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The Psychopharmacology Algorithm Project at the Harvard South Shore Program: An Update on Psychotic Depression

Hesham M. Hamoda, MD, and David N. Osser, MD

This new version of the psychotic depression algorithm has been developed by the Psychopharmacology Algorithm Project at the Harvard South Shore Program. The most effective treatment modality for inpatients with severe psychotic depression is electroconvulsive therapy. The first-line psychopharmacological treatment is a combination of an antidepressant (either a tricyclic or a selective serotonin reuptake inhibitor) and an antipsychotic. If one of these combinations has failed, consider switching to the other. If both combinations have failed, the next psychopharmacological option would be to augment the combination with lithium. Another option, though with limited evidence, is monotherapy with clozapine. If there is a good reason to avoid combination therapy with an antipsychotic, then a trial of monotherapy with a TCA or an SSRI can be supported. If that fails, adding an antipsychotic or ECT should be considered. (HARV REV PSYCHIATRY 2008;16:235–247.)

Keywords: affective disorders, psychopharmacology, psychotic, psychotic depression

Interest in psychopharmacology practice guidelines and algorithms has been increasing. There has been much recent discussion of how they are to be used, the extent to which they are used, and the studies that have been done to assess the value of following them compared to usual care.[1–5]

The Psychopharmacology Algorithm Project at the Harvard South Shore Program (PAPHSS) is a publicly available, Internet-based, interactive heuristic for clinical consultation on evidence-supported psychopharmacology. The Web site is www.mhc.com/Algorithms/. It began online in 1996 with the Algorithm for the Pharmacotherapy of Depression,[6–9] which addressed the major subtypes of depression, including unipolar nonpsychotic, psychotic, and bipolar depressions. In 1998 the first version of the Consultant for the Pharmacotherapy of Schizophrenia was completed, followed in 1999 by the Algorithm for the Pharmacotherapy of Anxiety Disorders in the Context of Substance Abuse. Since then, usage analysis has indicated that downloads have been initiated from at least 66 countries, and portions have been translated into Chinese, Greek, and Russian.

This article presents a new version of the PAPHSS algorithm for major depression with psychotic features, also known as psychotic or delusional depression. Psychotic depression occurs in about 14%–18% of patients with depressive episodes[10,11] and in approximately 25% of patients hospitalized for major depressive disorder.[12] The prevalence of psychotic depression in elderly patients may be as high as 45%.[13]

Among depressed patients, this group is one of the most difficult for which to devise a treatment algorithm. The difficulty starts with diagnosis. The diagnostic criteria have changed over the years, with the consequence that the

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treatment results in patients diagnosed one way do not necessarily apply to others diagnosed differently. The term "delusional depression" described patients with depression who also had delusions. Important studies from the mid-1980s that employed tricyclic antidepressants and first-generation antipsychotics diagnosed patients this way.[14,15] The 1980, third edition of the *Diagnostic and Statistical Manual of Psychiatric Disorders* (DSM-III),[16] however, proposed the term "major depression with psychotic features." These patients met criteria for major depression and also had delusions, hallucinations, or "depressive stupor (the patient is mute and unresponsive)." Patients did not have to be delusional, however, or even psychotic in the usual sense of the term. In the revised, 1987 DSM-III-R,[17] the option of depressive stupor was removed from the definition, but patients could have either delusions or hallucinations. Since 1994, with the DSM-IV,[18] this definition continued with the added provision that the condition had to be "severe." Important recent studies involving selective serotonin reuptake inhibitors (SSRIs) and atypical antipsychotics have used this definition.[19]

Despite these definitional confounds, accumulated data suggest that major depression with psychotic features is a distinct clinical entity even though debate continues on its most appropriate classification.[20,21] It differs from nonpsychotic major depression in biological factors,[22–29] neuropsychological features,[30,31] morbidity and mortality,[32,33] and structural brain imaging;[34,35] it responds differently to psychopharmacological treatment;[36] and its course is also different, with psychotic depression being associated with more previous episodes of psychotic depression.[37,38] A recent study showed that adherence to current guidelines for the treatment of psychotic depression is low and emphasized the importance of continuing clinician education on the identification and treatment of this condition.[39]

In the interval since the last revision of the PAPHSS psychotic depression algorithm,[7] there have been important new studies, meta-analyses of the literature, and algorithms published by other groups. The authors reviewed these data and analyses to prepare the current revision.

CONSTRUCTING THE ALGORITHM

There are various methods of constructing evidence-based algorithms.[2,3] The PAPHSS approach is to model the cognitive process of a psychopharmacology consultation. The algorithm is a series of questions that a consultant would ask, in the order they would to be asked, for the consultant to efficiently reach a recommendation. The evidence supporting the recommendations is provided and appraised, and the consultant avoids speculating based on clinical experience. The algorithm notes, too, when the evidence is contradictory or inadequate.

Initial drafts of the PAPHSS algorithms are prepared by one to three authors. These drafts are sent to other experts for critique and comment. Revised drafts are submitted for publication, where further review occurs. Before and after publication, the algorithms are presented in conferences and poster sessions. After this multistage revision process, they are converted to the computer format and uploaded to the Web site. Updates occur as required by new developments, and presentations at meetings continue on a regular basis.

