

New Approaches to Managing Psychotic Depression

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Major depression with psychotic features, while fairly common, is frequently misdiagnosed. Symptoms seen in these patients are those of an overall severe depressive disorder with psychomotor impairment (retardation or agitation), guilt, suicidal preoccupation, and neuropsychological impairment. A number of biological characteristics and behavioral symptoms are specific to patients suffering from psychotic depression and differ significantly from those of nonpsychotic depression. Psychotic depression is seen in patients of all ages, and it has a high short-term morbidity and risk of suicide. Data support the use of antipsychotics in combination with antidepressants for major depression with psychotic features, but other treatments may have as great or greater efficacy for the disorder. This article focuses on recognizing the features of psychotic depression, the success of current treatment options, and new treatments under investigation.

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Although major depression with psychotic features represents about 25% of consecutively admitted depressed patients,¹ it is frequently overlooked.² Patients are often careful about revealing cognitive deficits and delusions and will sometimes deny thoughts of suicide,³ which makes this disorder difficult to diagnose. Similarities in the symptoms of psychotic depression, schizophrenia, and schizoaffective disorder also make diagnosis more difficult.² Data have shown that psychotic depression is more similar to schizophrenia than to nonpsychotic depression.⁴

In the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, psychotic depression is classified as a major depressive disorder, severe, with psychotic symptoms. This classification requires the usual criteria for a major depressive episode with the additional symptoms of hallucinations or delusions, which can be either mood-congruent or -incongruent. Some researchers have argued that psychotic depression should be classified as a

distinct clinical entity due to a number of biological and behavioral symptoms that are specific to the disorder.^{5,6}

DIAGNOSIS

While symptoms of psychotic depression can be profound, differentiation from other disorders and detection of undisclosed symptoms often require extensive examination of the patient. Responding to data that patients with delusional depression were less responsive to tricyclic antidepressants than were patients with nondelusional depression, Glassman and Roose⁷ conducted a study to differentiate symptoms of psychotic and nonpsychotic depression. They found that patients with psychotic depression are more likely to show clinically significant psychomotor agitation than their nonpsychotic counterparts. These findings have been confirmed in subsequent studies.^{5,8–10}

The delusions experienced by psychotically depressed patients are typically guilty,^{5,7,10} paranoid,^{3,5} and somatic⁵; and their hallucinations are auditory, visual, or somatic.⁵ Studies conducted to test the neurovegetative symptoms of psychotic depression have shown symptoms of severe depression^{5,9} and fixed depressive thought content^{5,10} and both higher levels of retardation⁵ and higher levels of cognitive disturbance⁵ according to Hamilton Rating Scale for Depression (HAM-D) scores and compared with nonpsychotic patients. In studies,^{4,11} Stroop Color and Word Test scores indicated that psychotically depressed patients' attention and response inhibition were impaired. Patients also had impaired immediate and delayed recall memory for semantically organized information but were able to retain verbal material normally. These data suggest

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an attentional component to the problems with recall. Patients with psychotic depression have shown a higher rate of errors of commission on verbal memory tests.^{11,12} Serretti et al.¹³ found that these patients had a higher rate of cluster A personality disorder and a lower level of education compared with patients with nonpsychotic depression.

Other features characteristic of psychotic depression compared with nonpsychotic depression include a history of past delusions¹⁰ but fewer previous episodes,⁷ a positive family history of mental disorder,¹⁴ previous suicide attempt,¹⁴ greater suicidal ideation and intent,¹⁰ and reduced or absent diurnal variation of depressive symptoms.⁵ Psychotic depression is often considered a disorder of the elderly, but at least one study has reported that younger age was found to be a more common characteristic of psychotic rather than nonpsychotic depression.^{9,10} In comparison with patients with schizophrenic disorders, patients with psychotic depression have shown greater emotional impact features and greater volitional dyscontrol.¹⁵ If a patient's psychotic depression is further complicated by agitation, determining whether the patient is suffering from agitated psychosis, severe anxiety, or a dysphoric manic state may be difficult. A number of questions can help in the differential diagnosis. Does the patient suffer from insomnia? If so, does the patient believe that he or she needs less sleep than usual? If delusions are present, are they guilt-ridden as in a depressive state or pleasure-seeking as in a hypomanic or manic state? Has the psychosis been present in the absence of affective symptoms? Is there a family history of psychotic or affective illness?

