An Open Study of Olanzapine and Fluoxetine for Psychotic Major Depressive Disorder: Interim Analyses

John D. Matthews, M.D.; Kathryn A. Bottonari, B.A.; Laura M. Polania, B.A.; David Mischoulon, M.D., Ph.D.; Christina M. Dording, M.D.; Robert Irvin, M.D.; and Maurizio Fava, M.D.

Background: Although atypical antipsychotic agents are commonly used in the treatment of psychotic depression, there are no published prospective studies on their use in this condition. The aim of this study was to assess, by interim analyses, the efficacy of the atypical antipsychotic agent olanzapine in combination with the selective serotonin reuptake inhibitor antidepressant agent fluoxetine.

Method: We enrolled 27 patients (17 women [63.0%] and 10 men [37.0%]; mean ± SD age: 41.2 ± 14.7 years) with DSM-IV–defined major depressive disorder with psychotic features into an open trial of olanzapine, 5 to 20 mg/day, plus fluoxetine, 20 to 80 mg/day. Patients were assessed at each visit with the 17-item Hamilton Rating Scale for Depression and both the psychotic and mood modules of the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition. We are reporting the results of the first 6 weeks of treatment.

Results: Twenty-two (81.5%) of the 27 enrolled patients completed the 6-week open trial, and 5 (18.5%) dropped out, with only 2 (7.4%) dropping out due to side effects. Of the 27 patients, 74.1% (N = 20) met criteria for melancholic features, 14.8% (N = 4) had delusions alone, 18.5% (N = 5) had hallucinations alone, and 66.7% (N = 18) reported both delusions and hallucinations. In addition, the overall rates of response for the intent-to-treat group were as follows: depression response rate, 66.7% (N = 18); psychosis response rate, 59.3% (N = 16); psychotic depression response rate, 55.6% (N = 15); and psychotic depression remission rate, 40.7% (N = 11).

Conclusion: The combination of olanzapine and fluoxetine appears to be a promising, safe, and effective treatment for psychotic depression. Double-blind studies are needed to confirm this impression.

(J Clin Psychiatry 2002;63:1164–1170)

Received Oct. 17, 2001; accepted Aug. 27, 2002. From the Depression Clinical and Research Program, Massachusetts General Hospital, Boston.

Study supported by a grant from Eli Lilly and Company (Dr. Fava).

These data were previously presented by Dr. Matthews at the 153rd annual meeting of the American Psychiatric Association, May 13–18, 2000, Chicago, Ill.

Dr. Fava has received research support and/or honoraria from Lilly, SmithKline Beecham, Pfizer, Wyeth-Ayerst Laboratories, Organon, Bristol-Myers Squibb, Pharmacia Upjohn, GlaxoWellcome, Solvay, Forest, Sanofi/Synthelabo, Janssen, Lundbeck, Knoll, Parke-Davis, Somerset, Pharmavite, Abbott, Roche, Novartis, Lorex, and Litchwer Pharma GmbH.

The authors acknowledge Nicole Neault, B.A., and Grace Rubenstein, B.A., for their assistance in the preparation of the manuscript.

Corresponding author and reprints: John D. Matthews, M.D., Department of Psychiatry, WACC 812, 15 Parkman St., Massachusetts General Hospital, Boston, MA 02114 (e-mail: jmatthews@partners.org).

Psychotic major depressive disorder is defined by DSM-IV as major depressive disorder with delusions, hallucinations, or both.[1] The psychotic symptoms may be either mood congruent or incongruent. Delusions occur without hallucinations in between one half and two thirds of adults with psychotic major depressive disorder, whereas hallucinations occur without delusions in between 3% and 25%.[2–8] The types of delusions most commonly observed include persecution, suspiciousness, paranoia, sin, guilt, ideas of reference, and somatic.[8] A formal thought disorder occurs in only 20% of adult patients.[8] The most common types of hallucinations are auditory and visual, and they occur with equal frequency.[2,5,6] Tactile and olfactory hallucinations may occur, but usually with other hallucinations.[2,5,6] Depending on the population studied, between 16% and 54% of depressed adults with major depressive disorder exhibit psychotic features; inpatients have higher rates than outpatients.[2,8,9–13]

Clinicians as far back as the turn of the century, and before, reported that depressed patients with psychotic symptoms responded poorly to available treatments.[14] Glassman et al.[15] in the mid-1970s were among the first to demonstrate that the response rate to tricyclic antidepressants (TCAs) was low in delusional depression. In a review including mostly retrospective and uncontrolled prospective studies of 1054 psychotically depressed patients, Chan et al.[16] found response rates of 67% for TCAs

in patients with nonpsychotic major depressive disorder and 35% in patients with psychotic major depressive disorder. Several retrospective and open prospective studies between 1978 and 1981 demonstrated response rates between 60% and 80% for combined antidepressant and antipsychotic treatment in psychotic major depressive disorder.[6,17–20] Spiker et al.[21] carried out the first randomized, double-blind, prospective study for the treatment of psychotic major depressive disorder. They found response rates of 41% (7/17), 19% (3/16), and 78% (14/18) for patients treated with amitriptyline alone, perphenazine alone, and amitriptyline plus perphenazine, respectively.