For the present revision, a PubMed search was conducted to identify relevant studies and reviews. The keywords used were affective disorders, psychotic; psychotic depression; delusional depression; pharmacological treatment; and psychopharmacology. EMBASE was searched from 1974 to November 2007. Abstracts were reviewed, and all relevant articles were obtained. Reference lists from the identified articles were consulted. Original studies, meta-analyses, and review articles were evaluated for the quality of the evidence and also to assess the conclusions of others about the importance of the studies. Only studies published in English were examined.

This algorithm, depicted in Figure 1, focuses on psychopharmacological treatment of psychotic depression and does not cover psychotherapy treatment options. The Arabic numerals refer to nodes in the algorithm flowchart. We will review each step and discuss the pertinent evidence, including its limitations.

NODE 1: THE POTENTIAL USE OF ECT

The first decision point in the algorithm is to decide whether the patient is appropriate for electroconvulsive therapy (ECT) as the initial treatment. The algorithm recommends consideration of ECT for hospitalized, severely ill patients. ECT is perhaps the most effective treatment modality for this disorder. In an observational study by Petrides and colleagues,[40] patients with psychotic depression ($n = 77$) who received bilateral ECT achieved a remission rate of 95%. The rate was 83% for nonpsychotic depressed patients ($n = 176$; $p < .01$). Remission criteria were a score of ≤ 10 on the 24-item Hamilton Rating Scale for Depression (HAM-D-24) after two consecutive treatments, and a decrease of at least 60% from baseline. Improvement in symptomatology was greater and appeared sooner in patients with psychotic depression than in nonpsychotic patients.

In a chart review comparing 14 patients receiving ECT and 12 unmatched patients receiving an antidepressant/antipsychotic combination, a favorable overall response to treatment occurred in 86% of ECT patients but only in 42% of patients receiving an antidepressant/antipsychotic combination ($p < .05$).[41] ECT responders also experienced a nearly two-week earlier resolution of their depressive symptoms ($p < .05$).[42] However, it is difficult to draw broad

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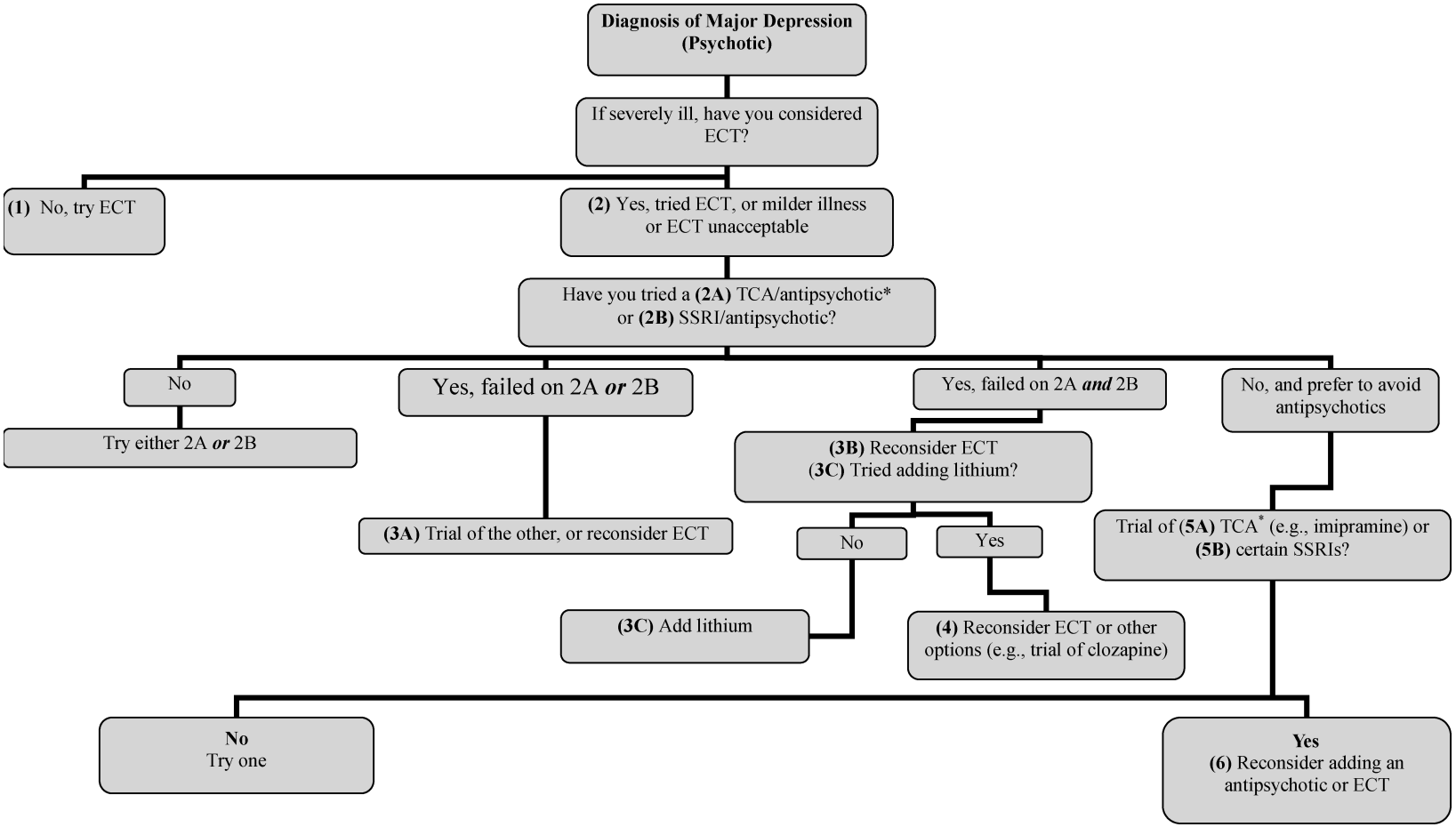

FIGURE 1. Flowchart of the algorithm for psychotic depression. ECT, electroconvulsive therapy; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
*Patients with psychotic depression are at a higher risk of suicide/overdose.

