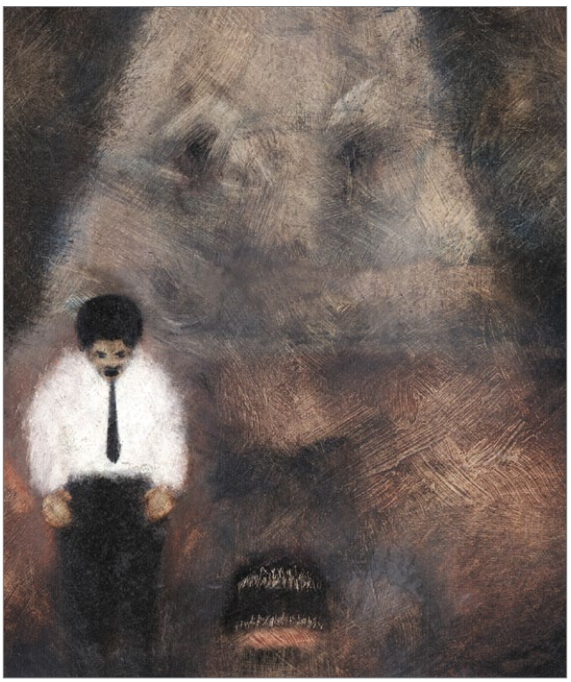
Current PSYCHIATRY

Treating 'depression' in patients with schizophrenia

A thorough differential diagnosis determines the best treatment approach



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Approximately 25% of schizophrenia patients experience course-related depression.[1-4] Depression in patients with schizophrenia is linked to reduced social and vocational functioning, increased likelihood of psychotic relapse and rehospitalization, and other problems.[2-4] Depression in patients with schizophrenia also has been linked to undesirable life events, especially "exit events" such as losing people in their lives, as well as suicidal ideation, suicide attempts, and completed suicides. Overall, it has been noted that approximately 10% of patients with schizophrenia commit suicide.[5] Depressed schizophrenia patients are at particularly high risk for suicide the first few months after diagnosis and after hospital discharge.

Confirm the diagnosis

The best approach to treating depressive symptoms in schizophrenia patients is to formulate a thorough differential diagnosis (***Table 1, page 36***).

Organic etiologies such as medical illnesses—including anemia, cancer, endocrinopathies, infections, and autoimmune, metabolic, cardiovascular, and neurologic disorders—may contribute to a patient's depressive symptoms. "Depression" also can be a side effect of medications used to treat medical conditions, such as antihypertensive and antineoplastic agents, steroidal and nonsteroidal anti-inflammatory agents, and sedative hypnotics, or could be secondary to dose reduction or discontinuation of other agents, such as corticosteroids or psychostimulants. Substance abuse also can play a role in depressive symptoms, either through acute or chronic use or

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Negative symptoms, such as anhedonia, social withdrawal, low energy, and reduced speech or activity, share features with depression

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Table 1

Differential diagnosis of 'depression' in schizophrenia

Organic factors
Antipsychotic-induced dysphoria
Akinesia
Akathisia
Negative symptoms
Acute disappointment reactions
Chronic disappointment reactions
Prodrome of psychotic relapse
Depression

discontinuation. In particular, chronic cannabis abuse can lead to an anergic state that resembles depression, and cocaine withdrawal typically features depression-like symptoms. Additionally, withdrawal from caffeine or nicotine—substances patients with schizophrenia often use heavily—can lead to dysphoric states that are difficult to distinguish from depression.

Antipsychotic-induced dysphoria. Blockade of dopamine receptors is an important feature of all antipsychotics; however, dopamine neurotransmission also is involved in the brain's "pleasure" pathways. Individuals who take antipsychotics may experience reduced joy from once-pleasurable activities. Results of studies on the link between depression and antipsychotics have been mixed.[2,4] Although some researchers have found depressed mood common among patients receiving antipsychotics, others have failed to show differences between patients treated with antipsychotics and those randomized to placebo.

Akinesia, a parkinsonian side effect of antipsychotics, can be blatant or subtle. The blatant form involves large muscle groups; these patients present with diminished arm swing, stooped posture, and parkinsonian gait. Easily spotted, such patients are unlikely to be considered depressed.

The more subtle form of akinesia is easier to confuse with depression. It can affect small muscle groups, such as in the face or vocal cords. Lack of responsiveness of facial expression is easily confused with blunted affect, low mood, lack of interest, or emotional unresponsiveness. Subtle akinesia also can impair a patient's ability to initiate or sustain motor behavior. Many activities, from striking up a conversation to changing television channels, involve initiating and sustaining motor behavior, which these patients' basal ganglia are underequipped to do. Life becomes boring and patients criticize themselves for "being lazy." Patients with akinesia also are prone to dysphoria.[6,7] When the lack of spontaneous motor behavior found in subtle akinesia is combined with diminished experience of pleasure due to antipsychotic blockade of dopamine, a patient may feel that "nothing is worth the effort."

