

# The Emergency Treatment of Depression Complicated by Psychosis or Agitation

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With the availability of newer, safer antidepressants in the past decade, initiation of definitive treatment for depression in the emergency setting has become an accepted practice. However, the use of newer antidepressants and atypical antipsychotics in depression complicated by psychosis or agitation has not yet been well studied. This article will review relevant data and make recommendations for the emergency management of psychotic and agitated depressive syndromes.

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Although antidepressant medications do not work immediately and conventional wisdom has until recently suggested that antidepressant treatment should not be started in the emergency room,<sup>1,2</sup> the initiation of antidepressant medication in the emergency setting to treat uncomplicated major depressive episodes is rational and appropriate.<sup>3,4</sup> While changes in mental health care access have been part of the catalyst for the shift of psychiatric emergency care toward a definitive treatment and away from a triage model,<sup>5</sup> the main reason it is now acceptable to start antidepressants in the emergency setting is that the newer medications make it easier and safer to do so. Can the initiation of treatment for depression complicated by psychosis or severe agitation also be undertaken in the emergency setting? Most of the published material on the treatment of psychotic and agitated depression focuses on the use of older drugs such as tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and typical neuroleptics, and few double-blind placebo-controlled studies have investigated newer antidepressants or atypical antipsychotic agents in these subsets of depression. This article will review available data on the management of these complicated forms of depression by discussing the current thinking about agitated and psychotic depression from a diagnostic and etiologic point of view, summarizing the treatment studies that have been

done, and describing some anecdotal experiences in managing these subsets of depression with newer agents. Treatment recommendations for the emergency setting will be outlined.

## PSYCHOTIC DEPRESSION

Psychotic depression is defined as the occurrence of delusions or hallucinations in the setting of a major depressive episode.<sup>6</sup> Texts suggest that psychotic features occur in about 15% of all depressed patients,<sup>7</sup> and psychosis has been reported to occur in up to 25% of consecutively admitted depressed patients.<sup>8</sup>

There are a number of questions and controversies in the literature about the clinical features of depression with psychotic features and whether this disorder represents a subtype of major depression or a distinct syndrome. When compared with nonpsychotic depression, psychotic depression is more severe as measured by higher Hamilton Rating Scale for Depression scores, is more likely to include psychomotor disturbances, and is often associated with greater feelings of guilt and greater cognitive impairment.<sup>9</sup> It may be associated with greater risk of suicide, although this is less clear. In hospitalized patients, there is a higher rate of suicide, but studies that have looked at psychotically depressed patients postdischarge have failed to show that these patients are at greater risk of suicide.<sup>10</sup> There are limited data on psychotic depression in the less severely ill from the Epidemiologic Catchment Area study. In this community sample, patients with psychotic depression did not have more symptoms nor did they have different patterns other than the presence of a thought disorder, but they did differ significantly in morbidity at 1 year, including frequent suicide attempts.<sup>9</sup>

While some believe psychosis is more common in the elderly depressed patient,<sup>11,12</sup> psychotic depression is not consistently associated in any way with patient age or age

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at onset of depression, patient sex, or patient socioeconomic status.<sup>10</sup> Data do suggest that psychotic depression in the young adult may be the first episode of bipolar disorder.<sup>9</sup> Finally, psychotic depression appears to be the most consistent unipolar subtype across episodes.<sup>10</sup>

Psychotic depression may differ biologically from major depression without psychotic features. A number of studies, although not all, of hypothalamic-pituitary-adrenal (HPA) axis activity have shown greater HPA activity in psychotic versus nonpsychotic depressions.<sup>9,10</sup> In a 1992 *American Journal of Psychiatry* article arguing that psychotic major depressive disorder should be a distinct syndrome, Schatzberg and Rothschild<sup>9</sup> hypothesized that the effects of hypercortisolemia on the dopaminergic system may explain the presence of psychotic symptoms in these patients. A limited number of studies looking at ventricle-to-brain ratios in psychotic and nonpsychotic depression have also consistently demonstrated that patients with psychotic features have significantly larger ratios.<sup>9,10</sup>

Family studies have also shown some difference between psychotic and nonpsychotic depression. First-degree relatives of patients with psychotic major depression demonstrate higher rates of depression and of the psychotic subtype of depression than do members of families of patients with nonpsychotic major depression.<sup>9</sup> An increased incidence of psychotic depression in relatives of patients with psychotic depression has been reported,<sup>10</sup> and relatives of patients with psychotic major depression are 6 times more likely to have bipolar disorder than are relatives of patients with nonpsychotic major depression.