With the introduction of the selective serotonin reuptake inhibitors (SSRIs) in the late 1980s and the atypical antidepressant and atypical antipsychotic medications throughout the 1990s, new strategies evolved for the treatment of psychotic major depressive disorder. The strategies include SSRIs plus typical antipsychotics,[22,23] SSRIs alone,[24–26] atypical antipsychotics alone,[27–32] atypical antipsychotics plus antidepressants,[33,34] and atypical antipsychotics plus SSRIs.[35] In spite of the fact that psychotic major depressive disorder occurs as frequently as bipolar disorder and schizophrenia, there is a paucity of research studies addressing the treatment of this severe disorder. Tollefson et al.[36] reported that the combination of fluoxetine and olanzapine was superior to placebo in treating both depression and psychosis. The combination was also significantly superior to olanzapine monotherapy in treating depression, but the combination was only equally effective to olanzapine monotherapy in treating the psychotic symptoms. In addition, the combination of olanzapine and fluoxetine has been shown to be more effective and to have a more rapid onset of action than either medication alone in treatment-resistant depression.[37] Our study is the first published prospective open study that evaluates the efficacy, safety, and tolerability of the combination of the atypical antipsychotic olanzapine and the SSRI fluoxetine in the treatment of psychotic major depressive disorder.

METHOD

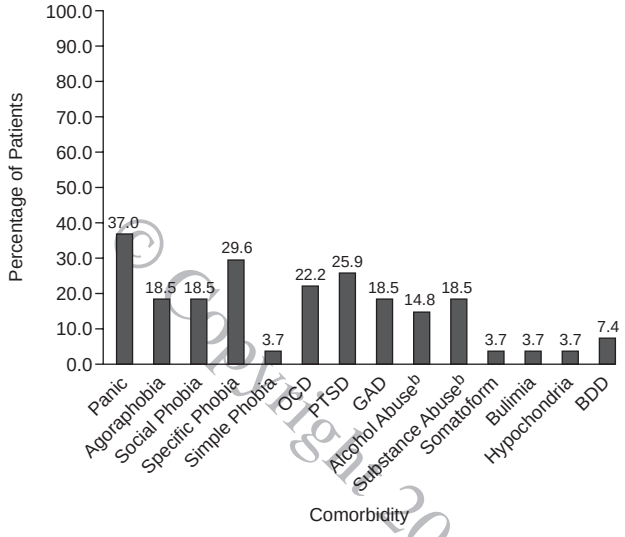
Twenty-seven male and female patients (aged 18–80 years) with a prior diagnosis of major depressive disorder with psychotic features were recruited from the Massachusetts General Hospital inpatient and outpatient services. After a full description of the study procedures and potential side effects to each potential subject by one of the study psychiatrists, written informed consent was obtained. Each subject was administered the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-I/P)[38] to determine index and comorbid DSM-IV diagnoses; all enrolled subjects met DSM-IV criteria for major depressive disorder with psychotic features. The severity of depression was measured by the 31-item Hamilton Rating Scale for Depression (HAM-D-31)[39]; a HAM-D-24 score ≥ 16 was required for inclusion into the study. Study psychiatrists obtained a psychiatric and medical history on each subject; this was followed by a complete physical and neurologic examination. Pretreatment laboratory tests included chemistry profile, urinalysis, urine toxicology screen when clinically indicated, complete blood count with differential, thyroid-stimulating hormone, and electrocardiogram. Exclusion criteria included meeting DSM-IV criteria for major depressive disorder without psychotic features, schizophrenia, bipolar disorder, schizoaffective disorder, substance use disorder (active use within the last 6 months), or organic mental disorders; being considered a serious suicide risk; a history of seizure disorder, an unstable physical disorder, or a physical disorder judged to significantly affect central nervous system function; female patients who were pregnant or of childbearing potential who were not using medically accepted means of contraception; and female patients who were breastfeeding.

