Olanzapine in Refractory Schizophrenia After Failure of Typical or Atypical Antipsychotic Treatment: An Open-Label Switch Study

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Background: When patients with schizophrenia fail to respond to an atypical antipsychotic, they are sometimes switched to another atypical compound. However, the benefits of such a switch have not been adequately studied. We present an open-label prospective 14-week trial with olanzapine in patients with schizophrenia and schizoaffective disorder whose treatment resistance to clozapine, olanzapine, risperidone, and haloperidol had been determined prospectively.

Method: The subjects were 45 inpatients with DSM-IV schizophrenia or schizoaffective disorder who failed to respond to treatment during a 14-week double-blind trial comparing clozapine, olanzapine, risperidone, and haloperidol. The patients had been selected for participation in the double-blind trial on the basis of a history of suboptimal response to previous treatment. Inclusion criteria for the present study were (1) completion of at least 8 weeks of the 14-week double-blind trial, (2) treatment resistance to 1 of the 4 compounds tested as evidenced by a decrease in total PANSS score of less than 20%, and (3) total PANSS score ≥ 60. Subjects were cross-titrated from the previous double-blind treatment to open-label olanzapine, 10 to 40 mg/day, and were treated for 14 weeks without concomitant psychotropic medication. Patients were evaluated weekly with the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impressions scale, and Extrapyramidal Symptom Rating Scale.

Results: Open-label olanzapine treatment yielded no significant change in PANSS total, positive subscale, or negative subscale scores. There was a significant improvement for the PANSS cognitive factor (mean ± SD change = 0.92 ± 2.27; F = 7.5, df = 1,44; p < .009) and a marginally significant worsening for the excitement factor (mean change = –1.36 ± 4.64; F = 4.0, df = 1,44; p < .053). Nine percent of patients (N = 4) were classified as responders using the Kane et al. criteria. The worsening in the PANSS excitement factor was significantly associated with the length of illness (t = –2.10, df = 44, p < .04). There was a nonsignificant decrease in extrapyramidal side effects and a significant increase in weight (mean increase = 3.5 ± 6.2 kg [7.8 ± 13.8 lb]; F = 5.29, df = 1,42; p < .0005).

Conclusion: Our results indicate that in patients with treatment-resistant schizophrenia, a switch to olanzapine after treatment failure with an atypical agent or haloperidol may not reduce psychopathology in general, but may improve symptoms related to cognitive function.

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Whether patients with schizophrenia who have failed to respond to an atypical antipsychotic benefit from a switch to another atypical compound has not been adequately studied. Most switch studies are retrospective or conducted in medication-responsive patients. In addition, whether olanzapine is helpful in patients who are treatment-resistant to other atypicals has not been fully examined. Sanders and Mossman[1] reported

an open 12-week olanzapine trial with 16 patients, 13 of whom had previously received either olanzapine, up to 20 mg/day, or risperidone. Only 2 patients showed improvement. A number of patients developed mild-to-florid mania and an increase in positive symptoms. Given that the atypical antipsychotics show differences in their respective receptor affinity profiles, we were interested to examine whether patients who had prospectively failed to respond to 1 of the 3 atypical antipsychotics clozapine, risperidone, or olanzapine, or to the typical antipsychotic haloperidol,[2] would show a response when switched to olanzapine, 10 mg/day, and then titrated to 20 mg/day. Olanzapine was chosen because the original hypothesis in our double-blind study stated that clozapine and olanzapine would show superior efficacy over risperidone and haloperidol in patients with treatment-refractory schizophrenia. In addition, we were interested to know whether a compound with a molecular structure similar to that of clozapine could have beneficial effects in nonresponders. We present the findings of an open-label prospective 14-week trial with olanzapine in patients with schizophrenia or schizoaffective disorder whose treatment resistance to clozapine, olanzapine, risperidone, or haloperidol was prospectively established during a 14-week double-blind trial immediately preceding the current study.

METHOD

The subjects were 45 inpatients with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder who had failed to respond to treatment during a double-blind trial that compared clozapine, olanzapine, risperidone, and haloperidol.[2] To be eligible for the double-blind trial, subjects had to have a history of suboptimal response to previous antipsychotic treatment. Suboptimal response was defined as persistence of positive symptoms after at least 1 adequate trial with a typical antipsychotic and poor level of functioning over the past 2 years. Patients with a history of unambiguous prior failure to respond to clozapine, olanzapine, or risperidone were not included. The 14-week double-blind trial enrolled 157 subjects from 4 state psychiatric hospitals; details are described elsewhere.[2] The eligibility criteria for the present open-label crossover olanzapine study were (1) completion of at least 8 weeks of the 14-week double-blind trial, (2) treatment resistance to 1 of the 4 compounds tested as evidenced by a decrease in total Positive and Negative Syndrome Scale (PANSS)[3] score of less than 20%, and (3) total PANSS score ≥ 60. Patients who had been randomly assigned to olanzapine during the double-blind phase had to meet an additional criterion for ethical reasons: they could not have deteriorated by more than 10% on total PANSS score from baseline. Seventy-eight patients met these criteria; 45 of these patients gave written consent to participate in the open-label study and were enrolled immediately after having reached their endpoint in the double-blind study.