The prognosis of major depressive disorder with psychotic features may also differ from that of major depressive disorder without psychotic features. The short-term outcome in psychotic depression is worse.<sup>9,10</sup> It is questionable if this difference holds or whether it dissipates over time.<sup>10</sup>

Psychotic depression also responds to treatment differently. It responds quite poorly to placebos.<sup>9</sup> Psychotic depression also responds poorly or very slowly to TCAs alone,<sup>9,13,14</sup> and this relative ineffectiveness appears to extend to treatment with MAOIs and selective serotonin reuptake inhibitors (SSRIs) alone as well.<sup>10</sup> Addition of an antipsychotic agent or use of amoxapine (a cyclic antidepressant with inherent antipsychotic properties) by itself is associated with substantially higher likelihood of recovery.<sup>9,10,13-15</sup> American Psychiatric Association practice guidelines now strongly suggest combination pharmacotherapy for psychotic depression.<sup>15</sup> If an episode of psychotic depression does not respond to a TCA/antipsychotic combination, it often will respond to electroconvulsive therapy (ECT), and ECT may lead to a more rapid response than any medication regimen.<sup>16</sup> While most well-designed studies on the treatment of psychotic depression use TCAs and typical antipsychotic combinations or ECT, Rothschild and colleagues<sup>17</sup> found that the combination of fluoxetine

and perphenazine was as effective in treating patients with psychotic depression as was a TCA/typical antipsychotic combination, amoxapine, or ECT in an open trial involving 30 patients. Availability of newer antidepressant and antipsychotic agents opens new therapeutic options, but little has been done to test these drugs in psychotic depression. Nonetheless, the available data appear to support some antidepressant efficacy with atypical neuroleptic agents, at least as adjuncts to standard antidepressants.

The early clinical trials in schizophrenia indicated that olanzapine produced a moderate decrease in depressive symptoms (6-point decline in Montgomery-Asberg Depression Rating Scale [MADRS] score compared with 3-point decline with haloperidol,  $p = .001$ ).<sup>18</sup> In depressed schizoaffective patients, MADRS scores improved by 8.6 points with olanzapine and worsened by 6.6 points with haloperidol ( $p = .002$ ).<sup>19</sup>

A retrospective review<sup>20</sup> of 150 patients treated with olanzapine at McLean Hospital reported similar response rates (moderate-to-marked improvement on the Clinical Global Impressions of Improvement [CGI-I] scale) in bipolar (83%,  $N = 47$ ) and schizoaffective disorders (74% for bipolar type,  $N = 23$ ; 47% for depressed type,  $N = 17$ ) as in schizophrenia (76%,  $N = 29$ ).

Later studies began to assess olanzapine's antidepressant effects more directly. In a study of 30 patients with unipolar psychotic depression, Rothschild and colleagues<sup>21</sup> found that olanzapine was superior to typical neuroleptic agents as add-on treatment to antidepressants (10/15 olanzapine-treated patients responded vs. 4/15 typical neuroleptic-treated patients,  $p = .04$ ). In another open study of unipolar psychotic depression, which had no comparison group, Koenig and associates<sup>22</sup> reported similarly high response rates (73%) with olanzapine added to SSRIs.

Recently, the first double-blind controlled study of olanzapine's antidepressant effects was reported as a scientific abstract.<sup>23</sup> In 28 patients with unipolar nonpsychotic major depressive disorder who had already failed 6 weeks of treatment with fluoxetine monotherapy, Shelton and colleagues<sup>23</sup> reported that the combination of olanzapine and fluoxetine was more effective than either agent alone (based on statistically significant differences using the MADRS).