The drug washout period varied among the subjects. Seventeen of the patients had no exposure to any psychotropic medication prior to 6 months before entering the study. Three patients had their antidepressants discontinued 3 weeks prior to entering the study (nefazodone; sertraline plus mirtazapine; fluoxetine). One patient discontinued valproic acid 2 weeks prior to entering the study. One patient discontinued St. John's wort, *Ginkgo biloba*, and ginseng 11 days before entering the study. Three patients had their medications discontinued 7 days prior to entering the study (citalopram; citalopram plus haloperidol; nortriptyline). Two inpatients were switched to study medications without a washout period (diazepam; clomipramine plus gabapentin). Thus, 21 (78%) of the 27 patients had their medications discontinued 2 weeks or more before starting study medications.

Subjects were started on treatment with fluoxetine, 20 mg/day, and olanzapine, 5 mg/day, simultaneously. In those instances in which the initial dose caused substantial side effects, the dose of the medication considered to be responsible for causing the side effects was reduced (10 mg/day for fluoxetine and 2.5 mg/day for olanzapine). The dosing schedules were flexible over the 6-week period, with maximum doses of 20 mg/day for olanzapine and 80 mg/day for fluoxetine. The subjects' clinical status was monitored weekly for the 6-week period. At each visit, a study psychiatrist administered the HAM-D-31, the SCID modules for psychosis and depression, and the Clinical Global Impressions-Severity of Illness and -Improvement scales.[40]

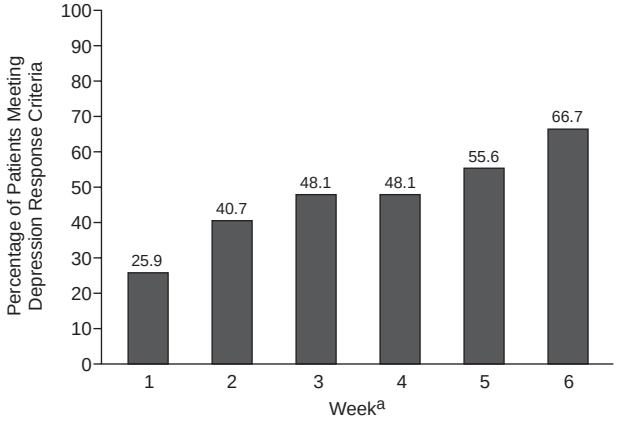
Since we were interested in evaluating the independent time course of improvement for depression and psychosis, as well as the combined time course, we defined the following responses: depression response was determined by a 50% reduction in HAM-D-17 score, psychosis

Figure 1. Lifetime Axis I Comorbidity (intent-to-treat; N = 27)[a]



[a]Abbreviations: BDD = body dysmorphic disorder, GAD = generalized anxiety disorder, OCD = obsessive-compulsive disorder, PTSD = posttraumatic stress disorder.
[b]Persons with current alcohol or substance abuse were not enrolled.

Figure 2. Depression Response Times (N = 27)



[a]Percentage of patients meeting criteria was assessed at the end of each week shown.

response was determined by the absence of delusions and/or hallucinations as assessed by the SCID psychosis module (subthreshold symptoms were therefore excluded), and psychotic depression response was determined by both depression and psychosis responses being present. We also determined the psychotic depression remission rate, which we defined as a HAM-D-17 score of less than 8, plus the absence of delusions and hallucinations.

Statistical Analyses

Descriptive statistics were used to assess patient demographic and characteristic variables as well as response rates and remission rates.

RESULTS

Subjects' Clinical Characteristics

Twenty-seven patients were enrolled into the study (10 men and 17 women; mean ± SD age = 41.2 ± 14.7 years). Of these, 22 (7 men and 15 women; mean age = 41.1 ± 14.9 years) completed the first 6 weeks of treatment. The following subject clinical characteristics are limited to the intent-to-treat group. With regards to ethnicity, 55.6% (N = 15) were white, 25.9% (N = 7) were Hispanic, and 18.5% (N = 5) were black. The mean age at onset for the first episode of major depressive disorder without psychosis was 30.2 ± 17.6 years, and the mean age at onset for the first episode of major depressive disorder with psychotic features was 33.6 ± 17.4 years. The mean number of episodes of major depressive disorder without psychotic features was 2.7 ± 4.4, and the mean number of episodes of major depressive disorder with psychotic features was 1.0 ± 0.4 (N = 23; 4 subjects had too many episodes to count); 14 (51.9%) of 27 subjects experienced previous nonpsychotic episodes. The mean pretreatment scores for the HAM-D-24 and the HAM-D-17 were 34.6 ± 7.7 and 28.9 ± 5.2, respectively, which are in the severe range. Seventy-four percent (N = 20) of the patients met criteria for melancholia, 11.1% (N = 3) met criteria for atypical depression, and 7.4% (N = 2) met criteria for dysthymia. Delusions and hallucinations occurred in 66.7% (N = 18) of the patients, whereas the frequency of delusions alone was 14.8% (N = 4) and the frequency of hallucinations alone was 18.5% (N = 5). The frequencies of the types of hallucinations are as follows: auditory, 66.7% (N = 18); visual, 48.1% (N = 13); and olfactory, 44.4% (N = 12).

