Depression in schizophrenia

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INTRODUCTION

Depressive symptoms are frequent clinical features in patients with schizophrenia. Depression is associated with a less favorable patient course and poorer outcomes compared with patients with schizophrenia without depression.

The diagnosis of depression in schizophrenia is complicated by a differential diagnosis that includes depression-like extrapyramidal side effect symptoms of antipsychotic drugs, negative symptoms of schizophrenia, and general medical conditions. In addition to thorough assessment, treatment trials can be used to differentiate these conditions.

The epidemiology, clinical manifestations, diagnosis, and treatment of depression in patients with schizophrenia are discussed here. Depression and schizophrenia as individual, noncomorbid disorders are discussed separately. Other common comorbidities of schizophrenia are also discussed separately.

- (See "Anxiety in schizophrenia" and "Unipolar depression in adults: Epidemiology" and "Unipolar major depression in adults: Choosing initial treatment" and "Schizophrenia in adults: Clinical features, assessment, and diagnosis".)
- (See "Schizophrenia in adults: Maintenance therapy and side effect management".)
- (See "Anxiety in schizophrenia" and "Unipolar depression in adults: Epidemiology" and "Unipolar major depression in adults: Choosing initial treatment" and "Schizophrenia in adults: Clinical features, assessment, and diagnosis".)
- (See "Unipolar depression in adults: Assessment and diagnosis".)

- (See "Anxiety in schizophrenia" and "Unipolar depression in adults: Epidemiology" and "Unipolar major depression in adults: Choosing initial treatment" and "Schizophrenia in adults: Clinical features, assessment, and diagnosis".)
- (See "Co-occurring schizophrenia and substance use disorder: Epidemiology, pathogenesis, clinical manifestations, course, assessment and diagnosis".)
- (See "Anxiety in schizophrenia" and "Unipolar depression in adults: Epidemiology" and "Unipolar major depression in adults: Choosing initial treatment" and "Schizophrenia in adults: Clinical features, assessment, and diagnosis".)
- (See "Unipolar depression in adults: Course of illness".)

EPIDEMIOLOGY

Estimates of the lifetime prevalence of depression in schizophrenia vary widely – from 6 to 75 percent – based on differing study characteristics including varying definitions of depression, patient settings, and durations of observation [1-6]. Overall, studies have found a modal prevalence of approximately 25 percent, well above the rate of depression in the general population. (See "Unipolar depression in adults: Epidemiology".)

Risk factors for depression in schizophrenia include family history of depressive disorder [7], high levels of family and personal expectations for success in life, critical family attitudes, high levels of family expressed emotion, stigma, intelligence and insight, multiple hospitalizations, recent hospital discharge, and lack or loss of psychosocial support or support of self-esteem.

PATHOGENESIS

Depression occurring in schizophrenia can be conceptualized in several ways. These include depression as a component of the underlying psychopathology of schizophrenia itself, a domain on a spectrum of pathology which extends from "purely affective" at one extreme to "purely psychotic" at the other, or co-occurrence of affective and psychotic pathology in the same individual.

What is known about the pathogenesis of schizophrenia and depression as individual disorders provides a starting point toward understanding the pathogenesis of this comorbidity. (See "Schizophrenia in adults: Epidemiology and pathogenesis", section on 'Pathogenesis' and "Unipolar depression: Pathogenesis".)

TERMINOLOGY

The term "depression" is used to describe several different phenomena. It can refer to an affect, a symptom, or a syndrome [8].

- As an affect, "depression" refers to a nonpathologic, transient feeling state of low mood.
- As a symptom, "depression" refers to an exaggerated feeling state of low mood, exaggerated in that it occurs in the absence of sufficient stimulus, is more severe than appropriate, or lasts longer than would otherwise be expected.
- As a syndrome, "depression" refers to a persisting clinical condition that features low mood or anhedonia along with elements such as low energy, self-reproach, impaired concentration, pessimism, guilt, lack of confidence, sleep or appetite disturbances, psychomotor agitation or retardation, or notions of self-harm, death, and suicide [9].