Similar data exist with risperidone. In an open study of 10 patients with unipolar psychotic depression or schizoaffective disorder, depressed type, Hillert and colleagues<sup>24</sup> reported response with risperidone monotherapy in 7 patients (70%). Another open uncontrolled study by Keck and colleagues<sup>25</sup> found risperidone more effective in schizoaffective disorder, depressed type (94% response,  $N = 18$ ) than in schizoaffective disorder, bipolar type (63%,  $N = 41$ ;  $p = .02$ , Fisher exact test) when used as an adjunct to thymoleptic agents (antidepressants or mood stabilizers). However, in a large double-blind, controlled

study<sup>26</sup> of 123 patients with unipolar psychotic depression; schizoaffective disorder, depressed type; and schizophrenia with comorbid depressive symptoms, risperidone monotherapy, while useful, was somewhat less effective than the combination of haloperidol and amitriptyline (37% response on the Brief Psychiatric Rating Scale and 51% response on the Bech Rafaelson Melancholia scale in the risperidone group vs. 51% and 70% responses on the 2 scales, respectively, in the other group,  $p < .01$ ).

Taken together, these studies suggest that olanzapine, and probably risperidone, have some antidepressant properties, although only moderately so, and mainly serve as add-on treatment to standard mood stabilizers.

### AGITATED DEPRESSION

Agitated depression is harder to define, and treatment options are less clear than in psychotic depression. However, most clinicians who deal with depressed patients recognize this subset of depression. Patients with agitated depression by definition have increased psychomotor activity and restlessness<sup>7</sup> and may exhibit pacing, hand-wringing, nail biting, hair pulling, incessant smoking, and incessant talking.<sup>27</sup> The prevalence of agitated depression increases with the severity of the depression, but not with age.<sup>28</sup> In patients admitted for depression, agitation is seen in as many as 60% to 70%.<sup>29</sup> The relationship between anxiety and the agitation is often unclear in these patients,<sup>28</sup> and it can be difficult to differentiate agitated depression from depression with severe anxiety.

It can also be quite difficult to distinguish agitated depression from a mixed episode of bipolar illness.<sup>28,30,31</sup> Patients with both disorders have psychomotor agitation, but in unipolar agitated depression, this psychomotor agitation is often purposeless and worse in the early morning.<sup>28</sup> Patients with both disorders have an increase in their thoughts, but the unipolar agitated depression patients complain of this mostly at night and describe that it is ruminative in nature.<sup>28</sup> Both groups report decreased sleep, but bipolar patients also report intact or increased energy, while those with agitated unipolar illness report decreased energy. Distractibility may be present in both groups, but in depressed patients it is internally driven with focus on health or guilt, whereas in bipolar patients it is often externally driven.<sup>28</sup> An agitated depressed patient lacks manic symptoms<sup>30</sup> and thus should not demonstrate grandiosity, decreased need for sleep, external distractibility, increased goal-directed activities, or increased interest in pleasurable activities.<sup>28</sup> The course of the illness may also help to distinguish these 2 disorders. The dysphoric manic patient may give a history of euphoric hypomania or mania, leading to increased agitation, dysphoric mood, and paranoia.<sup>31</sup> Unfortunately, in about one half of cases, bipolar patients will not have insight into their manic symptoms and will thus underreport them.<sup>2</sup> It is important to obtain

third-party information (family, other mental health professionals) to avoid the misdiagnosis of bipolar illness.<sup>3</sup>

The treatment of agitated depression has not been well studied. There are few controlled trials of management options. Historically, when an antidepressant alone is not sufficient, treatments have included benzodiazepines,<sup>28,32,33</sup> neuroleptics,<sup>11,28,31</sup> or lithium added to the antidepressant.<sup>28</sup> Divalproex sodium may be useful in agitated depression as well, as reported in 2 cases.<sup>28</sup> While no clinical trials on the treatment of agitated depression with atypical antipsychotics have been reported, a 1996 case report<sup>34</sup> describes a man with an "agitated depressive crisis" who had been unresponsive to a number of agents, but responded well and rapidly with decreased agitation in just 2 days when risperidone was added to phenelzine.

Because the newer antidepressants, particularly the SSRIs, can increase anxiety and agitation, there is some discussion in the literature about their use in patients with agitated depression. An industry-sponsored study compared imipramine and fluoxetine in a double-blind, randomized trial<sup>35</sup> of 124 agitated depressed patients and showed that both agents were equally effective but that fluoxetine was actually better tolerated. A post hoc analysis<sup>29</sup> of 9 antidepressant clinical trials ( $N = 279$ ) found that SSRI responders were more anxious and agitated at baseline than were norepinephrine reuptake inhibitor responders.