After consent to participate in the current trial was obtained from subjects, the dose of the double-blind medication was gradually tapered to a specified daily dose prior to the start of the cross-taper with olanzapine as follows: 150 to 300 mg of clozapine, 10 mg of olanzapine, 4 mg of risperidone, and 10 mg of haloperidol. The duration of the taper depended on the final dose achieved during the double-blind phase and lasted approximately 2 weeks.

Olanzapine, 10 mg/day, was then initiated and increased to 20 mg/day while the double-blind medication dose was gradually reduced to zero over a 10-day period. The olanzapine dose was first fixed at 20 mg/day for 4 weeks, then clinically titrated upward in 5-mg steps every 2 weeks to a maximum dose of 40 mg/day if there was lack of improvement (improvement was defined as a drop of at least 5 points between current and previous [most recent] PANSS score) and if side effects permitted such dose increases. A continuous lack of improvement, therefore, resulted in a dose of 40 mg/day in the last 4 weeks of the trial. No concomitant psychotropic medication was used except benztropine mesylate for extrapyramidal symptoms and chloral hydrate and lorazepam on an as-needed basis for agitation. All evaluations were conducted weekly by trained clinical raters who had reached intraclass correlation coefficients of 0.80 or higher on the PANSS prior to the study. Measures included the PANSS,[3] Clinical Global Impressions scale (CGI),[4] and Extrapyramidal Symptom Rating Scale (ESRS).[5] White blood cell count (WBC) was obtained weekly when the dose of olanzapine was raised over 20 mg. Weight was measured at baseline and endpoint.

The main outcome measures were the PANSS total score; the positive, negative, and general psychopathology subscale scores; and the 5 PANSS factor scores.[6] PANSS factor scores were the sum of item scores of the respective factors found in the original factor analysis by Lindenmayer et al.[6] Improvement was examined by using analysis of covariance both for absolute point improvement (raw score difference between baseline and endpoint measures) and for percentage improvement using baseline scores as a covariate. We used the last observation carried forward, basing the present analysis on an intent-to-treat strategy. Repeated-measures analyses of variance were used to investigate improvement over time within a study group on the basis of the preswitch medication given during the double-blind study. All patients included in the analysis received at least 3 weeks of open-label treatment. Categorical improvement was calculated by using the Kane et al. criteria[7]: a 20% drop in Brief Psychiatric Rating Scale (BPRS)[8] score (extracted from the PANSS) plus a final BPRS score of 35 or less or a final CGI score of 3 or less. Correlates of improvement were examined by using regression analysis for age, gender,

Table 1. Comparison of Eligible Patients From the Previous Double-Blind Trial Who Crossed Over (N = 45) and Did Not Cross Over (N = 33) at End of Double-Blind Treatment[a]

Variable	Crossed Over	Did Not Cross Over
Age, y	42.2 (8.46)	44.1 (8.82)
Duration of illness, y	21.6 (8.02)	21.1 (8.37)
PANSS score[b]		
Total	90.3 (12.4)	90.2 (16.32)
Positive	18.4 (3.71)	18.8 (6.00)
Negative	17.6 (5.41)	17.5 (5.34)
Excitement	9.7 (4.24)	10.4 (4.95)
Cognitive	15.8 (3.78)	15.9 (3.59)
Depression/anxiety	9.7 (3.56)	8.7 (2.38)
ESRS score[b]		
Total	29.5 (19.50)	23.2 (14.95)
Akathisia	0.7 (1.01)	0.4 (0.64)

[a]Values expressed as mean (SD). Comparisons between groups on all measures are nonsignificant. Abbreviations: ESRS = Extrapyramidal Symptom Rating Scale, PANSS = Positive and Negative Syndrome Scale.
[b]Scores at end of double-blind treatment.

duration of illness, and the dose of olanzapine in the last week of treatment.

