Psychosis in adults: Initial management

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INTRODUCTION

Psychosis is a condition of the mind broadly defined as a loss of contact with reality. Psychotic symptoms can increase patients' risk for harming themselves or others or being unable to meet their basic needs.

Psychosis may be seen in many psychiatric disorders. It is the core feature of schizophrenia and other conditions in the schizophrenia spectrum and may occur in bipolar disorder and major depression with psychotic features. Psychosis may also be a manifestation of substance use or underlying medical disease.

This topic will address initial management of psychosis. The epidemiology, pathogenesis, clinical manifestations, comorbid conditions, and initial evaluation of psychosis in adults are discussed elsewhere. Maintenance treatment of schizophrenia, management of side effects from antipsychotic medications, and management of mood disorders with psychosis are also discussed elsewhere.

- (See "Schizophrenia in adults: Epidemiology and pathogenesis".)
- (See "Schizophrenia in adults: Clinical features, assessment, and diagnosis".)
- (See "Schizophrenia in adults: Maintenance therapy and side effect management".)
- (See "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects".)
- (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

- (See "Schizophrenia in adults: Pharmacotherapy with long-acting injectable antipsychotic medication".)
- (See "Schizophrenia in adults: Psychosocial management".)
- (See "Co-occurring schizophrenia and substance use disorder: Psychosocial interventions".)
- (See "Evaluation and management of treatment-resistant schizophrenia".)
- (See "Brief psychotic disorder".)
- (See "Anxiety in schizophrenia".)
- (See "Depression in schizophrenia".)

INITIAL MANAGEMENT

The initial management of patients with psychosis should include an assessment of the safety risk and level of care indicated. For most patients, treatment involves antipsychotic medication and psychosocial interventions. It is essential to consider collateral information obtained from family members, psychosocial supports, and other providers during initial management decisions.

Safety risk and level of care — Treatment of psychosis should take place in the least restrictive environment where safety can be maintained. Inpatient psychiatric hospitalization is needed when the patient is at risk to harm themselves or others. This should be assessed through direct questions about homicidal and suicidal ideation (see "Suicidal ideation and behavior in adults"). Other considerations include the patient's ability to secure basic needs, such as food and shelter, to protect oneself from harm, and the presence of family members or other supports who can monitor the patient and alert emergency services if needed.

Psychiatric hospitalization can be either on a voluntary or involuntary basis, subject to legal restrictions that vary by jurisdiction. Clinicians, especially those in emergency settings, should become familiar with involuntary treatment criteria and procedures within their legal jurisdictions.

Psychiatric consultation — Any patient with an initial or recurrent onset of psychosis should be evaluated by a psychiatrist. Consultation may occur in the emergency department setting, in the inpatient setting, or in the form of an urgent outpatient evaluation.

Antipsychotic therapy

Indications — For most causes of psychosis, even those in which the psychiatric disorder or underlying medical condition causing the psychosis has not yet been established, we

recommend initial symptomatic treatment with an antipsychotic medication. Notable exceptions include patients with psychosis due to central nervous system stimulant intoxication or patients with catatonia, both of which should be treated initially with benzodiazepines. (See 'Psychosis due stimulant intoxication' below and 'Catatonia' below.)

Antipsychotics have been extensively studied and shown to be effective in the treatment of schizophrenia [1-3]. A network meta-analysis of 402 studies with over 50,000 participants examined the efficacy of over 30 different first- and second-generation antipsychotics in patients with acute symptoms of schizophrenia or related disorders [3]. All antipsychotics were found to reduce overall symptoms more than placebo. Studies used different rating scales for determining symptom improvement; the estimated individual effect sizes for overall symptom improvement ranged from -0.89 to -0.03 standardized mean difference compared with placebo (mean -0.42). Benefits were also reported for positive symptoms (eg, hallucinations, paranoia, delusions), depressive symptoms, and social functioning.

While antipsychotics have been most extensively studied in the treatment of schizophrenia, the medications appear to effectively reduce psychotic symptoms due to many different causes. For example, meta-analyses have found antipsychotics are effective in the treatment of psychotic mania in bipolar disorder [4], major depressive disorder with psychotic features (when combined with an antidepressant) [5], delirium [6], psychosis in Parkinson disease [7], and psychosis in Alzheimer disease [8]. The use and effectiveness of antipsychotic drugs for individual disorders and diseases are discussed separately.

