Olanzapine Response in Psychotic Depression

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***Background*:** Psychotic depression is more common than is generally realized, occurring in an estimated 16% to 54% of depressed patients. In controlled studies of patients with schizophrenia, the atypical antipsychotic olanzapine has been shown to be superior in efficacy to haloperidol at doses of 10 mg/day. Since olanzapine may have antidepressant effects in addition to its antipsychotic properties, the purpose of this study was to assess the safety and efficacy of olanzapine in the treatment of psychotic depression.

***Method*:** Hospitalized patients with the discharge diagnosis of DSM-IV psychotic depression (major depression with psychotic features or bipolar I disorder, depressed phase...with psychotic features) who had been treated with olanzapine during the first 9 months of its availability in the United States were identified. An age- and sex-matched sample of hospitalized patients with psychotic depression treated with other antipsychotics during the same time period was also identified. The medical records were expunged of all references to medication treatment and then reviewed and scored in a blind fashion for indications, doses, response, and side effects.

***Results*:** Fifteen psychotic depression patients (10 women, 5 men), aged 36.9 $\pm$ 10.1 years, who were treated with olanzapine were retrospectively compared with 15 psychotic depression patients (10 women, 5 men), aged 35.0 $\pm$ 8.2 years, treated with other antipsychotics. Ten (67%) of 15 patients taking olanzapine were much or very much improved upon discharge compared with only 4 (27%) of 15 patients taking other antipsychotics (Fisher exact test, $p = .037$). Olanzapine was well tolerated: no patient discontinued the medication because of side effects. Twelve (80%) of 15 patients in each group were taking antidepressants in addition to the antipsychotic. Of the 3 patients taking olanzapine but not taking an antidepressant, 2 were much or very much improved (1 patient taking olanzapine alone, 1 taking olanzapine plus valproate sodium).

***Conclusion*:** Olanzapine appears to be effective and safe for patients with psychotic depression. Further prospective studies are warranted to ascertain whether olanzapine's unique pharmacologic profile may make it particularly useful for the treatment of psychotic depression either alone or in combination with antidepressants.

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The most efficacious treatments for patients who suffer from major depression with psychotic features (psychotic depression, delusional depression) include amoxapine, electroconvulsive therapy (ECT), or the combination of an antidepressant and an antipsychotic.[1,2] Unfortunately, conventional antipsychotic medications expose patients to the development of tardive dyskinesia and extrapyramidal side effects, which may occur more frequently in patients with affective disorders than in those with schizophrenia.[3] Novel antipsychotic agents (e.g., clozapine, risperidone, olanzapine), which possess unique pharmacologic properties including central dopamine-2 and serotonin-2 ($5\text{-}HT_2$) receptor antagonist activity, should in theory be of therapeutic value in patients with both psychotic and depressive symptoms.[2] A few case reports and chart review studies have suggested that clozapine may be useful in the treatment of psychotic depression,[2] with one study[4] suggesting that it may be more effective for bipolar psychotic depression patients than for unipolar psychotic depression patients.

Olanzapine is a novel antipsychotic agent for the treatment of schizophrenia that has many of the pharmacologic properties of clozapine but a better side effect profile.[5] Its potential antidepressant as well as antipsychotic properties and its demonstrated superiority over conventional antipsychotics in exhibiting fewer extrapyramidal symptoms and side effects make it an ideal medication to study in patients who suffer from psychotic depression. The purpose of this study was to assess the safety and efficacy of olanzapine for the treatment of psychotic depression.

METHOD

All hospitalized patients treated at the University of Massachusetts Medical Center during the first 9 months of

olanzapine's availability (October 1996 through June 1997) with the discharge diagnosis of DSM-IV psychotic depression (major depression with psychotic features or bipolar I disorder, depressed phase...with psychotic features) were retrospectively identified by cross-matching the pharmacy database with discharge diagnoses. Psychotic depression patients previously exposed to typical antipsychotics in the current episode were excluded from the sample. An age- and sex-matched sample of hospitalized patients with psychotic depression treated with other antipsychotics during the same time period was also identified.

Demographic data and illness and treatment history were obtained by one rater, and the medical records were then expunged of all references to medication treatment. The records were then reviewed and scored in a blind fashion by a second rater for response to treatment (using a 7-point Likert rating scale: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse) and side effects. The discharge diagnosis of psychotic depression was confirmed by a detailed review of the medical record by a rater blind to the treatment the patient received. Data were analyzed using the Fisher exact test.

