Switching From Clozapine to Olanzapine in Treatment-Refractory Schizophrenia: Safety, Clinical Efficacy, and Predictors of Response

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Background: In our experience, many of our schizophrenic patients treated with clozapine request the newer atypical antipsychotic agents in order to eliminate the weekly blood monitoring. However, there are few guidelines available to clinicians interested in switching patients successfully treated with clozapine to olanzapine.

Method: The goal of this study was to collect preliminary data on the safety, clinical effectiveness, and predictors of response of switching clozapine patients to olanzapine. In an open trial, 19 patients receiving clozapine were switched to olanzapine.

Results: Eight (42%) of 19 patients were considered responders. Seven patients decompensated seriously enough to require hospitalization. All 7 of these patients were restabilized on clozapine treatment in the hospital, and olanzapine was discontinued. In an additional 4 patients, clinical status worsened, and clozapine doses were titrated upwards and olanzapine was slowly discontinued. Overall, mean total Brief Psychiatric Rating Scale (BPRS) scores increased significantly from baseline to final assessment ($p = .02$). Responders had been treated for a significantly shorter period of time with clozapine prior to the switch compared to nonresponders ($p = .04$) and were receiving a lower dose of clozapine ($p = .05$). The final olanzapine dose did not differ between responders and nonresponders. All responders have remained on olanzapine treatment and are stable.

Conclusion: In this open trial, the crossover from clozapine to olanzapine was generally well tolerated and resulted in a successful transition for 8 of the 19 patients. However, mean scores on the total BPRS and negative symptom and depressive symptom subscales significantly increased. Caution must be taken in determining which patients may benefit from the switch to olanzapine because of the risk of decompensation and hospitalization. Because this was an open trial, these findings require replication in a controlled trial.

(J Clin Psychiatry 1998;59:585–588)

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Clozapine, an atypical antipsychotic medication, was effective in 30% of treatment-refractory schizophrenia patients at 6 weeks in a controlled trial and in up to 60% at 6 months in uncontrolled studies.[1,2] Clozapine also produces substantially fewer extrapyramidal side effects compared with conventional antipsychotic agents, possibly owing to clozapine's lower occupancy of dopamine receptors in the nigrostriatal pathways at therapeutic doses. As a result, clozapine is often effective for schizophrenic patients who respond poorly to conventional agents or are unable to tolerate side effects such as akathisia or parkinsonian symptoms.

Several atypical antipsychotic agents have been developed, and 3 are currently available in the United States. Recent evidence suggests that olanzapine, an atypical antipsychotic agent that blocks dopamine D_2 and serotonin 5-HT_2 receptors, is at least as effective for positive symptoms and more effective for negative symptoms while producing fewer extrapyramidal side effects compared with haloperidol.[3–5] Olanzapine has a pharmacologic profile of activity similar to that of clozapine, but without significant risk of seizures or agranulocytosis.[5,6] It is not known if the similar patterns of receptor activity confer a similar pattern of clinical response, such that efficacy of clozapine in an individual patient might predict efficacy with olanzapine.

Clozapine, although effective in the treatment refractory population, is not without side effects, which include seizures, sedation, weight gain, orthostatic hypotension, and sialorrhea. Weekly white blood cell monitoring required for detection of agranulocytosis may present compliance difficulties. Because of these side effects, patients and clinicians are often hopeful that newly released atypical antipsychotic agents will be as effective as clozapine without the risk of agranulocytosis. In our experience, many of our patients request the newer agents in order to eliminate the weekly blood monitoring. However, there are few guidelines available to clinicians interested in

switching patients successfully treated with clozapine to olanzapine. The goal of this open clinical trial was to collect preliminary data on the safety, clinical effectiveness, and predictors of response of switching clozapine patients to olanzapine.

METHOD

The study was conducted in the outpatient clinic of an urban mental health center. Criteria for participation were a minimum of 1 year of treatment with clozapine, diagnosis of chronic schizophrenia or schizoaffective disorder, any subtype, and the desire to attempt a switch to olanzapine based on patient request or clinician recommendation. Diagnosis was confirmed by the treating clinician, chart review, and the research psychiatrist using DSM-IV criteria. All patients provided written informed consent.

