The Treatment of Psychotic Depression

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Psychotic depression is marked by increased severity, longer episodes, greater incapacity, and a lower likelihood of placebo response. Psychotic features often recur in subsequent episodes and interepisode intervals are shorter when psychotic features have been previously present. Among the treatment options for psychotic depression, electroconvulsive therapy is particularly effective. Conventional pharmacotherapy consists of tricyclic antidepressants combined with antipsychotics; recovery with tricyclic antidepressant monotherapy is less likely. Serotonin selective reuptake inhibitors may prove useful but the relevant literature is scant. Pharmacokinetic interactions are likely in combination treatment; as are side effects that may mimic the underlying condition. Little is known regarding the importance of antipsychotics to maintenance therapy.

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Second, psychotic episodes are more likely to be incapacitating, to feature unvarying dysphoria, and to persist for longer periods. The likelihood of placebo response in depression generally correlates inversely with severity and, accordingly, depressed patients with psychotic features are much less likely to respond to placebo than are other depressed patients.

Finally, psychotically depressed patients are much more likely to exhibit an abnormal plasma cortisol escape from dexamethasone suppression. A recent meta-analysis showed the presence or absence of psychotic features to be a much more consistent predictor of dexamethasone nonsuppression than endogenous or melancholic subtyping.

Follow-up studies show that the presence of psychotic features has a significance that extends well beyond a given episode. This is most clearly shown by the high likelihood that psychotic features will recur in new episodes. The tendency is sustained across multiple episodes, making psychotic depression the most stable of the phenomenologically based subtypes. Thus, the psychotic-nonpsychotic distinction appears to be more consistent across episodes than is the endogenous-nonendogenous distinction.

Patients with psychotic depression experience a shorter time to recurrence than do those with nonpsychotic depression, regardless of whether the immediately preceding episode includes psychotic features. The presence of psychotic features in any episode therefore indicates an illness with a persistently high risk of recurrence. The higher number of recurrences and the likelihood that many of these recurrences will involve psychosis with longer durations combine to produce a persistently greater depressive morbidity. Figure 1 uses data from a study by the National Institute of Mental Health Collaborative Depression Study (Clinical Branch) to show that patients who began this prospective follow-up with psychotic major depressive disorder experienced a higher likelihood of a full depressive syndrome throughout 10 years of follow-up. The substantial short- and long-term morbidity experienced by patients with psychotic depression, together with their failure to show placebo responses, underscores the importance of optimal treatment selection.

<table>
<thead>
<tr>
<th>Table 1. Hallucinations as the Sole Psychotic Feature in Psychotic Major Depressive Disorder (MDD)</th>
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<tr>
<td>Number of Patients With Hallucinations Only N</td>
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<tr>
<td>Lykouras et al (1986)</td>
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<td>Parker et al (1991)</td>
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<td>Anton and Burch (1993)</td>
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<tr>
<td>Coryell and Zimmerman (Unpublished data)</td>
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*Derived from database described in reference 3.

*Data from reference 10.

p < 0.1.

p < 0.05.

p < 0.01.

ACUTE TREATMENT

Tricyclic Antidepressants With and Without Antipsychotics

Research interest in psychotic depression as a distinct subgroup originated with the observation that psychotic features predicted poor outcome in antidepressant trials of conventional length. It is now broadly accepted that the short-term effectiveness of tricyclic antidepressants (TCAs) combined with antipsychotics exceeds that of TCAs alone, although a meta-analysis has failed to show this difference to be statistically significant across studies.

Psychotic features also predict a poorer short-term outcome with monoamine oxidase inhibitor (MAOI) therapy. Janicak et al., (1988) assigned 52 depressed inpatients to a 4-week trial of phenelzine. Twenty-one (68%) of those with nonpsychotic depression (N = 31), but only 3 (21%) of those with definite psychotic features (N = 14) were considered responders at the end of the trial.