### MANAGEMENT OF THE PSYCHOTIC OR AGITATED DEPRESSED PATIENT IN THE EMERGENCY SETTING

As with any agitated or psychotic, and potentially violent, patient, the first step in managing the psychotic or agitated depressed patient in the emergency room is to assure his or her safety and the safety of others. The patient should be approached in a nonthreatening way, and a show of force, seclusion, or restraint should be used as needed. If the agitation is severe enough, or if the patient's psychosis is interfering with the assessment, emergency treatment with a neuroleptic,<sup>1,36</sup> benzodiazepine,<sup>31</sup> or a combination of the 2<sup>31</sup> should be considered. Intramuscular medication may be needed if the patient is noncooperative.

The next step is the assessment leading to provisional and differential diagnosis. Agitation is usually easily recognized, but sorting out whether the patient is psychotic, is having severe anxiety, or is in a dysphoric manic state can be more difficult. Start with a careful mental status examination concentrating on certain key issues: Is there psychosis? Is the patient disturbed by insomnia? Is the patient guilt-ridden and ruminative? Or are they or have they been pleasure-seeking as in a hypomanic or manic state? Other historical information, which may need to be obtained from family or others, may also be helpful. Is the time course of the illness consistent with an affective disorder

or schizophrenia or schizoaffective disorder? Is there a family history of psychotic or affective illness? If depressive disorder leads the differential diagnosis list, secondary causes of depression, such as medical conditions and substances, must be ruled out by appropriate physical examination and laboratory studies.

The decision about whether to hospitalize the patient with depression complicated by psychosis or agitation will often depend on the severity of the episode and the suicide risk assessment. Patients who are not functioning and are unable to care for themselves, who lack social support, who do not have the possibility of rapid outpatient follow-up, or who have a past history of rapid deterioration will require hospitalization.

While many patients with complicated and severe forms of depression will require hospitalization, if hospitalization is not needed, definitive treatment should begin in the emergency setting. Trustworthy family or friends must be involved in the treatment plan so that, if there is deterioration, the patient can be brought back to the emergency room. Treatment must include both an antidepressant and an antipsychotic agent in the psychotically depressed patient. Although there have been few good studies, the early evidence indicates that both newer atypical antipsychotics and newer antidepressant agents are as effective in psychotic depression as are TCAs and neuroleptics, and they are much easier to use and better tolerated by patients. The agitated, but not psychotic, patient may be treated with an antidepressant alone, but can benefit from addition of a benzodiazepine or an antipsychotic. Before antidepressant therapy is initiated, however, careful attention should be given to ruling out a mixed bipolar episode. Antidepressant treatments will worsen a mixed bipolar episode and thus should be avoided. Anticonvulsant treatment with divalproex would be first-line therapy in that instance, with or without a concomitant neuroleptic. Again, the available data suggest that atypical antipsychotics and SSRIs are effective and well tolerated in depressed patients with agitation.

Both the antidepressant and the additional agent (antipsychotic or benzodiazepine) can be started at the same time. Drug-drug interactions should be considered before specific agents are chosen. When the differential diagnosis of unipolar agitated depression versus a mixed bipolar episode is entirely unclear, the use of an atypical neuroleptic alone may be reasonable, with close follow-up to clarify the diagnosis. The patient can be directed to return to the emergency department in a day or 2 for reassessment. Antidepressant treatment can be initiated at that time, if indicated.

### CASE REPORT

A 34-year-old, single woman was referred to the Psychiatric Emergency Service (PES) by the psychologist

she had been seeing off and on for 10 years. Her psychologist explained to the PES staff that Ms. A had struggled with dysthymia for some time and that he had viewed her as obsessive and somewhat suspicious of others, but never as paranoid. Six weeks before the referral, her boyfriend had moved out of their home and announced that the relationship was over. In the setting of the end of this intimate relationship, she had developed depressive symptoms including insomnia, loss of interest, decreased concentration at work, lack of energy, and loss of appetite. She had also become increasingly suspicious and paranoid about her coworkers and was now convinced that they were talking about her and making fun of her work. She also told her psychologist that she believed her coworkers had spoken to her neighbors and that everyone in her neighborhood was also talking about her behind her back. Her psychologist became concerned about her paranoia in the setting of a major depressive episode and asked her to go to the PES so that medications could be started immediately.

