How Long Should Patients With Psychotic Depression Stay on the Antipsychotic Medication?

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Background: Patients who have major depression with psychotic features have greater morbidity and mortality than patients with nonpsychotic major depression. In particular, relapse and recurrence have been reported to occur more frequently in patients with psychotic depression than nonpsychotic depression. Despite the frequent relapse and recurrence in major depression with psychotic features, there are few studies of the efficacy of continuation and maintenance treatments.

Method: Forty patients with a diagnosis of unipolar DSM-III-R major depression with psychotic features were treated with fluoxetine and perphenazine for 5 weeks after granting written informed consent. The patients who responded to treatment continued to receive the combination for an additional 3 months. If a patient was stable for 4 months on treatment with the combination, the patient was then gradually tapered off perphenazine treatment. For patients who exhibited impending relapse, perphenazine was restarted. Impending relapse was defined as any of the following: (1) symptoms meeting DSM-IV criteria for major depressive disorder (with or without psychotic features), (2) a total score of ≥ 17 on the HAM-D, or (3) the presence of any psychotic symptoms. After 1 year of taking fluoxetine, patients were tapered off fluoxetine treatment. Data were gathered from 1992 to 1997.

Results: Thirty patients responded to the initial 5 weeks of treatment with perphenazine and fluoxetine. After taper of perphenazine following 4 months of treatment with fluoxetine and perphenazine, 22 (73%) of the 30 patients exhibited no signs of relapse over the next 11 months (8 months of fluoxetine monotherapy followed by a taper of fluoxetine and 3 additional months of assessment). Patients who showed signs of relapse after taper of the antipsychotic were more likely to have had a longer duration of the current episode and a history of more frequent past episodes and were more likely to be younger (under the age of 30 years).

Conclusion: The data from this study suggest that a majority of patients who have major depression with psychotic features do not require treatment with antipsychotic medication for more than 4 months.

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Patients with major depression with psychotic features have greater morbidity and mortality than patients with nonpsychotic major depression.[1] In particular, relapse and recurrence have been reported to occur more frequently in patients who have major depression with psychotic features than nonpsychotic depression,[2–14] although not all studies are in agreement.[15,16] Patients who have major depression with psychotic features (when compared with nonpsychotically depressed patients) have increased use of services, greater disability, and poorer clinical course at both short-term[10,17] and longer-term follow-up.[11] In the Epidemiological Catchment Area Study, patients who had major depression with psychotic features had a greater number of attempted suicides and lifetime hospitalizations than nonpsychotic depressed patients.[18] A 25-year retrospective analysis of suicides among patients hospitalized previously for major depression demonstrated that patients who had delusions during their index episode of depression had a 5-fold increased likelihood of suicide compared with patients with nonpsychotic depression.[19]

Despite the frequent relapse and recurrence in major depression with psychotic features, there are few controlled studies of the efficacy of continuation and maintenance treatments. In a retrospective study of 52 patients who had major depression with psychotic features,[8] 29% of the first-year relapses occurred during or shortly after an antipsychotic taper while the patient was maintained on treatment with stable doses of antidepressant or lith-

ium. The mean duration of antipsychotic exposure prior to relapse was 5.0 months, and mean time to relapse after a dose reduction or discontinuation was 2.0 months. In an open-label prospective study of elderly patients who had major depression with psychotic features,[20] 8 (53.5%) of 15 electroconvulsive therapy (ECT) responders had a relapse or recurrence on nortriptyline monotherapy during the 2-year follow-up phase compared with 1 (25%) of 4 responders to nortriptyline, perphenazine, and lithium who were tapered off perphenazine treatment at 16 weeks ($p = .58$, NS).

Presently, it is the strong recommendation of the American Psychiatric Association Practice Guideline for Major Depressive Disorder in Adults[21] that major depressive disorder with psychotic features should be treated pharmacologically using an antipsychotic combined with an antidepressant, although the duration of antipsychotic treatment is not discussed. Two studies have suggested that it may not be necessary for the antipsychotic medication to be prescribed during continuation treatment. In the first study, Zanardi and colleagues[22] described good outcomes using fluvoxamine monotherapy for maintenance treatment of major depression with psychotic features. Of 25 patients selected on the basis of favorable short-term response to fluvoxamine (300 mg/day) and high risk of relapse (at least 1 previous episode), none relapsed during the 6-month follow-up, and only 5 (20%) had a single recurrence during the subsequent 2 years of maintenance phase follow-up. In a recent study in an older population, Meyers and colleagues[23] reported on 28 patients with major depression with psychotic features who received either continuation treatment with nortriptyline plus perphenazine or nortriptyline plus placebo under randomized double-blind conditions after achieving remission with ECT. The relapse frequency was nonsignificantly greater with combination therapy compared with nortriptyline monotherapy, although the combination subjects had significantly more extrapyramidal symptoms, an increased incidence of tardive dyskinesia, and a greater number of falls. Interestingly, in a study of the treatment of an acute episode of major depression with psychotic features in older adults, Mulsant and colleagues[24] found that the addition of a moderate dose of perphenazine to nortriptyline did not improve efficacy.