Although many studies support this conclusion, few have employed a prospective design to compare combination treatment to TCAs used alone. Of the three available studies, one included fewer than five subjects in each cell and another was restricted to patients with schizoaffective disorder as defined by the authors. That sample was comprised exclusively of patients with Schneiderian first-rank symptoms and included an unquantified portion with DSM-IV schizoaffective disorder. Nevertheless, results agree closely with those of the remaining study (Table 2). In both studies, three quarters of those given combination therapy, but slightly less than half given TCA monotherapy, responded.

Clinicians undertaking combination therapy should remember that conventional antipsychotics may interfere with the metabolism of TCAs, substantially raise plasma levels, and lengthen the time needed to reach steady state. Because toxicity resulting from excessive TCA
levels may be confused with the signs and symptoms of depression or psychosis.\(^4^6\) TCA plasma level monitoring is warranted at both 1 to 2 weeks and at 4 to 6 weeks of combination treatment.

The treating physician should also carefully monitor extrapyramidal symptoms. Stiffness and akathisia can be easily confused with psychomotor retardation and akathisia closely resembles psychomotor agitation.

Potential side effects and the feasibility of blood level monitoring should determine the choice of medicines used in combination treatment. Antipsychotics with prominent anticholinergic effects (i.e., thioridazine, mesoridazine, or chlorpromazine) are poor choices because such effects, as well as orthostatic blood pressure changes, are additive to those of TCAs.

Studies have shown only that TCA monotherapy is relatively ineffective. Two have described placebo response rates of zero for delusional depression. If the 30% placebo response rate generally assumed for nonpsychotic depression is subtracted from the 65%–75% recovery rate associated with active drug treatment, the figure approximates the 40% response rate typically seen for TCA monotherapy in psychotic depression. Thus, true responses to TCA monotherapy may be equally likely in psychotic and nonpsychotic depression. Spiker and Kuper (1988),\(^12\) in fact, demonstrated statistically significant drug effects for amitriptyline monotherapy in psychotic depression. Moreover, Nelson et al. (1986)\(^37\) described a statistically significant relationship between plasma desipramine levels and response in delusional depression.

### Electroconvulsive Therapy

In contrast to TCA or MAOI monotherapy, psychotic features have not been associated with poorer electroconvulsive therapy (ECT) outcomes. Rather, some studies have found that psychotic features are a positive predictor of ECT response.\(^38\)–\(^41\) Particularly noteworthy are two sham-controlled trials of ECT.\(^42\)–\(^44\) In these, the procedure for simulated ECT was identical to that for real ECT except that current was not applied. This allowed for double-blind outcome assessments and for control of the potentially powerful placebo effects of the ECT procedure. In both trials, clear outcome differences between real and simulated ECT emerged for delusional depressives. Statistically significant differences were absent for those who lacked both delusions and psychomotor retardation\(^43\) (Figure 2).

Such studies avoid the confounds of simple response predictor studies in which the features associated with placebo response are indistinguishable from those associated with true treatment effects. The association of delusions with a low placebo response would tend to cancel an association with specific responses to treatment. Sham control studies, though, indicate that psychotic depression is a particularly robust indicator for ECT.

The results from the few direct comparisons of ECT and TCA-antipsychotic combination therapy have been inconsistent.\(^30\)–\(^45\)–\(^46\) A meta-analysis of physical treatment trials in psychotic depression, however, revealed a strong trend toward a higher effect-size (ES) for ECT (ES = 2.3) than for combination therapy (ES = 1.6).\(^28\) This analysis also noted a higher effect-size for bilateral than for unilateral electrode placement. Findings of Pande et al. (1990)\(^41\) echo this; the superiority of bilateral over unilateral electrode placement was much more obvious for delusional than for nondelusional patients.