- (See "Schizophrenia in adults: Clinical features, assessment, and diagnosis".)
- (See "Schizophrenia in adults: Maintenance therapy and side effect management".)
- (See "Evaluation and management of treatment-resistant schizophrenia".)
- (See "Brief psychotic disorder".)
- (See "Treatment of delusional infestation".)
- (See "Treatment of postpartum psychosis".)
- (See "Management of neuropsychiatric symptoms of dementia".)
- (See "Unipolar major depression with psychotic features: Epidemiology, clinical features, assessment, and diagnosis".)
- (See "Acute bipolar mania and hypomania in adults: General principles of pharmacotherapy".)
- (See "Delusional disorder".)

Although some patients presenting with psychosis (eg, those with brief psychotic disorder) can recover spontaneously without medication, there are no features that can reliably identify such patients at the time of presentation. (See "Brief psychotic disorder", section on 'Treatment'.)

Selection

Preference for second-generation agents — We suggest using a second-generation antipsychotic as first-line treatment in most cases of psychosis (table 1). Selection among the second-generation antipsychotics is often based on clinician familiarity with specific agents, patient comorbidities, psychiatric symptoms such as level of agitation, and potential side effects of medications. In many cases, aripiprazole or risperidone are appropriate choices due to their relatively favorable side effect profiles; however, specific features may prompt selection of other second-generation antipsychotics, and in some cases (eg, severe agitation), a first-generation antipsychotic such as haloperidol may be appropriate. Patient-specific considerations in selecting an antipsychotic are discussed in the sections that follow. Specific side effects associated with the various antipsychotic agents are listed in the table (table 2).

Second-generation antipsychotics are preferred because they tend to cause fewer extrapyramidal symptoms (EPS; ie, akathisia, dystonia, parkinsonism) than first-generation antipsychotics [1,2,9,10]. Meta-analysis comparing overall efficacy and effects of antipsychotics showed less EPS associated with all second-generation antipsychotics studied compared with the first-generation antipsychotic, haloperidol [9]. Aside from this distinction, therapeutic effects and adverse effects are not significantly different between first- and second-generation antipsychotics and likelihood of specific adverse effects are heterogenous within each group. Although clozapine is more effective than other agents, it is reserved for patients who have not responded to other antipsychotics because it has significant side effects and medical risks that require careful monitoring. (See "Schizophrenia in adults: Maintenance therapy and side effect management" and "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects" and "Second-generation antipsychotic medications: Pharmacology, administration, and side effects" and "Schizophrenia in adults: Guidelines for prescribing clozapine".)

Additional patient-specific considerations

Psychiatric symptoms — Certain psychiatric features may be a reason for selection of a particular antipsychotic or a particular property of an antipsychotic:

- **Negative symptoms** – Negative symptoms of schizophrenia, such as diminished emotional expression and lack of motivation, have proven particularly difficult to treat. Most classes of medications tested have not shown clinically meaningful effects on negative symptoms [11], but cariprazine has shown positive effects in a clinical trial [12]. (See "Schizophrenia in adults: Clinical features, assessment, and diagnosis", section on 'Negative symptoms'.)

In a meta-analysis of 168 randomized trials involving 12,318 individuals with schizophrenia, the effects of several different classes medications on negative symptoms were examined [11]. Small, statistically significant reductions in negative symptoms were found for second-generation antipsychotics, antidepressants, glutamatergic agents, and combinations of these medications, but not for first-generation antipsychotics or brain stimulation. None of the beneficial effects for any of the medication strategies were considered to be of a clinically significant magnitude. (See "Schizophrenia in adults: Clinical features, assessment, and diagnosis", section on 'Negative symptoms'.)

In a clinical trial of 461 patients with stable schizophrenia with predominant negative symptoms, cariprazine was compared with risperidone over a 26-week period [12]. Cariprazine-treated patients had a modestly greater reduction in negative symptoms on the Positive and Negative Syndrome Scale (difference in mean change from baseline -1.46, 95% CI -2.4 to -0.5 on a 42 point scale) and improvement in domains of self-care, and social relationships and activities on the Personal and Social Performance Scale (difference in mean change from baseline 4.6, 95% CI 2.7-6.6 on a 100 point scale). Cariprazine did not have a differential effect on positive symptoms, depression, or EPS. (See 'Negative symptoms' below.)