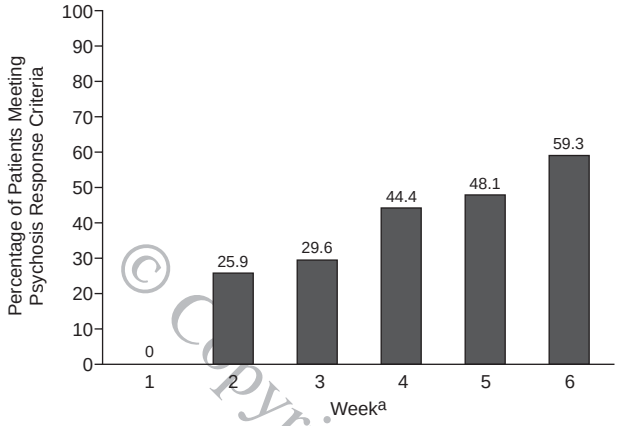
Lifetime Axis I Comorbidity

The most common DSM-IV comorbid diagnoses for the 27 patients were panic disorder (N = 10, 37.0%), specific phobias (N = 8, 29.6%), and posttraumatic stress disorder (PTSD) (N = 7, 25.9%). Figure 1 shows the prevalence of comorbid Axis I disorders within the intent-to-treat group.

Treatment Response

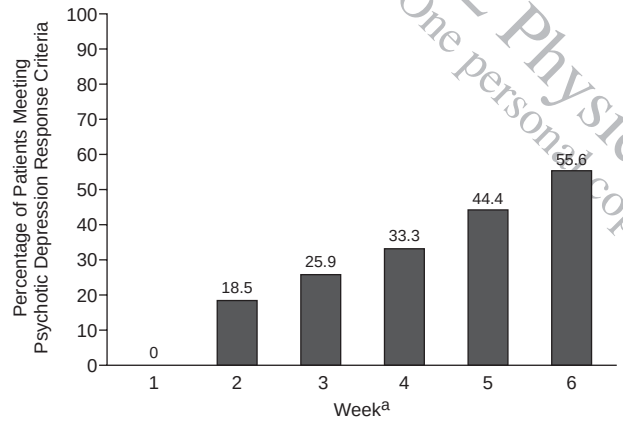
Figure 2 shows the time course for the depression response to the combined treatment. Sixty-seven percent (18/27) of the intent-to-treat group responded during the acute phase, whereas 68.2% (15/22) of the completers were responders. Eleven (40.7%) of the 27 enrolled patients responded within the first 2 weeks of treatment. Figure 3 shows the time course for the psychosis response. Fifty-nine percent (16/27) of the intent-to-treat

Figure 3. Psychosis Response Times (N = 27)



[a]Percentage of patients meeting criteria was assessed at the end of each week shown.

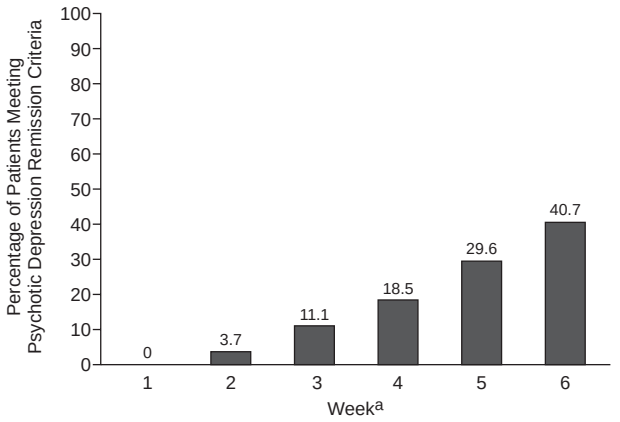
Figure 4. Psychotic Depression Response Times (N = 27)



[a]Percentage of patients meeting criteria was assessed at the end of each week shown.

group responded during the acute phase, whereas 63.6% (14/22) of the completers were responders. Twenty-six percent (7/27) of the intent-to-treat group showed resolution of their psychotic symptoms by the end of week 2. Figure 4 shows the time course for psychotic depression response. Nineteen percent (5/27) of the intent-to-treat group had a response of both depression and psychosis by the end of the second week. The psychotic depression response rate at endpoint was 55.6% (15/27) for the intent-to-treat group and 59.1% (13/22) for the completers. Figure 5 shows the time course for psychotic depression remission. Three patients achieved full remission by the end of week 3, but most achieved full remission between weeks 4 and 6. The psychotic depression remission rate at endpoint was 40.7% (11/27) for the intent-to-treat group and 40.9% (9/22) for the completers.