While ECT may be particularly efficacious for psychotic depression, the diagnostic caveats mentioned earlier are quite important when ECT is being considered. Both pseudohallucinations and a prior history of unsatisfactory responses to antidepressant treatment are common among patients with somatization disorder or with borderline personality disorder. Because antidepressant nonresponse is a widely accepted indication for ECT, such patients are frequently referred to this modality. While there are no formal studies of ECT in these disorders, in this author’s experience any improvements are quite transient.
and these patients are much overrepresented among those who claim long-lasting and disabling memory deficits consequent to ECT.

**Newer Antidepressants and Antipsychotics**

A direct comparison of amoxapine monotherapy and the combination of amitriptyline and perphenazine showed the two treatments to be equally effective. Amoxapine, however, has potent dopamine-receptor blocking properties, and its use entails all of the potential side effects associated with conventional antipsychotics. The advantages of monotherapy are offset by the loss of dosing flexibility.

There has been very little effort to determine the effectiveness of serotonin selective reuptake inhibitor (SSRI) monotherapy in psychotic depression. Recently, though, a four-cell comparison of fluvoxamine plus placebo, fluvoxamine plus haloperidol, desipramine plus placebo, and desipramine plus haloperidol, given to patients with psychotic depression over a 6-week trial, showed fluvoxamine alone to be as effective as the combination of desipramine and haloperidol. Surprisingly, fluvoxamine given with haloperidol was only as effective as desipramine alone and was less effective than fluvoxamine alone. The same investigators followed this with a larger, open trial of fluvoxamine monotherapy. In that study, 84% of 57 patients with psychotic depression met response criteria (a final 21-item HAM-D score less than 8) after 6 weeks of treatment with fluvoxamine. Six weeks is longer than the 4 or 5 weeks typical of acute treatment trials, and the authors did not describe time-to-recovery. Nevertheless, dropout rates were quite low (2 of 59 or 3%) and the recovery rate compared favorably with that typically reported for ECT.

At least one group has described a combined SSRI and antipsychotic trial. In this, 73% of 30 patients with mood-congruent psychotic features met the response criteria (50% or greater reduction in HAM-D scores) after 4 weeks of treatment with fluoxetine and perphenazine. There appear to be no other published comparisons of SSRI and TCA therapies, nor of SSRI therapy with and without antipsychotics.

SSRI effects on the dopamine system are apparently complex, and evidence is accumulating that these effects may be clinically important. Reports of akathisia during SSRI therapy indicate clinically manifest dopamine blockade in at least some areas, though SSRI-induced akathisia is not accompanied by extrapyramidal symptoms. On the other hand are reports of patients treated with fluoxetine who developed delusions which resolved promptly on discontinuation. It is therefore difficult to predict whether additional studies will confirm the efficacy of SSRI monotherapy in psychotic depression. Such trials are clearly warranted, though.

Caveats pertain to the coadministration of SSRIs and antipsychotics as they do to the combination of TCA and antipsychotics. While pharmacokinetic interactions between antipsychotics and SSRIs are not as well characterized as are those between TCAs and SSRIs, such interactions do occur, and antipsychotic levels may be increased by the coadministration of SSRIs. A recent review mentioned, in particular, the potential interactions between conventional antipsychotics and fluoxetine, paroxetine, and sertraline, and between clozapine and fluvoxamine.

**Atypical Antipsychotics**

A number of cases published in the last 5 years have suggested a role for atypical antipsychotics in the management of psychotic depression. The large majority of patients in these reports had bipolar affective disorder with psychotic features. Dwight et al. (1994) used risperidone as the sole treatment for six patients with DSM-III-R schizoaffective disorder, of whom four had a bipolar subtype; risperidone was added to a thymoleptic regimen in two other patients with bipolar schizoaffective disorder. The six with substantial depressive symptoms at the outset experienced reductions in depressive symptoms, but all of the bipolar patients had at least some increase in manic symptoms while taking risperidone. Hillert et al. (1992) successfully treated seven patients with psychotic depressive disorder but those were apparently all unipolar. In contrast, McElroy et al. (1991) included 14 patients with psychotic bipolar disorder in their series of patients treated with clozapine. They specifically mentioned neither antidepressant effects nor any tendency for mania to emerge or worsen. Dassa et al. (1993) presented a single patient with psychotic depression refractory to a variety of drug treatments and to ECT. Discharge took place 2 months after clozapine therapy was begun, and the HAM-D score at that point was 15. Thus, the scant literature so far developed suggests little role for clozapine as an antidepressant, but a possible one for risperidone. The use of risperidone in bipolar illness, though, may be problematic.