The Brief Psychiatric Rating Scale (BPRS)[7] was completed at baseline while patients were receiving a stable dose of clozapine. Olanzapine was started at 5 mg/day and titrated by 2.5 to 5 mg weekly to a maximum of 30 mg/day by the treating psychiatrist on the basis of clinical response. After the first week, clozapine doses were gradually decreased by increments of 25 to 50 mg per week, based on clinical status and as determined by the treating psychiatrist. The BPRS was repeated 2 to 4 weeks after clozapine was discontinued or at the time of clinical decompensation requiring hospitalization or an increase in clozapine. When ratings were not obtained at the time of psychiatric hospitalization (N = 4), final BPRS scores were obtained retrospectively by chart review and clinician interview by a research psychiatrist.

The criteria for response were successful discontinuation of clozapine and stable clinical status on olanzapine treatment alone for at least 2 weeks. Paired t tests were performed for the entire sample comparing baseline and end of study values for the BPRS total score and for psychotic (conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content), negative (emotional withdrawal, motor retardation, and blunted affect), and depressive (somatic concern, anxiety, guilt feelings, and depressive mood) symptom subscale scores of the BPRS.

Responders and nonresponders were compared at baseline and at final assessment according to BPRS total score and subscale (psychotic, negative, depression) scores, years treated with clozapine, initial dose of clozapine at the time of the study, final olanzapine dose, age, and duration of clozapine taper (in weeks) using unpaired t tests. Unpaired t tests were also used to compare groups according to the use of mood stabilizers (lithium, valproate) and antidepressants (fluoxetine, sertraline, paroxetine) on baseline and final BPRS total and subscale scores. Olanzapine responders and nonresponders were compared according to a previous history of resistance or intolerance to conventional neuroleptics by the Fisher exact test. All comparisons are 2-tailed.

RESULTS

Of 100 patients in the clozapine clinic, 19 met the inclusionary criteria and consented to participate. Ten were diagnosed with schizophrenia and 9 with schizoaffective disorder. Thirteen of the 19 patients requested a trial of olanzapine, and for the remaining 6 patients, a trial of olanzapine was recommended by the treating psychiatrist for the following reasons: noncompliance with clozapine (N = 1), continued psychotic or disorganized symptoms (N = 2), and clozapine side effects (N = 3). Nine (47%) of the patients were women. The mean ± SD age was 42.4 ± 9.1 years (range, 27–58). The mean ± SD dose of clozapine at baseline was 372.4 ± 159.8 mg/day, and the mean final dose of olanzapine was 17.1 ± 6.3 mg/day.

Overall, the mean ± SD total BPRS scores increased significantly from baseline to final assessment (36.6 ± 11.7 vs. 46.6 ± 11.6; $t = 2.60$, $df = 18$, $p = .02$). Eight (42%) of 19 patients were considered responders. Seven patients decompensated seriously enough to require hospitalization. All 7 of these patients were restabilized on clozapine treatment in the hospital, and olanzapine was discontinued. In an additional 4 patients, clinical status worsened, and clozapine doses were titrated upwards and olanzapine was slowly discontinued. Scores on the BPRS psychotic symptom subscale increased at a trend level of significance (9.3 ± 5.0 vs. 12.8 ± 5.7, $t = 2.04$, $df = 18$, $p = .06$). Scores on the BPRS negative symptom subscale increased significantly (7.1 ± 2.1 vs. 9.1 ± 2.8; $t = 3.74$, $df = 18$, $p = .002$) as did scores on the BPRS depressive symptom subscale (9.4 ± 4.2 vs. 11.8 ± 4.3; $t = 2.20$, $df = 18$, $p = .04$) in the entire sample.

Responders Versus Nonresponders

The results are highlighted in Table 1. Among responders, 6 requested a trial of olanzapine and 2 were recommended for olanzapine treatment by the treating psychiatrist (1 for clozapine noncompliance, 1 for continued psychotic symptoms). Among nonresponders, 7 requested a trial of olanzapine and 4 were recommended for olanzapine treatment by the treating psychiatrist (3 for clozapine side effects, 1 for continued psychotic symptoms).