RESULTS

Forty-five inpatients (7 women and 38 men) were enrolled in the study. Patients' mean age was 42.2 ± 8.5 years, and mean total PANSS score at baseline was 90.3 ± 12.4. Mean duration of illness was 21.6 ± 8.0 years. Eleven patients who crossed over to olanzapine treatment had experienced treatment failure with clozapine; 11, with olanzapine; 14, with risperidone; and 9, with haloperidol. Thirty patients completed the full open-label 14-week trial. Three patients dropped out because of clinical deterioration, 1 dropped out because of low WBC (olanzapine), 3 were dropped from the study because of protocol violations, 4 withdrew consent, 2 were discharged, and 2 were discontinued for administrative reasons. No patient dropped out during the cross-titration phase. The mean daily olanzapine dose in the last week of treatment was 30.5 ± 9.8 mg. We compared the patients from the double-blind study who were eligible for the trial but did not elect to enroll (N = 33) with those who were enrolled in the trial on all baseline characteristics prior to the start of the preceding double-blind phase. The 2 groups were comparable on all demographic and clinical variables (Table 1).

Olanzapine treatment yielded no significant change in PANSS total score (mean change = 0.2 ± 13.8), positive subscale score (mean change = –0.2 ± 4.8), or negative subscale score (mean change = –0.5 ± 4.5). The statistical effect sizes were 0.01, 0.04, and 0.11 (symptom increase) for the PANSS total and positive and negative subscale scores, respectively. However, when we investigated change in specific symptom domains using the 5 PANSS factors, we found a significant improvement in the PANSS cognitive factor (mean change = 0.92 ± 2.27; $F = 7.5$, df = 1,44; $p < .009$) and a marginally significant worsening in the PANSS excitement factor (mean change = –1.36 ± 4.64; $F = 4.0$, df = 1,44; $p < .053$). PANSS positive, negative, and depression/anxiety factor scores were unchanged (Table 2). Higher olanzapine dosages (> 20 mg/day) were associated with numerically less improvement in all outcome measures. Duration of illness and worsening in the PANSS excitement factor were significantly associated ($t = –2.10$, df = 44, $p < .04$). No other significant associations with demographic variables were found. We also examined the response of patients according to the compound they had been taking during the preceding double-blind study. The 4 groups did not differ in degree of response during the present trial ($F = 0.41$, df = 3,44; $p = .71$). The interpretation of this result is limited by the small number of subjects in each group. Using the Kane et al. categorical response criteria, only 4 patients (9%) could be considered responders. Two of these patients had been switched from risperidone, 1 had been switched from clozapine, and 1 had been switched from haloperidol.

Table 2. Change in PANSS Factor and Extrapyramidal Symptom Rating Scale (ESRS) Scores After 14 Weeks of Olanzapine Treatment[a]

Variable	Mean	SD	F[b]	p[c]
PANSS factor				
Positive	0.30	3.22	0.4	NS
Negative	0.26	4.59	0.2	NS
Excitement	–1.36	4.64	4.0	< .053
Cognitive	0.92	2.27	7.5	< .009
Depression/anxiety	–0.15	3.45	0.1	NS
ESRS	2.3	12.8	1.4	NS

[a]Negative values indicate worsening. Abbreviation: PANSS = Positive and Negative Syndrome Scale.
[b]df = 1,44.
[c]Time effect; repeated-measures analysis of variance.

Extrapyramidal symptoms showed a nonsignificant decrease (mean change in ESRS score = 2.3 ± 12.8). When the change in the level of akathisia was analyzed separately (score at end of double-blind phase minus score at end of open-label trial), a significant decrease was found for the total group ($F = 3.98$, df = 3,41; $p < .01$). Post hoc analyses (Tukey Studentized range test for pairwise comparisons) of change in akathisia levels between the 4 groups of patients on the basis of medication used in the double-blind trial (clozapine, haloperidol, olanzapine, or risperidone) showed that the subjects who had been on haloperidol treatment showed significantly greater improvement ($p < .05$) in akathisia than the patients who had been on clozapine treatment. There was a significant mean increase in weight of 3.5 ± 6.2 kg (7.8 ± 13.8 lb) during the duration of the trial ($F = 5.29$, df = 1,42; $p < .0005$), as well as an effect on the weight change by the mean dose in the last week of treatment

($F = 6.3$, $df = 1,42$; $p < .01$) and by olanzapine doses over 20 mg/day ($F = 3.9$, $df = 1,42$; $p < .05$).

DISCUSSION

Forty-five patients with schizophrenia or schizoaffective disorder refractory to a prospective 14-week double-blind trial with either an atypical antipsychotic (clozapine, olanzapine, or risperidone) or a typical antipsychotic (haloperidol) were switched to open-label olanzapine, which yielded no further change in PANSS total, positive, or negative scores after 14 weeks of olanzapine treatment. Only 9% of the sample fulfilled the criteria for response. Our results are similar to those of the Conley et al. study,[9] which found a response rate of 7% in a treatment-refractory sample after olanzapine treatment. Both studies used prospective determination of treatment failure.

This lack of change is in contrast to the results of our open-enrollment olanzapine study of patients with failure to respond to atypicals who had not been prospectively treated in a double-blind fashion with one of the atypicals.[10] In that study, we found a significant, although small, improvement in total PANSS score. The lack of effect found in the present study is probably due to the strict and prospective determination of treatment resistance. If treatment resistance is defined prospectively, finding a response in an additional treatment trial is unlikely.