As is the case for individuals who do not have schizophrenia, patients with schizophrenia can have "depression" in any of these three senses of the term. When we refer to depression in patients with schizophrenia in clinical practice or in the psychiatric literature, we are typically referring to the symptom or syndrome. (See "Unipolar depression in adults: Assessment and diagnosis".)

COURSE

The course of depressive symptoms occurring in schizophrenia varies based on the underlying cause of the condition and the treatment received. Environmental factors also influence the course of depression in both patients with and without schizophrenia.

Depressive symptoms can occur either during the prodrome of a new psychotic episode, during an acute psychotic episode or subsequently to it [1,10,11]. When depression occurs during the acute psychosis, its presentation is often less dramatic than the psychotic symptoms and it may therefore be less apparent. Depression occurring in the course of an acute psychotic episode frequently remits as the psychosis subsides in response to an antipsychotic agent. At other times, however, a depressive syndrome may persist (and consequently appear to emerge) as the psychosis improves. (See 'Prodrome of a psychotic episode' below.)

Depression has been found to be associated with a variety of undesirable outcomes in schizophrenia [1,3,12]. These include higher rates of relapse and early rehospitalization, longer durations of hospitalization, greater symptom burden, poorer responses to psychopharmacologic interventions, greater impairments in cognitive functioning, more impairments in social and vocational functioning, more personal suffering, increased family and

community burden, and more life events involving permanent loss or other unfavorable life occurrences. Depression in schizophrenia has been associated with increased rates of suicide attempts and completed suicides, the latter estimated at between 4 and 12 percent [13-15].

DIFFERENTIAL DIAGNOSIS

Diagnosis of a depressive syndrome in the context of schizophrenia requires the consideration of other diagnoses with overlapping presentations. The differential diagnosis of depression in schizophrenia includes general medical factors, features of schizophrenia, antipsychotic side effects, disappointment reactions, and a co-occurring depressive disorder.

Medical factors — There are many conditions that can biologically predispose schizophrenic patients to a depression or depression-like symptoms [16-18]. Medical conditions and other organic factors are summarized in the table and discussed in greater detail separately (table 1).

Antipsychotic drug-induced dysphoria — Antipsychotic medications have been observed to produce a dysphoria as a side effect [1,3,18]. This has been reported particularly with first-generation antipsychotic compounds, but has also been found to occur with second-generation antipsychotic agents. All antipsychotic medications interfere with dopamine neurotransmission as a component of their activity, and dopamine neurotransmission has been found to figure prominently in pleasure/reward pathways in the brain [3,19,20]. Blocking of dopamine transmission by antipsychotics may be responsible, at least in part, for the dysphoria experienced by a proportion of patients taking the medication. (See "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects" and "Second-generation antipsychotic medications: Pharmacology, administration, and side effects" and "Schizophrenia in adults: Maintenance therapy and side effect management".)

Extrapyramidal side effects of antipsychotics — First-generation and some second-generation antipsychotics are known to produce the extrapyramidal side effects of akinesia and akathisia. While blatant forms of akinesia and akathisia are distinctive, more subtle forms can be difficult to distinguish from depression. (See "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects" and "Second-generation antipsychotic medications: Pharmacology, administration, and side effects" and "Schizophrenia in adults: Maintenance therapy and side effect management".)

The subtle form of akinesia affects small muscle groups, typically the facial muscles of expression, producing an expressionless or "mask-like" appearance, and the larynx, decreasing

voice tone and expressiveness. Akinesia also can adversely affect the part of the basal ganglia responsible for initiating and sustaining motor behavior. Such patients behave as if their "starter motor" is broken, appearing to be nonspontaneous. The patient's subjective experience is that activities are "not worth the effort"; they often perceive themselves self-critically as being "lazy," which contributes to a negative effect on mood. It is easy to see how this combination of factors could lead to a combination of depression and depression-like symptoms on both a psychological and physiologic basis [21,22].

