacy differences between antipsychotics with regard to reducing hostility [24], those pale in comparison to receiving no treatment.
- Drug use – In some jurisdictions, probation and court-mandated treatment (e.g., random urine drug testing) instead of prison time can provide motivation. In some programs, entitlement benefits can be contingent on drug-free status.
- Residual psychosis – Use the most effective antipsychotics, including clozapine; clozapine also has anti-aggressive properties independent of its antipsychotic properties [25].
- Gun access – Ask about gun possession and take necessary steps to remove guns. In some jurisdictions, extreme risk protection orders (ERPOs) or red flag laws allow weapons to be removed preemptively from households if there is risk of violence [26].

Involuntary Treatment

Involuntary or coercive measures are most visible when somebody gets involuntarily committed to a hospital. Prior to the 1960s, involuntary civil commitments were largely left to the discretion of psychiatrists if there seemed to be a “need for treatment.” With the rise of the civil liberties movement, this prerogative has been severely curtailed, and patients today are mostly committed for “danger to self or others” and no longer for need for treatment. Many believe the pendulum has swung too far and rightly point to the difficulties in getting psychotic but non-dangerous patients appropriately treated if they refuse treatment. A purely individual rights-based approach that includes the right to refuse treatment negates the clinical reality of an anosognosia-like inability to see oneself as ill and in need of treatment (see Chap. 31 on insight).

Key Point

Currently, the threshold for involuntary intervention is high, usually dangerousness to self or others or clear inability to care for oneself. The dangerousness or inability to care for oneself must stem from a mental illness. Psychiatric (civil) commitment is usually a two-step process: the initial involuntary hospitalization, which can be initiated by a physician, for an emergency evaluation, followed by a petition to the court for psychiatric commitment, which may or may not be granted. Technically, it is not psychiatrists but judges who “commit” patients, a point often overlooked. State laws and local culture vary considerably on the details and outcomes of the process.

I view an involuntary hospitalization and treatment as the gateway to eventual voluntary treatment and as a tool to restore capacity lost during psychosis. There are three typical clinical situations in which you should seek involuntary hospitalization and treatment for psychotic patients who refuse treatment:

- Psychotic patients who are potentially violent, to acutely reduce risk to specific people or the community at large. This is the typical case of commitment for “danger to others” and refers to state-based and modifiable dangerousness due to symptoms of a psychiatric illness. You act as an agent of the state to protect the community, but you also act as the patient’s advocate to protect the patient from legal charges and criminalization or injury.
- Psychotic patients at acute risk for a suicide attempt. This is the case of commitment for “danger to self.”
- Patients who are unable to care for themselves while psychotic. This is the remnant of the in-need-for-treatment approach. Depending on the exact interpretation and wording of the respective statute, this can be very difficult to apply, and judges might have a threshold very different from yours or the patient’s family. Are you unable to care for yourself if you can line up in a shelter line and find the local soup kitchen?

Clinical Vignette

Franz was a promising college student who developed persecutory delusions and left college. Despite attempts to engage him and initiate treatment, he resisted as he was convinced that there was “nothing wrong” with him. An involuntary hospitalization was initiated, but the petition for civil commitment was not granted, as Franz was eloquent in his hearing and had neither been homeless, without food (he had moved back in with his parents), nor dangerous (he was basically just staying in his room). Months later, a second treatment attempt, after some admittedly vague threats in an argument with his mother, led to a period of involuntary hospitalization “for dangerousness” and treatment, leading to a full recovery.

This patient represents a subgroup of patients who fall through the cracks: clearly psychotic, yet resisting treatment and at the same time not clearly dangerous but also not doing well with their lives wrecked by decision made under the influence of psychosis. Often, the outcome of a hearing depends on the judge's view of mental illness and its treatments. Families might have little leverage in compelling such "quietly psychotic" family members to begin treatment, short of evicting their family member or withdrawing all resources (something most families would never do to their children).

In this case, the patient was grateful for the episode of involuntary treatment, after he had recovered. Some remain furious and cut off all contact to their family and psychiatric care: an outcome that is a risk of an involuntary commitment.

Sometimes you are asked (by the group home, the family, or the police) to simply hospitalize somebody because of some potential for violence sometime in the future. It is not your task as a physician to prevent the commission of violence by antisocial or angry people; your role is to treat patients who are dangerous because of psychiatric illness (character pathology and drug use are often excluded in state laws, so know the exact definition of mental illness in your state law). Be wary of colluding with anything that would more aptly be termed preventive detention. Preventive detention and involuntary confinement (without treatment) are police functions.

States continue to experiment with legislation and treatment models that entail an element of coercion but no longer use the blunt instrument of an involuntary inpatient admission. One guiding principle is the idea that involuntary treatment, if needed, ought to occur in the least restrictive setting, usually in the community. Mandated (involuntary) court-ordered outpatient treatments like assisted outpatient treatment (known as community treatment orders (CTOs) in Great Britain) have been implemented in many countries, amidst much criticism and with mixed results. One concern that is not easily dismissed is a tendency to use coercive measures once they are available; other treatment options are no longer pursued or even cut to save money, if they even existed in the first place. (Voluntary) ACT teams, for example, that would obviate the need for involuntary measure are often not available, despite a good track record of efficacy. One large trial in Great Britain (named OCTET) failed to show benefit from CTOs in a randomized trial [27]; outcome measures beyond hospitalization may be important considerations that materialize in some patients [28]. The actual availability of assisted treatment options short of involuntary hospitalization varies greatly by state or even by county. Table 33.2 shows the spectrum of involuntary interventions.

Society has given physicians significant powers vis-a-vis other people's lives that we should use judiciously. Psychiatry's history is a sobering reminder how easily humans can be co-opted to achieve inhuman goals (e.g., psychiatrists cooperating with Nazi Germany in sending psychiatric patients to concentration camps) [30].

Table 33.2 Assisted treatment options for psychotic disorders

Advanced (psychiatric) directives [29]	A document put together while well that specifies treatment preferences when ill. Problem: it can be revoked easily
Outpatient commitment	Patients are ordered by a court to comply with treatment to be allowed to stay in the community
Conditional-release arrangement	Patients are released from the hospital under the promise of compliance
Assertive community treatment (ACT)	A well-studied model of care in which patients are tracked down in the community if they miss appointments; this model of case management linked closely with treatment is most effective in reducing hospitalizations and became necessary during the period of deinstitutionalization (hospitals without walls)
Representative payee	Benefit payments are not given directly to patients but are used as incentives to adhere to treatment

Always remember that procedures that seem overly prescriptive today were often put in place to rectify a wrong from the past, as noted by Harvard lawyer Alan Dershowitz [31]. You may want to consider respecting forms documenting restraint even if they seem unnecessarily burdensome in the middle of the night.

Today's social control is hidden and at the same time ubiquitous, at least according to the French philosopher Michel Foucault [32]. We nudge, we hint at involuntary measures, we write letters to authorities who ask for a report, we withhold money (rep payee [33]), and we determine placement: there are many subtle and not so subtle ways in which we use leverage to control patient behavior [34]. Invisible, internalized rules about living in a group can give patients a feeling of being institutionalized in the community even though they are no longer physically locked up in a state hospital [35].

Appreciate that some patients may have a point when they avoid psychiatry for fear of some form of involuntary treatment. I had a patient who lamented that he would have been better off in life if psychiatry had never gotten involved at all; this is difficult to accept if you do not appreciate the downsides of our specialties' involvement, ranging from medication side effects to psychological suffering, loss of privacy, and the experience of social control.

Psychiatrists may have an important ethical imperative: working on reducing the amount of coercion used in psychiatry and speaking up when there is misuse of power. The use of restraint, for example, in inpatient units can be greatly reduced (assuming adequate staffing). Even if coercion cannot be avoided, increasing patient control to reduce the *perceived* level of coercion can be achieved. The perceived level of coercion is a much better predictor of treatment satisfaction than some objective measure of coercion (like a legal admission status) [36]. The clinical experience during an involuntary hospitalization may be critical for a good long-term outcome, and improving the experience with care may have practical ramifications beyond the ethical imperative. Patients who had a good experience (despite the circumstances) may be less likely to disengage from treatment after an involuntary

hospitalization compared to patients with a bad experience [37]. Locked-door policies that allow for more staff control deserve scrutiny [38]. Staff training and education about power and how easy power is abused may be an area where psychiatry can lead, including creating a culture where people are willing to speak up if inhumane treatment occurs. The old “total institutions” (Goffman’s term [39]) look different today (although we have come full circles with prisons), and eternal vigilance is needed to provide the most humane treatment possible.

In some circles, any form of involuntary commitment or treatment is challenged using a human rights argument with an almost exclusive emphasis on a patient’s preference alone – a challenge to current psychiatric practice where impaired capacity to make medical decisions is moral justification to intervene [40]. An extreme position of the human rights argument equates any form of involuntary psychiatric treatment with torture.

Tip

I find the ethics of coerced care in all its shades (not just involuntary hospitalizations) one of the more difficult aspects of being a public and community psychiatrist. The tension between appropriate supervision (including the use of coercion to prevent harm) and freedom (including the freedom to make mistakes) is familiar to those of us who are parents. When faced with a decision about coercion, I remind myself that I have several, potentially conflicting loyalties that create moral discomfort: the person I am treating is a *patient* (with the expectation to be treated according to our professional code of ethics); he is a *citizen* (with civil rights spelled out in our social contract); and last, he or she is a *neighbor* (with the hope to get help when in need).

Capacity Evaluations

Consultation-liaison psychiatrists typically are asked to evaluate patients with schizophrenia for “competence” if patients refuse a medical intervention deemed necessary by the medical treatment team. Sometimes all that is needed is spending a little more time to explain the risks and benefits to the patients. Evaluations of medical decision-making capacity (i.e., the capacity to make an *informed* choice) follow the same principles of patients with schizophrenia as for other patients (see Table 33.3) [41]. Be aware, however, that capacity evaluation requests can be hidden attempts to resolve moral dilemmas (e.g., wanting to protect a vulnerable person who wants to go home versus respect for a person’s wish to go home) [42].

Note the following points. Psychotic patients cannot be considered incompetent merely by virtue of their diagnosis or symptoms, or in the words of one patient, “I might have schizophrenia but I am not stupid.” Make sure, however, that psychosis is not responsible for treatment refusal. Other areas of dysfunction, for example, negative symptoms or cognitive problems, are as important to assess

Table 33.3 Four key elements of a capacity evaluation^a

1. Communicate a choice	Patient clearly (and consistently) indicates a preferred treatment option
2. Understand the factual information	Patient has meaningful understanding of his/her condition, its various treatment options, and the risks and benefits for each
3. Appreciate the situation	Patient understands the nature of his/her condition, particularly the likely outcomes for him/her, including for no treatment
4. Reason about treatment options	Patient can show that (from his/her perspective and based on his/her values) the choice is reasonable

Based on Ref. [41]

^aA sliding scale threshold is often used in which a higher degree of capacity needs to be shown for high-stakes decisions (i.e., refusing lifesaving treatment or accepting high-risk treatments with limited benefit)

as positive symptoms. Also, as with other patients, you are not trying to assess some “global” capacity, but capacity with regard to a very specific clinical question. While capacity evaluations have a legal flavor to them, there is a fundamentally clinical aspect to them (helping patients formulate choices, uncovering clinical reasons including noncognitive or shall we say psychological-emotional reasons for lack of capacity) [43].