Given that it remains the standard of care to treat an acute episode of major depression with psychotic features using either the combination of an antidepressant and an antipsychotic or ECT,[1] clinicians are left with the question of how long to maintain the patient on treatment with the antipsychotic medication. On the one hand, the clinician must be concerned with the high morbidity and mortality associated with relapse in patients with major depression with psychotic features. On the other hand, the clinician also needs to be concerned about the risk of tardive dyskinesia developing in patients with major depression with psychotic features who are maintained for long periods of time on treatment with conventional antipsychotic medications. One might argue that, given the decreased risk of the development of tardive dyskinesia with newer atypical antipsychotic medications, these drugs should be used for maintenance treatment in psychotic depression. Unfortunately, there are no data demonstrating the efficacy of atypical antipsychotics for maintenance treatment of psychotic depression, and only 1 recently completed double-blind, placebo-controlled study demonstrating the efficacy of an atypical antipsychotic for the treatment of acute episodes of psychotic depression.[25]

The results of our prospective study help to address the question of how long a patient who has major depression with psychotic features and is successfully treated with an antidepressant and antipsychotic during the acute episode should remain on treatment with the antipsychotic medication.

METHOD

Forty patients with the diagnosis of unipolar major depression with psychotic features who were participating in a longitudinal study of the relationship between hypothalamic-pituitary-adrenal axis measures and cognition were studied after granting written informed consent and after the study was approved by an Institutional Review Board. Data were gathered from 1992 to 1997. Patients were recruited from both inpatient units and outpatient settings.

Any patient with significant medical, neurologic, or endocrinologic illness was excluded. Patients with a history of nonresponse to a selective serotonin reuptake inhibitor were not enrolled in the study. Nonresponse was defined as a lack of response to at least 6 weeks of ≥ 40 mg/day of fluoxetine, ≥ 100 mg/day of sertraline, ≥ 40 mg/day of paroxetine, or ≥ 150 mg/day of fluvoxamine (citalopram was not available at the time of the study). Both female and male patients in the age range of 18 to 65 years were studied. Only patients who had been significantly depressed for at least 4 weeks and who had a minimum score of 18 on the 21-item Hamilton Rating Scale for Depression (HAM-D) were enrolled in the study. All subjects were medication-free for at least 2 weeks prior to the study. Patients were excluded if they had received ECT in the last 6 months or had a history of alcohol or substance abuse in the last 6 months.

During the baseline period, clinical assessments were performed using the Structured Clinical Interview for DSM-III-R (SCID).[26] A series of supplemental questions for psychosis based on the Schedule for Affective Disorders and Schizophrenia (SADS)[27] were asked. Diagnoses were determined on the basis of the intake SCID interviews and assigned using Research Diagnostic Criteria (RDC)[28] and DSM-III-R schemata. All patients partici-