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conclusions from this small study. ECT was compared to several different combinations of medications at varying doses and for different periods of time.

Other uncontrolled studies have suggested that psychotic depression responds better to ECT than to pharmacotherapy.[43,44] Olfson and colleagues found that ECT is more rapidly effective than pharmacotherapy, shortens hospital stays, and reduces treatment costs if initiated within five days of admission.[45] ECT has never been prospectively compared, however, to any medication regimen.

Birkenhager and colleagues[46,47] found that among patients who have responded to ECT, those with psychotic depression had lower relapse rates than those with nonpsychotic depression. Tsuchiyama and colleagues[48] tried to predict which patients would respond to ECT and found the response unrelated to the presence of psychotic features. Keller and colleagues[20] concluded that although ECT may be effective in initially treating psychotic depression, the data are unclear regarding the duration of this effect.

Although ECT is an effective treatment for psychotic depression, there are several drawbacks, and in many situations, patients and families will refuse ECT or the patient will not be an ideal candidate to receive ECT. Access to ECT may be limited in different areas in the United States and in other countries due to issues with availability or reimbursement. In locations where it is available for inpatients, it might not be available for outpatients for maintenance ECT. In contrast to the studies by Birkenhager and colleagues cited above, several studies have reported a high relapse rate in psychotic depression after a good response to ECT.[49,50] Memory impairment, particularly with bilateral ECT and older ECT techniques, can present a potential problem for patients.[51] ECT is also associated with increased costs if treatment is not initiated rapidly.[45]

NODE 2: ALTERNATIVES TO ECT

If the patient has a milder illness, refuses ECT, or is a less desirable candidate for ECT (e.g., because of increased medical risk due to unstable cardiac disease, a space-occupying lesion, or a recent intracerebral bleed),[52] the first-line psychopharmacological recommendation is a combination of an antipsychotic and an antidepressant. The American Psychiatric Association Practice Guidelines for Major Depression in 2000[53] and the British National Institute for Clinical Excellence in 2004[54] both supported this first-line recommendation for the treatment of psychotic depression. A recent Cochrane collaboration meta-analysis on psychotic depression,[55,56] however, concluded that both the antidepressant/antipsychotic combination and an antidepressant alone (adding an antipsychotic if the patient does not respond) are appropriate options. The Cochrane group suggested that the balance between risks and benefits favors the latter option for most patients.

We examined the available evidence and support the combination treatment as first-line. Our reasoning is explained in the discussion of nodes 2A and 2B below.

Node 2A: The Combination of a Tricyclic Antidepressant and an Antipsychotic

What is the evidence that the combination of a tricyclic antidepressant (TCA) and an antipsychotic is better than antidepressant monotherapy?

- The landmark study of the pharmacotherapy of psychotic depression was conducted by Spiker and colleagues.[14] In that study 51 inpatients with delusional depression were treated for six weeks after randomization to one of three regimens: a combination of amitriptyline and perphenazine, amitriptyline alone, or perphenazine alone. The combination of amitriptyline and perphenazine produced a 78% response rate ($n = 18$) and was superior ($p < .01$) to the 41% response rate with amitriptyline alone ($n = 17$) and 19% rate with perphenazine alone ($n = 16$). The HAM-D-17 was used to assess response, which required that the patient no longer be delusional or depressed (HAM-D ≤ 6). Patients on the combination of amitriptyline plus perphenazine received a mean dose of 170 mg/day and 54 mg/day, respectively. The patients taking amitriptyline alone received a mean dose of 218 mg/day. Patients on perphenazine alone received a mean dose of 50 mg/day. Twelve percent (7 out of 58) were dropouts: 4 from the amitriptyline plus perphenazine group, 2 from the amitriptyline group, and 1 from the perphenazine group. The limitations of this study were the small sample size and the absence of a placebo control group. In the intent-to-treat analysis, the response rates were 64% for amitriptyline plus perphenazine, 37% for amitriptyline alone, and 18% for perphenazine alone ($p = 0.11$ for the combination vs. the antidepressant).[55] It appears that patients enrolled in this study had a high severity of illness as suggested by their initial mean scores on the HAM-D-17, which ranged from 26.0 to 30.6 and the low response rate to perphenazine monotherapy, which the authors considered to be the nearest to placebo. Earlier studies with delusional depression had found that the response to 1–3 week placebo run-ins was very low, approaching 0%.[57,58] In more recent studies, however, placebo controls were included, and the placebo response rates after eight weeks were 28% to 32%.[19]