Akathisia is another movement disorder of the basal ganglia that can be triggered by antipsychotics. Whereas a patient with akinesia experiences having a "broken starter motor," the akathisia patient experiences "a starter motor that won't turn off." Akathisia can be blatant or subtle. A patient with blatant akathisia has difficulty remaining seated and often paces. In subtle akathisia, increased motor activity is less dramatic, and patients may simply wander or talk excessively. Akathisia also has a dysphoric component that, when the movement is interpreted as restlessness or agitation, may look like depression.[8]

Negative symptoms. Primary negative symptoms in schizophrenia have several features in common with depression, which can create diagnostic challenges.[9] These include anhedonia, social withdrawal, lack of initiative, lowered energy, diminished expectations and/or self confidence, and reduced speech or activity. The main feature that distinguishes the primary negative symptom syndrome from depression is prominent blue mood, which is present in depression but not in negative symptoms. Cognitive features—such as guilt, pessimism, and suicidal thoughts—are common in depression, but usually are absent in negative symptoms.

Acute disappointment reactions. Short-term reactions to negative life events can include depressed mood, pessimism, self-

Table 2

Antidepressant effects of antipsychotics in schizophrenia patients

Study	Design	Results
Marder et al, 1997[14]	In 2 double-blind trials, 513 patients with chronic schizophrenia received risperidone (2, 6, 10, or 16 mg/d), haloperidol (20 mg/d), or placebo for 8 weeks	Patients receiving risperidone showed greater reductions in anxiety and depression symptoms as measured by PANSS scores than patients receiving haloperidol or placebo
Tollefson et al, 1998[15]	In a prospective, blinded trial, 1,996 patients with schizophrenia received olanzapine (5 to 20 mg/d) or haloperidol (5 to 20 mg/d)	Among patients with depressive signs and symptoms, those who received olanzapine showed better improvement in MADRS scores than patients receiving haloperidol
Emsley et al, 2003[16]	Patients with schizophrenia (N = 269) who had not responded to 4 weeks of fluphenazine (20 mg/d) were randomized to receive quetiapine (600 mg/d) or haloperidol (20 mg/d) for 8 weeks	Quetiapine produced greater reduction on PANSS depression scores than haloperidol
Mauri et al, 2008[17]	In a retrospective study, 222 patients in the reexacerbation phase of schizophrenia received fluphenazine, haloperidol decanoate, haloperidol, clozapine, olanzapine, quetiapine, risperidone, or L-sulpiride monotherapy	All antipsychotics led to improvements in depressive symptoms as measured by the BPRS scale, but improvements were statistically significant only with fluphenazine, haloperidol, olanzapine, risperidone, and L-sulpiride

BPRS: Brief Psychiatric Rating Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; PANSS: Positive and Negative Syndrome Scale

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Depressive symptoms may occur during the early stages of psychotic decompensation

blame, impaired concentration, and sleep and appetite disturbances. With acute disappointment reactions, there is an identifiable proximal loss or disappointment, and the duration of the reaction is relatively brief, from a couple of hours to a few weeks.[4] While the acute disappointment reaction is ongoing, the emotional burden may be substantial. With bereavement or grief reactions the loss is clear; however, be vigilant for situations where the patient's loss may be idiosyncratic or symbolic.

Chronic disappointment reactions, also known as the demoralization syndrome, involve long-term convictions of defeat, despair, incompetence, and loss of control.[10] These reactions can be devastating and prolonged. These reactions are important to identify because they may be ameliorated by rehabilitative interventions or other psychosocial supports.

Prodrome of psychotic relapse. Longitudinal observations of patients with schizophrenia have found depressive symptoms may occur during the early stages of psychotic decompensation.[4,11,12] These symptoms include dysphoria, anxiety, agitation, sleep and/or appetite disturbances, impaired concentration, hopelessness, helplessness, feelings of loss of control or alienation, and social withdrawal. These features usually last a few days to a couple of weeks before they are overtaken by psychotic phenomena.

Depression may occur with similar frequency among patients with schizophrenia as the general population—an estimated 17%.[13] Once other possibilities for a depression-like syndrome have been considered, it is reasonable to speculate that a patient's symptoms might be the product of a traditional depression diathesis, and might respond to usual treatments for depression.

Treatment: A suggested approach

Based on my clinical experience in managing newly emergent "depression" episodes in patients correctly diagnosed with schizophrenia, I suggest the following approach:

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If depressive symptoms persist after lowering or changing the antipsychotic, consider a trial of an adjunctive antidepressant

First, assess the patient for medical disorders that could present with depressive features. Collaborate with the patient's primary care physician to determine which medications the patient is taking and whether there have been any recent changes in these agents or their doses, including adherence issues, potential substance use or abuse, and changes between brand name and generic agents. Thoroughly evaluate the patient's psychiatric status, including symptoms, suicidal risk, and changes in life circumstances. A patient who is at high risk of suicide may require hospitalization. Also assess for the presence of extrapyramidal side effects.