- **Agitation** – We consider agitation to be a psychiatric emergency. Agitation is a state of motor restlessness or excitement and is often accompanied by mental tension and irritability.

  - We typically treat agitated patients with an antipsychotic with prominent sedating effects. As examples, we often use olanzapine 5 to 10 orally or disintegrating tablet or haloperidol 2 to 10 mg orally (table 1). In individuals who refuse or are unable to take oral medication, each of these can be administered intramuscularly (IM) at the same dose as oral administration. However, when giving these medications IM, we administer them with benztropine or diphenhydramine in order to reduce the risk of severe EPS or dystonia. (See "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Medication adjustments'.)

  - For mild to moderate agitation in patients who are able to cooperate, another option is the sublingual formulation of the alpha-2 agonist, dexmedetomidine. In a trial, 380 participants with schizophrenia or schizoaffective disorder were randomly assigned to sublingual dexmedetomidine 180 µg, 120 µg, or matching placebo [13]. Subjects were instructed on the appropriate method of self-administration, and the study drug was administered under the supervision of a staff member. Treatment effects, as measured by the five-item, 35-point Positive and Negative Syndrome Scale-Excited Component,

were first observed at 20 and 30 minutes postdose with sublingual dexmedetomidine 180 µg and 120 µg, respectively. Participants in both sublingual dexmedetomidine treatment groups showed improvements as compared with participants in the placebo group at all measured timepoints for up to two hours. Drug-related adverse effects for the 180 µg group, the 120 µg sublingual group, and placebo group were 37, 40, and 15 percent, respectively. The most common side effects with the active drug included somnolence, dry mouth, hypotension, and dizziness. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Agitation'.)

The use of sublingual administration may help to avoid the use of IM administration and improve the patient's overall experience, thereby improving future cooperation between patients and their health care providers.

- For severely agitated patients, we use a benzodiazepine in combination with the antipsychotic. As an example, the combination of haloperidol 5 mg, lorazepam 2 mg, and benztropine 2 mg given IM is often effective for treating severe agitation. Although olanzapine is associated with metabolic effects and haloperidol is associated with a high likelihood of EPS, the benefits of reducing acute agitation likely outweigh the side effects of each. (See "Assessment and emergency management of the acutely agitated or violent adult".)

- **Insomnia** – For insomnia due to underlying psychosis, we suggest an antipsychotic with sedating properties. An example is quetiapine, which can be initiated at 25 mg twice daily and increased every few days by 25 mg twice daily to an initial target dose of 300 to 400 mg daily, depending on response (table 1). Insomnia may be a common symptom if psychosis is secondary to mood disturbance. Treatment of insomnia may lead to improvement in psychotic symptoms, including paranoia and hallucinations [14]. (See "Overview of the treatment of insomnia in adults", section on 'Psychotic disorders' and "Bipolar disorder in adults: Clinical features" and "Unipolar major depression with psychotic features: Epidemiology, clinical features, assessment, and diagnosis".)

Cardiovascular risk factors

- **Patients with or at risk for metabolic syndrome** – For patients with diabetes, obesity, dyslipidemia, or other uncontrolled cardiovascular risks, we are especially cognizant of choosing an agent that has a lower risk of metabolic side effects (table 2) [15]. The metabolic syndrome associated with antipsychotic treatment is a risk factor for consequent cardiovascular disease and a contributor to the early mortality experienced, on average, by patients with severe mental illness [16,17]. (See "Second-generation

antipsychotic medications: Pharmacology, administration, and side effects" and "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects".)

- **Patients at risk for QT prolongation** – In patients with congenital long QT and in those at risk for acquired long QT syndrome, we recommend avoiding medications that have a greater association with long QT syndrome (table 2). This includes patients with metabolic disorders such as hypokalemia or hypomagnesemia, patients with anorexia nervosa, and patients on other medications that can prolong QT intervals, such as antiarrhythmics. We try to avoid ziprasidone, quetiapine, chlorpromazine, and intravenous (IV) haloperidol, which are the antipsychotics that have the strongest association with prolonged QT interval, torsade de pointes, and potentially lethal arrhythmias. We suggest an electrocardiogram prior to, at three months, and yearly thereafter in all patients at baseline risk for QT prolongation and in those treated with antipsychotic medications associated with QT prolongation. (See "Acquired long QT syndrome: Clinical manifestations, diagnosis, and management".)