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- Spiker and colleagues[59] also reported that the patients on amitriptyline plus perphenazine had higher plasma levels of amitriptyline and of its pharmacologically active metabolite nortriptyline than the patients on amitriptyline alone. Clinical response was significantly correlated with amitriptyline/nortriptyline plasma levels. An analysis of covariance, however, showed that the patients treated with amitriptyline plus perphenazine still had a higher response rate than the monotherapies, even after controlling for the plasma levels of amitriptyline/nortriptyline.
- In another study comparing a TCA plus an antipsychotic to an antidepressant alone in the treatment of psychotic depression, Anton and Burch[60] treated 38 inpatients for four weeks with either amitriptyline plus perphenazine or amoxapine alone. Combination treatment had a small numerical advantage over monotherapy. Eighty-one percent of patients on amitriptyline plus perphenazine had a reduction in HAM-D of more than 50%, compared to 71% of the patients on amoxapine. Seventy-six percent of the patients on amitriptyline plus perphenazine had an improvement on the Brief Psychiatric Rating Scale (BPRS) of more than 50%, compared to 59% of the patients on amoxapine. This study also lacked a placebo control group and was single blind. The mean dose of perphenazine was only 32 mg, compared to a mean of 54 mg in the study by Spiker and colleagues.[14] Perhaps the most important thing to observe about this study is that the antidepressant (amoxapine) is actually a combination treatment—which is why the investigators selected it. Amoxapine is a metabolite of the antipsychotic loxapine and has some antipsychotic properties. The 7-hydroxy metabolite of amoxapine is a high-potency neuroleptic. Notably, amitriptyline plus perphenazine and amoxapine both produced high improvement rates, similar to the amitriptyline plus perphenazine combination in the Spiker study.
- Another study of the combination of a TCA and an antipsychotic suggests that both medications independently contribute to the clinical result. Nelson and colleagues[15] studied 35 patients with delusional depression, who received either haloperidol or perphenazine combined with desipramine. They found that the average dose of haloperidol in responders was 12 mg daily versus 6 mg daily in nonresponders ($p < .04$). Perphenazine performed better when the dose was over 48 mg daily. The number of responders when desipramine plasma levels were less than 100 ng/ml was 1 of 8 patients, compared to 15 of 23 patients when the levels were over 100 ng/ml ($p < .05$).
- Mulsant and colleagues[61] conducted a randomized, double-blind study of 52 psychotically depressed elderly inpatients (mean age = 72). All patients were started openly on nortriptyline monotherapy and titrated to a therapeutic plasma level. After two weeks, 44% responded, as defined by a HAM-D-17 score of less than 10 and essentially no psychotic symptoms on the psychosis items of the BPRS. These criteria for response were less rigorous than those of Spiker and colleagues, and the duration of this phase was only two weeks. The nonresponders were then randomly assigned to addition of perphenazine ($n = 17$) or placebo ($n = 19$) and treated for at least two more weeks. The dose of perphenazine (12–24 mg/day) was appropriate to this age group, but lower than that in the Spiker and colleagues study (54 mg/day) or the Anton and Burch study (32 mg/day). There were 3 dropouts from each group. Of the remaining patients, 50% ($n = 7$) of the nortriptyline plus perphenazine group responded, and 44% ($n = 7$) of the nortriptyline plus placebo group responded—a nonsignificant difference. The authors proposed that this lack of advantage for the combination might have been due to the presence of comorbid incipient dementia in many patients. When the treatment groups were divided according to Mini–Mental State examination scores, those with scores above 27 had a response rate almost twice as high as those patients with scores less than 27. Due to the small sample size, however, the difference was not statistically significant. One would be cautious to generalize the results of this study, because of its population of elderly and demented patients, along with the limited sample size.

The findings of this review of the key individual studies of psychotic and delusional depression can be summarized as follows: the percentages of patients improving on the combination therapy were 81%, 78%, and 50%, whereas on antidepressant monotherapy the percentages were 44% and 41%. The combinations appear more efficacious.

As noted, a Cochrane systemic review and meta-analysis concluded that starting with a combination of an antidepressant and an antipsychotic is an appropriate option. However, they found that the evidence of its superiority to antidepressant monotherapy was unconvincing and that the balance between risks and benefits favored starting with the monotherapy.[55,56]

To reach this conclusion, the Spiker and colleagues study[14] was pooled with the Mulsant and colleagues study.[61] The result was a finding of no statistically significant difference between a TCA plus an antipsychotic and a TCA alone (relative risk ratio = 1.44; 95% confidence interval, 0.86–2.41; $p = .16$). These two studies were quite dissimilar, however, in terms of both patient populations and methodologies. The Spiker and colleagues study compared

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a TCA/antipsychotic to a TCA alone and an antipsychotic alone. In the Mulsant and colleagues study, all participants received a TCA and then only those patients who did not respond were given either an antipsychotic or placebo, rather than starting the combination therapy initially. In addition, the target populations in the two studies were different: the average patient age in the Mulsant and colleagues study was significantly older than the Spiker and colleagues study (72 versus 44 years, respectively). As noted earlier, Mulsant and colleagues found a more robust numerical advantage for the combination treatment in the nondemented elderly patients, though it was not significant due to the small sample size. In summary, the conclusion of the Cochrane "meta-analysis" was based on only two studies. Since the Mulsant and colleagues study had a different design and an older patient population, it should not have been combined with the Spiker and colleagues study to evaluate the comparative efficacy of a TCA alone versus a combination treatment.

In a letter to the editor about the Cochrane analysis, Vattakatuchery[62] suggested that the relative risk ratio of 1.44 favoring the TCA/antipsychotic combination was impressive. Although the confidence interval for the relative risk included values below 1.0, the result was *statistically* nonsignificant because of the small sample sizes in the two studies. The difference nevertheless appears *clinically* significant, and the findings are consistent with other lines of evidence and with expert opinion expressed in practice guidelines.[14,15,19,21,53,54,60,63]

Node 2B: The Combination of an SSRI and an Antipsychotic

What is the evidence that the combination of an SSRI and an antipsychotic is better than monotherapy with an antidepressant? Unfortunately there are no head-to-head comparisons. However, there are studies suggesting the effectiveness of the combination as well as studies implying that the combination may be superior to monotherapy with an antipsychotic. We will discuss these studies in the following two subsections.