Tip

The most useful question to ask yourself is this one: “Does the patient appreciate the pragmatic consequences downstream of placing an act now (phrase courtesy of the late George B. Murray, MD)?” In other words, does the patient truly appreciate what it means tomorrow if he refuses to have surgery today? The key word is *appreciation*, in contradistinction to lip service. Patients with clinically relevant executive dysfunction will invariably fail this question as they only focus on some immediate aspect of care. In those cases, foresight is missing: action (not agreeing to surgery) is not only ill-advised but inconsistent with professed values (not wanting to die).

A common question is if a patient has the capacity to refuse treatment with antipsychotic medications. Less commonly, the issue of capacity to consent to treatment is raised, particularly if patients passively go along with treatment. This second scenario is equally problematic as informed consent is not only a legal requirement but also the ethical basis for treatment; it reflects our society’s basic value of respect for persons. You therefore need to routinely assess a patient’s understanding of his diagnosis (the sine qua non from which all else follows, simply by logic), the proposed treatment plan (including antipsychotics), and the risks and benefits of the proposed treatment with antipsychotics, alternative including no treatment. Acknowledging your diagnosis does not hinge on agreeing to “schizophrenia,” but some awareness of a psychiatric disorder is surely logically needed.

Table 33.4 The four-quadrant approach to guide medical decision-making

1. What does psychiatry have to offer?	The medical facts: diagnosis, differential diagnosis, treatment options (including no treatment), prognosis for the various options
2. What does the patient want?	Patient preference. Also important for patients under guardianship to minimize confrontation
3. What kind of life does the patient both hope for and fear?	Know how a proposed course of action would affect a patient's quality of life
4. Who and what else matters?	Many stakeholders (family, "systems") have a legitimate interest in the outcome. Laws need to be obeyed

Based on Ref. [45]

If patients are unable to recognize that they are ill, guardianship should be considered because such patients are unable to provide meaningful (legal) informed consent to treatment. Lip service assenting to treatment is not informed consent. Admittedly, there is a gray zone of recognizing that one is ill. Complete and firm denial of any mental or psychological problem (see anosognosia, in Chap. 31 on Insight) in a patient with established schizophrenia is not consistent with being able to consent to psychiatric treatment, a fact affirmed by the US Supreme Court. Patients under guardianship often benefit from the additional oversight and help with decisions, allowing them to live in the community (a less restrictive setting than a state hospital).

A different framework for making good clinical (and ethical) decisions about patient care is captured in the four-quadrant approach proffered by Jonsen and colleagues [44]. In this scheme, you consider the psychiatric facts, the patient's hopes and fears, and the concerns of others when making treatment recommendations. Applying this scheme will not compute "the solution"; it will, however, assure that all the facts are on the table and that everybody is heard. Importantly, while a patient's capacity is one consideration, a much broader lens of inquiry prevents a premature closure that often characterizes discussions when people make decisions for other people. The model is summarized in Table 33.4 using four questions.

Paternalism in Healthcare

Paternalism has gotten a bad reputation as it seemingly conflicts with patient autonomy. Helping patients make good decisions maybe be questioned as an unwanted intrusion into their lives. The right to fail at something is part of human freedom and a necessary experience in order to grow up.

Tip

Keep a check on your tendency to protect patients from themselves, “to avoid harm.” Simply having a diagnosis of schizophrenia changes your perception about somebody, according to the dictum, “It is twice as difficult to look half as normal if you have a mental illness.” This bias can result in an attitude of complete risk aversion for patients that you would not accept for yourself. Older patients face the same bias when their children insist on a “safe discharge” to a nursing home. Sometimes there might be more to life than death.

However, patient autonomy can be impaired by poor judgment, and focusing solely on autonomy ignores that obvious fact that physicians, as experts with experience, sometimes do know better and that patients make decisions that run counter to their own long-term interests. Physicians have always provided guidance (i.e., paternalism has always been constrained by the time-honored principles of nonmaleficence and benevolence). When viewed as a tool to advance true autonomy (in a Kantian sense, where decisions that ignore our debt to and embeddedness in society ultimately limit our autonomy), patients will in the end benefit. Sometimes accepting restrictions in one area means gaining freedom somewhere else. Insisting on a representative payee to manage benefit payments and avoid homelessness for lack of rent payment is an example of paternalism. True, the patient can no longer choose to spend the money on drugs and alcohol and will not sleep in a shelter because of lack of rent payment. However, help with money can be the first step toward more responsible budgeting and, ultimately, secure housing. What exactly is respected if your psychotic patient languishes in a homeless shelter, his or her “civil rights” seemingly intact? Who benefits if patients repeatedly offend and get criminalized simply for lack of moral commitment by the state to protect this vulnerable (and small) group [46]?

Key Point

Not pursuing assisted treatment options to do undue respect for a limited and atomistic view of autonomy can be a form of abandonment and ignores the equally important principle of nonmaleficence and benevolence. A lack of appropriate paternalism does not respect patient autonomy but constituted patient abandonment. The consequences of no treatment are victimization, homelessness, criminalization, or abandoned careers, to suggest a few. A patient’s welfare should be given some consideration when the pull of self-determination seems to lead a patient into social chaos.

References

1. Warren SD, Brandeis LD. The right to privacy. *Harv Law Rev.* 1890;4:193–220.
2. Arboleda-Florez J. Forensic psychiatry: contemporary scope, challenges and controversies. *World Psychiatry.* 2006;5:87–91.
3. Van Dorn R, Volavka J, Johnson N. Mental disorder and violence: is there a relationship beyond substance use? *Soc Psychiatry Psychiatr Epidemiol.* 2012;47:487–503.
4. Phillips JP. Workplace violence against health care workers in the United States. *N Engl J Med.* 2016;374:1661–9.
5. Volavka J, Citrome L. Heterogeneity of violence in schizophrenia and implications for long-term treatment. *Int J Clin Pract.* 2008;62:1237–45.
6. Witt K, van Dorn R, Fazel S. Risk factors for violence in psychosis: systematic review and meta-regression analysis of 110 studies. *PLoS One.* 2013;8:e55942.
7. Parke S, Baranoski M, Buchanan A, Norko MA. Violence risk assessments and management. *Psychiatr Ann.* 2018;48:109–14.
8. Winsper C, Singh SP, Marwaha S, Amos T, Lester H, Everard L, et al. Pathways to violent behavior during first-episode psychosis: a report from the UK national EDEN study. *JAMA Psychiatry.* 2013;70:1287–93.
9. Fazel S, Lichtenstein P, Grann M, Langstrom N. Risk of violent crime in individuals with epilepsy and traumatic brain injury: a 35-year Swedish population study. *PLoS Med.* 2011;8:e1001150.
10. Lake CR. Rampage murderers, part I: psychotic versus non-psychotic and a role for psychiatry in prevention. *Psychiatr Ann.* 2014;44:216–25.
11. Hirschtritt ME, Binder RL. A reassessment of blaming mass shootings on mental illness. *JAMA Psychiatry.* 2018;75:311–2.
12. Peterson J, Skeem JL, Hart E, Vidal S, Keith F. Analyzing offense patterns as a function of mental illness to test the criminalization hypothesis. *Psychiatr Serv.* 2010;61:1217–22.
13. Volavka J, Citrome L. Pathways to aggression in schizophrenia affect results of treatment. *Schizophr Bull.* 2011;37:921–9.
14. Swanson JW, Swartz MS, Van Dorn RA, Elbogen EB, Wagner HR, Rosenheck RA, et al. A national study of violent behavior in persons with schizophrenia. *Arch Gen Psychiatry.* 2006;63:490–9.
15. Buchanan A, Sint K, Swanson J, Rosenheck R. Correlates of future violence in people being treated for schizophrenia. *Am J Psychiatry.* 2019;176:694–701.
16. Scott CL, Resnick PJ. Evaluating psychotic patients' risk of violence: a practical guide. Investigate persecutory delusions and command hallucinations. *Curr Psychiatr Ther.* 2013;12:29–32.
17. Linden M, Noack I. Suicidal and aggressive ideation associated with feelings of embitterment. *Psychopathology.* 2018;51:245–51.
18. Skeem JL, Manchak SM, Lidz CW, Mulvey EP. The utility of patients' self-perceptions of violence risk: consider asking the person who may know best. *Psychiatr Serv.* 2013;64:410–5.
19. Krakowski MI, Czobor P. The denial of aggression in violent patients with schizophrenia. *Schizophr Res.* 2012;141:228–33.
20. Nordstrom K, Allen MH. Lessons to the practicing psychiatrist from emergency psychiatry: outpatient emergencies. *Primary Psychiatry.* 2009;16:37–40.
21. Montoya A, Valladares A, Lizan L, San L, Escobar R, Paz S. Validation of the excited component of the positive and negative syndrome scale (PANSS-EC) in a naturalistic sample of 278 patients with acute psychosis and agitation in a psychiatric emergency room. *Health Qual Life Outcomes.* 2011;9:18.

22. Jaber FS, Mahmoud KF. Risk tools for the prediction of violence: 'VRAG, HCR-20, PCL-R'. *J Psychiatr Ment Health Nurs.* 2015;22:133–41.
23. Frankle W, Shera D, Berger-Hershkowitz H, Evins AE, Connolly C, Goff D, et al. Clozapine-associated reduction in arrest rates of psychotic patients with criminal histories. *Am J Psychiatry.* 2001;158:270–4.
24. Volavka J, Czobor P, Derkis EM, Bitter I, Libiger J, Kahn RS, et al. Efficacy of antipsychotic drugs against hostility in the European First-Episode Schizophrenia Trial (EUFEST). *J Clin Psychiatry.* 2011;72:955–61.
25. Volavka J, Czobor P, Nolan K, Sheitman B, Lindenmayer JP, Citrome L, et al. Overt aggression and psychotic symptoms in patients with schizophrenia treated with clozapine, olanzapine, risperidone, or haloperidol. *J Clin Psychopharmacol.* 2004;24:225–8.
26. Frizzell W, Chien J. Extreme risk protection orders to reduce firearm violence. *Psychiatr Serv.* 2019;70:75–7.
27. Burns T, Rugkasa J, Molodynski A, Dawson J, Yeeles K, Vazquez-Montes M, et al. Community treatment orders for patients with psychosis (OCTET): a randomised controlled trial. *Lancet.* 2013;381:1627–33.
28. O'Brien AM, Farrell SJ, Faulkner S. Community treatment orders: beyond hospital utilization rates examining the association of community treatment orders with community engagement and supportive housing. *Community Mental Health J.* 2009;45:415–9.
29. Zelle H, Kemp K, Bonnie RJ. Advance directives in mental health care: evidence, challenges and promise. *World Psychiatry.* 2015;14:278–80.
30. Strous RD. Psychiatry during the Nazi era: ethical lessons for the modern professional. *Ann General Psychiatry.* 2007;6:8.
31. Dershowitz A. Rights from wrongs : a secular theory of the origins of rights. New York: Basic Books; 2005.
32. Foucault M. *La volonté de savoir.* Edition Gallimard: Paris; 1976.
33. Elbogen EB, Soriano C, Van Dorn R, Swartz MS, Swanson JW. Consumer views of representative payee use of disability funds to leverage treatment adherence. *Psychiatr Serv.* 2005;56:45–9.
34. Monahan J, Redlich AD, Swanson J, Robbins PC, Appelbaum PS, Petrina J, et al. Use of leverage to improve adherence to psychiatric treatment in the community. *Psychiatr Serv.* 2005;56:37–44.
35. Kontos N, Freudenreich O, Querques J. Outpatient institutionalization – 100 words. *Br J Psychiatry.* 2014;205:339.
36. Opjordsmoen S, Friis S, Melle I, Haahr U, Johannessen JO, Larsen TK, et al. A 2-year follow-up of involuntary admission's influence upon adherence and outcome in first-episode psychosis. *Acta Psychiatr Scand.* 2010;121:371–6.
37. Priebe S, Katsakou C, Yeeles K, Amos T, Morrissey R, Wang D, et al. Predictors of clinical and social outcomes following involuntary hospital admission: a prospective observational study. *Eur Arch Psychiatry Clin Neurosci.* 2011;261:377–86.
38. Shoefeld N, Ulman AM, Weiss M, Strous RD. To lock or not to lock patients' rooms: the key to autonomy? *Psychiatr Serv.* 2008;59:1100–2.
39. Asylums GE. Essays on the social situation of mental patients and other inmates. Garden City: Anchor Books; 1961.
40. Szumukler G. "Capacity", "best interests", "will and preferences" and the UN convention on the rights of persons with disabilities. *World Psychiatry.* 2019;18:34–41.
41. Appelbaum PS. Clinical practice. Assessment of patients' competence to consent to treatment. *N Engl J Med.* 2007;357:1834–40.
42. Kontos N, Freudenreich O, Querques J. Beyond capacity: identifying ethical dilemmas underlying capacity evaluation requests. *Psychosomatics.* 2013;54:103–10.