Age — Older adult patients (eg, patients older than 70 years) are more susceptible to side effects associated with antipsychotic medication. Particular attention should be paid to anticholinergic side effects such as dry mouth, blurry vision, urinary hesitancy, constipation, and cognitive effects (table 2). Other considerations include orthostatic hypotension (leading to increased risk of falls) and sedation.

In addition, for older patients, we suggest initiating antipsychotic therapy below or at the lower end of the dose range, for example, aripiprazole 5 to 10 mg per day and titrating every week to two weeks to therapeutic range. In these patients, we recommend careful review of medications and drug interactions prior to starting antipsychotic treatment. (See 'Initial dosing' below.)

Dementia or cognitive impairment — Antipsychotics are associated with risk of stroke, myocardial infarction, and death when used to treat behavioral symptoms in older adults with dementia, particularly those with underlying vascular disease. Given this increased risk, their use in patients with dementia should be reserved for patients with neuropsychiatric symptoms that are severe or pose safety risks [18].

Use and selection of antipsychotic therapy in patients with dementia is discussed in detail elsewhere. (See "Management of neuropsychiatric symptoms of dementia", section on 'Antipsychotic drugs'.)

Selection of antipsychotics in patients with dementia associated with Parkinson disease and parkinsonian disorders warrants additional consideration and is also discussed in detail

elsewhere. (See "Management of nonmotor symptoms in Parkinson disease" and "Cognitive impairment and dementia in Parkinson disease" and "Palliative approach to Parkinson disease and parkinsonian disorders".)

Administration

Initial dosing — In adults, most antipsychotic medications should be titrated from the initial dose to the therapeutic range as quickly as tolerated (table 1). Exceptions include older patients, patients with first episode of psychosis, and patients with relevant medical comorbidities. These patients may be more sensitive to side effects from medications and should be started at a lower dose and titrated slowly while monitoring for side effects. Dosing and titration in such patients is discussed elsewhere. (See 'Additional patient-specific considerations' above.)

Timeframe for titration may differ depending on specific properties of medications. As an example, iloperidone and quetiapine should be titrated gradually due to increased risk of orthostasis. Typically, sedation and orthostasis are the limiting factors in titration of antipsychotic medications.

If adequate response is achieved before the suggested range is reached, the patient should be monitored for continued response before further titration.

Once the dose reaches therapeutic range, we allow several days to one week at that dose to evaluate for effect before deciding to increase the dose further. Examples of initial dosing and titration include the following:

- Aripiprazole can be started at 10 mg per day to 15 mg per day. Patients should be monitored at this dose for several days before increasing further by 5 to 10 mg per day every few days to maximum dose of 30 mg per day.

- Risperidone can be started at 2 mg a day, administered either once daily or as 1 mg twice daily. This dose can be increased by 1 mg every one to two days until the initial therapeutic range of 4 mg is reached. We suggest monitoring at this dose for several days to a full week before considering further increase. If the patient shows no improvement the dose can be increased up to 8 mg daily with careful monitoring for side effects and clinical response. Doses above 8 mg per day are associated with substantial risk of EPS. (See "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Antipsychotic therapy'.)

The objective of dose titration is to maximize efficacy while minimizing adverse effects. Because of dose-related toxicities, antipsychotics should be used at the lowest dose that is sufficiently effective for an individual. In a meta-analysis of clinical trials investigating antipsychotic dosing for acute schizophrenia, medication increases within the therapeutic range were associated with a decrease in symptoms (total and positive symptoms) and a lower rate of medication discontinuation for ineffectiveness in a dose-dependent fashion [19]. However, dose increases were also associated with increased side effects such as akathisia, parkinsonism, and somnolence.

Most studies of doses above the recommended range have found no clear benefit. At higher doses, the adverse effects of an antipsychotic may surpass the marginal benefit of dosing increases. As a result, increasing the dose of an antipsychotic for a patient who is already experiencing significant EPS is unlikely to result in additional symptom reduction [20,21].