SSRIs and typical antipsychotics: What is the evidence for effectiveness? Two small studies examined the combination of an SSRI and a typical antipsychotic:

- The first study, by Rothschild and colleagues,[63] involved 30 patients who met DSM-III-R criteria for psychotic depression. They were treated with a combination of fluoxetine and perphenazine (20–40 mg and 32 mg, respectively). Twenty-two of the 30 patients (73%) had a reduction of HAM-D and BPRS scores of 50% or more after five weeks. Limitations of this study include the open-label design, small sample size, and lack of a placebo control group. In addition, not all patients enrolled had unipolar psychotic depression: 7 of the 30 patients were bipolar. It was not clear whether the patients were inpatients or outpatients, which is relevant to the severity of their disorders.
- In another study, by Wolfersdorf and colleagues,[64] 14 patients were treated with paroxetine (20 mg) and either zotepine (150–200 mg) (an atypical antipsychotic not available in the United States) or haloperidol (2.5–10 mg), or both. Of the 4 patients receiving a combination of paroxetine and haloperidol, 3 patients achieved a 50% or more reduction in HAM-D-24. This study had a very small sample size, was nonblind, lacked a placebo control group, and was relatively short in duration (three weeks only).

SSRIs and atypical antipsychotics: What is the evidence for effectiveness?

- Two double-blind, controlled trials were conducted by Rothschild and colleagues[19] at 27 sites. These studies had the largest sample size of all treatment studies of psychotic depression. There were 124 inpatients in trial 1, and 125 inpatients in trial 2, diagnosed with DSM-IV psychotic depression. Subjects were randomized to three groups: placebo; olanzapine plus placebo; and olanzapine combined with fluoxetine. They were followed for eight weeks. The noncompletion rate in these studies was high at 56% (139 out of 249), although there were no differences in noncompletion rates among the treatments. Response rate was defined as a $\geq$50% decrease from baseline HAM-D-24. In trial 1 the combination group ($n = 22$) had a significantly higher response rate (64%) than the placebo (28%; $n = 50$; $p = .004$) or olanzapine (35%: $n = 43$; $p = .027$) groups. In trial 2 there were no significant differences among treatment groups in their responses on the HAM-D-24. The combination group had a response rate of 48% ($n = 23$), compared to the response rates of placebo (32%; $n = 44$; $p = .20$) and olanzapine (36%; $n = 47$; $p = .35$). Fluoxetine inhibits olanzapine metabolism through the cytochrome P450 system, but levels of olanzapine increased only 15%–30%.[65,66] The response in the combination group is consequently unlikely to be explained by this drug interaction.
- A limitation of the study as identified by its authors included the absence of a fluoxetine monotherapy arm; it can therefore not be excluded that the combination effects were mostly attributable to the fluoxetine component. (Others have found that SSRI monotherapy can be effective in psychotic depression,[67–69] but, as will be discussed in node 5B, there are both methodological concerns about these studies and questions [see 5B]

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about the severity of illness of the patients.) Notably, the results in trial 1 were not replicated in trial 2 despite the absence of any significant differences in demographics or illness characteristics between the treatment groups in the two trials. In trial 2, there was actually a modest, but possibly clinically significant, effect size for the combination group, but it failed to attain statistical significance. The small sample size of the combination groups in these studies was due to the randomization schedule, which was 2:2:1 for olanzapine, placebo, and combination, respectively. The investigators intended that combination group would be an "exploratory pilot arm" in these trials; the primary goal of the studies was to evaluate olanzapine monotherapy for psychotic depression. No significant improvement was found in either trial with olanzapine alone.

- In the Wolfersdorf and colleagues study[64] cited above, a subgroup of 7 patients received paroxetine (20 mg) combined with zotepine. Four of the 7 patients achieved a $\geq$50% reduction in HAM-D-24 after three weeks.

In summary, a combination of an SSRI and either a typical or an atypical antipsychotic may be effective, though the effect size appears modest. Although comparisons versus SSRI monotherapy would be of interest, there are no such studies available.

Nodes 2A & 2B: Conclusions

Though the data are limited, it seems justified to conclude that the first-line psychopharmacological treatment recommendation is to use a combination of an antidepressant and an antipsychotic.

- *Which antidepressant is preferred in the combination: A TCA or an SSRI?* There are no head-to-head comparisons, but two studies are most relevant to this question: the Spiker and colleagues study,[14] which used a TCA, and the studies by Rothschild and colleagues,[19] which used an SSRI and had placebo control groups. The two studies are difficult to compare. They used different diagnostic criteria: Spiker and colleagues enrolled patients with delusional depression, whereas Rothschild and colleagues enrolled patients with DSM-IV psychotic depression. The Rothschild and colleagues studies had a larger sample size (251 vs. 51). They also used different versions of the HAM-D to evaluate response.