Although Ms. A had always been reluctant to see a psychiatrist and unwilling to consider psychotropic medications in the past, she agreed to come to the PES because she "felt so bad." She immediately explained to us that she had an uncle whose diagnosis she was unsure of but who had been in psychiatric hospitals on and off and who had developed problems that sounded like tardive dyskinesia by her description. She recognized that she was depressed and could even understand that her concerns about people at work might be unfounded at moments, but then immediately returned her to focus on how she was being talked about and ridiculed. On examination, she was appropriately groomed. Her speech was soft and slow. Her mood was sad, she was tearful, and her affect was blunted and mood congruent. She was quite suspicious of both her neighbors and coworkers and even became concerned that the emergency room staff might be communicating with the people who "did not like her." She denied hallucinations, ideas of reference, and both suicidal and homicidal ideation, although on careful questioning she did say that the thought of death had crossed her mind, but that she "had not let herself think about it." When we spoke to her about the possible benefits of hospitalization, she became more upset and stated she was frightened with the idea of being in the hospital and worried about what would happen to her dog if she was not home to take care of him.

While she acknowledged that the loss of her significant relationship, living alone now, and not trusting her coworkers or neighbors were hard to handle, she reported she still had several friends whom she could trust, and she thought she could have one of these women stay with her if we recommended it. We contacted this friend, who was willing to come to the emergency room and be part of the treatment plan for Ms. A.

Ms. A was sent home with her friend, who planned to stay with her for the next few days. Ms. A planned to take

the following day off work. Because Ms. A was reluctant to start medications in general, only one agent, risperidone, was started. She was instructed to take 1 mg at bedtime and to telephone the PES the next morning, Friday.

The next morning, Ms. A reported by phone that she had slept well and had no problem with the risperidone. She was instructed to take 2 mg of risperidone at bedtime on Friday, Saturday, and Sunday evenings and telephone the PES on Monday morning for reassessment and to determine if she could return to work.

On Monday she reported that she felt better and had been sleeping well. She was less concerned about her neighbors and coworkers and said she thought she had "overreacted" the week before. She was willing to try an antidepressant as well. Sertraline was started, an appointment was arranged in an outpatient clinic for the end of the week, and she was instructed to return to the emergency department during her lunch break on Wednesday. During her return visit on Wednesday, she reported no difficulty with sertraline and continued to feel better. She planned to continue at work and followed up with her psychologist as scheduled.

### CONCLUSIONS

Whether psychotic depression or agitated depression represent distinct syndromes or are simply more severe variants of major depression, their treatment differs from unipolar depression without psychosis or agitation. The addition of an antipsychotic agent is necessary in the depressed patient with psychosis and is often beneficial in the depressed patient with agitation. Careful attention should be paid to diagnosing the mixed bipolar episode versus agitated depression, however, and avoiding antidepressants in that setting.

Available data suggest that the newer agents, both antipsychotics and antidepressants, are effective and perhaps even better tolerated than TCAs and traditional neuroleptics in psychotic and agitated depression, although few randomized double-blind studies have been reported.

While depression complicated by psychosis or agitation often represents a severe form of depression for which hospitalization is needed, definitive treatment of both agitated and psychotic depression can be started in the emergency setting. The patient must be followed closely, and family or other social supports must be involved in the treatment plan.

*Drug names:* amitriptyline (Elavil and others), amoxapine (Asendin and others), divalproex sodium (Depakote), fluoxetine (Prozac), haloperidol (Haldol and others), olanzapine (Zyprexa), perphenazine (Trilafon and others), phenelzine (Nardil), risperidone (Risperdal), sertraline (Zoloft).

*Disclosure of off-label usage:* The authors have determined that, to the best of their knowledge, divalproex has not been approved by the U.S. Food and Drug Administration for the treatment of agitated depression.

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