Treatment for Major Depression With Psychotic Features (Psychotic Depression)

"I have a patient with psychotic depression (major depression with psychotic features). Can I treat her with medications?"

Reply from Anthony J. Rothschild, M.D.

Psychotic depression, or major depressive disorder with psychotic features, is a serious illness during which a person experiences the combination of depressed mood and psychosis, with the psychosis commonly manifesting itself as nihilistic or somatic-type delusions. You have already accomplished an important first step for the successful treatment of your patient in recognizing and diagnosing psychotic depression. Data from the National Institute of Mental Health (NIMH) Study of the Pharmacotherapy of Psychotic Depression (STOP-PD) (1) indicate that psychiatrists frequently miss the diagnosis of psychotic depression, in large part because they do not recognize the psychotic features. In the STOP-PD study, the diagnosis of psychotic depression was missed 27% of the time, which was likely a conservative estimate because patients with comorbid conditions, such as substance abuse in the past three months, or unstable medical conditions were excluded.

The American Psychiatric Association (APA) practice guidelines recommend with substantial clinical confidence (the highest ranking) that patients with psychotic depression be treated with the combination of an antidepressant and an antipsychotic or electroconvulsive therapy (ECT) (2). Although ECT has well-established efficacy as a treatment for psychotic depression (3, 4), its use is limited by several factors: a high rate of relapse following completion of ECT (5, 6), lower rates of response in nonacademic centers (7), significant disparities in its availability (8), and the fact that many patients prefer pharmacologic treatment.

In the United States, despite the APA practice guideline recommending the combination of an antidepressant and antipsychotic for the acute treatment of psychotic depression since 2000 (9), studies have shown that only 5% of patients with psychotic depression receive an adequate combination of an antidepressant and an antipsychotic (10). Efficacy has been demonstrated for only certain specific combinations of an antidepressant and antipsychotic; thus, whether the combinations discussed below are generalizable to all patients with psychotic depression or all combinations of antidepressant and antipsychotic medications is not known. Because there are no FDA-approved medications for the treatment of psychotic depression, all of the medications discussed below are off-label for this use.

Sertraline With Olanzapine

The largest study of the combination of an antidepressant and an antipsychotic for the treatment of psychotic depression to date, the NIMH STOP-PD, reported that the combination of sertraline and olanzapine was more efficacious than monotherapy with olanzapine alone (11). The study included 259 participants with psychotic depression, 142 participants ≥60 years old and 117 participants <60 years old. The target dose for sertraline was 150 mg/day and for olanzapine was 15 mg/day. Doses up to 200 mg/day for sertraline and 20 mg/day for olanzapine could be used if indicated. Combination therapy was comparably superior for both younger and older adults and, overall, tolerability was comparable across age groups. Both age groups had significant increases in cholesterol and triglyceride concentrations, but statistically significant increases in glucose occurred only with younger adults. Younger adults gained significantly more weight than older participants did.

Fluoxetine With Olanzapine

In two randomized, placebo-controlled trials (12), a combination of fluoxetine plus olanzapine was compared with olanzapine monotherapy or placebo in 229 hospitalized patients with psychotic depression. These two studies are the largest randomized controlled trials for the treatment of psychotic depression that included a placebo arm. In both studies, patients were randomized to placebo, olanzapine (mean doses: 11.9 and 14.0 mg/day) plus placebo, or olanzapine (mean doses: 12.4 and 13.9 mg/day) plus fluoxetine (mean doses: 23.5 and 22.6 mg/day) and followed for eight weeks. Pooled data from both studies showed a reduction in Hamilton Depression Rating Scale scores that was statistically greater in the combination group than in the olanzapine monotherapy group or the placebo group.

Venlafaxine With Quetiapine

A double-blind, randomized controlled study of 122 hospitalized patients (aged 18–65 years) with psychotic depression at eight sites in the Netherlands treated patients for seven weeks with imipramine (N=42), venlafaxine (N=39), or the combination of venlafaxine and quetiapine (N=41) (13). Dosages used were the following: The imipramine dose

was adjusted to adequate plasma levels of 200–300 ng/ml, the maximum venlafaxine dose was 375 mg/day, and the maximum venlafaxine-quetiapine doses were 375 mg/day for venlafaxine and 600 mg/day for quetiapine. The authors concluded that the combination of venlafaxine and quetiapine was more effective than venlafaxine alone on the primary outcome measure (response) and was well tolerated. The authors also stated that the venlafaxine-quetiapine combination was likely to be more effective than imipramine, but they could not conclude that from the data.

Older Medications

Studies using older medications have reported efficacy with the combination of amitriptyline and perphenazine (14) or amoxapine (15). Long-term use of perphenazine or amoxapine incurs a greater risk of the development of tardive dyskinesia than does the use of olanzapine or quetiapine.

Time to Recovery

Observational studies show that about 50% of patients with unipolar psychotic depression recover within two to three months, and the large majority of patients recover within six to 12 months (16–18).

How Long Should Patients Stay on Medications After They Are in Remission?

Determining the optimal continuation and maintenance therapy for psychotic depression is of special concern because of the high rate of relapse observed in naturalistic follow-up studies of psychotic depression, including relapse after ECT (5, 6, 19). Other concerns include a relapsing or chronic course of illness (20), high mortality rates (20, 21), a high risk of extrapyramidal symptoms and tardive dyskinesia with first-generation antipsychotics (22), risk of metabolic syndrome with second-generation antipsychotics (11), an increased use of health care services (23), and a high rate of disability (23). During maintenance treatment of unipolar psychotic depression with combination pharmacotherapy, the antidepressant is generally maintained longer than the antipsychotic. Most experts discontinue the antipsychotic after four months of sustained recovery from the episode of unipolar psychotic depression and continue the antidepressant (24–26). An NIMH study that addresses the question of how long a patient with psychotic depression who is in remission needs to stay on the antipsychotic medication is currently in progress (27). For patients who relapse while discontinuing the antipsychotic during maintenance treatment of prior episodes of psychotic depression, it is reasonable to maintain the antipsychotic for at least six to 12 months. I suggest slowly tapering the antipsychotic over one month to increase the probability of detecting incipient depressive and psychotic symptoms before a full-blown episode of psychotic depression recurs. Each week, I taper by approximately 25% of the dose used to achieve remission. As an example, olanzapine at 20 mg/day is reduced each week by 5 mg/day. If symptoms recur during the tapering, the dose is usually titrated back up to the full dose used initially to achieve remission. For patients with unipolar psychotic depression who successfully taper and discontinue the antipsychotic but subsequently relapse during maintenance treatment with antidepressant monotherapy, I suggest restarting the antipsychotic that was discontinued. Given the serious morbidity and mortality of psychotic depression, I recommend lifetime treatment with the antidepressant.

AUTHOR AND ARTICLE INFORMATION

Dr. Rothschild is the Irving S. and Betty Brudnick Endowed Chair and Professor of Psychiatry at the University of Massachusetts Medical School, Worcester (e-mail: anthony.rothschild@umassmemorial.org).

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