Figure 5. Psychotic Depression Remission Times (N = 27)



[a]Percentage of patients meeting criteria was assessed at the end of each week shown.

Drug Doses and Retention Rates

The dropout rate was 18.5% (5/27). Only 7.4% (2/27) dropped out due to adverse effects from the medications. The other 3 patients dropped out for the following reasons: 1 was lost to follow-up and 2 were nonresponders to the study medication and chose to discontinue. The mean dose of olanzapine for the 27 enrolled patients was 10.2 ± 6.0 mg/day, while the mean dose for the 22 completers was 10.2 ± 6.4 mg/day. The mean dose of fluoxetine for the 27 enrolled patients was 52.7 ± 19.7 mg/day, while the mean dose for the 22 completers was 56.4 ± 17.3 mg/day.

Adverse Events

The most common adverse events for both the intent-to-treat and completer groups included sedation, gastrointestinal distress, dizziness/light-headedness, weight gain, headache, fatigue/tiredness, increased appetite, body aches, dry mouth, and decreased appetite (prevalence shown in Table 1). The mean increase in weight during the 6 weeks of the study was 3.3 ± 6.6 lb (1.5 ± 3.0 kg) among the 27 enrolled patients (2.3 ± 4.6% increase) and 2.8 ± 5.9 lb (1.3 ± 2.7 kg) for the completers (1.9 ± 3.8% increase).

DISCUSSION

This open trial suggests that the combination of olanzapine and fluoxetine may be effective in the treatment of psychotic major depressive disorder. The 6-week psychotic depression response and remission rates for the 27 enrolled patients were 55.6% and 40.7%, respectively. The rapidity of improvement is impressive in view of studies that have shown a slow overall recovery rate for psychotic major depressive disorder.[41,42] These results

Table 1. Most Common Adverse Events (intent-to-treat and completer groups)[a]

Adverse Event	Intent-to-Treat (N = 27)	Completers (N = 22)
Sedation	11 (40.7)	10 (45.5)
Gastrointestinal distress	7 (25.9)	7 (31.8)
Body aches	7 (25.9)	7 (31.8)
Dizziness/light-headedness	6 (22.2)	4 (18.2)
Headache	6 (22.2)	6 (27.3)
Weight gain	4 (14.8)	3 (13.6)
Fatigue/tiredness	4 (14.8)	4 (18.2)
Increased appetite	3 (11.1)	3 (13.6)
Dry mouth	3 (11.1)	3 (13.6)
Decreased appetite	2 (7.4)	2 (9.1)

[a]All values shown as N (%).

also appear to be consistent with other studies that have found atypical antipsychotic agents, including olanzapine, to be effective in combination with antidepressants in the treatment of psychotic major depressive disorder.[33–35]

Overall, the combination of olanzapine and fluoxetine was well tolerated. Only 2 of 27 subjects dropped out due to adverse effects from the medications. The mean ± SD weight gain over the 6 weeks was 3.3 ± 6.6 lb (1.5 ± 3.0 kg). Two short-term studies, one in patients with an acute exacerbation of schizophrenia[43] and one in patients with bipolar disorder,[44] showed increases in mean weight from baseline of 2.2 ± 4.0 kg (4.8 ± 8.8 lb) over 6 weeks and 1.65 ± 2.54 kg (3.67 ± 5.64 lb) over 3 weeks, respectively. In addition, in placebo-controlled 6-week studies, 29% of olanzapine patients gained greater than 7% of their baseline weight,[45] compared with 11.1% of patients (3/27) in our study. Interestingly, our patients showed less weight gain over a 6-week time period. Although we cannot draw conclusions because of our small sample size, it may be that fluoxetine had a relative protective effect against possible olanzapine-related weight gain.

A number of clinical features of our patients are of interest. The mean initial HAM-D-17 score of our patient population was 28.9 ± 5.2, which is in the severe range. In addition to their depressive symptoms, 66.67% of our patients experienced both delusions and hallucinations. The most common hallucinations were auditory (66.7%) and visual (48.1%), which is consistent with other reports.[8,46] However, 44.4% of the intent-to-treat group experienced olfactory hallucinations. Results of magnetic resonance imaging of 2 patients with olfactory hallucinations were negative for any temporal lobe abnormalities. None of the patients with olfactory hallucinations reported a history of seizures. However, no electroencephalograms were obtained, so we cannot rule out that these patients had had seizures.