There was no significant difference in age (41.0 ± 9.7 vs. 43.6 ± 9.0; $t = .59$, $df = 17$, $p = .56$) or gender between responders and nonresponders. Five (50%) of 10 men and 3 (33%) of 9 women were responders. Comparing responders with nonresponders, baseline total BPRS (34.4 ± 11.5 vs. 38.3.0 ± 12.1, $t = .71$, $df = 17$, $p = .49$), negative symptom subscale (6.6 ± 2.3 vs. 7.5 ± 2.1; $t = .82$, $df = 17$, $p = .42$), psychotic subscale (7.6 ± 2.7 vs. 10.5 ± 5.9; $t = 1.3$, $df = 17$, $p = .21$), and depression

Table 1. Comparison of Olanzapine Responders With Nonresponders*

	Responders		Nonresponders				
Variable	Mean	SD	Mean	SD	t	df	p
Baseline BPRS score							
Total	34.4	11.5	38.3	12.1	.71	17	.49
Psychotic symptom subscale	7.6	2.7	10.5	5.9	1.3	17	.21
Negative symptom subscale	6.6	2.3	7.5	2.1	.82	17	.42
Depressive symptom subscale	9.4	5.4	9.5	3.4	.04	17	.97
Final BPRS score							
Total	38.1	8.9	52.7	9.4	3.4	17	.003[a]
Psychotic symptom subscale	8.9	4.1	15.6	5.0	3.1	17	.006[a]
Negative symptom subscale	8.1	3.3	9.8	2.3	1.3	17	.20
Depressive symptom subscale	9.8	3.2	13.3	4.4	1.9	17	.07
Time treated with clozapine, y	2.3	1.3	3.9	1.8	2.3	17	.04[a]
Baseline clozapine dose, mg	287.5	102.6	434.1	169.3	2.17	17	.05[a]
Final olanzapine dose	18.75	3.5	15.9	7.69	.97	17	.35
Titration time, wk	8.3	5.4	15.3	10.8	1.67	17	.10

*Abbreviation: BPRS= Brief Psychiatric Rating Scale.
[a]Statistically significant difference between olanzapine responders and nonresponders.

subscale scores (9.4 ± 5.4 vs. 9.5 ± 3.4; t = .04, df = 17, p = .97) did not differ between groups.

Final total BPRS scores differed significantly between responders and nonresponders (38.1 ± 8.9 vs. 52.7 ± 9.4; t = 3.4, df = 17, p = .003). The final BPRS psychotic subscale scores also showed a significant difference between responders and nonresponders (8.9 ± 4.1 vs. 15.6 ± 5.0; t = 3.1, df = 17, p = .006). Responders and nonresponders did not differ on the neg-ative symptom (8.1 ± 3.3 vs. 9.8 ± 2.3; t = 1.3, df = 17, p = .20) and depressive symptom scores (9.8 ± 3.2 vs. 13.3 ± 4.4; t = 1.9, df = 17, p = .07) at endpoint.

Responders had been treated for a significantly shorter period of time with clozapine prior to the switch compared with nonresponders (2.3 ± 1.3 years vs. 3.9 ± 1.8 years; t = 2.3, df = 17, p = .04) and were receiving a lower dose of clozapine (287.5 ± 102.6 mg/day vs. 434.1 ± 169.3 mg/day; t = 2.17, df = 17, p = .05). The final olanzapine dose did not differ between responders and nonresponders (18.75 ± 3.5 mg/day vs. 15.9 ± 7.69 mg/day; t = .97, df = 17, p = .35). Responders remained on the combination of clozapine treatment and olanzapine treatment during the titration period for a nonsignificantly shorter period than nonresponders (8.3 ± 5.4 weeks vs. 15.3 ± 10.8 weeks; t = 1.67, df = 17, p = 10). Responders and nonresponders did not differ in diagnosis or in the use of mood stabilizers or antidepressants (p > .1).

Four patients were considered treatment intolerant with conventional neuroleptics before being treated with clozapine. Three (75%) of the 4 responded to olanzapine, and the fourth patient experienced a severe withdrawal dyskinesia and a worsened clinical status. Fifteen patients were considered treatment resistant before starting clozapine. Five (33%) of the 15 responded to olanzapine.