Biological symptoms that have been found to be indicators of psychotic depression are related to excessive hypothalamic/pituitary/adrenal (HPA) axis activity.⁴ This is reflected in high levels of 24-hour urinary free cortisol,¹⁶ high rates of dexamethasone nonsuppression,^{11,17-20} and high post-dexamethasone cortisol levels.^{11,18}

CURRENT TREATMENTS

Psychotic depression is also a difficult-to-treat disorder, and in general, patients with psychotic depression are inadequately treated. In a survey of 187 patients referred for electroconvulsive therapy (ECT), Mulsant and colleagues²¹ reported high rates of inadequate treatment. They found that only 2 (4%) of 53 patients with psychotic depression received at least one adequate medication trial. In contrast, 70 (52%) of 134 patients with nonpsychotic depression received at least one adequate trial. Of patients with psychotic depression, 25 (47%) received either no antipsychotic medication or treatment for less than 3 weeks.

Antidepressants

Tricyclic antidepressant (TCA) monotherapy, other than amoxapine, is generally ineffective for psychotic

depression. Amoxapine is a dibenzoxazepine TCA with antidepressant and antipsychotic effects that has shown effectiveness in patients with delusional depression.²² The serotonin-2 antagonist and mild dopamine-2 antagonist properties of amoxapine have led some to argue that amoxapine should be considered an atypical antipsychotic.²³ Anton and Burch²² compared the combination of amitriptyline and perphenazine with amoxapine in 38 patients with psychotic depression in a 4-week double-blind study. Patients in each group showed similar improvement in depression and psychosis.

There are some positive data on selective serotonin reuptake inhibitors (SSRIs) as monotherapy for the treatment of psychotic depression. In a double-blind European trial comparing sertraline with paroxetine for delusional depression, 75% of patients treated with sertraline and 46% of patients treated with paroxetine were considered responders.²⁴ A trial of fluvoxamine monotherapy for delusional depression showed a response rate similar to that of antidepressants plus antipsychotics and of ECT.²⁵ Of the 57 patients who completed the 6-week trial, 48 patients recovered. American investigators have been skeptical of the efficacy of SSRI monotherapy.

Atypical Antipsychotics

Atypical antipsychotics alone may be effective for psychotic depression. The earliest observation of atypical antipsychotic monotherapy treatment reported that risperidone seemed to be effective in 10 patients with schizodepressive disorders or a psychotic major depressive episode.²⁶ In a more recent, multicenter, double-blind, parallel group trial,²⁷ the efficacy of risperidone was compared with a combination of haloperidol and amitriptyline in 123 patients over 6 weeks. Although overall, the combination treatment showed greater efficacy, risperidone produced a 37% reduction in patients' Positive and Negative Syndrome Scale-derived Brief Psychiatric Rating Scale (BPRS) scores and a 51% reduction in patients' Bech-Rafaelsen Melancholia Scale total scores. A case report²⁸ of a female patient with psychotic depression suggests that risperidone monotherapy can be efficacious in some patients who have not responded to other treatments. The patient was first treated with a combination of fluoxetine and flupenthixol, and then a regimen of fluoxetine, trifluoperazine, and bilateral ECT 3 times a week, both of which were unsuccessful. Risperidone monotherapy was initiated, which resulted in an improvement in psychotic as well as mood disturbances without emergence of side effects after 1 week of treatment.

Olanzapine has also been found successful as monotherapy in psychotic depression. DeBattista et al.²⁹ reported a substantial improvement in symptoms of psychotic depression in a patient taking olanzapine monotherapy, and a case report in Germany also found olanzapine effective for psychotic depression.³⁰

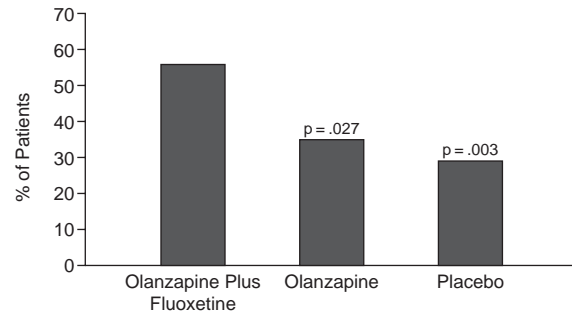
Antidepressant-Antipsychotic Combinations

The drug treatments that have typically been most effective for psychotic depression include combinations of antidepressants with antipsychotics. Traditionally these treatments have included TCAs combined with conventional antipsychotics. In a double-blind study by Spiker et al.,³¹ the combination of amitriptyline and perphenazine was significantly more effective for psychotic depression than either drug alone. A meta-analysis³² of 597 patients showed a 77% response rate to TCAs combined with antipsychotics, and 3 retrospective chart reviews³³⁻³⁵ revealed good responses to TCA and antipsychotic combinations. The SSRI fluoxetine combined with perphenazine showed efficacy similar to that reported for amoxapine, ECT, and TCA-antipsychotic combination therapy in a 5-week trial.³⁶ Of 30 patients, 22 had a 50% or greater reduction in their total HAM-D score by week 5.