  The Rothschild and colleagues studies using an SSRI had high placebo response rates. It could be argued that these high placebo response rates (trial 1, 28%; trial 2, 32%) suggest a population with a less severe form of psychotic depression. The mean HAM-D-24 score was between 34.3 and 38.4, however, which does not indicate a sample with only mild illness. The mean HAM-D-17 in the Spiker and colleagues study[14] was between 26.0 and 30.6, which is also a severe level of illness. In this latter study (which did not have a placebo arm), the response rate in the perphenazine monotherapy group was 19%, which is lower than the placebo response in the Rothschild and colleagues studies. Notably, whereas these Rothschild studies were conducted for eight weeks, the Spiker and colleagues study was for six weeks, and it is known that the proportion of patients that respond to placebo increases with trial length.[70–72] Rothschild and colleagues also proposed that the high placebo response rate was consistent with a pattern of escalating placebo response rates in recent antidepressant trials. This pattern was identified by Walsh and colleagues[72] in a meta-analysis of 75 placebo-controlled medication trials for outpatients with major depression. However, none of these trials involved patients with psychotic depression. Also, there have been changes in the way that patients are selected for nonpsychotic depression trials that may have increased the placebo response rate. In particular, the use of nonclinical patient samples recruited by advertising has increased. This selection issue may not apply in the psychotic depression studies. The latter have all used inpatient clinical populations.

  In conclusion, based on the evidence cited, it seems that in the TCA era, delusional depression responded well to a TCA plus an antipsychotic, compared to perphenazine alone as a control. In the SSRI era, DSM-IV psychotic depression has responded fairly well to an SSRI plus an antipsychotic compared to placebo. Thus, TCAs remain a strong option for use in combination—perhaps not as the first-line option due to TCAs' potential side effects, but in any event as an alternative if an SSRI in combination is ineffective. It should also be noted that patients with psychotic depression have a higher rate of suicidal ideation,[73] suicide attempts,[10] and completed suicide[74] compared to patients with nonpsychotic depression. An overdose with a TCA is more than five times as likely as an overdose with an SSRI to result in death.[75] Therefore, for patients with psychotic depression (especially outpatients and those inpatients likely to relapse while on maintenance TCA), the risk for TCA overdose should be considered in choosing between a TCA and an SSRI. Thus, if a TCA is unacceptable due to a medical contraindication, doctor/patient preference (e.g., because of potential side effects), or risk of overdose, commencing with an SSRI is certainly reasonable.

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There is no evidence to support the use of other antidepressant groups such as monoamine oxidase inhibitors in psychotic depression.

- *Which antipsychotic should be used in the combination?* There are no head-to-head studies to guide the choice between a typical versus an atypical antipsychotic, or to help determine which specific antipsychotic might be preferred within each subgroup. No advantage in efficacy for a typical versus an atypical antipsychotic has been suggested by any of the studies we reviewed. It should be noted that the only atypical antipsychotic that has been studied in a randomized, placebo-controlled, double-blind study is olanzapine.[19] Given the increased risk of tardive dyskinesia with typical antipsychotic use in the population of patients with affective psychosis,[76] atypicals are preferred. This recommendation should nevertheless be weighed against the risks involved with atypical antipsychotics, including metabolic risks,[77,78] particularly with olanzapine.[79]
- *Should treatment with a combination be continued beyond the acute phase?* This algorithm addresses the treatment of acute psychotic depression. There is no adequate evidence regarding maintenance treatment and whether the use of an antipsychotic should be continued beyond the acute phase. One naturalistic study followed 52 patients with delusional depression who had remitted after receiving ECT or medications.[80] These patients were kept on a variety of maintenance regimens. The authors found that there were more relapses in the follow-up period (average 32 months) when a neuroleptic was tapered down from combination treatment, than when medication regimens were kept stable. The authors concluded that continuation therapy with antidepressant alone was associated with a greater risk of relapse compared to the combination treatment. Another study, however, found no difference in relapse rates. It was a randomized, double-blind comparison of an antidepressant plus a typical antipsychotic versus an atypical alone in 29 patients who had achieved remission after ECT.[50] The combination was associated with significant adverse effects.

NODE 3

Node 3A: Switch the Antidepressant If a Combination Trial Has Failed

If the patient has failed on an SSRI/antipsychotic combination, we would propose switching the antidepressant to a TCA, as discussed in the 2A/2B node conclusions. The evidence was interpreted there as suggesting that TCAs may have greater efficacy than SSRIs. We must again offer the caveat, however, that patients in the earlier TCA studies, especially the important Spiker and colleagues study,[14] had delusional depression. The SSRI-treated patients had DSM-IV psychotic depression.[19] This difference limits their comparability and therefore the confidence we can have in the recommendation, which is also limited, as we have noted, by other problems with the quantity and quality of the available data.

Another possibility would be a switch to a dual-action antidepressant such as venlafaxine, which might be expected to have TCA-like efficacy with a better safety profile. There is no evidence, however, supporting the combination treatment of psychotic depression using venlafaxine as the antidepressant. The lack of data is surprising given that this option has been available for many years, and if the combination had been found effective, one would have expected to see published reports.

If the patient was initially treated with a TCA/antipsychotic and did not respond, it is less clear whether a switch to an SSRI as the antidepressant would be advantageous. In the study by Rothschild and colleagues,[63] a subgroup of eight patients—prior to entering the study—had relapsed while on full dosages of a combination therapy with a TCA plus a typical antipsychotic. Of these, five (62%) responded to the SSRI/antipsychotic. Other than that, we could find no other reports of a TCA to SSRI switch. It is notable that some other experts, including the authors of the 2007 update of the Korean Psychopharmacology Algorithm Project,[81] do recommend an antidepressant switch at this point in the algorithm. Also, in the treatment of nonpsychotic depression, there is evidence that some patients respond when a TCA is switched to an SSRI and vice versa.[82]

Despite the paucity of direct or even indirect evidence to support switching antidepressants, this evidence appears slightly stronger than the evidence supporting augmentation strategies with combined antidepressant/antipsychotic therapy, to be discussed later at node 3C.