RESULTS

The medical records of 30 psychotic depression patients who met DSM-IV criteria for major depression with psychotic features or bipolar I disorder, depressed phase... with psychotic features were analyzed. None of the patients had any substantial medical problems including cardiovascular, neurologic, or endocrinologic diseases. Fifteen psychotic depression patients (10 women, 5 men; 11 unipolar, 4 bipolar), aged 36.9 ± 10.1 years, who were treated with olanzapine were compared with 15 psychotic depression patients (10 women, 5 men; 11 unipolar, 4 bipolar), aged 35.0 ± 8.2 years, treated with other neuroleptics. The mean ± SD dose of olanzapine in the 15 psychotic depression patients was 12.0 ± 4.8 mg/day (range, 5–20 mg/day). The mean ± SD chlorpromazine equivalent dose of other neuroleptics used was 293.4 ± 98.7 mg/day. There were no significant differences between the patients treated with olanzapine and those treated with other neuroleptics for number of previous episodes, length of current episode, length of illness, age, or sex.

The response of psychotic depression patients to olanzapine compared with other neuroleptics is shown in Table 1. Ten (67%) of 15 patients taking olanzapine were much or very much improved upon discharge compared with only 4 (27%) of 15 patients taking other antipsychotics (Fisher exact test, p = .037). When the data were analyzed for patients receiving 14 days or fewer of antipsychotic therapy (length of stay in the hospital ≤ 14 days), 10 (91%) of 11 patients taking olanzapine were much or very much improved compared with 4 (36%) of 11 patients taking other antipsychotic medications (Fisher exact test, p = .012). There was no difference in total length of hospitalization between those patients who received olanzapine and those who received other neuroleptics.

Table 1. Response of Patients With Psychotic Depression to Olanzapine Versus Other Neuroleptics[a]

	At Discharge[b]		Treatment ≤ 14 Days[c]	
Treatment	Favorable Response	Poor Response	Favorable Response	Poor Response
Olanzapine	10	5	10	1
Other neuroleptics	4	11	4	7

[a] Favorable response was defined as much or very much improvement; poor response was defined as minimal improvement, no change, or worsening.
[b] Fisher exact test, p = .037.
[c] Fisher exact test, p = .012.

Twelve (80%) of 15 patients in both the olanzapine and other antipsychotic group were taking antidepressants in addition to the antipsychotic. There were no statistically significant differences in the type of antidepressants used with olanzapine (selective serotonin reuptake inhibitors [SSRIs]: 5; heterocyclic antidepressants: 3; other antidepressants [bupropion, nefazodone, venlafaxine, monoamine oxidase inhibitors]: 4) when compared with other neuroleptics (SSRIs: 8; heterocyclic antidepressants: 1; others: 3) (Fisher exact test, NS). Of the 3 patients taking olanzapine but not taking an antidepressant, 2 were much or very much improved (1 patient taking olanzapine alone, 1 taking olanzapine plus valproate sodium). When the data were analyzed for the unipolar psychotic depression group alone, 8 (73%) of 11 patients treated with olanzapine were much or very much improved at discharge compared with 3 (27%) of 11 patients treated with other neuroleptics (Fisher exact test, p = .043).

Of the 15 psychotic depression patients treated with olanzapine, 9 reported no side effects, 3 reported sedation, 2 reported tremors or rigidity, 1 reported dry mouth, and 1 had postural hypotension. Of the 15 psychotic depression patients treated with other antipsychotics, 6 reported no side effects, 6 reported tremor or rigidity, 5 reported sedation or dizziness, 2 reported oculogyric crises, and 1 reported nasal congestion.

DISCUSSION

Inpatients with psychotic depression had greater response rates at discharge when treated with olanzapine and an antidepressant compared with other neuroleptics and an antidepressant. We did not observe a greater response in bipolar psychotic depression patients compared with unipolar psychotic depression patients as has been reported with clozapine.[4] Olanzapine alone was also effective for the treatment of psychotic depression in some pa-

tients. Since olanzapine has both 5-HT_2 and dopamine antagonism, it is conceivable that it may exert both antidepressant and antipsychotic effects. Whether or not olanzapine alone is effective for the treatment of psychotic depression remains to be studied. However, since the current standard of treatment for psychotic depression patients when using medications is to combine an antidepressant with an antipsychotic, it may be preferable to use an atypical antipsychotic as the neuroleptic for greater efficacy and fewer side effects.

Our data also suggest that psychotic depression patients may improve more rapidly when treated with olanzapine compared with other neuroleptics. The lack of a difference in overall length of hospitalization between olanzapine-treated versus other neuroleptic–treated patients in this study is most likely due to the multiple factors that determine length of hospitalization in our setting, including degree of family support, availability of a day program, and presence and type of managed care. For these reasons, we analyzed the data both at discharge from the hospital and after 14 days or fewer of treatment. Although raters in this study were blind to which treatment the patient had received, our study was retrospective and so definitive conclusions regarding olanzapine's efficacy in psychotic depression must wait for prospective double-blind studies. These studies appear warranted to ascertain whether olanzapine's unique pharmacologic profile may make it particularly useful for the treatment of psychotic depression either alone or in combination with antidepressants.

Drug names: amoxapine (Asendin), bupropion (Wellbutrin), clozapine (Clozaril), haloperidol (Haldol and others), nefazodone (Serzone), olanzapine (Zyprexa), risperidone (Risperdal), venlafaxine (Effexor).

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