43. Kontos N, Querques J, Freudenreich O. Capable of more: some underemphasized aspects of capacity assessment. *Psychosomatics*. 2015;56:217–26.
44. Sokol DK. The “four quadrants” approach to clinical ethics case analysis; an application and review. *J Med Ethics*. 2008;34:513–6.
45. Freudenreich O, Querques J, Kontos N. Four questions to guide clinical decisions. *Curr Psychiatr Ther*. 2011;10:86.
46. Lamb HR, Weinberger LE. Meeting the needs of those persons with serious mental illness who are most likely to become criminalized. *J Am Acad Psychiatry Law*. 2011;39:549–54.

Additional Resources

Websites

<https://www.treatmentadvocacycenter.org/> – The Treatment Advocacy Center’s (TAC) website. TAC advocates for psychiatric treatment for vulnerable populations, as opposed to letting patients go untreated so they can live psychotic in the streets, as if it were a choice. E. Fuller Torrey started TAC over 20 years ago with the goal to reform psychiatric treatment laws and remove barriers to psychiatric treatment, particularly for patients with serious mental illness who are unaware that they are ill.

Books

Earley P. *Crazy : a father's search through America's mental health madness*. New York: G. P. Putnam's Sons; 2006. – Earley, journalist and father, chronicles the sad story of his son with mental illness, as both move through the American legal system. After reading the book, you will appreciate the shortcomings of our current approach to refusal of treatment for mental illness.

Szmukler G. *Men in white coats : treatment under coercion*. Oxford: Oxford University Press; 2018. – Every psychiatrist needs to read one book about coercion in our field. This single-author book written by a prominent British community psychiatrist is a good starting point if you ever wondered if our current laws are non-discriminatory and consistent with human rights.

Article

Saya A, Brugnoli C, Piazzi G, Liberato D, Di Ciaccia G, Niolu C, et al. Criteria, procedures, and future prospects of involuntary treatment in psychiatry around the world: a narrative review. *Front Psych*. 2019;10:271. – This article describes how involuntary treatment differs around the world, reminding us that what may appear normal and customary to us could be seen as barbaric and antiquated (or progressive) somewhere else. If there is variance in medicinal practice, it usually means that there is no one best solution.

Chapter 34

History of Schizophrenia Care



Essential Concepts

- You cannot understand the state of current healthcare without looking through the lens of history.
- Our discipline has its roots in asylum care which always had a custodial aspect to it even if this may not have been the intended purpose.
- Goal displacement (a feature of dysfunction in Weber's systems of bureaucracy) has led to the misuse and demise of institutional care when state hospitals became places of social control and warehousing instead of psychiatric treatment. As a consequence, high-quality and longer inpatient care, if needed, can no longer be provided by the public sector in many states since most state hospitals have closed.
- Community psychiatry as the predominant treatment paradigm today is the result of attempts to reform institutional psychiatry beginning with deinstitutionalization in the 1950s. Since community-based services were never adequately funded, community psychiatry struggles to provide services for increasingly complex outpatients with multimorbidities.
- Many patients who used to live in state hospitals were merely “dehospitalized” (discharged) and “transinstitutionalized” (moved into the criminal justice system); they never reaped the benefit from deinstitutionalization as intended. They literally and figuratively lost their asylum – the place they cannot be expelled from.
- The antipsychiatry movement was *also* a group of reform-minded psychiatrists in the 1960s who tried to improve the care of institutionalized patients who had no voice.

- The behaviors of psychiatrists that led the killing of psychiatric patients in Nazi Germany (Aktion T4) are important reminders that medical practice can be terribly subverted unless the interest of patients and their welfare are of paramount value.
- Any healthcare design needs to pay attention to these areas: patient-centered care, transitional age youth, med-psych integration, community psychiatry (including full continuum of care), multimorbidity (including substance use), workforce development, and technology.
- Professional commitment to humanism and commitment to individual patient welfare must be the basis for all decisions regarding the organization of healthcare.

“Today, any form of the concrete world, of human life, any transformation of the technical and environment is a possibility [...]. This would mean the *end of utopia*, that is, the refutation of those ideas and theories that use the concept of utopia to denounce certain socio-historical possibilities.” [1]

– Herbert Marcuse, 1898–1979; German-American philosopher
of the Frankfurt School

From a lecture delivered in 1967 at the Freie Universität in West Berlin.

Societies since antiquity have grapples with the management and treatment (those are not identical concepts) of those who used to be identified as “mad” or “deranged.” Many patients with serious mental illness in the United States today receive psychiatric treatment not in state-run institutions like the asylums of old anymore but in the community. However, we also have large numbers of patients who are managed in another state-run institution instead, prisons or left to their own devices with no care, homeless in the streets of our inner cities.

I conclude this book with a brief chapter on the history of schizophrenia care and our current mental healthcare system since the availability, accessibility, and affordability of services have an impact on *any* clinical decision you make. This chapter is not a comprehensive or coherent history of psychiatry; refer to the standard text by Shorter listed under Additional Resources [2]. Instead, I selected key institutions and movements that define our current practices. I am going to emphasize our profession’s origins in asylums and the influential community psychiatry movement (that has not yet ended). I also include a section on the antipsychiatry movement and on psychiatry during the German 3rd Reich as both have relevance for ethical practice. How we manage schizophrenia today (i.e., which systems of care are available to us) is the result of historical developments and decisions that people before us made, based on their values and economic realities [3]. If our current system is understood in this way, we need to honestly acknowledge that any system could change – if we want change. This chapter skips healthcare financing and the business of medicine, which are both clearly important technical areas but ultimately more a reflection of what a society prioritizes. There is nothing inevitable about our current healthcare system, and accusations of “utopianism” are often a mere smoke screen for lack of interest in change (see epigraph).

Asylum Psychiatry

Schizophrenia is a young disease, first described in its current, recognizable form by Emil Kraepelin a little more than 100 years ago [4]. Named dementia praecox by Kraepelin in 1893 (in the 4th edition of his textbook [5]), Eugen Bleuler gave schizophrenia its current name [6]. The basic concept of schizophrenia as a non-episodic psychiatric illness characterized by the predominance of typical symptoms of psychosis has not changed much since these early pioneers described this disease entity. What has changed is the way we manage schizophrenia. In Kraepelin's days, psychiatrists (or rather "alienists," as they were called because they tried to help patients overcome their mental "alienation" [7]) practiced in state hospitals. Most patients with schizophrenia, once admitted to a state hospital, would live out their natural lives in these "total institutions" (a term the sociologist Erving Goffman [8] used to describe settings where people are taken care of in their totality, e.g., prisons or the military, in a weaker form a residency would count). The rules that govern behaviors in total institutions are examples of structural violence (see Chap. 32). With deinstitutionalization (see below), state hospitals have fallen out of favor, and many states by now have closed most of their state hospitals.

Asylum psychiatry was not a fundamentally bad idea – it is an example of good intentions gone bad [2]. The first asylums with recognizable state hospital architecture in the United States were set up in the nineteenth century with enlightenment principles in mind: to provide humane care for vulnerable people who had no place in society; rather than chaining them, a healthy environment, away from the stressors of modern life ("moral treatment"), was thought to be conducive to healing and eventual reintegration in society [9]. By World War I, asylums had been turned into the hellholes that many younger psychiatrists associate with them. Why asylum psychiatry failed is a lesson in bureaucratic dysfunction, specifically goal displacement according to Weber's model of bureaucracy: a system set up for a particular purpose gets usurped for different goals [10]. When we began to send people with problems other than mental illness (poverty, sociopathy, alcoholism) to asylums, the link between confinement and treatment was broken, leading to warehousing and overcrowding [11]. To this day, psychiatry has not recovered from this nihilistic and purely custodial image, perpetuated by highly influential movies like "One flew over the cuckoo's nest," released in 1975. This has had tragic consequences for the small but real group of seriously ill patients who require what corresponds to intensive care, even for prolonged periods of time. While nobody wants to bring back the dysfunctional asylums, modern state hospitals are a needed piece in a full continuum of care [12]. Unfortunately, closing yet another state hospital (i.e., reducing psychiatric inpatient beds) appears to be a source of pride for politicians, with a domino effect of many unintended consequences.

Perhaps the most dramatic consequence of the reduction in psychiatric beds has been a move of patients into the correctional setting. Increasingly, the correctional system is being tasked with providing mental health services, down to the job of being "road runners" by shuttling psychiatric patients to psychiatric facilities [13].

(No patient with a heart attack or stroke is transported by the police to a treatment facility.) This task shifting is the result of seriously limited community treatment options and dire shortage of psychiatric beds. As a result, patients with psychiatric conditions only receive treatment once the correctional system has intervened. We seemed to have reached a sad point in our history where another Dorothea Dix needs to emerge to extricate our patients from the correctional system [14].

I also like to point out the diametrically opposed associations that people have when they conjure up images of an “asylum” or the “community.” It should not be forgotten that state hospitals were once seen as “asylums,” as places from which vulnerable people could not be expelled, as one meaning of asylum. The view of asylums changed when what was once a good idea was turned upside down by over-crowding, as noted earlier. Conversely, while “community” conjures up images of peace and happiness, patients can be institutionalized in the community in the middle of downtown Boston, not partaking in civic life but wasting away in poorly run group homes, with little to no interaction with the community at large. A small subgroup of very vulnerable patients no longer has the option of living in an asylum. Not surprisingly, patients create their own places that function as asylums. Is it surprising that the same group of patients frequents emergency rooms, a place from where they cannot be expelled immediately, but have to be listened to and given at least temporary respite?