Recent data suggest that the combination of SSRIs and atypical antipsychotics might be particularly effective for the treatment of psychotic depression. Olanzapine was reported to be effective in combination with citalopram in a case report of a patient who was resistant to other treatments.³⁰ Another case report³⁷ found the combination of olanzapine and sertraline effective for severe depression with psychotic features in a suicidal patient who had failed treatment with the combination of mirtazapine and haloperidol as well as venlafaxine and haloperidol. The patient's condition deteriorated when olanzapine was withdrawn but quickly improved when olanzapine therapy was restarted.

Beyond case reports, more substantial data for the combination of olanzapine and fluoxetine in the treatment of psychotic depression have recently been presented. Dubé et al.³⁸ conducted 2 parallel, 8-week, double-blind trials that compared treatment with olanzapine plus fluoxetine to olanzapine or placebo in 249 patients with psychotic depression. While 110 patients completed the acute phase, rates of study discontinuation due to adverse events were higher for the olanzapine-fluoxetine combination compared with placebo (6.0%, $p = .016$) but not different from the rate with olanzapine alone (8.9%, $p = .085$). Mean changes in HAM-D scores were significantly greater for the olanzapine-fluoxetine combination than for either placebo or olanzapine alone. The response rates were 56% for the combination, 36% for olanzapine alone, and 30% for placebo (Figure 1), and 20% of patients in the combination group remitted (Table 1). Rothschild et al.³⁹ retrospectively compared olanzapine against typical antipsychotics in 15 inpatients with psychotic depression, most of whom were also taking antidepressants. Response to treatment was evaluated by reviewing and scoring patient records using a 7-point Likert rating scale. Ten of the 15 patients taking olanzapine compared with 4 of 15 patients taking other antipsychotics were considered much or very much improved upon discharge. However, there have been re-

Figure 1. Percentage of Patients Considered Responders ($\geq 50\%$ Improvement) to Olanzapine-Fluoxetine Combination Treatment According to HAM-D Scores^a



^aReprinted with permission from Dubé et al.³⁸
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

ports of the induction and exacerbation of psychotic symptoms by fluoxetine⁴⁰ and sertraline⁴¹ in patients with psychotic depression who are taking antipsychotics.

Other Treatments

While ECT is a remarkably effective treatment for psychotic depression,^{33,34,42,43} requirements for its use are stringent, and public perception about the overall appropriateness of shock treatment is negative.

Lithium has shown some effectiveness as an augmentation strategy in patients with psychotic depression who do not respond to the combination of tricyclic antidepressants and neuroleptics.⁴⁴ In an open comparison of lithium plus amitriptyline and haloperidol plus amitriptyline, Ebert⁴⁵ described fewer side effects and better improvement of some depressive symptoms in patients taking the lithium combination.

HPA Axis Inhibition

An emerging area of study for treating patients with psychotic depression is based on the markedly abnormal HPA axis and high cortisol levels in those patients.^{4,5,12} Clinicians have hypothesized for a number of years that psychosis and the cognitive disturbance seen in these patients may be due to excessive glucocorticoids and that inhibition of the HPA axis might be an effective treatment. There are 2 types of receptors for cortisol. One is the mineralocorticoid receptor, which is a high-affinity receptor that is responsible for much of the diurnal variation of cortisol metabolism and secretion. The other receptor is the low-affinity glucocorticoid receptor (GR) that tends to be activated only under high levels of stress.⁴⁶

Mifepristone is a potent GR antagonist that has shown potential for rapidly reversing psychotic symptoms in delusional depression. Belanoff et al.⁴⁷ conducted a small, double-blind, placebo-controlled, crossover study of mifepristone in 5 patients with psychotic major depression.