If used, trials of higher doses should be limited to three months. Unless clear improvement is seen, higher doses should not be continued [22].

Expected response — Resolution of psychotic symptoms generally begins within several days of reaching an effective dose but may take as much as four to six weeks for full improvement. Most patients who will improve on an antipsychotic show the most rapid improvement during the first two weeks [23]. Evidence suggests that if the patient shows only minimal response to an antipsychotic during the first two weeks, it is unlikely that the individual will have a robust response [24]. (See 'Adjustments for poor response to initial treatment' below.)

Initial effects of antipsychotic medication are often sedation, restlessness, or postural hypotension. It is important to explain to the patient and their family that these side effects are common, or they may conclude that the medication is ineffective or worsening their condition.

Adjustments for poor response to initial treatment — If there is no improvement in psychotic symptoms after two to four weeks of a therapeutic dose, we generally suggest changing to a different antipsychotic medication, although this is not always effective. Switching antipsychotics can be helpful when a poor response is related to side effects. It is less clearly beneficial when the initial medication lacked effectiveness. Patients who respond poorly to one antipsychotic may likely be poor responders to another antipsychotic. A meta-analysis investigating treatment of patients who do not respond to the initially prescribed antipsychotic did not find a difference in benefit between increasing the same medication and switching to a different antipsychotic [25]. However, the overall quality of the evidence was low.

For patients who are actively psychotic who are switching from an ineffective medication to another choice, we suggest maintaining full dose of the current medication as the new medication is increased. Once the second medication has reached its target dose, the first medication may be gradually decreased and discontinued. In most cases, this change can be managed over two weeks.

Clinicians often add a second antipsychotic when patients have suboptimal response to a single drug. We typically do not add a second agent as little empirical evidence supports this practice [26]. Exceptions are discussed elsewhere. (See "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Partial response or recurrence of symptoms' and "Evaluation and management of treatment-resistant schizophrenia", section on 'Augmentation with medication'.)

Patients who have not responded adequately to two or more trials of antipsychotics at therapeutic dose (eg, >600 mg chlorpromazine or its equivalent) are considered treatment resistant. (See "Evaluation and management of treatment-resistant schizophrenia".)

Duration of pharmacologic therapy — The recommended duration of antipsychotic therapy varies according to the underlying etiology: In chronic schizophrenia, antipsychotics should be offered indefinitely to reduce the risk of relapse [27]. With time-limited psychoses (such as delirium), antipsychotic therapy can be continued for two weeks after the resolution of symptoms and then tapered off gradually. (See "Schizophrenia in adults: Maintenance therapy and side effect management" and "Delirium and acute confusional states: Prevention, treatment, and prognosis".)

In many cases of psychosis, particularly at initial stages of the illness, the diagnosis is uncertain. In these cases, we consider additional factors that inform the likely diagnosis and subsequent duration of antipsychotic therapy. These factors include patient age, premorbid characteristics such as interpersonal traits, and psychosocial functioning including employment history. Additionally, the severity of symptoms (eg, suicidality) and extent of disruption to daily life functioning should be weighed. As an example, a 20-year-old patient with acute onset of psychosis, chronic mild paranoia, and social isolation will likely need chronic treatment with antipsychotics after initial stabilization because of a relatively high likelihood of schizophrenia. In contrast, a 40-year-old patient with acute onset of psychosis, no premorbid history, and stable psychosocial functioning will likely be treated for several months followed by a trial of discontinuation of medications. In most cases, longitudinal monitoring is needed to make an accurate diagnosis and treatment plan. (See "Schizophrenia in adults: Maintenance therapy and side effect management".)

Psychosocial interventions — We recommend psychosocial treatment as an adjunct to antipsychotic medication. Our approach is to implement the most comprehensive psychosocial interventions available; these include cognitive and social training, cognitive-behavioral therapy (CBT), and family-based interventions. Most of the evidence for efficacy is in patients with schizophrenia; this is discussed elsewhere. (See "Schizophrenia in adults: Psychosocial management".)

Cognitive remediation and social skills training — These interventions attempt to improve cognitive weaknesses, such as attention and planning, and apply training to focus on specific situations, problems, or activities. The ultimate goal is to generalize the learned skills to community-based activities and improve overall functioning. (See "Schizophrenia in adults: Psychosocial management", section on 'Cognitive remediation' and "Schizophrenia in adults: Psychosocial management", section on 'Social skills training'.)