The most common comorbid psychiatric disorders were panic disorder, social phobia, and PTSD. Currently, there are no data on comorbid disorders in psychotic major depressive disorder with which to compare our results.

The SCID psychotic module was our only measure of the presence of psychosis. One could argue that since the SCID is a qualitative rather than a quantitative instrument, a patient may have a degree of psychosis that is not adequately measured by the SCID. However, on the SCID, a score of 1 on each of the psychosis items means complete absence of that particular psychotic symptom, a score of 2 means the psychotic symptom is subthreshold, and a score of 3 means that the psychotic item is present. In our study, a score of 2 on a SCID item was interpreted as psychosis being present; thus, we used a score of 1 for complete absence of that particular psychotic item. This would suggest that the SCID psychotic module is a relatively conservative tool to evaluate response in these patients.

Although other work has found higher rates of psychotic major depressive disorder in the elderly, the mean age at onset of the disorder in our study is consistent with a recent large (N = 674) study by Thakur et al.[47] They found that the young adult and middle-aged group was more commonly associated with psychotic rather than nonpsychotic depression. In their depressed population, the proportion of psychotic major depressive disorder was 37.1% in the group aged 18 to 39 years, whereas the proportion of psychotic major depressive disorder was 25% in the group aged 40 years or older. Nelson et al.[48] found no significant difference in mean age at onset in 39 delusional and 70 non-delusional unipolar depressed patients over 60 years of age. However, Brodaty et al.[49] found that rates of psychotic major depressive disorder and major depressive disorder with melancholia increased with age.

Because of the relatively young age at onset and the frequent relapses in some of the patients, a diagnosis of schizoaffective disorder needs to be considered. Evidence that argues against a diagnosis of schizoaffective disorder in our population includes no formal thought disorder in any of our patients, the presence of nonpsychotic depressive episodes in 51.9% of our patients, and the high rates of comorbid anxiety disorders. The high relapse rate in some of our patients is consistent with the psychotic major depressive disorder literature. Aronson et al.,[50] in a 3-year retrospective study, found that the first year after recovery from the index episode was a vulnerable period for relapse. They found that 45 (86%) of 52 patients with psychotic major depressive disorder relapsed over the 3-year period of follow-up. Among the 45 patients who relapsed, there were 98 episodes of relapse. Eighty-two (82.5%) of the 98 episodes occurred within the first year, and 26 (26.5%) of the 98 episodes occurred within the first 3 months of discharge from inpatient treatment.

Although our remission rate for psychotic major depressive disorder compares favorably with remission rates for nonpsychotic major depressive disorder, in a re-

view by Solan et al.,[51] electroconvulsive therapy (ECT) response rates for psychotic major depressive disorder ranged from 58% to 100%, with a mean of 76%. More recently, Sobin et al.[52] found ECT response rates of 64.8% immediately post–ECT series. There are few other studies assessing remission rates for ECT in psychotic major depressive disorder. Petrides et al.[53] found an ECT remission rate of 95% among 77 psychotically depressed patients. Although ECT appears to be relatively more effective than combined antidepressant and antipsychotic medications on the basis of these reported remission rates, randomized studies comparing remission rates of ECT and combined SSRIs and atypical antipsychotic medications are needed.

Our study has several limitations. We used an open and uncontrolled design, and, therefore, we cannot draw firm conclusions on whether our findings are due to the effect of these medications. However, since the placebo response rate tends to be rather low in psychotic major depressive disorder studies,[12,16,54] it is unlikely that the improvement observed in our population was due to nonspecific, placebo-like effects. This sample has a higher rate (44%) of olfactory hallucinations than has been reported elsewhere[2,5,6]; it is unclear whether our results can be extrapolated to other psychotic major depressive disorder samples. Most of the patients were outpatients (22/27; 81.5%), and, therefore, our findings may not be generalizable to inpatient populations. The study's main sampling bias is due to the fact that patients with current or recent substance abuse were excluded. However, many of our patients did have a lifetime history of such disorders. Finally, the age range was limited to adults, and we cannot infer that these treatments may be effective in older or younger populations.

In summary, our open study suggests that the combination of fluoxetine and olanzapine is a well-tolerated and effective treatment for psychotic major depressive disorder. Further controlled, double-blind studies are warranted.