When separate domains of psychopathology were examined using the PANSS factors, significant improvement was found in the PANSS cognitive factor, and marginally significant worsening was found in the excitement factor. The symptoms that make up the cognitive factor are poor attention, conceptual disorganization, difficulty in abstract thinking, mannerisms and posturing, and disorientation. We found a significant improvement in the cognitive factor in the present study as well as in our open-enrollment olanzapine study.[10] These findings may point to an ameliorative effect of olanzapine on impaired cognitive functions. Studies with olanzapine have found significant ameliorative effects on some of these cognitive functions, particularly on attention, executive function, and spatial and new learning skills.[11] Our clinical measure of cognitive symptoms cannot be equated with cognitive measures derived from neurocognitive testing. However, such testing was implemented in the double-blind study preceding the current open-label olanzapine trial; these tests demonstrated improvements of executive functioning and attention with olanzapine.[12]

The group as a whole showed a trend toward deterioration in terms of the excitement factor, which consists of excitement, hostility, poor impulse control, and tension. We do not think that this effect is related to psychotic worsening, as there was only a minimal concomitant increase in positive symptoms. Furthermore, our patients were carefully cross-tapered from their previous antipsychotic medication to olanzapine to avoid an abrupt reduction in dopamine D_2 blockade, which could have led to rapid psychotic decompensation and increased excitement. Akathisia is also an unlikely cause for the worsening of excitement symptoms, given that our patients improved significantly in terms of akathisia. We found a significant deterioration in the excitement factor in our open-enrollment olanzapine study[10] as well, pointing to a possible activating effect of long-term treatment with olanzapine in treatment-refractory patients. Sanders and Mossman[1] also found an increase in excitement symptoms in a similar cohort of treatment-refractory patients treated with olanzapine. However, in light of the fact that we carried out multiple tests, this finding needs to be confirmed by additional studies.

There was an association of higher olanzapine dose with worsening in most symptom domains. This finding was surprising and dissimilar to case report findings with high-dose olanzapine in patients with schizophrenia.[13] This observation most likely reflects the instruction to the study psychiatrists to raise the olanzapine dose in the absence of a reduction of the total PANSS values. Our design does not allow us to draw generalizable conclusions about dose-response relationships. This question should be further explored with a fixed-dose/response design. Demographic correlates of improvement were generally nonsignificant. The only positive finding was an association of length of illness with worsening of excitement symptoms.

Even at a mean dosage higher than the maximum recommended dose of 20 mg/day, olanzapine was associated with a numerical improvement of extrapyramidal side effects. This improvement did not reach statistical significance for any extrapyramidal side effects except akathisia. There was superior improvement in akathisia in patients who had been on haloperidol treatment during the double-blind phase. There was a significant weight gain over the 14-week duration of the trial, which was dose related. This weight gain has been noted by others.[14] The relationship between dose and weight gain indicated that patients taking doses lower than 20 mg/day gained more weight than patients taking higher doses. In accordance with study instructions, patients who showed improvement or lack of worsening did not have their dose increased over 20 mg/day, yet these patients gained more weight than those taking doses greater than 20 mg/day. We conclude, therefore, that patients who showed some improvement on olanzapine treatment were taking lower doses and showed more weight gain. In a related observation, Czobor et al.[15] report a significant positive relationship between improvement and weight gain in the patients assigned to olanzapine or clozapine in the preceding double-blind study.

Limitations of our study include the open-label design, the lack of a control group, and the small sample size. The exposure to well-defined, prospective previous failed trials with atypical antipsychotics and the adequate length

of the present trial may have helped to guard against a bias due to the lack of a control group. However, our limited sample size did not provide adequate power for a subanalysis to explore the characteristics of the responders. Also, our study does not shed light on the question of whether patients who failed to respond to olanzapine or risperidone would have responded better if switched to clozapine. Our results, however, can be helpful in the context of switching treatment-resistant patients from one atypical compound to another atypical compound. While the more typical switch may be from olanzapine to clozapine, there are situations where patients with a history of nonresponse have already experienced a failure on treatment with clozapine or another atypical compound and clinicians are considering a second atypical trial. It appears that a trial with olanzapine at that point may have some merit in patients whose psychopathology involves primarily the symptoms that make up the cognitive PANSS factor (enumerated above). In other patients, olanzapine is likely to have only limited effects at that point; an augmentation strategy directed at the specific nonresponding symptom domain may be a more promising treatment alternative for such patients.

Drug names: benztropine (Cogentin and others), clozapine (Clozaril and others), haloperidol (Haldol and others), lorazepam (Ativan and others), olanzapine (Zyprexa), risperidone (Risperdal).

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