ECT may also be reconsidered at this 3A node.

Node 3B: If A Patient Has Failed at Both Nodes 2A and 2B, What Should Be Done Next?

ECT should be reconsidered since it often works when patients do not respond to medications.[21]

- In a study of 15 patients hospitalized with severe psychotic depression (DSM-III criteria), 9 patients did not respond to a combination of TCAs and antipsychotics. Eight of these 9 patients then showed an excellent clinical response after receiving ECT.[83]
- In the Spiker and colleagues study,[14] all six patients who had failed on the combination treatment did well after completing a series of ECT.

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NODE 3C: What Should Be Done After Two Combinations Have Failed and ECT Has Also Failed or Cannot Be Given?

There is little evidence pertinent to this point in the algorithm. Consider augmentation with lithium:

- Some evidence suggests that augmenting the TCA and antipsychotic combination with lithium can be helpful. In a series of 20 patients with psychotic depression, 40% attained either a partial or marked response.[84]
- Another study of lithium augmentation involved 6 patients with delusional depression who were unresponsive to combined neuroleptic-tricyclic treatment.[85] Of the 6, 3 had a dramatic response, 2 had a more gradual response, and 1 was unresponsive.
- In Rothschild and colleagues' study,[63] of the 8 patients who did not respond to fluoxetine and perphenazine, 3 responded to augmentation with lithium.
- A small study showed that response after adding lithium appears to be better in bipolar psychotic depression than in unipolar psychotic depression.[86]

NODE 4: IF THE PATIENT HAS FAILED ON TRIALS OF BOTH COMBINATIONS 2A AND 2B, AND HAS ALSO FAILED LITHIUM AUGMENTATION, WHAT CAN BE DONE?

There is limited evidence available here. The best option would still be ECT. Otherwise, it may be worthwhile to consider clozapine, based on case series and case reports:

- In a case series of three patients with refractory psychotic depression, clozapine was initiated after multiple failed trials of antidepressant/antipsychotic combinations as well as ECT.[87] Both psychotic and mood symptoms responded well, although response was delayed in 1 case. No patient relapsed over a follow-up period of 4–6 years. In another case report, a patient with similar treatment history was given clozapine. Her BPRS score decreased from 63 at baseline, to 39 after four weeks on clozapine, and to 21 after four months.[88] Another case report described a woman who received clozapine after failure on a wide range of drug treatments and ECT.[89] She had improvement in her depressive symptoms and resolution of her psychotic symptoms.

NODE 5: TRIAL OF A TCA OR AN SSRI ALONE

The clinician or patient may sometimes prefer to avoid antipsychotics altogether. In the past, the risk of tardive dyskinesia in psychotic patients with mood disorders treated with typical antipsychotics led many clinicians to avoid or underdose them. With the atypical antipsychotics, however, the risk of developing tardive dyskinesia appears to be lower.[90,91] As discussed earlier, we conclude that some evidence, though not robust in quality, supports antidepressant monotherapy for psychotic depression. This evidence may be summarized as follows:

Node 5A: TCA Monotherapy

If an antidepressant is to be used alone, which one should be selected? The evidence seems to support a first choice of a tricyclic. Meta-analyses have concluded that TCAs are superior to placebo[92] and also superior to antipsychotics alone[14,56] in psychotic depression. In addition, evidence suggests that a TCA alone may be preferred to a non-TCA in patients with psychotic depression:

- A randomized, controlled study by Van Den Broek and colleagues[93] showed that imipramine 150–450 mg daily (plasma level of imipramine and desipramine, 192–521 ng/ml) was more effective than fluvoxamine, 150–1800 mg daily. According to the Cochrane review's analysis of this study,[55] which used data from the subgroup of patients in the study with a diagnosis of psychotic depression, 16 out of 25 patients (64%) on imipramine achieved a 50% reduction in HAM-D scores, compared to 7 of 23 patients (30%) on fluvoxamine ($p = .03$). There were 4 dropouts in the imipramine group, compared to 2 in the fluvoxamine group ($p = .4$).
- In another randomized, controlled study by Brujin and colleagues,[94] imipramine was superior to mirtazapine. According to the Cochrane review's analysis of this study,[55] which used data from the subgroup of patients in the study with a diagnosis of psychotic depression, 9 of the 15 patients (60%) on imipramine achieved a 50% reduction in HAM-D scores, compared to 3 of 15 patients (20%) on mirtazapine ($p = .05$). There were 4 dropouts in the imipramine group, compared to 8 in the mirtazapine group ($p = .2$).
- Amoxapine is also an antidepressant monotherapy option that can be considered.[60] We do not suggest it at this node of the algorithm, however, since as noted earlier, amoxapine has a major metabolite (7-hydroxy amoxapine) with strong typical antipsychotic properties. Thus, it is more similar to a combination therapy than a TCA monotherapy and would have the same risk for tardive dyskinesia.