Drug names: amitriptyline (Elavil, Endep, and others), citalopram (Celexa), clomipramine (Anafranil and others), diazepam (Valium and others), fluoxetine (Prozac and others), gabapentin (Neurontin), haloperidol (Haldol and others), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Aventyl and others), olanzapine (Zyprexa), perphenazine (Trilafon and others), sertraline (Zoloft), valproic acid (Depakene and others).

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
2. Coryell W, Zimmerman M. Demographic, historical, and symptomatic features of the nonmanic psychoses. J Nerv Ment Dis 1986;174:585–592
3. Jorgensen P. Manic-depressive patients with delusions. Acta Psychiatr Scand 1985;72:364–368
4. Agren H, Terenius L. Hallucinations in patients with major depression: interactions between CSF monoaminergic and endorphinergic indices. J Affect Disord 1985;9:25–34
5. Frangos E, Athanassenas G, Tsitourides P, et al. Psychotic depressive disorder: a separate entity? J Affect Disord 1983;5:259–265
6. Charney DS, Nelson JC. Delusional and nondelusional unipolar depression: further evidence for distinct subtypes. Am J Psychiatry 1981;138: 328–333
7. Coryell W, Pfohl B, Zimmerman M. The clinical and neuroendocrine features of psychotic depression. J Nerv Ment Dis 1984;172:521–528
8. Dubovsky SL, Thomas M. Psychotic depression: advances in conceptualization and treatment. Hosp Community Psychiatry 1992;43:1189–1198
9. Frances A, Brown RP, Kocsis JH, et al. Psychotic depression: a separate entity? Am J Psychiatry 1981;138:831–833
10. Lykouras E, Christodoulou GN, Malliaras D. Type and content of delusions in unipolar psychotic depression. J Affect Disord 1985;9:249–252
11. Nelson WH, Khan A, Orr WW. Delusional depression: phenomenology, neuroendocrine function, and tricyclic antidepressant response. J Affect Disord 1985;9:297–306
12. Glassman AH, Roose SP. Delusional depression: a distinct clinical entity? Arch Gen Psychiatry 1981;38:424–427
13. Avery D, Lubano A. Depresssion treated with imipramine and ECT: the DeCarolis study reconsidered. Am J Psychiatry 1979;136:559–562
14. Goshen CE. Documentary History of Psychiatry. New York, NY: Philosophical Library; 1967
15. Glassman AH, Kantor SJ, Shostak M. Depression, delusions, and drug response. Am J Psychiatry 1975;132:716–719
16. Chan CH, Janicak PG, Davis JM, et al. Response of psychotic and nonpsychotic depressed patients to tricyclic antidepressants. J Clin Psychiatry 1987;48:197–200
17. Nelson JC, Bowers MB. Delusional unipolar depression: description and drug response. Arch Gen Psychiatry 1978;35:1321–1328
18. Minter RE, Mandel MR. The treatment of psychotic major depressive disorder with drugs and electroconvulsive therapy. J Nerv Ment Dis 1979; 167:726–733
19. Minter RE, Mandel MR. A prospective study of the treatment of psychotic depression. Am J Psychiatry 1979;136:1470–1472
20. Kaskey GB, Nasr S, Meltzer HY. Drug treatment in delusional depression. Psychiatry Res 1980;1:267–277
21. Spiker DG, Weiss JC, Dealy RS, et al. The pharmacological treatment of delusional depression. Am J Psychiatry 1985;142:430–436
22. Rothschild AJ, Samson JA, Bessette MP, et al. Efficacy of the combination of fluoxetine and perphenazine in the treatment of psychotic depression. J Clin Psychiatry 1993;54:338–342
23. Wolfersdorf M, Barg T, Konig F, et al. Paroxetine as an antidepressant in combined antidepressant-neuroleptic therapy in delusional depression: observation of clinical use. Pharmacopsychiatry 1995;28:56–60
24. Gatti F, Bellini L, Gasperini M, et al. Fluvoxamine alone in the treatment of delusional depression. Am J Psychiatry 1996;153:414–416
25. Zanardi R, Franchini L, Gasperini M, et al. Double-blind controlled trial of sertraline versus paroxetine in the treatment of delusional depression. Am J Psychiatry 1996;153:1631–1633
26. Zanardi R, Franchini L, Gasperini M, et al. Long-term treatment of psychotic (delusional) depression with fluvoxamine: an open pilot study. Int Clin Psychopharmacol 1997;12:195–197
27. Dassa D, Kaladjian A, Azorin JM, et al. Clozapine in the treatment of psychotic refractory depression. Br J Psychiatry 1993;163:822–824
28. Hillert A, Maier W, Wetzel H, et al. Risperidone in the treatment of disorders with a combined psychotic and depressive syndrome: a functional approach. Pharmacopsychiatry 1992;25:213–217
29. Zarate CA, Tohen M, Baldessarini RJ. Clozapine in severe mood disorders. J Clin Psychiatry 1995;56:411–417
30. Ranjan R, Meltzer HY. Acute and long-term effectiveness of clozapine in treatment-resistant psychotic depression. Biol Psychiatry 1996;40: 253–258
31. Lane HY, Chang WH. Risperidone monotherapy for psychotic depression unresponsive to other treatments [letter]. J Clin Psychiatry 1998;59:624
32. Muller-Siecheneder F, Muller MJ, Hillert A, et al. Risperidone versus haloperidol and amitriptyline in the treatment of patients with a combined psychotic and depressive syndrome. J Clin Psychopharmacol 1998;18: 111–120
33. Kaiya H, Takeda N. Sulpiride in the treatment of delusional depression [letter]. J Clin Psychopharmacol 1990;10:147
34. Rothschild AJ, Bates KS, Boehringer KL, et al. Olanzapine response in psychotic depression. J Clin Psychiatry 1999;60:116–118
35. Adli M, Rossius W, Bauer M. Olanzapine in the treatment of depressive disorders with psychotic symptoms. Nervenarzt 1999;70:68–71