Key Point

State hospitals (asylums) are no longer fashionable, but they play a key role in a functioning public sector healthcare system that provides high-quality psychiatric care. For a small minority of patients, a longer-term hospitalization would allow for meaningful diagnosis and long-term care planning that is currently all but impossible, including *elective* admissions for necessary stepped care (e.g., a clozapine trial for a complex patient). Many seemingly available inpatient beds are not available as they are reserved for forensic patients. As an unintended consequence of state hospital closures, patients have lost their asylum – a place from which they cannot be ejected.

Community Psychiatry Movement

Today, most patients are cared for in the community. This is the result of medical progress (chlorpromazine became widely available for clinical use in 1954), societal changes (human rights), and legislation (President John F. Kennedy signed the Community Mental Health Centers Act in 1963); together, it allowed for an emptying of state hospitals, known as deinstitutionalization. From a high of 558,000 public psychiatric beds in 1955 (340 bed per 100,000), we had 35,000 beds in 2018 (11 beds per 100,000); this number is woefully inadequate to provide a full continuum of care [15]. Even worse, it could be argued that we did not have successfully dein-

stitutionalize our state hospital population in the United States but merely succeeded in “dehospitalization,” with most people who used to be institutionalized in state institutions now at best be “institutionalized in the community,” or worse “transinstitutionalized” into jails and prisons, or homeless [16].

Penrose Hypothesis

An interesting proposition referred to as the Penrose hypothesis is that each society only tolerates a certain, fixed amount of deviance or pathology that will be actively managed; whether a deviant person (in the sociological sense) is dealt with through the penal system or the medical system depends only on the availability of beds in either system. If psychiatric beds are scarce, rather than being brought to a hospital, patients are arrested and diverted into the criminal justice system, a phenomenon known as “criminalization of the mentally ill.” This inverse relationship between psychiatric and nonpsychiatric beds has been partially confirmed in modern studies (see Fig. 34.1 for a depiction of this relationship) [17].

For many, the promises and hopes of deinstitutionalization never materialized. As anyone treating the typical ambulatory patient with schizophrenia in a community mental health center will discover quickly, high-quality services beyond acute care beds are simply not widely available, and patients often receive little more than medications. An increasingly deskilled workforce is often not qualified to provide behavioral interventions for patients who are among the most difficult patients in psychiatry. Those rehabilitation services that exist are often underfunded and poorly

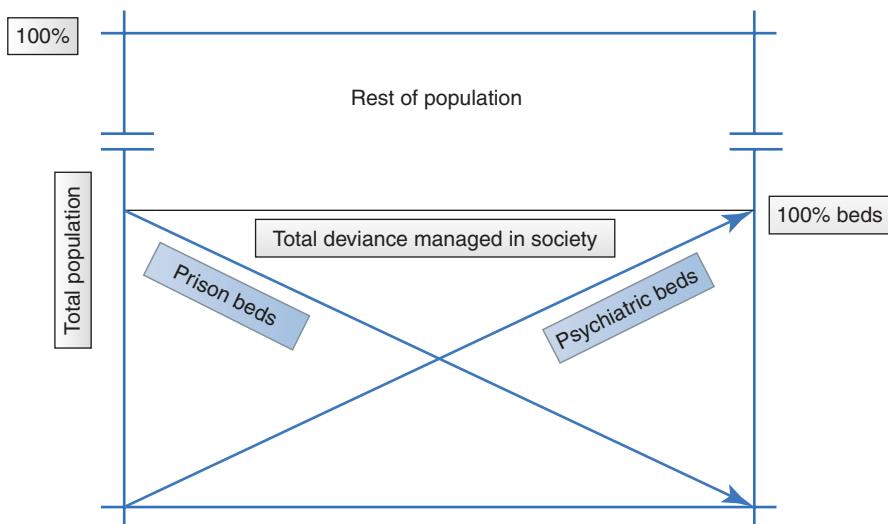


Fig. 34.1 Penrose hypothesis

staffed. Too often, you succeed for brief periods not because of the support of a comprehensive treatment system but because of your persistence and individual, random act of kindness, for example, an insurance person extending a direly needed hospital stay for another 3 days. Sadly, dedication alone and working harder, without financial support and a larger system of care to back you up, seems to be the current American solution for the long-standing mental health crisis. The well-documented burnout in medicine and psychiatry [18] is surely in part due to the organizational chaos in the trenches of today's psychiatric care.

There are great differences in the financing and hence provision of mental healthcare between the states. States that have opted out of the Medicaid expansion (a provision in the Affordable Care Act that increased the number of low-income patients who could receive healthcare through Medicaid), for example, provide less money for their public sector and safety net services. Other states lean philosophically toward a more communitarian responsibility for caring for patients with a serious mental illness who need our support. I suspect disparities in availability of services and access to healthcare between the states due to different levels of funding (moral commitment) will still be an issue in the next edition of this book.

Antipsychiatry Movement

We may be the only specialty that faces sustained critique from a movement, the so-called antipsychiatry movement – there is no anti-cardiology movement. If you go to a major psychiatry meeting, there is usually a protest against psychiatry, often staged by the Citizens Commission on Human Rights (a branch of scientology).

However, we would be foolish to summarily dismiss any critique of our practices as “antipsychiatry.” Other than extreme groups who deny any possible benefit from psychiatric care, psychiatric care, the main people that are usually put into the antipsychiatry bin include psychiatrists and sociologists. The psychiatrists, as far as I can tell, were often reform-minded physicians, and all had a point, just like the sociologists who studied the structure of institutions (Goffman) and state power (Foucault) (see Table 34.1).

In order to understand antipsychiatry we again cannot ignore our field’s history. As noted above, psychiatry as a specialty came out of institutional care that, while

Table 34.1 Lasting contributions from “antipsychiatry”

Proponent	Main point
Franco Basaglia	Patients are citizens who also have rights
Erving Goffman	Total institutions (e.g., state hospitals) also have a control function
Thomas Szasz	Psychiatric diagnosis is also socially constructed
Michel Foucault	Societies control behaviors, including patients, in subtle yet effective ways
RD Laing	There are also pathologies of society, and psychosis is also understandable

set up with the best of intentions, also functioned as systems of exclusion and control which is unique among the medical specialties. The early psychiatrists were all alienists in state hospitals. Today's American Psychiatric Association (APA) was named the "Association of Medical Superintendents of American Institutions for the Insane" when it was founded in 1844. I consider Goffman's insights into the less benevolent aspect of total institutions (prisons, state hospitals, the military) to be important reminders that we behave according to assigned roles and that power needs to always be checked [8]. If you have ever visited a group home, you recognize elements of total institutions [19].

Antipsychiatry was an international phenomenon that emerged in 1960 which in the West was a period of great social change and student protests [20] in which authority and state power was questioned, including by some psychiatrists. An episode in the history of my alma mater, Heidelberg University, in 1970/1971, is instructive (this was before my time). In Germany, the Sozialistische Patientenkollektiv (SPK) was a group of patients and their psychiatrist who ended up breaking away from the university to form their own clinic. SPK was one of the earliest attempts at self-governance and self-help. For the first time in Europe, patients with psychiatric illnesses were given a voice (nobody in a state hospital had one). Importantly, the group was not against psychiatry or treatment but against the dehumanizing conditions in German "Anstaltspsychiatrie" (institutional psychiatry) of the 1970s. Due to the SPK's real or perceived closeness to radical elements in Germany (including the terrorist group RAF), the German state felt threatened and crushed the group with the full force of German law. In Italy, the psychiatrist Franco Basaglia was more successful in his efforts to humanize institutional Italian psychiatry when, more a revolution than reform, he convinced the legislature to close all state hospitals and move Italy to community-based care (Law 180) [21].

Like most ideas, when taken to an extreme, they become absurd. While making a diagnosis is clearly a sociological process (for any diagnosis, not just psychiatry) in which at some point a group in power decided what counts as disease and what not, it does not negate the reality of serious psychiatric illness, even if the diagnostic labels are constructed as noted by the psychiatrist/psychoanalyst Thomas Szasz [22]. Having seen a grossly psychotic patient makes you wonder about the common sense of critics who insist that this illness is a myth. The suffering for patients and their families appears rather real, even if the name of the ailment is constructed and the MRI looks (more or less) normal. Diagnoses come and go, not just in psychiatry but also in medicine as knowledge changes and as societal attitudes change. Psychiatry is often belittled because in 1973 the APA *voted* to remove homosexuality as a disorder from our classification system [23]. And yet other professional societies vote as well. How else did the American Medical Association decide a few years ago if obesity should be considered a disease or not [24]?

What is the legacy of the antipsychiatry movement(s)? One could argue that better civil rights protection of patients today, the peer movement (self-governance), or shared decision-making (end of paternalism) are at least in part due to their stirrings. Dismissing antipsychiatry summarily forgets that psychiatric treatment is not always treatment and not always benign. In countries that never had psychiatry

reforms, reform is needed (or needed again: in the United States, an aforementioned new Dorothea Dix needs to again move patients out of correctional settings). Compulsory treatment while not unknown to medicine is something that psychiatry has had to grapple with since the founding of the specialty in state hospitals. Without civil-minded psychiatrists (and lawyers), would we have policed ourselves and would we continue to try and reduce coercion in psychiatry? For better or worse, at least our field has some outside review. In a free society, justifying your actions, particularly if it involves coercion seems only fair.

Psychiatry in Nazi Germany

To some readers, this may seem to be a curious inclusion. We live in the United States, and Nazi Germany is becoming a distant historical aberration on a different continent. However, I believe general lessons for psychiatry need to be remembered, as psychiatrists function, more than other specialties, also as agents of the state which can lead to particularly severe forms of abuse of power. It is not widely known that Nazi psychiatrists were rather willing, to the point of anticipatory obedience, to cooperate with the Nazi regime and advance the state's eugenic agenda of "racial purification" and betterment of mankind in parallel with their academic careers, with catastrophic costs for Jews but also patients with mental retardation and serious psychiatric illnesses who became defined as subhuman and being an economic burden, like parasites for society. This utilitarian, pseudoscientific genetic race thinking (which was by the way not limited to Nazi Germany but was an area of active research in the United States [25]) and deeply anti-humanistic stance led to the sterilization and forced euthanasia of between 200,000 and 300,000 patients, killed by their psychiatrists in German psychiatric institutions during the so-called Aktion T4 (after an address, Tiergartenstrasse 4, in Berlin where the administrative office was located) [26]. In addition to actively killing patients, many psychiatric patients starved to death. While difficult to be sure about the exact numbers for this psychiatric genocide, at least three quarters of patients with schizophrenia living in Germany between 1939 and 1945 were either sterilized or killed [27]. As a sad coda, psychiatry and the T4 program must be considered a test run for the later development of the six extermination camps, on the occupied Polish territory in the East.

How was this possible? Germany was a modern society with a clear medical code of ethics that, even by today's standards, was progressive. Many assumptions on how this could have happened do not hold up to closer scrutiny. It is simply untrue, for example, that killing your patients was ever an ethically justifiable position in Germany [28] and that psychiatrists were justified what they did against the moral and social norms of their time. Further, many people participating were not sociopaths or "evil," a dangerously reductionist view. Rather, what the German experience showed is that the values of care and compassion can be eroded, *regardless* of what is written in laws and documents; this knowledge from history demands constant vigilance [29] as we today contemplate how to implement our healthcare policies, including coercive measures. Are there groups of patients that are treated

differently *today*, defined as “other,” with all the risks associated with outsider status? Does scientific progress always take the second row vis-à-vis individual patient welfare? What is the historical and intellectual context of the mass incarceration crisis in the United States [30]?