Overall, few side effects were reported with olanzapine. Five patients complained of a worsening of constipation (3 responders, 2 nonresponders) and sedation (3 responders, 2 nonresponders) with the initial dose of olanzapine. However, over the course of several weeks on olanzapine treatment, sedation, constipation, and hypersalivation decreased. One patient, a nonresponder who experienced both sedation and constipation, also experienced a significant withdrawal dyskinesia during the study. Another patient, who experienced obsessive-compulsive symptoms secondary to clozapine, experienced a resolution of these symptoms upon reduction of clozapine. However, within 8 weeks of olanzapine alone, the obsessive-compulsive symptoms returned.

Although the 8 patients who responded to olanzapine showed an initial worsening in BPRS total and subscale scores, their clinical status appeared to stabilize 4 to 8 weeks after the switch. Three of the 8 actually showed improvement at the time the final BPRS total was obtained. All 8 patients have remained on olanzapine treatment (without other antipsychotic medications) and are clinically stable.

DISCUSSION

In this open trial, the crossover from clozapine to olanzapine was generally well tolerated and resulted in a successful transition for 8 of the 19 patients. However, mean scores on the total BPRS and negative symptom and depressive symptom subscales significantly increased. Because this was an open trial, these findings require replication in a controlled trial.

Responders and nonresponders did not differ in baseline BPRS scores but differed significantly on final assessment for BPRS total and psychotic symptom subscale scores. Responders also showed a significant increase in total BPRS scores compared with baseline. Despite the increase in symptoms, responders were clinically stable on olanzapine treatment alone and have remained on this regimen.

Responders had been treated with clozapine for a shorter duration of time. The clinical significance of this is unknown. However, it is possible that the nonresponders represented a group with a more severe illness. BPRS scores before clozapine was initiated in these patients were not available. When clozapine initially became available, only the most severely treatment-refractory patients received a trial. Over time, less severely treatment-refractory and intolerant patients received trials. Therefore, it is possible that some patients receiving trials of clozapine in the most recent years were less ill and may be

more likely to benefit from olanzapine. It would be helpful to know the severity of illness before patients were treated with clozapine to determine if this predicts response to olanzapine.

Responders to olanzapine were stable taking significantly lower doses of clozapine before the trial. Although serum clozapine levels were not available, it is possible that the lower doses prescribed for responders reflect less severe illness.

Another interesting finding in this open trial was that responders required a shorter time to discontinue clozapine compared with nonresponders, although the final olanzapine dose did not differ between the 2 groups. This may, in part, be due to the lower clozapine doses for responders at baseline. However, it indicates that rapid taper of clozapine was not responsible for poor outcome. The slow taper of clozapine was designed to reduce decompensation and hospitalization. However, in this study, the slow taper was not protective for nonresponders and may not have been necessary for responders.

It is recommended that moderate to high doses of olanzapine be used initially and then adjusted once clinical stability is achieved. Although responders showed worsening on final BPRS scores, they eventually stabilized with a moderate to high dose range. The risk of underdosing may result in decompensation and restart of clozapine for some patients who would otherwise respond.

Despite the anticholinergic and histaminic side effects of olanzapine and clozapine, only 5 patients complained of worsening constipation and sedation, which improved upon reduction of the clozapine dose. Although clozapine and olanzapine have α-adrenergic activity, no patients complained of dizziness or hypotension.

Treatment-intolerant patients are clinically different from treatment-resistant patients. Although the small number of treatment-intolerant patients does not allow for determination of a statistically significant relationship between intolerance of clozapine and subsequent response to olanzapine, 3 of 4 treatment-intolerant patients responded to olanzapine in this trial. It may be reasonable to offer a trial of olanzapine to clozapine patients who were intolerant of conventional neuroleptics. Care should be taken, however, in determining the nature of conventional neuroleptic intolerance to assure olanzapine has a lower potential for the particular side effect.

In summary, 8 of 19 clozapine patients responded to olanzapine. Treatment-intolerant patients appear to be the best candidates for such a trial, as well as patients who respond to the lower doses of clozapine. Finally, the less severe treatment-refractory clozapine patient may also merit a trial of olanzapine.

Drug names: clozapine (Clozaril), fluoxetine (Prozac), haloperidol (Haldol and others), olanzapine (Zyprexa), paroxetine (Paxil), sertraline (Zoloft).

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