Do not change your patient's medication regimen at this early stage, but provide him or her structure and support, and schedule an early appointment for the next visit (eg, 1 week later). A planned telephone call before the appointment may be helpful as well. If the "depression" is an acute disappointment reaction, it may run its course and resolve. However, if your patient's depressive symptoms are a prodrome of psychotic relapse, the quick follow-up contact will improve the chances of preventing a psychotic episode by increasing the antipsychotic dosage or making other reasonable changes in pharmacotherapy.

If at the follow-up visit the patient's psychotic symptoms have not progressed but depressive symptoms persist, evaluate for the possibility of parkinsonian symptoms, which may be subtle and difficult to rule out. If your patient is restless or tends to be physically active, a trial of a benzodiazepine can be added to treat akathisia. If the patient is underactive, consider a trial of an anticholinergic antiparkinsonian agent, such as benztropine, for akinesia. Dosages of benztropine can be raised in a stepwise manner up to 6 mg/d if there are no side effects, such as constipation, dry mouth, blurry vision, or memory impairment. Advantages of treating extrapyramidal side effects first include:

- response to antiparkinsonian medications occurs rapidly—if your patient shows no response within a week, future response at this dose is unlikely
- the presence of anticholinergic side effects is a biologic marker indicating that the treatment dose is adequate
- the clinician has more time to get to know the patient and his or her condition before committing to lowering, raising, or changing the antipsychotic dosage.

Once extrapyramidal symptoms have been ruled out, consider the possibility of antipsychotic-induced dysphoria. If the patient does not have current psychotic symptoms, cautious lowering of the antipsychotic can be tried. Lower the dose gradually and closely monitor for emerging psychotic symptoms. If your patient has evidence of psychotic symptoms or if the antipsychotic can't readily be lowered, switching antipsychotics is a reasonable approach. Several second-generation antipsychotics have been associated with reduced symptoms of "depression," (***Table 2, page 37***)[14-17] although it is not entirely clear whether the real difference is in depression or in negative or extrapyramidal symptoms.[1,2,17,18]

Antidepressants. If depressive symptoms persist after lowering or changing the antipsychotic, consider a trial of an adjunctive antidepressant. Titrate antidepressants to the recommended dose over 1 month, and continue antiparkinsonian medications. See patients frequently, and ensure that they receive psychosocial support.

No randomized trials have compared the efficacy of antidepressants for treating patients with schizophrenia; therefore, it is unclear if there is a preferred agent. Newer antidepressants often are used in depressed patients with schizophrenia because they are less likely to cause anticholinergic side effects. However, anticholinergic activity may be desirable, eg, for patients with akinesia. Caution is required when combining a selective serotonin reuptake inhibitor with clozapine because metabolism interactions could lead to toxic clozapine levels in some patients.[19]

If your patient's depressive symptoms improve after adding an antidepressant, continue that agent along with the antipsychotic and any antiparkinsonian medications. Only 1 study has evaluated maintenance adjunctive antidepressant therapy for depressed patients with

schizophrenia who initially responded to antidepressants. It found that imipramine appeared to protect patients from depressive relapse, and patients who received maintenance adjunctive imipramine were less likely to experience worsening psychotic symptoms.[20]

Depressed schizophrenia patients are most likely to improve if they receive optimal psychosocial intervention,[21] which consists of nonspecific support and, when indicated, psychosocial rehabilitation services. Change, even positive change, can be stressful, and patients with schizophrenia need every advantage they can get to be successful in moving their lives in a positive direction.

Related Resources

- Rybakowski JK, Vansteelandt K, Szafranski T, et al. Treatment of depression in first episode of schizophrenia: Results from EUFEST [published online ahead of print May 22, 2012]. Eur Neuropsychopharmacol. doi:10.1016/j.euroneuro.2012.04.001.
- Addington D, Addington J. Calgary Depression Scale for Schizophrenia. www.ucalgary.ca/cdss.

Drug Brand Names

Benztropine • Cogentin
Clozapine • Clozaril
Fluphenazine • Permitil, Prolixin
Haloperidol • Haldol
Imipramine • Tofranil
Olanzapine • Zyprexa
Quetiapine • Seroquel
Risperidone • Risperdal

Disclosure

Dr. Siris reports no financial relationships with any company whose products are mentioned in this article or with manufacturers of competing products.

Clinical Point

Depressed schizophrenia patients are most likely to improve if they receive optimal psychosocial intervention

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Bottom Line

Depressive symptoms are common among patients with schizophrenia. A thorough differential diagnosis can help identify organic factors, movement disorders, and other conditions that can cause these symptoms. Treatment options include addressing the underlying causes, prescribing adjunctive antidepressants, switching antipsychotics, and initiating psychosocial interventions.