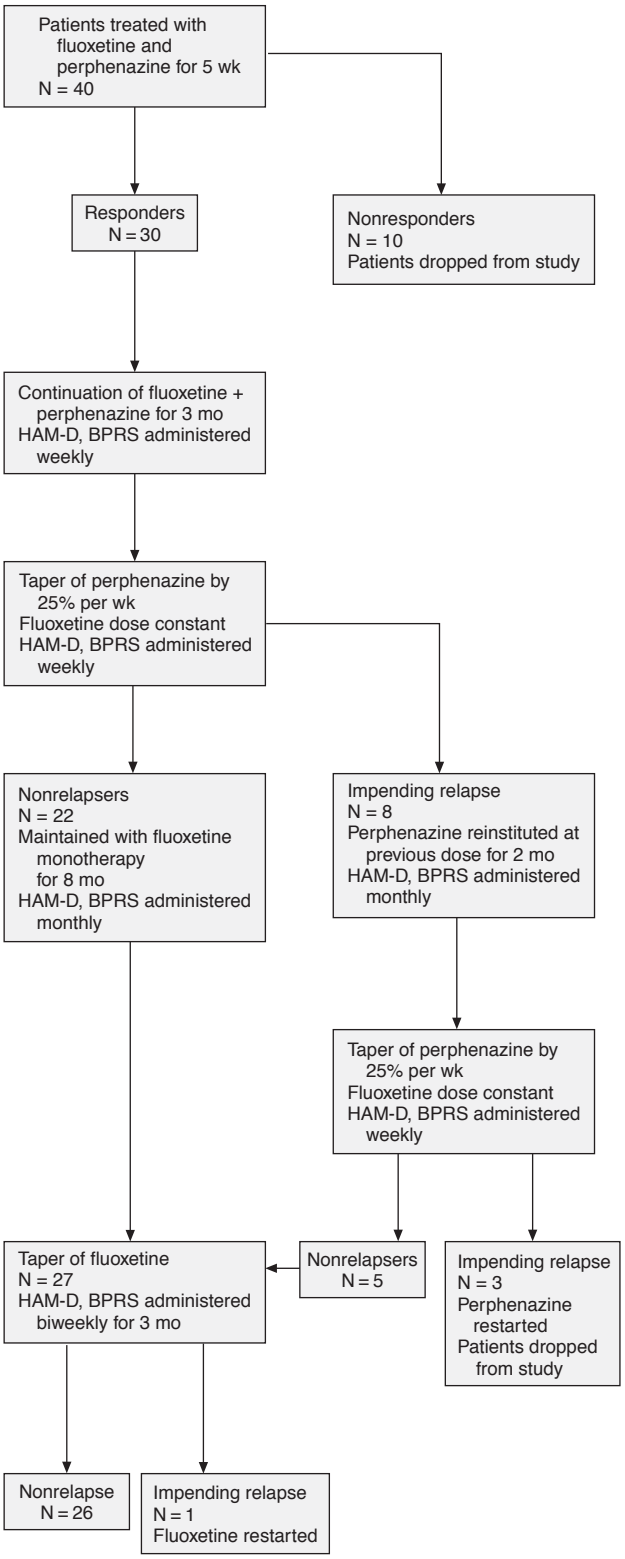
pating in the study had delusional symptoms (i.e., there were no patients whose only psychotic symptoms were hallucinations). At baseline, patients were also administered the 21-item HAM-D[29] and the Brief Psychiatric Rating Scale (BPRS).[30]

Patients were treated with the combination of fluoxetine and perphenazine. On day 2 of the study, patients were treated with 8 mg of perphenazine at bedtime and on day 4 began taking 20 mg of fluoxetine in the morning. The perphenazine dose was increased by 8 mg every 3 days as tolerated to a total daily dose of 32 mg at bedtime. The fluoxetine dose remained at 20 mg/day for 3 weeks. If there was no therapeutic response (with response defined as a 50% reduction in HAM-D and BPRS scores and a final HAM-D score less than 12) within 3 weeks, the fluoxetine dose was increased to 40 mg in the morning. If a patient did not meet response criteria by the end of 5 weeks, he or she was deemed a nonresponder and dropped from the study.

For patients who continued to meet response criteria for an additional 3 months (4 months total fluoxetine plus perphenazine treatment), the perphenazine dose was reduced each week by 25% of the total dose for 4 weeks (Figure 1). A gradual dose reduction schedule was chosen to allow for recognition of symptoms of impending relapse and to minimize discontinuation side effects. Patients remained on treatment with their current dose of fluoxetine. Patients were administered the HAM-D and BPRS on a weekly basis for the next 2 months (months 5 and 6). Impending relapse was defined as any of the following: (1) symptoms meeting DSM-IV criteria for major depressive disorder (with or without psychotic features), (2) a total score of ≥ 17 on the HAM-D, or (3) the presence of any psychotic symptoms. For patients who exhibited impending relapse, perphenazine was immediately restarted, and the patients were titrated to their previous dose within 1 week (see Figure 1). All patients were administered the HAM-D and BPRS on a monthly basis for the next 2 months (months 7 and 8). At the 8-month timepoint, an attempt was made to taper perphenazine for those patients who were still taking it using the same schedule that was used after 4 months of treatment (see Figure 1). All patients were maintained on fluoxetine treatment for 12 months and administered the HAM-D and BPRS on a monthly basis (months 9–12). Twelve months after the index episode and after 1 year of treatment with fluoxetine, patients were tapered off fluoxetine treatment (see Figure 1). Patients taking more than 20 mg/day of fluoxetine decreased their fluoxetine dose by 20 mg every 3 days. The HAM-D and BPRS were administered every other week for the next 3 months (months 12–15).