Patients with akathisia are fidgety and feel unable to stop moving; they can find the experience to be intensely dysphoric [23]. In a subtle manifestation of akathisia, patients may be observed to be "action-prone," over-talkative, and/or having the tendency to wander into other people's space [24]. A dysphoric, subtle akathisia can be difficult to distinguish from the syndrome of depression. Akathisia has also been noted to be a possible risk factor for suicide [25].

Negative symptoms of schizophrenia — The "negative symptoms" syndrome of schizophrenia includes a number of features which are similar to components of the depression syndrome [26-28]. These features include anhedonia (lack of pleasure), anergia (lack of energy), alogia (lack of having things to say or lack of content in what is said), blunted affect, social withdrawal, and loss of drive or motivation. (See "Schizophrenia in adults: Clinical features, assessment, and diagnosis", section on 'Negative symptoms'.)

A depressive syndrome is distinguished from negative symptoms in schizophrenia by the presence of cognitive features of depression (guilt, shame, low self-esteem, ideas of worthlessness, notions of helplessness, pessimism, and suicidal thoughts), and the prominent affective manifestations of depressed mood (such as intense low mood or tearfulness).

Prodrome of a psychotic episode — Studies have reported the presence of depression-like symptoms in 28 to 76 percent of such patients. These patients are often dysphoric and socially withdrawn. They may experience sleep or appetite irregularities, manifest variations in their energy levels, lose interest in their surroundings, have trouble concentrating, express thoughts of hopelessness, helplessness, or self-blame, and anticipate punishment or catastrophe. The prodrome of a psychotic episode generally lasts days to a couple of weeks at most. By then, psychosis has typically become more evident with the emergence or exacerbation of hallucinations, delusions, thought disorder, and/or the eruption of disjointed fragments of behavior.

Disappointment reactions — An acute disappointment reaction can occur in response to a loss or failure of plans to work out. Persons with schizophrenia, for example, may be disappointed about the way in which their lives are progressing (or not progressing). A negative

subjective reaction to the advent of a new episode of decompensation would certainly qualify as such a disappointment [29]. In this circumstance, "insight" into their situation can be a contributing factor as well [30].

What distinguishes an acute disappointment reaction from a depressive syndrome is the presence of an unpleasant event or precipitating circumstance and the fact that such a reaction does not last for an extended period (generally a few hours or days, up to a couple weeks). Patients with schizophrenia may have a limited capability for self-expression or idiosyncratic interpretations of events, requiring patient, careful listening to understand them.

Chronic disappointment reactions can also occur and this situation is sometimes referred to as the "demoralization" syndrome [31,32]. This state can present depressive symptoms in that the patient feels chronically discouraged and dispirited, expresses pessimism, has a sense of loss of control, is preoccupied with past failures and their consequences, pleads incompetence, and behaves in an avoidant manner. Again, "insight" into the situation may be a contributing factor for "depression" [30].

Depression in schizophrenia — A depressive disorder may be diagnosed in the context of schizophrenia when a patient, who has otherwise been diagnosed as having schizophrenia and is currently not floridly psychotic, manifests a depression syndrome (meeting DSM-5-TR criteria for a depressive disorder [9]), and other items in the differential diagnosis have been excluded. Postpsychotic depressive syndrome is a historically used term to describe depression occurring in schizophrenia when the patient is no longer floridly psychotic. (See "Unipolar depression in adults: Assessment and diagnosis".)

Schizoaffective disorder — Schizoaffective disorder is a condition in which the patient meets the diagnostic criteria for both schizophrenia and a major mood disorder, and both sets of symptoms are prominent in the patient's course of illness [33]. The diagnosis requires the patient to have had at least one two-week period of illness during which they experience hallucinations and/or delusions in the absence of any prominent mood episode.