**Other Therapies**

Though lithium enhancement of ongoing antidepressant therapy is perhaps the best studied of the pharmacologic options for treatment-resistant depression, few have described its use in psychotic depression. Nelson and Mazure (1986) reviewed the records of psychologically depressed patients who received ECT or the addition of lithium following unsuccessful treatment with desipramine and a neuroleptic. Eight of 9 bipolar patients, but only 3 of 12 unipolar patients, recovered with lithium enhancement (p = .003, Fisher’s exact test). Among those with unipolar depression who were given ECT, 9 (60%) of 15 responded, as did 3 (50%) of the 6 unipolar patients who failed to respond to lithium enhancement. These findings suggest that the unipolar/bipolar distinction should be strongly considered in treatment selection when psychotic depression fails to improve with the conventional antidepressant
antipsychotic regimen. However, other researchers at the same center described lithium enhancement without ongoing antipsychotic therapy. Only 6 (24%) of the 25 patients with psychotic depression had a “marked response” and bipolar patients fared as poorly as unipolar ones.

A high proportion of patients with psychotic depression exhibit hypercortisolism. High corticosteroid levels have adverse effects on cognitive performance and are suspected to play a key role in the long-term morbidity of psychotic depression. Several researchers have tested the antidepressant effects of corticosteroid suppression with some success. Optimal doses and safeguards have yet to be established, nor have controlled studies been accomplished.

Maintenance Treatment

Intervals between episodes appear to be shorter for patients with psychotic depression. This, combined with the likelihood that psychotic features will redevelop in subsequent episodes, makes prophylaxis particularly important. There are no published, controlled trials of prophylaxis in psychotic depression, however. This leaves unanswered the important question of when antipsychotics should be discontinued after symptom resolution. On the one hand, risks for tardive dyskinesia increase substantially with as little as 3 months of lifetime exposure to conventional antipsychotics. On the other hand is the observation of several naturalistic follow-up studies that risks for relapse seem to increase after the elimination of antipsychotics, despite the continuation of antidepressants.

One solution to this dilemma is the gradual tapering of antipsychotic during the maintenance of full-dose antidepressant. Family members should be recruited to monitor the early reemergence of depressive symptoms or psychotic features typical of that patient’s illness. Early signs are often easily reversed by a return to higher antipsychotic doses. If several trials of discontinuation are unsuccessful, at the minimum effective dose can be established and cumulative neuroleptic exposure minimized.

Maintenance ECT should be considered when repeated prophylactic efforts fail. Preliminary results from an ongoing study suggest that this approach should come into wider use. Of 7 patients randomly assigned to receive continuation pharmacotherapy after ECT, 3 have relapsed. Of the 12 assigned to ECT, only 1 has relapsed. Maintenance ECT typically begins with weekly treatments. Intervals can be gradually increased, but, as with the downward titration of medications, this should be done only with careful surveillance and the readiness to introduce an additional ECT treatment on short notice.

SUMMARY

Severity, long episodes, and high recurrence all characterize psychotic depression and make treatment selection critical. Two modalities, ECT and the combination of an antipsychotic and a tricyclic antidepressant, have the best documented efficacy, though SSRIs, with or without antipsychotics, show promise. Diagnostic alternatives to psychotic depression should be carefully considered before ECT or combination therapy is undertaken. Also, pharmacokinetic interactions are likely in combination treatment and side effects may be confused with symptoms of psychotic depression. The necessity of antipsychotic therapy in maintenance has not been formally established and must be determined on a case-by-case basis.

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