Chi-square and Student t tests were used to compare the demographic and clinical characteristics between patients who suffered a relapse and those who did not when the perphenazine was tapered.

Figure 1. Flow Chart Showing Treatment of 40 Patients With Major Depressive Disorder With Psychotic Features



Abbreviations: BPRS = Brief Psychiatric Rating Scale, HAM-D = Hamilton Rating Scale for Depression.

Table 1. Demographic and Clinical Characteristics of Patients With Psychotic Depression Who Did and Did Not Relapse After Taper of Perphenazine Following 4 Months of Treatment With Perphenazine and Fluoxetine*

	Total (N = 30)		Relapse (N = 8)		No Relapse (N = 22)		Analysis	
Variable	Mean	SD	Mean	SD	Mean	SD	t[a]	p
Age, y	42.4	11.7	29.6	2.1	47.1	10.1	–4.82	.000
Age at onset, y	38.1	11.2	26.5	2.3	42.3	10.0	–4.35	.000
Duration of current episode, mo	7.5	2.0	8.9	2.4	7.0	1.7	3.39	.024
Duration of illness, mo	49.1	36.9	37.6	16.6	53.3	41.5	–1.03	NS
Number of previous episodes of psychotic depression	1.6	0.9	2.3	0.7	1.4	0.9	2.48	.019
Duration between episodes of psychotic depression, mo	36.4	14.5[b]	33.8	15.0	37.6	14.6[c]	0.61[d]	NS
Baseline HAM-D score (prior to treatment)	29.0	6.2	31.0	6.4	28.3	6.1	1.07	NS
Baseline BPRS score (prior to treatment)	43.4	5.6	42.6	4.7	43.7	6.0	–0.47	NS
Remission HAM-D score (at 5 weeks)	6.7	2.2	7.0	1.3	6.5	2.4	0.50	NS
Remission BPRS score (at 5 weeks)	24.3	2.5	24.0	2.4	24.4	2.6	–0.34	NS

*Gender distribution was as follows: total:18 women, 12 men; relapse: 5 women, 3 men; no relapse: 13 women, 9 men. Statistical analysis was as follows: $\chi^2 = .028$, df = 1, p = NS.
[a]df = 28 unless otherwise noted.
[b]N = 26 (4 subjects had no prior episodes).
[c]N = 18 (4 subjects had no prior episodes).
[d]df = 24.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, HAM-D = Hamilton Rating Scale for Depression.

RESULTS

Forty patients with major depression with psychotic features (24 women, 16 men) were enrolled in the study at baseline. At entry into the study, 25 were inpatients and 15 were outpatients. Patients ranged in age from 27 to 64 years (mean ± SD age = 40.7 ± 13.1 years). At baseline, mean ± SD HAM-D scores were 28.7 ± 6.1, and mean ± SD BPRS scores were 43.3 ± 8.9. After 5 weeks of treatment with fluoxetine and perphenazine, 30 (75%) of the patients with psychotic depression achieved remission criteria (50% reduction in HAM-D and BPRS scores, a final HAM-D score less than 12, and no psychotic symptoms) and entered the continuation and maintenance phase of the study (see Figure 1). In the responders, the mean ± SD dose of fluoxetine was 32.0 ± 10.0 mg/day and the mean ± SD dose of perphenazine was 30.7 ± 3.7 mg/day. There were no significant differences in mean fluoxetine and mean perphenazine doses between responders and nonresponders.

No patients relapsed during the next 3 months of treatment with fluoxetine and perphenazine. After taper of the perphenazine (after 4 months of treatment with fluoxetine and perphenazine), 22 (73%) of the 30 patients remained well and did not exhibit signs of relapse over the next 11 months. Eight (27%) of the 30 patients exhibited signs of an impending relapse within 2 months of the perphenazine taper (see Figure 1). Five patients exhibited psychotic symptoms only, 2 patients exhibited psychotic symptoms and a total HAM-D score ≥ 17, and 1 patient exhibited a total HAM-D score ≥ 17 without psychotic symptoms. None of the patients required hospitalization or made a suicide attempt. These 8 patients were placed back on perphenazine treatment (added to the fluoxetine) for a minimum of an additional 2 months of combined treatment. All 8 patients had a remission of their symptoms with reinstitution of perphenazine. At the 8-month timepoint, 5 of these 8 patients were able to taper off perphenazine without signs or symptoms of impending relapse (see Figure 1).