ASSESSMENT AND MANAGEMENT

Assessment and treatment of depression in patients with schizophrenia are closely intertwined and performed in tandem, guided by the differential diagnosis. Periods of observation and clinical interventions can be used to identify or rule out possible diagnoses.

When a patient with schizophrenia presents with a new episode of depression, after addressing safety concerns, the first step is watchful waiting. During this time, the patient can be assessed

and carefully monitored. The medical history, physical exam, and laboratory testing can identify or rule out general medical factors potentially contributing to depression.

If the depression lasts for more than two weeks, and the patient's clinical state remains relatively unchanged, then a prodrome of a psychotic disorder and an acute disappointment reaction have largely been ruled out. Treatment is then guided by the remaining diagnostic possibilities. (See "Unipolar depression in adults: Assessment and diagnosis".)

Antipsychotic medication effects — The next step is to determine through intervention whether the depression is a product of the patient's antipsychotic medication, either as a direct mood effect or as an extrapyramidal side effect. (See "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects" and "Second-generation antipsychotic medications: Pharmacology, administration, and side effects" and "Schizophrenia in adults: Maintenance therapy and side effect management".)

- If possible, a cautious downward titration of the antipsychotic medication dose should be attempted first, with continuing close monitoring of the patient for exacerbation of psychosis and change in depressive symptoms. This can be tried in patients who are not experiencing an acute exacerbation of psychotic symptoms and are receiving more than the minimally recommended antipsychotic dose or, if the patient's history of antipsychotic treatment is known, more than the minimal dose that has been historically required to control their psychotic symptoms.

- For the patient with EPS where an antipsychotic dose reduction is not possible or inadequate, an appropriate antiparkinsonian agent may be added, or increased if already present, to treat or rule out extrapyramidal symptoms.

- For akinesia, we suggest treatment with an anticholinergic antiparkinsonian medication. Benztropine may be started at 1 to 2 mg/day in divided doses and increased gradually every three to four days to 6 to 8 mg/day in the absence of substantive side effects such as constipation, blurry vision, dry mouth, or the history or presence of glaucoma.

  If the patient experiences anticholinergic side effects, nonanticholinergic antiparkinsonian medications may be employed, such as amantadine, 100 mg orally two to three times daily.

- Managing akathisia is discussed separately. (See "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Akathisia'.)

An alternative to adding a medication to treat EPS would be a change of antipsychotic medications. If a patient is on an antipsychotic drug likely to cause EPS (eg, haloperidol), for example, substituting an antipsychotic with a lower risk of EPS (eg, quetiapine) may be helpful [2,34-37]. A positive response to this intervention may leave unclear whether improvement was due to a reduction in EPS, a decrease in negative symptoms, or an antidepressant effect of the SGA.

Demoralization — Although not extensively studied, the syndrome of demoralization may be responsive to psychosocial interventions [38-40]. A meta-analysis of cognitive interventions suggests a possibly helpful role for such patients [40]. In our clinical experience, demoralization may respond favorably to interventions incorporating skill-building, success experiences, and exercises in positive thinking that are often a component of cognitive behavioral therapy and motivational interviewing.

Pharmacotherapy for major depressive disorder — Although evidence from clinical trials has multiple limitations, its findings are consistent with our clinical experience that adjunctive antidepressant treatment can reduce symptoms of major depression when an episode occurs in patients with antipsychotic-treated schizophrenia [41]. Depressive-symptom reduction is more likely when psychotic symptoms are not currently florid and symptom causes other than depression have been treated or ruled out. (See 'Antipsychotic medication effects' above.)