Cognitive-behavioral therapy — CBT attempts to reduce the intensity of distress related to delusions and hallucinations. CBT promotes active participation of the individual through cognitive reframing, with the ultimate goal of reducing relapse and social disability. (See "Schizophrenia in adults: Psychosocial management", section on 'Cognitive-behavioral therapy'.)

Family-based interventions — Family interventions seek to establish a collaborative process involving patient, family, and clinician. Patients with psychosis and their families are educated about the nature and course of psychosis, including increased risk of harm to self or others and warning signs of recurrence. Families or caregivers should be advised about effective means of interacting with patients with psychosis. These include reducing environmental stimulation, encouraging healthy lifestyle, providing calm and gentle empathy, and not arguing with delusional ideas. (See "Schizophrenia in adults: Psychosocial management", section on 'Family-based Interventions'.)

Early identification and intervention — Early identification and intervention programs seek to identify individuals with prodromal or first episode of psychosis. Efforts are aimed at preventing progression of prodromal syndrome or recurrent psychosis. These include:

- Education of primary care providers and community outreach to secondary schools and colleges. Referral to mental health programs for diagnosis and treatment is encouraged.
- Provision of diagnosis-specific multimodal treatment including psychosocial and pharmacologic interventions.
- Multidisciplinary teams of mental health professionals that work in an integrated fashion and follow patients longitudinally.

Meta-analyses of randomized clinical trials have found that early intervention services lead to better clinical outcomes for patients with early phase psychosis compared with treatment as usual [28,29]. In one meta-analysis of 10 trials and over 2000 patients, subjects were randomized to receive early intervention services or treatment as usual. Patients in early intervention had superior results on all outcomes studied including any psychiatric hospitalization (relative risk 0.74, 95% CI 0.61-0.90), involvement in school or work (relative risk 1.13, 95% CI 1.03-1.24), and total symptom severity (standardized mean difference -0.32, 95% CI -0.47 to -0.17). Preliminary evidence has also suggested that extended early intervention for up to five years may result in fewer patients disengaging from treatment, although the certainty of the evidence is very low and more studies are needed [30].

Special circumstances

First episode of psychosis — Choice of antipsychotic medication in a patient with a first episode of psychosis is the same as for psychosis in general. However, we suggest patients with a first episode of psychosis be treated with an antipsychotic at the lower end of the recommended dose range. For example, for a first episode of psychosis, we recommend starting aripiprazole at 5 mg per day or risperidone starting at 1 mg per day. These can be increased over one week to the lower end of the therapeutic range (ie, 10 mg per day aripiprazole, 2 mg per day risperidone) while monitoring for response. Patients in a first psychotic episode tend to have higher response rates than patients who have experienced multiple psychotic episodes. These individuals respond to lower antipsychotic doses and have greater vulnerability to side effects such as weight gain [31].

Psychosis due stimulant intoxication — When the underlying cause of psychosis or agitation is thought to be stimulant related, we suggest initial treatment with a benzodiazepine rather than an antipsychotic medication. For example, lorazepam can be given at a dose of 2 to 4 mg IV and repeated every 10 minutes. In milder cases, it may be given orally or IM. Antipsychotics can be used as an adjunctive therapy when high doses of benzodiazepines (eg, more than 20 mg of lorazepam in 30 minutes) do not adequately control agitation. Although antipsychotics are reported to be safe and effective in this setting [32-35], they may interfere with heat dissipation, lower the seizure threshold, and prolong QT interval. (See "Methamphetamine: Acute intoxication" and "Methamphetamine use disorder: Epidemiology, clinical features, and diagnosis".)

Catatonia — Antipsychotic medications should be avoided as they can precipitate or worsen catatonia. Catatonia is a syndrome manifested by inability to move normally. It can present as either extreme negativism (eg, passive resistance to movement), mutism, or catatonic excitement (eg, excessive, purposeless motor activity). The presence of catatonia should alert

the clinician to the possibility of an underlying medical disorder and should be thoroughly investigated. Treatment of catatonia is reviewed in more detail elsewhere. (See "Catatonia: Treatment and prognosis" and "Catatonia in adults: Epidemiology, clinical features, assessment, and diagnosis".)