Key Point

They are some lessons learned from psychiatry during the Nazi era: values of compassion can be eroded by false theories and a commitment to “Volksgesundheit” (health of a society) and “Vorsorge” (prevention) over individual Fürsorge (welfare). Medical and social theories of the time (ideologies about health, disease, and personhood), perceived societal or peer pressure, and simple careerism can be enough for atrocities to be committed, particularly when powerful organizations are silent (psychiatry, the Church). Since anti-humanistic forces *always* exist in any society, constant vigilance and a willingness to defend the weak remain of utmost importance.

Schizophrenia Care in the Twenty-First Century

Some harsh realities for patients with serious mental illness have not been effectively addressed since I wrote the first edition of this book a decade ago. Rectifying uneven access to high-quality psychiatric care that is timely, phase-specific, and lifelong, for example, remains a largely aspirational goal. However, I also believe the past decade has led to conceptual progress and clarification of goals for the next decade. Table 34.2 provides a summary of broad treatment principles that need be kept on a whiteboard in any systems redesign.

Table 34.2 Broad treatment principles

<i>Recovery orientation</i>
Patient-centered care ^a
Patient/peer involvement in disease self-management
Holistic care (mens sana in corpore sano; no health without psychiatric health)
<i>Prevention principles</i>
Timely care ^a
Stepped care
Medical prevention (no health without medical health)
<i>High-quality medical care</i>
Effective care ^a
Safe care ^a
Efficient care ^a
Integrated medical-psychiatric care
<i>Accessible care</i>
Equitable care ^a

^aBased on Ref. [31]

What follows is a list of seven specific areas related to systems of care where we made progress and where we should continue to spend our efforts in order to improve care for patients with serious illness.

- *Emphasis on Patient-Centered Care.* A clear emphasis on patient-centered care, shared decision-making, and peer involvement is visible in my home state and in many other states. New programs will need to be designed to help real patients; there can no longer be programs designed for the ideal patient (and convenient for staff). I also have the impression that orthopsychiatry and the recovery movement have had a rapprochement of sorts and that they are no longer locked into a mutually hostile and unproductive grip.
- *Emphasis on Transitional Age Youth.* I suspect that the transitional age youth group will increasingly become a focus of attention as many psychiatric disorders begin in late adolescence/early adulthood. The “early intervention movement” has led to an invigorated prevention effort to improve the long-term outcome of schizophrenia patients. Making early intervention and first-episode programs available to all young patients in all states to minimize the duration of untreated illness and optimally treat the first psychotic episode is an achievable goal.
- *Emphasis on Med-Psych Integration.* The mortality gap between patients with serious mental illness and their peers in the general population has been clearly documented. Now action is needed. The next decade will continue to experiment with new models of med-psych integration that close this gap.
- *Emphasis on Community Psychiatry.* Strengthened community-based psychiatry will remain to be at the center of systems redesign. Paradoxically, a full care continuum that includes sufficient long-term hospital beds is going to be a necessary component of community care unless we want to overburden community care systems with patients who require higher-level services (another example of goal displacement leading to a dysfunctional bureaucracy). While I appreciate the need to improve the interface between the criminal justice system and the psychiatric healthcare system, I am unsure if building more jails and providing psychiatric treatment behind bars is the best ways forward. Ultimately, one goal of the penal system is to punish and to control, not to provide psychiatric care, leading to inevitable role conflict for the institution itself and also for people working in it. As noted earlier, systems become dysfunctional if they are used for purposes they were not intended for. Morally, the push ought to be for strengthening psychiatric outpatient care, not correctional psychiatric care. I suspect the prison-industrial complex is going to be difficult to beat.
- *Emphasis on Multimorbidity.* Today’s patients are complex, suffering from primary psychiatric disorders, substance use disorders, and medical diseases [32]; they are no longer just “dual diagnosis” patients. Many patients have also experienced trauma as a child or live chronically stressful lives. In my own hospital, substance use disorders are now systematically screened for and addressed across the whole spectrum of medical and psychiatric care. Combining funding streams for what are currently different care systems (medical care, psychiatric care, substance use treatment, social entitlement programs) is going to be a complex but necessary endeavor.

- *Emphasis on Workforce Development.* A key question for the next decade will be who should do what? Already, psychiatrists are often limited to prescribing medications. Should we move to a pure specialist model, where psychiatrists provide a very limited number of services themselves, merely supervising care provided by other people, including primary care doctors? Such a model is unlikely to become the dominant model for patients with serious mental illness where, in my opinion, significant knowledge and experience are required. The risk of using a deskilled and cheaper workforce to manage patients with serious mental illness is a concern. Finally, effective, long-term solutions to address burnout are critical; proving free yoga sessions are insulting to hardworking (and probably reasonably resilient) physicians.
- *Emphasis on Technology.* Technology will undoubtedly be applied to schizophrenia care. Apps for symptoms monitoring and patient engagement are already available, and their usability will improve. Concerns about introducing technology will be the inappropriate replacement of humans with technology, misuse of monitoring technology, particularly for minority groups, lack of access to technology (as a health disparity), and patient privacy.

Professionalism and Physician Leadership

We may not always appreciate that physicians, despite many chances in society, remain a respected profession. When we speak up collectively, our voice cannot be ignored.

Increasingly, professionalism demands of us “alienists” to fight for a more just resource allocation on behalf of our patients with serious mental illnesses [33]. Advocacy for social justice in its many forms is part of our job description and not optional (see Table 34.3). While the task of improving care for patients with serious mental illness is daunting (I have been to many care redesign meetings where reform efforts stopped cold in their tracks once the matter of financing them was raised), each one of us can choose if he or she wants to adopt an attitude of hopefulness and get engaged or one of futility and stay on the sidelines. Professionalism clearly demands action.

Table 34.3 Fundamental principles of professionalism

Primacy of patient welfare	Serve the interest of your patient Guard against market forces, societal pressures, and administrative exigencies
Patient autonomy	Respect patient autonomy Empower patients to make informed decisions about their care
Social justice	Promote justice in healthcare system Work toward fair resource distribution Work actively to eliminate discrimination in healthcare

Based on Ref. [33]

I had included a section on psychiatry during the Nazi era as it provides us with perhaps the most important lesson of history vis-à-vis schizophrenia care: humanism matters, particularly for diseases where we have no cure and patients are dependent on the good will and mercy of their neighbors. The welfare of the individual patient sitting across from you must come first. However, George E. Thibault who held a leadership position at Harvard medical education warned that “It will be hard to have humanism in medicine if there is no humanism in the world around us. Human interest, values, and dignity must predominate [34].” Without humanism in a society, people die. In Germany, moderate forces eventually lost control over anti-democratic forces that they had invited and allowed to grow, with the catastrophe of Nazi Germany. There are signs in the United States today that humanism as a guiding principle in the implementation of health policies is under threat. Sometimes it feels as if Enlightenment failed and as if the French Revolution never ended.

Tip

Albert Schweitzer who was a physician developed his humanistic philosophy of “Ehrfurcht vor dem Leben” (reverence for life) [35]. Humanism as a foundational principle of medicine must be the “Leitidee” or guiding principle when we decide how to care for patients with schizophrenia in the next decade.

I am going to end this book with an inspiration and obligation that I discovered as an inscription on a fountain in Cambridge, Massachusetts. These are the words of President John F. Kennedy from his address to the Massachusetts Legislature 11 days before his inauguration, on January 9, 1961:

When at some future date the high court of history sits in judgment on each of us ... our success or failure in whatever office we hold will be measured by the answers to four questions:

*Were we truly men of courage ... ? Were we truly men of integrity ... ?
Were we truly men of judgment ... ? Were we truly men of dedication?*

*The enduring qualities of Massachusetts –
the common threads woven by the Pilgrims and the Puritans,
the fisherman and the farmer, the Yankee and the immigrant –
are an indelible part of my life, my convictions,
my view of the past, and my hopes for the future.*

References

1. Kellner D, Pierce C, editors. Marxism, revolution, and utopia: collected papers of Herbert Marcuse. Abingdon: Routledge; 2014.
2. Shorter E. A history of psychiatry: from the era of the asylum to the age of Prozac. New York: Wiley; 1997.

3. Shorter E. History of psychiatry. *Curr Opin Psychiatry*. 2008;21:593–7.
4. Jablensky A. Living in a Kraepelinian world: Kraepelin's impact on modern psychiatry. *Hist Psychiatry*. 2007;18:381–8.
5. Adityanjee AYA, Theodoridis D, Vieweg VR. Dementia praecox to schizophrenia: the first 100 years. *Psychiatry Clin Neurosci*. 1999;53:437–48.
6. McGlashan TH. Eugen Bleuler: centennial anniversary of his 1911 publication of dementia praecox or the group of schizophrenias. *Schizophr Bull*. 2011;37:1101–3.
7. Diamond SA. Who were the alienists? *Psychology Today*. 2018. Available from: <https://www.psychologytoday.com/us/blog/evil-deeds/201801/who-were-the-alienists>. Accessed on 7/1/2019.
8. Goffman E. Asylums. Essays on the social situation of mental patients and other inmates. Garden City: Anchor Books; 1961.
9. King LJ. A brief history of psychiatry: millennia past and present—part II. *Ann Clin Psychiatry*. 1999;11:47–54.
10. Marcos LR. Dysfunctions in public psychiatric bureaucracies. *Am J Psychiatry*. 1988;145:331–4.
11. Kosky R. From morality to madness: a reappraisal of the asylum movement in psychiatry 1800–1940. *Aust N Z J Psychiatry*. 1986;20:180–7.
12. Sisti DA, Segal AG, Emanuel EJ. Improving long-term psychiatric care: bring back the asylum. *JAMA*. 2015;313:243–4.
13. Treatment Advocacy Center. Road runners 2019. Available from: <https://www.treatmentadvocacycenter.org/road-runners>. Accessed on 7/1/2019.
14. Haas LF. Dorothea Lynde Dix (1802–87). *J Neurol Neurosurg Psychiatry*. 1994;57:1465.
15. Treatment Advocacy Center. Beyond beds. The vital role of a full continuum of care 2017. Available from: <https://www.treatmentadvocacycenter.org/beyond-beds>. Accessed on 7/1/2019.
16. Schildbach S, Schildbach C. Criminalization through transinstitutionalization: a critical review of the Penrose hypothesis in the context of compensation imprisonment. *Front Psych*. 2018;9:534.
17. Mundt AP, Chow WS, Arduino M, Barriouevo H, Fritsch R, Girala N, et al. Psychiatric hospital beds and prison populations in South America since 1990: does the Penrose hypothesis apply? *JAMA Psychiatr*. 2015;72:112–8.
18. Maslach C, Leiter MP. Understanding the burnout experience: recent research and its implications for psychiatry. *World Psychiatry*. 2016;15:103–11.
19. Kontos N, Freudenreich O, Querques J. Outpatient institutionalization – 100 words. *Br J Psychiatry*. 2014;205:339.
20. Berlim MT, Fleck MP, Shorter E. Notes on antipsychiatry. *Eur Arch Psychiatry Clin Neurosci*. 2003;253:61–7.
21. Babini VP. Looking back: Italian psychiatry from its origins to Law 180 of 1978. *J Nerv Ment Dis*. 2014;202:428–31.
22. Kelly BD, Bracken P, Cavendish H, Crumlish N, MacSuibhne S, Szasz T, et al. The myth of mental illness: 50 years after publication: what does it mean today? *Ir J Psychol Med*. 2010;27:35–43.
23. Drescher J. Out of DSM: depathologizing homosexuality. *Behav Sci*. 2015;5:565–75.
24. Frelick M. AMA declares obesity a disease: medscape psychiatry. 2013. Available from: <https://www.medscape.com/viewarticle/806566>. Accessed on 7/1/2019.
25. Reilly PR. Eugenics and involuntary sterilization: 1907–2015. *Annu Rev Genomics Hum Genet*. 2015;16:351–68.
26. Lifton RJ. The Nazi doctors: medical killing and the psychology of genocide. New York: Basic Books; 1986.
27. Torrey EF, Yolken RH. Psychiatric genocide: Nazi attempts to eradicate schizophrenia. *Schizophr Bull*. 2010;36:26–32.
28. Strous RD. Psychiatry during the Nazi era: ethical lessons for the modern professional. *Ann General Psychiatry*. 2007;6:8.