At the 1-year timepoint, 27 patients remained in remission on fluoxetine monotherapy. After taper of the fluoxetine at 1 year, 1 of the 27 patients (a patient who had required reinstitution of perphenazine at month 5) showed signs of impending relapse over the next 3 months and required reinstitution of fluoxetine (see Figure 1).

Side effects reported by patients during the acute phase of treatment (first 5 weeks of treatment) included dry mouth (13 [33%]), blurry vision (8 [20%]), constipation (7 [18%]), orthostatic hypotension (4 [10%]), and dizziness (4 [10%]). One patient (3%) developed headache, and 1 patient (3%) complained of nausea. Eight patients (20%) experienced mild-to-moderate tremor or rigidity. No patients developed akathisia or tardive dyskinesia. There were no significant differences between responders and nonresponders on frequency of side effects during the acute phase of treatment. During the next 3 months of treatment, side effects diminished. After 4 months of combined fluoxetine and perphenazine treatment, 1 patient (3%) complained of dry mouth; 1 (3%), of blurry vision; and 2 (5%), of dizziness. Two patients (5%) had orthostatic hypotension, and 3 (8%) still experienced mild-to-moderate tremor or rigidity. No patients developed tardive dyskinesia.

The clinical characteristics of the patients who relapsed and those who did not when perphenazine was tapered are shown in Table 1. Patients who relapsed were more likely to have had a longer duration of the current episode, a greater number of previous episodes, and an earlier age at onset and were more likely to be younger (under the age

of 30 years). There were no significant differences between patients who relapsed and those who did not on dose of perphenazine, dose of fluoxetine, side effects, duration of illness, mean time between episodes of psychotic depression, gender, or baseline HAM-D, baseline BPRS, HAM-D or BPRS scores prior to antipsychotic taper.

DISCUSSION

Consistent with previous studies,[31] 75% of patients with major depression with psychotic features responded to combination treatment with fluoxetine and perphenazine for the acute episode. Furthermore, the data from this study suggest that a majority of patients with major depression with psychotic features do not require treatment with antipsychotic medication for more than 4 months. Seventy-three percent of patients with major depression with psychotic features treated with the combination of fluoxetine and perphenazine for 4 months were tapered off perphenazine treatment at 4 months without relapse over the next 11 months. Of the 27% of patients who needed to be maintained on perphenazine treatment for more than 4 months, 62.5% were able to be tapered off perphenazine treatment after 8 months of combined therapy and remained well without treatment with the antipsychotic during the remaining 7-month follow-up period. These findings are particularly important in light of recent studies that reported a 43% incidence of tardive dyskinesia in geriatric patients with major depression with psychotic features who were treated with perphenazine plus nortriptyline for 6 months.[23]

Our observation of no relapses in the first 4 months of continuation treatment with fluoxetine and perphenazine in major depression with psychotic features is similar to the 0% relapse rate observed over 6 months with fluvoxamine monotherapy[22] and the 13.4% relapse rate in the 1-year naturalistic follow-up for patients taking stable doses of antidepressant plus antipsychotic.[8] The relapse rate is lower than the 33% relapse rate over 6 months of nortriptyline and perphenazine therapy[23] and the 53% relapse/recurrence rate over 2 years of nortriptyline monotherapy[20] observed in geriatric patients with major depression with psychotic features. The higher rate of relapse observed in these 2 studies may be due in part both to the fact that the remission of the acute episode of major depression with psychotic features was achieved using ECT and to the substantially older age of the sample. Previous studies of patients with major depression with psychotic features have suggested a high post-ECT relapse rate,[5,7] although not all studies are in agreement.[32] Although the 2 studies of geriatric patients with psychotic depression[20,23] excluded patients who were known nonresponders to nortriptyline, they did not know whether the patients would be nortriptyline responders after ECT. In contrast, in the present study, as well as a few previous studies,[8,20,22] patients remained on treatment with the same medications that had successfully treated the acute episode of major depression with psychotic features. This may have resulted in a lower rate of relapse/recurrence during continuation and maintenance treatment.