Negative symptoms — Negative symptoms have a detrimental impact on outcomes and quality of life in individuals with schizophrenia. Negative symptoms appear to cluster in two main components: diminished expression (eg, reduced display of affect and speech) and motivational or volition-apathy symptoms including apathy, asociality, and decreased capacity for pleasure. Most medications have not shown clinically meaningful effects on them [11]. (See "Schizophrenia in adults: Clinical features, assessment, and diagnosis", section on 'Negative symptoms' and 'Additional patient-specific considerations' above.)

- Noninvasive brain stimulation (NIBS) may be effective in treating negative symptoms. In a network meta-analysis of 48 trials involving 2211 participants with schizophrenia, treatment over the left dorsolateral prefrontal cortex with excitatory NIBS led to larger reductions in negative symptoms than sham control intervention [36]. NIBS protocols and their effect included: high-definition transcranial random noise stimulation (standardized mean difference -2.19, 95% CI -3.36 to -1.02), intermittent theta-burst stimulation (standardized mean difference -1.32, 95% CI -1.88 to -0.76), anodal transcranial direct current stimulation (standardized mean difference -1.28, 95% CI -2.55 to -0.02), high-frequency repetitive transcranial magnetic stimulation (rTMS; standardized mean difference -0.43, 95% CI -0.68 to -0.18), or extremely high-frequency rTMS (standardized mean difference -0.45, 95% CI -0.79 to -0.12). The comparative efficacy of different NIBS protocols for relieving negative symptoms remains unclear. Further studies are warranted.

- Psychosocial treatment with a combined program of motivational interviewing and CBT may lead to improvements in negative symptoms in individuals with schizophrenia. In a trial, 79 subjects with schizophrenia and moderate to severe negative symptoms were randomly assigned to 12 weeks of group treatment with combined motivational interviewing and CBT versus 12 weeks of active control group with mindfulness-based stress reduction [37]. At treatment end, individuals in the treatment group showed lower measures on the Clinical Assessment Interview for Negative Symptoms, Motivation and Pleasure subscale (CAINS-MAP) a nine-item measure of motivation and pleasure, as compared with those in the control group (endpoint scores 1.42 versus 2.05, respectively). Gains were maintained through follow-up, though the benefit for the treatment group was attenuated as compared with control group (follow-up score 1.59 versus 1.75, respectively). Additionally, individuals in the treatment group showed a trend towards

greater improvement on the Specific Level of Functioning (SLOF) scale, a 43-item scale for daily functioning and behavior across a range of domains than those in the control group. (See "Schizophrenia in adults: Psychosocial management".)

Comorbidities — Psychosis can occur in the setting of other psychiatric comorbidities such as mood disorders, substance use disorders, and other medical or neurologic disorders. In these cases, the underlying disorder should be treated as appropriate for that particular disorder. These issues are discussed separately.

- (See "Unipolar major depression with psychotic features: Acute treatment".)
- (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy".)
- (See "Pharmacotherapy for co-occurring schizophrenia and substance use disorder".)
- (See "Psychosis in adults: Epidemiology, clinical manifestations, and diagnostic evaluation", section on 'Factors differentiating medical versus psychiatric causes'.)

Patients who refuse medications — The approach to patients who refuse medications is driven by the acuity of the symptoms. Patients with agitation or symptoms that put them at risk for dangerous behaviors (eg, severe paranoia leading to agitation or hallucinations commanding violence) often refuse or are unable to take medications. In these cases, we recommend IM or IV treatment; the medication choice depends on the clinical situation. (See "Assessment and emergency management of the acutely agitated or violent adult".)

In cases where the acuity of the psychosis does not warrant IM or IV treatment (eg, mild paranoia), we suggest frequent education of the patient about potential benefits of medication and discussion of reasons for refusal. It is often helpful to engage family members and other supports in order to build alliance with the patient. In cases where adherence becomes problematic, long-acting injectable medications are suggested. (See "Schizophrenia in adults: Pharmacotherapy with long-acting injectable antipsychotic medication".)

Monitoring and follow-up — We recommend follow-up monitoring on a weekly basis with a mental health team to provide pharmacologic and psychosocial treatment. After three months, the frequency can be monthly if the patient continues to be in remission.