29. Seeman MV. Psychiatry in the Nazi era. *Can J Psychiatr.* 2005;50:218–25.
30. Appleman LI. Deviancy, dependency, and disability: the forgotten history of eugenics and mass incarceration. *Duke Law J.* 2018;68:417–78.
31. Institute of Medicine (IOM). Crossing the quality chasm: a new health system for the 21st century. Washington, DC: National Academy Press; 2001.
32. Langan J, Mercer SW, Smith DJ. Multimorbidity and mental health: can psychiatry rise to the challenge? *Br J Psychiatry.* 2013;202:391–3.
33. ABIM Foundation, American College of Physicians-American Society of Internal Medicine, European Federation of Internal Medicine. Medical professionalism in the new millennium: a physician charter. *Ann Intern Med.* 2002;136:243–6.
34. Thibault GE. Humanism in medicine: what does it mean and why is it more important than ever? *Acad Med.* 2019;94(8):1074–7.
35. Schweitzer A. Aus meinem Leben und Denken. Frankfurt: Fischer Taschenbuch; 1995. p. 1931.

Additional Resources

Books

Kotowicz ZRD. Laing and the paths of anti-psychiatry. London: Routledge; 1997. – While written around R. D. Laing, this book brings the reformist spirit of the 1960s to life, including other writers and movements of the time.

Scull A. Madness: a very short introduction. Oxford: Oxford University Press; 2011. – The author who is a sociologist brings to life in this small volume from Oxford University Press's Very Short Introduction series how societies since antiquity have understood and coped with “madness,” or with people suffering from a serious mental illness, as we refer to them today.

Shorter E. A history of psychiatry: from the era of the asylum to the age of Prozac. New York: John Wiley & Sons, Inc; 1997. – A well-organized and logical history of psychiatry that includes the origins of asylum psychiatry, the asylum era itself, and subsequent social reforms and attempts to establish a more scientifically-based biological psychiatry.

Articles

Freudenreich O, Kontos N. “Professionalism, physicianhood, and psychiatric practice”: conceptualizing and implementing a senior psychiatry resident seminar in reflective and inspired doctoring. *Psychosomatics.* 2019;60:246–54. – Summary of a course on professionalism that I taught together with my friend and colleague for ten years.

Marcos LR. Dysfunctions in public psychiatric bureaucracies. *Am J Psychiatry.* 1988;145:331–4. – One of the most important articles I read that opened my eyes to the importance of functioning bureaucracies (a term that has gotten a bad reputation because many bureaucracies are dysfunctional). The author helpfully applies Max Weber's theory of bureaucracies to public sector psychiatry in order to explain many frustrations that you will be quite familiar with.

Strous RD. Psychiatry during the Nazi era: ethical lessons for the modern professional. *Ann Gen Psychiatry.* 2007;6:8. – An important call to continue to teach ethics in medicine that is informed by the lessons from history.

Index

A

- ABCs of estimating adherence, 417
- ABCs of suicide, 403
- Abnormal involuntary movement scale (AIMS), 192
- Absolute neutrophil count (ANC), 234–236
- ACLAIMS trial, 254
- Acute and transient psychotic disorders (ATPD), 70, 74
- Adjunctive medications
 - anticholinergics, 270–272
 - antidepressants, 264–266
 - anxiolytics, 266–267
 - acute treatment phase, 266
 - depressive symptoms, 265
 - post-psychotic depressive episodes, 264
 - antiepileptic drugs, 268–270
 - carbamazepine and oxcarbazepine, 269
 - lamotrigine, 268
 - topiramate, 269–270
 - valproate, 268
 - lithium, 267
 - sedative-hypnotics, 267
 - insomnia, 267
 - obstructive sleep apnea, 267
- Aggression, 59, 174, 233, 234, 268, 269, 366, 439
- Alcohol Use Disorders Identification Test for Consumption (AUDIT-C), 354
- American Psychiatric Association (APA), 457
- The American Society of Sleep Medicine, 267
- Anticholinergic load, 281
- Antipsychiatry, 456
- Antipsychotic adherence, 415
- Antipsychotic combination treatment, 291
- Antipsychotic drug metabolism, 278–280

- anticholinergic load, 281
- with antidepressants, 284
- with benzodiazepines, 285
- olanzapine and clozapine, 280
- inducers/inhibitors, 281
- and mood stabilizers, 284–285
- pharmacogenomics, 279–280
 - clozapine-induced agranulocytosis, 280
 - complete metabolic pathway, 280
- therapeutic monitoring, 284
 - clozapine serum levels, 283
 - drug blood level determinations, 282
 - point-of-care, 283
- Antipsychotic-induced motor side effects, 187
- Antipsychotics, 172
 - dopamine blockade, 172
 - first-generation antipsychotics, 175
 - cogwheeling, 176
 - D2 blockade, 176
 - mechanism of action, 172–175
 - antipsychotic clozapine, 174
 - biological mechanism, 172
 - clinical efficacy, 172
 - dopamine receptors, 172
 - dopamine storm, 172
 - parkinson's disease, 172
 - neurotoxicity and neuroprotection, 181
 - cortical thinning, 181
 - morbidity and mortality, 181
- non-dopaminergic antipsychotics, 180
 - dopamine-blocking agents, 180
 - 5-HT1a receptor, 180
 - NDMA receptors, 180
 - pimavanserin, 180
- second-generation antipsychotics, 177–178
 - clozapine, 178

- A**
- Antipsychotics (*cont.*)
 - CPZ-Eq, 177
 - 5-HT2a-D2 antagonists, 177
 - QTc interval, 178
 - serotonin 5-HT2a antagonism, 177
 - third-generation antipsychotics, 178–180
 - antipsychotic efficacy, 179
 - brexipiprazole, 179
 - dopamine receptors, 179
 - low-dopaminergic states, 178
 - receptor-binding property, 179
 - Antipsychotic target dose, 146
 - Assessment of executive function, 390
 - Assisted treatment options, 443
 - Auditory hallucinations (AH), 7
- B**
- Barnes Akathisia Rating Scale (BARS), 189
 - Bell's mania, 5
 - Benign ethnic neutropenia (BEN), 234
 - Brief Assessment of Cognition in Schizophrenia (BACS), 389
 - Brief Negative Symptoms Scale (BNSS), 379
- C**
- Capacity evaluation, 445
 - Capgras syndrome, 5
 - Care integration, 345
 - Catatonia, 13–14
 - Charles Bonnet syndrome, 5
 - Childhood-onset schizophrenia (COS), 90
 - Clinical antipsychotic trials, 219
 - Clinical antipsychotic trials of intervention effectiveness (CATIE), 62, 175, 216, 326, 352, 389, 438
 - Clinical Assessment Interview for Negative Symptoms (CAINS), 379
 - Clinical effectiveness, 216
 - CATIE, 217–218
 - clozapine, 217
 - CUtLASS 1, 217
 - randomized trial, 217
 - discontinuing antipsychotics, 224–225
 - antipsychotic reduction, 225
 - dyskinesias, 225
 - supersensitivity psychosis, 225
 - evidence-based prescribing, 216–220
 - morbidity and mortality, 227–228
 - quality of life, 227
 - CUtLASS trial and RAISE trial, 227
 - depression, 227
 - objective markers, 227
 - schizophrenia treatment goals, 220
 - selecting antipsychotics, 220–222
 - age, 221
 - ethnicity, 221
 - gender, 221
 - pharmacogenetic testing, 221
 - shared decision making, 225–227
 - switching antipsychotics, cross-titration, 222–224
 - trials beyond CATIE, 218–220
 - bipolar disorder, 218
 - psychopharmacology, 218
- Clinical indications, 234, 266
- Clinical staging, 122
 - early treatment, 122
 - functional remission, 124
 - phase-specific treatment, 122
 - recovery, 124
 - stepped treatment, 122
 - symptomatic remission, 123–124
- Clozapine, 232
 - agranulocytosis and clozapine registry, 238–239
 - granulocytopenia, 235
 - neutrophil kinetics, 234
 - atypical properties, 232
 - augmentation, 242–243
 - ariPIPrazole, 242
 - dopamine binding, 242
 - benign ethnic neutropenia, 236
 - constipation and ileus, 240
 - indications, 233–234
 - broad-spectrum antipsychotic, 233
 - course-stabilizing properties, 233
 - psychiatric and neurological cases, 233
 - suicidality, 233
 - metabolism and dosing, 236–238
 - complex receptor profile, 236
 - cytochrome P450 enzymes, 236
 - inter-individual variability, 237
 - nor-clozapine, 237
 - REMS guidelines, 237
 - morbidity and mortality, 241–242
 - myocarditis, 239
 - orthostatic hypotension, 239–240
 - refractory psychosis, 233
 - seizures, 239
 - sialorrhea, 240
 - urinary incontinence, 240–241
- Clozapine black box warnings, 238
- Clozapine side effects, 241
- Clusters of schizophrenia, 110
- Cognitive deficits, 386
 - clinical approach, 393–395
 - brain healthy, 394–395
 - educate family members, 393