In our study, 27% of the patients showed signs and symptoms of impending relapse after taper of perphenazine following 4 months of treatment with the combination of fluoxetine and perphenazine. This observation is consistent with the naturalistic study by Aronson and colleagues[8] that found that 29% of relapses in patients with major depression with psychotic features during the first year after the index episode occurred during or shortly after the tapering of the antipsychotic medication. However, there are several important differences between the present study and the naturalistic study by Aronson and colleagues. The study by Aronson et al. included patients whose medications were stopped secondary to noncompliance or who may have had their medications tapered while still symptomatic, as well as the lack of certainty in the retrospective chart review that the patients were in remission from the acute episode.

The rate of impending relapse in the present study (27%) after antipsychotic taper and treatment with fluoxetine monotherapy (after 4 months of combined treatment) is higher than the 0% rate reported by Zanardi and colleagues[22] with fluvoxamine monotherapy for 6 months. In the present study, when the patients exhibiting signs and symptoms of impending relapse received further treatment with combined perphenazine and fluoxetine treatment for an additional 4 months (8 months total), 27 (90%) of the 30 patients were able to taper off perphenazine treatment and remain well on fluoxetine monotherapy for the next 4 months (12 months after the index episode), and 26 (87%) of the 30 did well taking no medication for the next 3 months (15 months after the index episode). These rates of relapse/recurrence are comparable to those in the study by Zanardi and colleagues,[22] in which 22 (88%) of 25 patients remained well on fluvoxamine monotherapy 15 months after the index episode, and the study of Flint and Rifat,[20] in which 3 (75%) of 4 elderly patients with major depression with psychotic features remained well over a 2-year period after responding to the combination of nortriptyline and perphenazine and taper of the perphenazine after 16 weeks.

Taken together, published studies of continuation and maintenance treatment of major depression with psychotic features appear to suggest differing strategies. Two studies have suggested that an antipsychotic medication does not provide additional benefit when added to an antidepressant for continuation treatment in young[22] and older[23] patients and may increase morbidity secondary to side effects.[23] Other studies suggest a higher rate of relapse after discontinuation of the antipsychotic medication.[8] The present study suggests that, for the majority of patients

with major depression with psychotic features, the antipsychotic can be tapered after 4 months of combined antidepressant and antipsychotic treatment without relapse on antidepressant monotherapy. However, in the present study, there did exist a significant minority of patients who required longer treatment with the antipsychotic. In particular, those patients with a longer duration of the current episode, a history of previous episodes, and an earlier age at onset of illness and who were under the age of 30 years during the current episode were more likely to exhibit signs of relapse during the antipsychotic taper. Previous prospective[22,23] and retrospective[8] studies have found no particular risk factors for relapse in major depression with psychotic features, including current age, age at onset of illness, duration of illness, number of previous episodes, and gender,[22] although the sample sizes did not always permit systematic assessment for specific risk factors.[23]

The use of atypical antipsychotics for maintenance treatment of major depression with psychotic features remains an open question. A recent study suggests that the combination of olanzapine and fluoxetine was significantly more effective than placebo for treatment of the acute episode of major depression with psychotic features.[25] Future studies appear warranted to determine the efficacy and safety of atypical antipsychotics for the maintenance treatment of major depression with psychotic features. In addition, a comparison of the side effects of atypical antipsychotic medications (e.g., weight gain, hyperprolactinemia) with the side effects of typical antipsychotic medications (e.g., tardive dyskinesia) during the long-term management of patients with major depression with psychotic features would be of great importance.

In summary, the majority of patients with major depressive disorder with psychotic features remained stable after taper of the antipsychotic medication following 4 months of combined antidepressant and antipsychotic treatment. Given the open nature of this study, our findings must be considered preliminary. However, given the serious morbidity and mortality associated with major depressive disorder with psychotic features and the risk of tardive dyskinesia from long-term treatment with typical antipsychotic medications, further studies appear warranted to determine the appropriate length of time of antipsychotic therapy in major depressive disorder with psychotic features.

Drug names: citalopram (Celexa), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), nortriptyline (Aventyl and others), paroxetine (Paxil), perphenazine (Trilafon and others), sertraline (Zoloft).

Disclosure of off-label usage: The authors of this article have determined that, to the best their knowledge, fluoxetine, fluvoxamine, lithium, nortriptyline, paroxetine, perphenazine, and sertraline are not approved by the U.S. Food and Drug Administration for the treatment of major depression with psychotic features.

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