Medication benefits, side effects, and adherence should be discussed at each visit. Additionally, lipid profile, metabolic profile, and, for patients on a medication associated with QT prolongation, an electrocardiogram should be monitored at regular intervals (table 3). Side effect monitoring for patients taking long-term antipsychotic medication is discussed elsewhere. (See "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Duration of antipsychotic therapy'.)

Patients who have recovered from a first episode of psychosis have a high rate of recurrence following medication discontinuation [37,38]. For those whose antipsychotic treatment is discontinued, we continue to monitor for relapse in symptoms. (See 'Duration of pharmacologic therapy' above and "Schizophrenia in adults: Maintenance therapy and side effect management".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Psychotic disorders".)

SUMMARY AND RECOMMENDATIONS

- **Safety risk and level of care** – Patients with psychosis are at elevated risk for agitated and aggressive behaviors. All patients with psychosis should be evaluated for risk of harm to themselves or others and their ability to take care of themselves. Patients who are unable to care for themselves or pose a risk to themselves or others should be hospitalized. Severely agitated patients with psychosis may need sedation or physical restraint. (See 'Safety risk and level of care' above.)

- **Antipsychotic therapy** – Antipsychotic medications are an effective symptomatic treatment of psychosis, regardless of underlying cause, and are the standard initial treatment for most cases. Important exceptions include patients with stimulant-related psychosis or catatonia, for whom antipsychotic medications are not given unless the underlying condition is treated. (See 'Indications' above.)

- **Selection** – Antipsychotic drugs are largely similar in efficacy and selection among them is typically made on the basis of patient presentation, the medication's side effect profile and formulations available (table 1 and table 2). For most patients, we suggest a second-generation rather than a first-generation antipsychotic (**Grade 2B**). Aripiprazole or risperidone are appropriate choices for most patients. However, specific features of the presentation may warrant a different antipsychotic choice (table 2). (See 'Selection' above.)

  - **For agitation** – For patients with agitation, an antipsychotic with prominent sedating effects, such as olanzapine 5 to 10 mg orally or haloperidol 2 to 10 mg orally may be useful. These can be given intramuscularly (IM) if refused orally. For more severe agitation, they can be combined with lorazepam. A sublingual formulation of

dexmedetomidine is available for individuals with agitation who can self-administer under supervision. (See 'Psychiatric symptoms' above.)

- **For insomnia** – For patients with insomnia due to underlying psychosis, an antipsychotic with sedating properties such as quetiapine can be a useful option. Quetiapine can be started at 25 mg twice daily and increased to an initial target dose of 300 to 400 mg nightly. (See 'Psychiatric symptoms' above.)

- **For patients with cardiovascular risk factors** – For patients with diabetes, obesity, dyslipidemia, or other uncontrolled cardiovascular risks, we are especially cognizant of choosing an agent that has a lower risk of metabolic side effects (table 2). (See 'Cardiovascular risk factors' above.)

- **Administration** – In adults, most antipsychotic medications are titrated from the initial dose to the therapeutic range as quickly as tolerated (table 1). Exceptions include older patients, patients with first episode of psychosis, and patients with relevant medical comorbidities. (See 'Administration' above.)

- **Patients who refuse medication** – In patients who refuse medications, IM or intravenous medication may be needed for those with agitation or symptoms that put them at risk for dangerous behaviors (eg, severe paranoia leading to agitation or hallucinations commanding violence). Otherwise, we continue to educate patients who refuse medications about potential benefits and discuss reasons for refusal. (See 'Patients who refuse medications' above.)

- **Psychosocial interventions** – Psychosocial interventions are an important adjunctive therapy to antipsychotic medications. These interventions include cognitive and social training, cognitive-behavioral therapy, and family-based interventions. (See 'Psychosocial interventions' above.)

- **Comorbidities** – Psychosis can occur in the setting of other psychiatric comorbidities such as mood disorders, substance use disorders, and other medical or neurologic disorders. In these cases, antipsychotic medications are administered in combination with treatment for the underlying or comorbid medical or psychiatric disorder. (See 'Comorbidities' above.)

- **Monitoring and follow-up** – We recommend follow-up monitoring on a weekly basis with a mental health team to provide pharmacologic and psychosocial treatment. After three months, the frequency can be monthly if the patient continues to be in remission. (See 'Monitoring and follow-up' above.)

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