- rely on routines, 394
sufficient time, 394
- clinical assessment, 388–391
attention/vigilance, 390
cognitive battery, 389
diagnostic criteria, 388
frontal lobe functions, 390
functional neuroimaging, 391
MATRICS, 389
premorbid IQ, 391
processing speed, 390
verbal learning and memory, 390
working memory, 390
- impairments, 386–388
behavioral disinhibition, 388
neuroanatomical model, 387
neuropsychological testing, 387
prefrontal systems, 387
pre-morbid IQ, 387
social cognition, 387
stimulus-bound responses, 388
top-down cognitive control, 388
- negative symptoms, 386
- Pfropfschizophrenie*, 386
- social skills groups, 392
- treatment, 392–395
cognitive rehabilitation, 393
cognitive test scores, 392
neurocognitive disorders, 392
pro-cognitive effects, 392
risperidone, 392
- Cognitive domains, 389
- Comparison of antipsychotics for metabolic problems (CAMP), 222, 343–344
- Conrad's stage model, 93
- Coping strategies, 308
- Coping styles, 309
attitudinal-based coping, 309
emotion-based coping, 309
problem-based coping, 309
- Cotard's syndrome, 5
- Course of schizophrenia, 89
- CUtLASS 1 (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study), 227
- D**
- De Clérambault syndrome, 5
- Delirium
clinical presentation, 27–28
hallucinations, 28
psychosis, 28
- diagnosis, 28–31
catatonia, 31
- confusion assessment method, 29
- dementia, 28
- depression, 28
- mania, 28
- psychosis, 28
- risk factor model, 31
- etiologies, 29
intoxication, 29
medical conditions, 29
psychiatric conditions, 29
withdrawal, 29
- initial work-up, 30
ancillary tests, 30
blood tests based on clinical situation, 30
laboratory work-up, 30
- prevention, 33
nonpharmacological measures, 33
sleep-wake cycle, 33
- treatment, 31–33
antipsychotics, 31
benzodiazepines, 32
haloperidol, 31
pharmacological approaches, 32
pharmacotherapy, 32
- Diagnosis of psychosis, 70
- Diagnostic assessment of schizophrenia
assessment, 108
assessment of functional capacities, 108
diagnostic medical assessment, 108
diagnostic psychiatric assessment, 108
risk assessment, 108
substance use assessment, 108
- diagnostic criteria, 102–104
checklist psychiatry, 103
prototype approach, 103
- diagnostic features, 103
active-phase symptoms, 103
duration of symptoms, 103
functional decline, 103
- diagnostic mistakes, 105–106
diagnostic omissions, 106–107
comprehensive assessment, 107
dimensional assessment, 108–109
functional assessment, 109–111
quality of life, 111
rating scales, 111
dissociative symptoms, 105
longitudinal symptoms, 105
peculiarities, 106
psychosis continuum concept, 106
racial stereotypes, 106
transient psychotic experiences, 105
florid psychopathology, 104

- Digit-symbol substitution test (DSST), 390
 Drug-induced psychosis, 38
 cocaine and amphetamines, 43–44
 diagnosis, 38–41
 dextromethorphan, 38
 drug intoxication, 39
 substance-induced psychosis, 39
 LSD and hallucinogens, 44–45
 PCP and ketamine, 45
 psychopathology, 39–40
 adulterated drugs, 40
 model psychosis, 39
 Schneiderian symptoms, 39
 visual hallucinations, 40
 substances of misuse, 41–45
 alcohol and sedatives, 41–42
 cannabis and cannabinoids, 42–43
 clinical vignette, 42
 treatment, 41
 urine drug testing, 40–41
 benzodiazepine levels, 41
 false positive drug test, 41
 serum alcohol level, 41
 serum cocaine levels, 41
 urine drugs screens, 40
- Dual diagnosis, 351
 assessment, 353–355
 hair testing, 354
 laboratory screening, 354
 caffeine intoxication, 352
 treatment, 355–357
 antidipsomanic medication, 356
 clozapine, 356
 cocaine, 356
 community support programs, 355
 disulfiram, 356
 health care system, 355
 psychosocial services, 355
- Duration of untreated psychosis (DUP), 94
- E**
 Early course schizophrenia, 142
 Early intervention, 139
 Ekbom's syndrome, 5
 Electroconvulsive therapy (ECT), 77
 Electroencephalogram (EEG), 56
 Emergency management
 appropriate disposition, 134
 initial and differential diagnosis, 131–133
 delirium, 131
 frequent flyer with psychosis, 133
 medical clearance, 132
 older patient with recent onset of psychosis, 132
- patients with long-standing history of psychotic illness, 133
 young patient with first episode of psychosis, 132
 young, combative patients, possibly psychotic, 132
 stabilization, 128–131
 agitation, 128
 benzodiazepines, 130
 cardiac toxicity, 130
 chemical restraint, 129
 intramuscular droperidol, 129
 loxapine, 129
 neuroleptization, 130
 sublingual asenapine, 129
 verbal de-escalation, 129
 treatment specific for diagnosis, 133–134
 Entitlement and welfare programs, 331
 Eponyms of psychotic conditions, 5
 Etiological factors, 293
 EUFEST (European First-Episode Schizophrenia Trial), 145
 EAGLES (Evaluating Adverse Events in a Global Smoking Cessation Study) trial, 366
 Extrapyramidal side effects (EPS), 62, 270
- F**
 Fading of psychosis, 147
 First episode psychosis, 118, 138
 acute phase, ancillary medications, 144–146
 antipsychotic choice, 145–146
 EUFEST trial, 145
 second-generation antipsychotics, 145
 antipsychotic dose, 146
 antipsychotics due to non-response
 amisulpride, 147
 injectable antipsychotics, 148
 OPTiMiSE trial, 147
 antipsychotics due to non-response, 147–148
 components, 151
 course, 140
 diagnosis, 139
 frank psychosis, 140
 longitudinal development, 139
 manic episode, 140
 prodromal period, 140
 prototypical course, 140
 diagnostic uncertainty, 141
 duration of antipsychotic, 149–150
 first-episode services, 150–152
 medical examination, 141

- phase-specific treatment goals, 141–150
prodromal phase, 142–144
 biological markers, 143
 BLIPS, 142
 frank psychotic symptoms, 143
 NEURAPRO trial, 143
 syndromal diagnosis, 143
stabilization phase, 146–148
stable phase (maintenance phase), 148–150
- First-episode schizophrenia
 laboratory tests, 55
 neuroimaging, 55
- First-generation antipsychotics (FGAs), 174, 176
- Fluorescent treponemal antibody absorption test (FTA-Abs), 56
- Food and Drug Administration (FDA), 161, 175
- Forensic aspects
 capacity evaluations, 444–446
 involuntary treatment, 440–444
 involuntary confinement, 442
 psychiatric commitment, 441
 psychiatric illness, 442
 psychological suffering, 443
 staff training and education, 444
 narrow forensic issues, 436
 paternalism in health care, 446–448
 violence risk assessment, 437–439
 cultural scripts, 437
 limbic warning system, 438
 structured professional judgment model, 439
 violence risk reduction, 439–440
 criminalization, 440
 gun access, 440
 non-adherence, 440
 residual psychosis, 440
 socio-toxic consequence, 440
- Formal thought disorder, 12
- 4-quadrants approach, 446
- Functional assessment, 110
- G**
- Ganser syndrome, 5
- Global Smoking Cessation Study, 366
- Granulocyte colony-stimulating factor (G-CSF), 236
- H**
- Hallucinogen persisting perception disorder (HPPD), 45
- Health and Recovery Peer (HARP) program, 307
- Hearing Voices Networks (HVN), 7
- History of schizophrenia, 88–91
 childhood-onset schizophrenia, 90
 chronic period, 89
 chronic phase, 94–95
 first-episode of psychosis, 94
 late-onset schizophrenia, 90–91
 clinical features, 90
 delusional disorder, 91
 long-term outcome, 95–97
 post-partum psychosis, 91
 premorbid phase, 91–92
 prototypical illness, 90
 psychotic relapse, 95
 role of culture, 97
 schizophrenia prodrome, 92–94
- Hopkins Verbal learning Test (HVLT), 389
- Human immunodeficiency virus (HIV), 61
- Hyperprolactinemia, 205
- I**
- Illness insight, 412–414
 acceptance of need for treatment, 413
 acknowledgement of illness, 413
 actual compliance behavior, 418–419
 awareness of symptoms, 413
 barriers to adherence, 418
 cognitive-behavioral therapy, 413
 medication adherence, 414–421
 assessment of, 416–419
 health belief model, 415–416
 health care access problems, 415
 neuropsychiatric and cognitive deficits, 415
 neuropsychiatric deficits, 414
 optimization, 419–421
 environmental supports, 420
 long-acting injectable antipsychotics, 420
 positive drug experience, 420
 psychoeducation, 420
 professed drug attitude, 417–418
- Indications for benzodiazepines, 266
- Intensive family involvement, 316
- International Classification of Diseases (ICD), 103
- Interpersonal deficits, 325
- InterSePT (International Suicide Prevention Trial), 404, 405
- Intravenous haloperidol, 32
- J**
- Jerusalem syndrome, 5

K

Kleist-Leonhard classification, 73
Korsakoff's psychosis, 5
Kraepelin-Morel disease, 5

L

Late-onset schizophrenia (LOS), 90, 91
Lhermitte's (peduncular) hallucinosis, 5
Long-acting injectable antipsychotics (LAIs), 250, 255–256
ACLAIMS trial, 254
advantages, 250–252
oral aripiprazole, 251
REMIND trial, 251
aripiprazole lauroxil, 257
contraindications for, 254
harm reduction, 253
indications, 252
limitations, 258–259
long-acting risperidone, 254
low-dose approach, 258
oral antipsychotic, 254
patient selection, 252–254
PRELAPSE trial, 250
Looseness of associations (LOAs), 11
Lysergic acid diethylamine (LSD), 38

M

Magnetic resonance imaging (MRI), 52
Medical morbidity and mortality
antipsychotic-associated weight gain, 336
causes of, 337–338
cancer mortality, 337
RAISE trial, 337
smoking, 337
medical prevention mindset, 338–339
blood-borne infections, 339
body mass index, 339
screening, 339
verbal intervention, 338
metabolic disease prevention, 339–345
antipsychotic-naïve patients, 340
disease-intrinsic motivational deficits, 340
mortality gap, 336
primary prevention, 340–342
STRIDE, 341
therapeutic lifestyle changes, 341
reverse integrated care, 345–347
secondary prevention, 342–343
antipsychotic-induced weight gain, 343
guideline-concordant screening, 342
metabolic screening bundle, 342

SGA drugs, 342

tertiary prevention, 343–345
Medication assisted treatment (MAT), 356
Metabolic monitoring, 242, 343
Metabolic pathways, 279
Metabolic risk management, 344
Methamphetamine, 43
Methylenedioxymethamphetamine (MDMA), 43
Mini Mental State Examination (MMSE), 390
Montreal Cognitive Assessment (MoCA), 390
Motor side effects
acute dystonic reaction, 188
emergency room, 189
parenteral benzotropine, 188
akathisia, 189
extrapyramidal symptoms, 190
mirtazapine, 190
neuroleptic malignant syndrome, 196–197
neuroleptic-induced dysphoria, 196
parkinsonism, 190
tardive dyskinesia, 191–192
anticholinergics, 194
botulinum injections, 195
deutetrabenazine, 195
diagnosis, 192
valbenazine, 195
Münchhausen syndrome, 5

N

National Alliance of Mental Illness (NAMI), 316
National Institute on Drug Abuse (NIDA), 40
Negative symptom domains, 376
Negative symptoms, 375
anticipatory pleasure, 377
clinical assessment, 377–379
goal setting, 378
primary/secondary distinction, 378
ratings scales, 379
cognitive impairment, 377
consummatory pleasure, 377
differential diagnosis, 379
DSM-5, 376
environmental stimulation, 382
secondary causes of, 381–382
anhedonia, 381
parkinsonism, 381
self-rating scale, 381
social competence, 382
treatment, 379–382
bitoperkin, 380
cariprazine, 380
deficit syndrome, 380