Node 5B: An SSRI

What about using an SSRI alone? There are reports that SSRIs alone are effective in the treatment of psychotic depression. These reports involve fluvoxamine,[67] sertraline,[68] and,

with lesser effect, paroxetine[68] and the dual-action agent venlafaxine.[69]

- A double-blind, controlled study by Zanardi and colleagues[68] compared the response rates to monotherapy with two SSRIs in 66 patients with psychotic depression (DSM-III-R). Twenty-four received sertraline, and 22 received paroxetine, for six weeks. The rating instruments were the 21-item HAM-D and the Dimensions of Delusional Experience Rating Scale (DDERS). The response rates were 75% for sertraline and 46% for paroxetine. This difference was not statistically significant for the subjects who completed the protocol ($p = .16$). Problems with this study included its lack of a placebo control group, its dropout rate of 41% in the paroxetine group, and its enrollment of 14 bipolar patients.
- In another randomized, double-blind trial from the same research group, 28 inpatients meeting DSM-IV criteria for psychotic depression were assigned to receive 300 mg of fluvoxamine or 300 mg of venlafaxine for six weeks.[69] Clinical response was defined as a reduction of scores in the 21-item HAM-D to 8 or below and in the DDERS to 0. The response rate was 78.6% ($n = 11$) and 58.3 % ($n = 7$) for fluvoxamine and venlafaxine, respectively. No significant difference was found between the drugs ($p = .40$). The sample size for this study was small, 6 of the patients were bipolar, and there was no placebo control.

Despite their flaws, these two studies produced surprisingly good results for SSRI monotherapy. The studies were criticized for lacking a placebo control group and clear criteria for delusions. The adequacy of the diagnoses and the validity of the DDERS were questioned. There was some uncertainty regarding whether a standard diagnostic instrument, such as the Structured Clinical Interview for the DSM-III-R (SCID), was used.[20,95] Zanardi and colleagues replied[96] that the absence of a placebo group was required by the hospital's ethics committee because of the severity of illness and the risk of suicide. It was also explained that the SCID was used, but not in all patients, because of the peculiar and severe psychopathological condition of some.

We conclude that there may be some efficacy for SSRI monotherapy. The evidence appears stronger for TCA monotherapy, and the strongest evidence supports a combination of an antidepressant and an antipsychotic.

NODE 6: IF THE TRIAL OF AN ANTIDEPRESSANT ALONE HAS FAILED, WHAT IS NEXT?

In cases where the trial of an antidepressant alone has failed, there are several options:

- The clinician should reconsider adding an antipsychotic. This option was extensively discussed in nodes 2A and 2B, and is also the recommendation of the Cochrane Review that suggested adding an antipsychotic if antidepressant monotherapy failed.[55,56]
- It is conceivable that there would be patients who are still not appropriate for any antipsychotic usage. In such cases, ECT should be reconsidered. In the DeCarolis study,[97] while 40% of the patients with psychotic depression responded to imipramine, 83% of the nonresponders responded to ECT.
- Monotherapy with a different antidepressant could be tried.

FINAL COMMENTS

The aim of algorithms is not to substitute for clinical judgment, but rather to provide the available evidence in a format that is accessible and available for consultation in making a clinical decision that takes into account multiple considerations. Evidence from algorithms should be a necessary contributor to, but never a sufficient basis for, clinical decision making. With that understanding, we believe that this algorithm is appropriate for use by any prescribing clinician who treats patients with psychotic depression.

Algorithms derived from the available evidence are ultimately limited by the quantity and quality of that evidence. This limitation is especially evident with psychotic depression. Head-to-head prospective trials of different treatment options have not been done, and there are few quality studies on psychotic depression that could be used as a basis for a guideline. Nevertheless, this algorithm was created to best present the existing evidence in a clinically relevant fashion. The alternative for many physicians would be to rely solely on clinical experience, which can be unreliable and not conform with the available evidence.[98] New studies, as they appear, should be evaluated to see if minor or significant changes in the layout of this algorithm should be made. For example, the Study of the Treatment of Psychotic Depression—a multisite, National Institute of Mental Health–funded, randomized, controlled trial that was recently completed, comparing sertraline plus olanzapine to olanzapine alone—will substantially add to the evidence base.[99]

Rothschild and colleagues[32] suggested that the systematic study of psychotic depression has been limited by several factors: (1) the disorder does not exist as a distinct diagnostic subtype in DSM-IV, (2) few psychiatric researchers have made the study of psychotic depression a priority, (3) there have always been difficulties enrolling patients with this disorder in research studies, and (4) the diagnosis is often missed by clinicians.

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The potential for an algorithm to improve clinical outcome depends on the extent to which the evidence-based recommendations in the algorithm are similar to, or different from, "treatment as usual." If the steps suggested in an algorithm are similar to what prescribers would have done normally, then it is unlikely that following the algorithm will change clinical outcome. In the pharmacotherapy of psychotic depression, the available evidence suggests that usual care often does not involve the combined use of an antidepressant and an antipsychotic—the treatment recommended in this algorithm. Andreescu and colleagues[39] recently found that only 57% of 100 patients with psychotic depression received at least one combination of an antidepressant and an antipsychotic, and only 5% received a full dose of the antipsychotic. A similar result was found by Mulsant and colleagues[100] in 1997; only 4% of 53 patients received an adequate antidepressant/antipsychotic combination. We believe that practitioners need to be educated about the evidence available for guiding their selection and dosing of medications in the treatment of patients with psychotic depression. This algorithm presents that evidence in a systematic manner.

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