A meta-analysis of randomized clinical trials of patients with schizophrenia treated with antipsychotic medication found that adjunctive treatment with an antidepressant led to reductions in depressive symptoms (standardized mean difference: -0.25, 95% CI -0.38 to -0.12) and in negative symptoms (SMD: -0.30, 95% CI -0.44 to -0.16) compared with placebo or no treatment [42]. A total of 82 trials with 3602 patients were included in the analysis. The number needed to treat (NNT) to show benefit was five (NNT, 95% CI 4-7). No particular problems were found with emergent side effects in the patients receiving antidepressants compared with controls. There was no difference between the two groups in emergent psychotic symptoms. A study that examined maintenance adjunctive-antidepressant treatment found that patients receiving an antidepressant experienced fewer psychotic exacerbations compared with the placebo control group [43].

The trials had multiple limitations [44]. The samples were not limited to schizophrenia patients with major depression, although trials with inclusion criteria for baseline levels of depressive symptoms had superior results [42]. Many were relatively small; only one attempted to exclude patients who might have been suffering from neuroleptic-induced akinesia [45]. Most of the trials involved tricyclic antidepressants rather than the newer serotonin agents.

There have been no published head-to-head comparisons between different antidepressants in schizophrenia and it remains unclear if there are meaningful differences among the various available agents. Both selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) have been reported to be effective in this role, although SSRIs might be expected to be associated with fewer side effects.

The addition of antidepressant medication to the antipsychotic regimen of acutely psychotic schizophrenic patients may delay the antipsychotic response time [46]; however, this does not seem to occur in patients where the psychosis is only residually active. Since the depressive symptoms which are observed in the midst of an acute psychotic episode frequently fade away as the psychotic episode subsides, there is no advantage to be gained by attempting to treat symptoms of depression with antidepressant medications in schizophrenia during an acute psychotic episode. Psychosocial supports would be better suited for that circumstance.

For a patient experiencing major depression and schizophrenia, who is not floridly psychotic, we suggest treatment of depression with one of the SSRIs. The antidepressant should be titrated gradually up to a therapeutic dose (or level if applicable) with maintenance of a steady antipsychotic-drug dose. As an example of treatment with an SSRI, sertraline 50 mg can be added to an ongoing regimen of antipsychotic medication for a schizophrenic patient with depression, and increased by 50 mg/day per week to a final dose of 150 to 200 mg/day (the higher dose in the absence of side effects). The medication should be continued at this dose for at least six weeks. Dose of antidepressants in the treatment of depression are found on the table (table 2).

Some SSRIs (especially fluvoxamine) interact with clozapine leading to toxic clozapine levels in some individuals [47]. Fluvoxamine should be avoided in patients receiving clozapine. Other SSRIs should be used with caution and accompanied by monitoring of clozapine drug levels.

If the patient's clinical response to the SSRI trial is inadequate, then the SSRI can be tapered and an adjunctive TCA could be given instead. The evidence is strongest for adjunctive imipramine, which can be started at 50 mg/day for the first week, and increased by 50 mg/day per week to a final dose of 150 to 200 mg/day (depending on side effects). Six weeks at this dose would constitute an adequate trial, although more time may be required to achieve the maximum benefit.

If SSRIs or tricyclic antidepressants are not helpful or well tolerated, other categories of antidepressants may be tried as adjunctive agents, but there is an absence of controlled trials assessing their efficacy.

In selecting an antidepressant to treat depression in a patient with schizophrenia, the patient's history should be carefully reviewed for antidepressants or antidepressant-antipsychotic combinations that the patient has responded to in the past. The medication history of a close biologic relative with these conditions may also provide useful guidance.

During an antidepressant trial, antipsychotic medication should be continued because antidepressant treatment in the absence of co-treatment with an antipsychotic agent in persons with schizophrenia has been associated with exacerbation of psychosis [2,48].

For patients who respond favorably to the addition of adjunctive antidepressant medication, long-term maintenance treatment with this combination is recommended. A small randomized trial suggested that continuation of an adjunctive antidepressant could prevent relapse in patients with schizophrenia who had initially responded to the antidepressant with a reduction in depressive symptoms [43]. If the antidepressant is to be discontinued, a gradually tapering of the medication over the course of a month is recommended.