Table 1. Percentage of Patients Achieving Response or Remission While Taking Placebo, Olanzapine Alone, or Olanzapine Plus Fluoxetine^a

Treatment	% Responders (≥ 50% Improvement in HAM-D Total Score)	Median Days to Response ^b	% Remitters (HAM-D Total Score ≤ 8)	Median Days to Remission ^b
Olanzapine-fluoxetine combination	55.6	12	20.0	20
Olanzapine	35.6 ^c	12	13.3	56
Placebo	29.8 ^d	20	10.6	24

^aReprinted with permission from Dubé et al.³⁸ Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

^bMedian days to response/remission based on Kaplan-Meier survival analysis.

^cp = .041 vs. olanzapine-fluoxetine combination.

^dp = .005 vs. olanzapine-fluoxetine combination.

Patients were given 600 mg/day of mifepristone for 4 days. All patients completed the protocol and no adverse effects were observed or reported. All patients showed substantial improvements in their HAM-D scores while receiving mifepristone, and 4 of the 5 patients showed substantial improvement in their BPRS scores.

In a more recent study, Belanoff et al.⁴⁸ conducted an open-label trial of mifepristone in 30 inpatients with psychotic major depression. Patients were randomly assigned to receive 50 mg, 600 mg, or 1200 mg of mifepristone once daily for 7 days. Patients taking both the 600-mg/day and 1200-mg/day doses showed significant reductions in their psychosis in 1 week or less. More than 40% of patients taking the 2 higher doses had a greater than 50% reduction in their HAM-D scores, and over 60% demonstrated at least a 30% reduction in BPRS scores. This strategy may open up some alternative methods for treating delusional depression that are more acceptable than ECT. A GR antagonist may have more rapid effects than atypical antipsychotic-antidepressant combination therapy, which may not separate from placebo for several weeks.

My colleagues and I have used mifepristone for psychotic depression acutely then switched patients over to antidepressant monotherapy or an antidepressant-antipsychotic combination.⁴⁶ The clinical improvement achieved with the GR antagonist seems to be maintained after patients are switched; however, in an attempt to demonstrate that sustained effect in a controlled study, we are now conducting longer-term, placebo-controlled trials of mifepristone. In these studies, patients are assessed for response after 1 week of treatment with mifepristone. Patients are then switched to antidepressant monotherapy or an antidepressant-antipsychotic combination and response is assessed again after 4 weeks of treatment.

A disadvantage of most of the drugs that are currently available for GR antagonism is that they are progesterone antagonists as well. Particularly in younger women, problems with long-term treatment could include delayed menses and potential breakthrough bleeding. GR antagonists have been used long term at lower doses for meningiomas, uterine fibroids, and chronic pelvic pain.⁴⁹ In younger

women, frequent monitoring may be important when progesterone is blocked for prolonged periods (months) because unopposed estrogen could lead to menstrual problems.

CONCLUSION

Psychotic depression may be difficult to detect and to treat, but there are specific psychological and biological symptoms that clinicians can become familiar with in order to identify this disorder. Symptoms of a severe, debilitating depressive disorder should prompt a clinician to examine the patient

more closely for delusions or other symptoms of psychosis. Hospitalization and stabilization may be necessary for severely psychotic and suicidal depressed patients. Often, patients with paranoid delusions will be more willing to accept treatment with a single medication rather than a combination. For this reason, it may be optimal to stabilize the patient with an antipsychotic agent and add an antidepressant to the treatment after the patient is more willing to accept additional medication. Olanzapine and fluoxetine may be a useful combination. While there are sufficient data to recommend ECT for the treatment of psychotic depression, there are both real and perceived drawbacks to ECT; therefore, it may be best considered after other options have failed. Limited data confirm the efficacy of options such as HPA axis inhibition for the treatment of psychotic depression. These options may also be best considered after standard therapies have failed.

Drug names: amitriptyline (Endep, Elavil, and others), amitriptyline and perphenazine (Etrafon and others), citalopram (Celexa), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), haloperidol (Haldol and others), mifepristone (Mifeprex), mirtazapine (Remeron), olanzapine (Zyprexa), paroxetine (Paxil), perphenazine (Trilafon and others), risperidone (Risperdal), sertraline (Zoloft), trifluoperazine (Stelazine and others), venlafaxine (Effexor).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, amitriptyline, amoxapine, citalopram, fluoxetine, fluvoxamine, haloperidol, lithium, mifepristone, mirtazapine, olanzapine, paroxetine, perphenazine, risperidone, sertraline, trifluoperazine, and venlafaxine are not approved by the U.S. Food and Drug Administration for the treatment of psychotic major depression.

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