36. Tollefson GD, Sanger TM, Andersen SW. The use of an olanzapine:fluoxetine combination in the treatment of major depression with psychotic features: results form a large, prospective, double-blind trial. Presented at the 40th annual meeting of the American College of Neuropsychopharmacology; Dec 9–13, 2001; Waikoloa, Hawaii
37. Mathew S, Shelton RC, Paul S, et al. Olanzapine-fluoxetine combination in treatment-resistant depression. Presented at the 40th annual meeting of the American College of Neuropsychopharmacology; Dec 9–13, 2001; Waikoloa, Hawaii
38. Spitzer RL, Williams JBW, Gibbon M, et al. Structured Clinical Interview for DSM-IV Axis I Disorders User's Guide and Interview (SCID-I, Research Version). New York, NY: Biometric Research, New York State Psychiatric Institute; 1995
39. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
40. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
41. Tsuang D, Coryell W. An 8-year follow-up of patients with DSM-III-R psychotic depression, schizoaffective disorder, and schizophrenia. Am J Psychiatry 1993;150:1182–1188
42. Coryell W, Leon A, Winokur G, et al. Importance of psychotic features to long-term course in major depressive disorder. Am J Psychiatry 1996;153: 483–489
43. Beasley CM, Sanger T, Satterlee W, et al. Olanzapine versus placebo: results of a double-blind, fixed-dose olanzapine trial. Psychopharmacology (Berl) 1996;124:159–167
44. Tohen M, Sanger T, McElroy S, et al, for the Olanzapine HGEH Study Group. Olanzapine versus placebo in the treatment of acute mania. Am J Psychiatry 1999;156:702–709
45. Zyprexa (olanzapine). Physicians' Desk Reference. Montvale, NJ: Medical Economics; 2001:1788–1793
46. Schatzberg A, Rothschild AJ. Psychotic (delusional) major depression: should it be included as a distinct syndrome in DSM-IV? Am J Psychiatry 1992;149:733–745
47. Thakur M, Hays J, Ranga K, et al. Clinical, demographic and social characteristics of psychotic depression. Psychiatry Res 1999;86:99–106
48. Nelson JC, Conwell Y, Kim K, et al. Age at onset in late-life delusional depression. Am J Psychiatry 1989;146:785–786
49. Brodaty H, Luscombe G, Parker G, et al. Increased rate of psychosis and psychomotor change in depression with age. Psychol Med 1997;27: 1205–1213
50. Aronson TA, Shukla S, Gujavarty K, et al. Relapse in delusional depression: a retrospective study of the course and treatment. Compr Psychiatry 1988;29:12–21
51. Solan WJ, Khan A, Avery DH, et al. Psychotic and nonpsychotic depression: comparison of response to ECT. J Clin Psychiatry 1988;49:97–99
52. Sobin C, Prudic J, Devanand DP, et al. Who responds to electroconvulsive therapy? a comparison of effective and ineffective forms of treatment. Br J Psychiatry 1996;169:322–328
53. Petrides G, Fink M, Husain MM, et al. ECT remission rates in psychotic versus nonpsychotic depressed patients: a report from CORE. J ECT 2001; 4:244–253
54. Anton RF, Burch EA. Amoxapine versus amitriptyline combined with perphenazine in the treatment of psychotic depression. Am J Psychiatry 1990; 147:1203–1208