Contrary to some beliefs, anticholinergic antiparkinsonian medication can be safely administered concurrently with antidepressant and antipsychotic medication [43], although it would be prudent to obtain an EKG before embarking on this combined medication trial.

Other depressive disorders — There is little research to guide the decision to treat depressive disorders other than major depression (eg, dysthymia). A reasonable approach would be to weigh the potential risk of medication side effects versus the potential benefit of the added adjunctive antidepressant.

Monitoring — Patients with schizophrenia who are undergoing medication changes to treat depression or depression-like symptoms should also receive increased structure and support. Increased energy, initiative, and confidence may emerge in response to treatment with antidepressant medication, and the patients (and/or the patient's family) may need help in keeping these factors within the framework of constructive adaptation. Patients should also be monitored with increased frequency for signs of emerging psychotic symptoms resulting from treatment changes.

As with other patients experiencing a major depression, patients with depression comorbid with schizophrenia should be assessed and monitored for suicidal ideation, intent, and means. A history of past suicidality and suicide attempts should be obtained. (See "Suicidal ideation and behavior in adults".)

Standard rating scales have often been used to quantify and monitor the course of depressive symptomatology in patients with schizophrenia. The Calgary Depression Scale was specifically

developed for use in patients with schizophrenia, highlighting affective and cognitive aspects of depression and focusing away from "negative" and motoric symptoms which could come from other sources in the schizophrenic population (figure 1) [49].

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".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Schizophrenia (The Basics)" and "Patient education: Schizoaffective disorder (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Epidemiology** – The lifetime prevalence of depression in schizophrenia has been estimated to be 25 percent; findings have varied with the patient population studied, definition of depression used, and duration of observation. (See 'Epidemiology' above.)
- **Differential diagnosis** – A patient with schizophrenia may be diagnosed with a depressive disorder if they meet criteria for the disorder and other possible causes of depression or depression-like symptoms (listed below) have been excluded including general medical factors, side effects of antipsychotic medications, negative symptoms of schizophrenia,

prodrome of a psychotic event, disappointment reaction. (See 'Differential diagnosis' above.)

- **Assessment and management** – In patients with schizophrenia and major depression who are floridly psychotic, we continue to address the psychosis rather than adding an antidepressant as our next step. The addition of antidepressant medication to the antipsychotic regimen of a patient with schizophrenia who is acutely psychotic may delay the antipsychotic response time. Depressive symptoms which are observed in the midst of an acute psychotic episode frequently fade away as the psychotic episode subsides in individuals with schizophrenia. There is no advantage to be gained by attempting to treat symptoms of depression with antidepressant. Psychosocial supports would be better suited for that circumstance.

  In patients with schizophrenia and major depression who are not floridly psychotic two weeks of watchful waiting, if possible (eg, no suicidal thoughts or other behaviors that put the patient or others at risk) can allow for diagnosing or ruling out a prodrome of a psychotic episode or acute disappointment reaction. (See 'Assessment and management' above.)

  Our next step is to determine, through intervention, whether depression is a product of the patient's antipsychotic medication either as a direct mood effect or as an extrapyramidal side effect. We do this by a cautious downward titration of the antipsychotic medication, or when not possible, through an antiparkinsonian agent or a change in antipsychotic medication to one with less risk of extrapyramidal symptoms. (See 'Antipsychotic medication effects' above.)

  In patients with schizophrenia and major depression, who are not floridly psychotic, and in whom other causes have been ruled out, we suggest treatment with an adjunctive antidepressant medication (**Grade 2C**) rather than other medications or psychosocial interventions. (See 'Pharmacotherapy for major depressive disorder' above.)

- For patients who respond to antidepressant treatment, long-term maintenance treatment is recommended. If the antidepressant is to be discontinued, a gradual taper over the course of a month is advised. (See 'Pharmacotherapy for major depressive disorder' above.)

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