- L-methylfolate, 380
mirtazapine, 380
standard folic acid supplementation, 380
NEURAPRO trial, 143
Neuroleptic malignant syndrome (NMS), 186
New-onset psychosis, 51
Nicotine facts, 369
Nicotine replacement therapy (NRT), 365
N-methyl-D-aspartate (NMDA), 59
Nonmotor side effects, 202
 anticholinergic side effects, 209
 cardiac toxicity, 207–209
 dose-related QTc, 207
 intravenous haloperidol, 207
 QT interval, 207
 R-R interval, 207
 ziprasidone, 207
 ZODIAC trial, 208
eye and dental care, 209–210
 pigmentary retinopathy, 209
 serial slit-lamp examinations, 209
hyperprolactinemia and sexual side effects, 204–207
 antipsychotic-induced amenorrhea, 206
D2-binding, 205
prolactin levels, 206
prolactin-related side effects, 205
prolactin-sparing antipsychotic, 205–206
mortality from antipsychotics, 210–211
sedation, 202
weight gain and metabolic side effects, 203–204
 antipsychotic-naïve, 204
BMI calculations, 203
CATIE cohort, 203
meta-analysis of, 203
metabolic monitoring guidelines, 203
olanzapine, 203
- O**
Obsessive-compulsive disorder (OCD), 81, 107
Open dialogue (OD), 319, 320
OPTiMiSE (Optimization of Treatment and Management of Schizophrenia in Europe) trial, 147
Othello syndrome, 5
- P**
Patient Health Questionnaire (PHQ-9), 111
Patient Outcomes Research Team (PORT), 203
Penrose hypothesis, 455
Pharmacotherapy, 365–369
 clinical problems, 369–371
drug interactions, 369–370
nicotine withdrawal, 370
patient concerns, 370–371
maintenance treatment, 368–369
smoking cessation treatment, 365–368
 bupropion, 365
 EAGLES trial, 366
 nicotine replacement therapy, 366
 tolerability, 365
 vaping, 368
 varenicline, 366
Polypharmacy, 290
 anticipate resistance, 296
 antipsychotics, 291
 brown bag examination, 297
 counterproductive pattern, 296
 diagnosis, 292–294
 cross-taper, 293
 fragmentation, 293
 maintenance medications, 293
 unrecognized pseudo-refractoriness, 292
 efficacy, 291
 mythological views, 296
 non-medication alternatives, 297
 prevention, 294–296
 hedonistic approach, 295
 hippocratic medicine, 295
 rule and the Holmes rule, 295
 socio-cultural context, 295
 psychological support, 291
 supplemental symptom control, 291
 treatment intolerance, 291
Prevention
 early detection, 119
 duration of untreated psychosis, 119
 neurocognitive problems, 119
 RAISE cohort, 119
 early intervention, 118–119
 critical illness period, 118
 full-blown psychosis, 118
 neurodevelopmental disorder, 118
 preventing relapse, 120–122
 primary prevention, 118
 psychosocial toxicities, 117
 secondary prevention, 118
 tertiary prevention, 119
PRELAPSE trial, 250
PRIDE (Paliperidone Palmitate Research in Demonstrating Effectiveness) trial, 252
PROACTIVE (Preventing Relapse Oral Antipsychotics Compared to Injectables Evaluating Efficacy) trial, 251
Professionalism, 461

- Prodromal symptoms, 92
- Prolactin-sparing antipsychotics, 205
- Psychiatric interview, 17
- concepts, 17
 - delusions, 20
 - hallucinations, 20
 - history and mental status, 18–21
 - maligner psychosis, 24
 - mental status examination, 18
 - mistakes, 22–24
 - paranoia, 20
 - past psychosis, 21
 - patient observation, 19
 - review of systems, 20
 - Schneiderian first-rank symptoms, 20
 - unwilling patients, 24
- Psychiatric rehabilitation, 324
- recovery, 331–333
 - personal recovery goals, 333
 - recovery-oriented care, 333
 - recovery-oriented rehabilitation, 331
 - rehabilitation goals and assessment, 325–328
 - rehabilitation tools, 328–331
 - ACT programs, 329
 - pre-vocational training, 329
 - social skills training, 328
- terminology, 324–325
- first-episode programs, 324
 - skill building, 324
 - wellness movement, 327
- Psychiatric rehabilitation tools, 328
- Psychological treatment, 302
- cognitive-behavioral therapy, 305–306
 - behavioral experiments, 305
 - benefit of, 306
 - broken brain model, 305
 - delusions, 306
 - goals and techniques, 303–305
 - positive psychology and resilience, 307–309
 - cognitive impairment, 309
 - coping mechanisms, 308
 - 3rd wave of CBT, 308
 - Victor Frankl's logotherapy, 308
- psychoanalysis, 302
- psychoeducation, 306–307
- supportive therapy, 302–305
- Psychological treatments
- expressed emotions, 317–319
 - family involvement, 314–315
 - open dialogue, 319, 320
 - selection of families, 315–316
 - crisis intervention, 317
 - emotions model, 316
 - family work, 316
 - first-episode treatment, 316
- Psychopharmacology, 131
- first-line oral options, 131
 - first-line parenteral options, 131
 - second-line options, 131
 - third-line options, 131
- Psychosis, 77
- Psychosocial history, 429
- Psychotic signs and symptoms
- behavioral disorganization and catatonia, 13–14
 - delusions, 3–6
 - formal thought disorder, 10–12
 - hallucinations, 6–10
 - hallucinosis, 8
 - impaired reality testing, 3
 - overvalued idea, 6
 - Schneiderian first-rank symptoms, 8–10
- Q**
- Quality of life, 111
- R**
- RAISE (Recovery After an Initial Schizophrenia Episode) trial, 227
- Rare and uncommon diseases, 54
- Receptors, 173
- Remedies for nonadherence, 420
- REMIND trial, 251
- S**
- Scale for the Assessment of Negative Symptoms (SANS), 379
- Scheme of movements disorder, 186
- Schizophrenia care
- antipsychiatry movement, 456–458
 - psychiatry reforms, 457–458
 - asylum psychiatry, 453–454
 - community treatment, 454
 - continuum of care, 453
 - moral treatment, 453
 - nonepisodic psychiatric illness, 453
- care in the 21st century
- community psychiatry, 460
 - med-psych integration, 460
 - multimorbidity, 460
 - patient-centered care, 460
 - physician leadership, 461–462
 - technology, 461
 - transitional age youth, 460
 - workforce development, 461

- community psychiatry movement, 454–456
dehospitalization, 455
penrose hypothesis, 455–456
professionalism, 461–462
psychiatry in Nazi Germany, 458–459
genetic race thinking, 458
moral and social norms, 458
- Schizophrenia subtypes, 377
- Schizophrenia spectrum disorders, 71–74
atypical psychoses, 73–74
autism, 81–83
Asperger's syndrome, 82
neurodevelopmental difficulties, 81–82
syndromal diagnosis, 82
- catatonia, 78–79
classification, 79
periodic catatonia, 79
- delusional disorders, 74–76
Ekblom syndrome, 74
Othello syndrome, 74
- folie à deux, 78
- mood disorders, 76–78
- personality disorders, 79–81
- psychotic depression, 76–77
antidepressants, 77
bipolar depression, 76
delusions level, 77
psychomotor retardation, 76
- psychotic mania, 78
mood-congruent, 78
- schizoaffective disorder, 72–73
bipolar disorder, 72
cross-sectional symptoms, 72
mood and psychotic symptoms, 72
mood stabilizers, 72
non-pharmacological approaches, 72
- schizophrenia, 71
biomarkers, 71
gluten-sensitivity, 71
treatment approach, 71
- Schneiderian first-rank symptoms, 9
- Secondary schizophrenia
autoimmune diseases, 57–58
clinical presentation, 52–53
olfactory hallucinations, 53
Schneiderian first-rank symptoms, 53
- clinical vignette, 52
autoimmune multisystem disease, 52
Huntington's disease, 52
- diagnosis, 53–56
autoimmune inflammatory brain diseases, 56
first-episode, 54
- multiple sclerosis, 53
silent brain tumor, 56
- differential diagnosis, 50–52
- endocrine diseases, 57
- genetic disorders, 56–57
- infections, 61
- metabolic diseases, 57
- narcolepsy, 58
- neurologic conditions, 58–60
autoimmune inflammatory brain diseases, 59
basal ganglia diseases, 59
brain tumors, 60
dementias, 60
demyelinating diseases, 59
seizures, 58
stroke, 58
- toxins, 61
- treatment, 61–62
antipsychotics, 62
cholinesterase inhibitors, 61
Parkinson's disease, 62
vitamin deficiencies, 60
- Second-generation antipsychotics (SGAs), 62, 177, 216
- Selective serotonin reuptake inhibitors (SSRIs), 265
- Shared decision making, 226
- Simpson-Angus Rating Scale (SARS), 190
- Smoking cessation treatment, 352, 363
bupropion, 367
varenicline, 367
- Social adversity, 426–428
anxiety and depression, 427
assessment, 428–429
microaggressions, 429
psychological ramifications, 429
racism, 429
- economic disadvantage, 426
- social selection theory, 426
- stigma, 429–432
broken brain model, 430
non-discriminatory policies, 431
psychoeducation, 431
self-stigmatization, 430
vicious cycle, 430
- structural violence, 427
natural illness course, 427
social advocacy, 428
- Social determinants of health (SDOH), 426
- SOHO (Schizophrenia Outpatients Health Outcomes), 109
- Sozialistisches Patientenkollektiv (SPK), 457

- Spectrum of symptoms in NMS, 197
- Suicide, 400
- assessment, 402–404
 - ABCs of suicide, 403
 - CDC, 402
 - Columbia scale, 404
 - relapse and hospitalization, 400
 - risk factors for, 400–402
 - anomic suicide, 402
 - depressive symptoms, 401
 - Mann's stress-diathesis model of suicide, 402
 - neurocognitive impairment, 402
 - post-psychotic depression, 401
 - psychosis, 401
 - state-dependent stressor, 402
 - treatment
 - high placebo-response rate, 405
 - interSePT trial, 404, 405
 - psychopharmacologic treatment, 404
 - subsyndromal depressive symptoms, 405
- Suicide assessment, 403
- Supplemental Security Income (SSI), 330
- Supportive therapy, 303
- Symptomatic remission, 123
- Systemic lupus erythematosus (SLE), 57
- T**
- Tardive dyskinesia, 193
 - Tetrahydrocannabinol (THC), 42
 - Third-generation antipsychotics, 180
 - Tobacco use disorder
 - average life expectancy, 360
 - cascade framework, 362
 - chronic relapsing substance, 362
 - long-term smokers, 360
 - psychiatric treatment, 361
 - smoking status assessment, 360, 362–365
 - help to quit, 364–365
- history, 362
- motivate to quit, 363–364
- smoking cessation, 361
- Tom Sawyer approach, 315
- Toxin-induced psychosis, 45–46
- Traumatic brain injury, 60
- Treatment Response and Resistance in Psychosis (TRRIP), 158
- Treatment-resistant schizophrenia (TRS), 158, 159
- antipsychotic trial, 160–162
 - dopamine blockade, 162
 - OPTiMiSE trial, 162
 - clozapine augmentation, 165–166
 - evidence-based treatments, 165
 - pimavanserin, 165
 - reserpine, 166
 - clozapine non-response, 164–167
 - clozapine trial, 163–164
 - cognitive-behavioral therapy, 166–167
 - electroconvulsive therapy, 165
 - rule-out pseudo-refractoriness, 159–162
 - symptomatic improvement, 160
 - therapeutic drug monitoring, 161
- V**
- Visual hallucinations, 7
- W**
- Wellness Recovery Action Plan (WRAP), 307
 - Wernicke's encephalopathy, 5
 - World Health Organization (WHO), 270, 412
- Z**
- ZODIAC (Ziprasidone Observational Study of Cardiac Outcomes) trial, 208