Switching Clozapine Responders to Olanzapine

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Background: Clozapine is an atypical antipsychotic indicated for the management of severely ill patients with schizophrenia who have failed to respond adequately to standard drug treatment. The significant risk of agranulocytosis and seizure associated with clozapine has led to the restrictions in its use. Additionally, drug-induced sedation, sialorrhea, enuresis, and weight gain are often cited as problematic consequences of clozapine treatment. Our primary objective was to determine the effectiveness and safety of a method of slow cross-titration from clozapine to olanzapine among patients responsive to clozapine treatment but experiencing medication-induced adverse events.

Method: Changes in symptomatology, mood, subjective response, and safety were examined in 20 outpatients meeting DSM-IV criteria for schizophrenia or schizoaffective disorder who converted from clozapine to olanzapine. Patients were considered clozapine-responsive as evidenced by improved social function and decreased symptoms with clozapine therapy; however, they were interested in alternative pharmacologic treatment because of clozapine-related side effects.

Results: Equivalent efficacy of olanzapine to clozapine was found in 90% of the patients (18/20) in the study group, without rehospitalization or suicidal behavior in any of the patients. Also notable was a reduction in drug-induced side effects and improved subjective response to pharmacotherapy.

Conclusion: The successful conversion from clozapine to olanzapine has the potential to provide great benefits for the patient, including reducing drug-induced side effects while maintaining symptom control. These preliminary results suggest that further research on converting clozapine responders to olanzapine is warranted.

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The introduction of clozapine marked a turning point in the treatment of schizophrenia. Vastly different from conventional antipsychotics, clozapine was found to be effective with treatment-refractory patients[1] and efficacious for negative symptoms.[1] More recently, it was reported to be effective in treatment-refractory mood disorder.[2] Concurrently, it displays low incidences of extrapyramidal side effects, neuroleptic malignant syndrome, and tardive dyskinesia.[3] Despite such benefits, clozapine patients typically complain of adverse events such as sedation, sialorrhea, orthostasis, anticholinergic effects, weight gain, and the inconvenience of routine blood monitoring. Additionally, there are concerns of seizure risk and possible hematologic complications with clozapine use. The subsequent development of other atypical antipsychotics (risperidone, olanzapine, and quetiapine) has generated considerable interest regarding their potential to demonstrate clozapine-like efficacy without the associated side effect burden. Crossing over from clozapine to other agents poses considerable risks because of possible symptom exacerbation and potential withdrawal syndrome.

While the exact mechanism of clozapine discontinuation syndrome is unknown, it has a set of characteristic symptoms including a dramatic increase in psychosis and a variety of physical manifestations including diaphoresis, confusion, nausea, vomiting, headache, diarrhea, agitation, extrapyramidal symptoms, and restlessness.[4]

The receptor binding profile of olanzapine makes it pharmacologically similar to clozapine. Tollefson and colleagues[5] hypothesized that the use of olanzapine may prevent or decrease the severity of clozapine discontinuation syndrome. They conducted a randomized, double-blind comparison of placebo and olanzapine for 3 to 5 days following the abrupt discontinuation of clozapine in 106 patients. They found that 24.5% of the patients given placebo experienced discontinuation symptoms compared with 7.5% of patients given olanzapine. Lingle et al.[6] conducted an open-label study with 6 patients who had been previously responsive to clozapine but were intolerant of drug side effects. All patients responded well to olanzapine and reported fewer side effects. However, Haskins and colleagues[7] found that, at 8 weeks, only 7 of 23 clozapine-treated inpatients were able to tolerate changing to olan-

zapine. In another study, Henderson et al.[8] noted that 8 of 19 patients with schizophrenia and schizoaffective disorder were considered olanzapine responders, while the remaining 11 required reinstitution of clozapine. Most recently, Weiss and colleagues[9] reported the successful treatment of 5 clozapine responders with olanzapine. All patients had experienced clozapine-induced side effects and had become noncompliant with their medication. Subsequently, they were rehospitalized, and olanzapine was initiated. The group was restabilized and returned to the community. Implicit in these differing reports is the need for additional information regarding the associated risk/benefit profile of cross-titration to olanzapine among clozapine-responsive patients.

METHOD

Twenty clozapine-treated patients, aged 18 to 55 years and meeting DSM-IV criteria for schizophrenia or schizoaffective disorder, were recruited and gave informed consent for participation in a 24-week outpatient study designed to gradually convert them to olanzapine therapy. The patients were treated with clozapine by other prescribers who reported the primary reason for clozapine treatment to be treatment resistance to conventional antipsychotic therapy as evident by poor symptom control. The patients were classified as clozapine responders (baseline total Positive and Negative Syndrome Scale [PANSS][10] score of 79.84). Patients received a maintenance dose of clozapine with no dosage adjustments 30 days prior to study entry. Employment status was recorded at baseline and endpoint as a measure of social functioning. The PANSS and Young Mania Rating Scale (YMRS)[11] were conducted at baseline and every 4 weeks thereafter (last observation carried forward [LOCF]).

Criteria for switching to olanzapine included the following objective and subjective factors: (1) excessive sedation, (2) excessive weight gain (≥ 20% of the upper limit of ideal body weight), (3) clozapine-induced grand mal seizures, (4) clozapine-induced hypertension, (5) poor quality of life secondary to clozapine-related adverse events (sialorrhea, enuresis, and urinary incontinence), and (6) dissatisfaction with mandatory white blood cell (WBC) count monitoring. The most common reasons for inclusion were sedation (N = 9; 45%), poor quality of life (N = 9; 45%), and dissatisfaction with WBC count monitoring (N = 7; 35%). Excessive weight gain occurred in 25% of the sample (N = 5). Least common were hypertension (N = 3; 15%) and seizures (N = 1; 5%). Fifty-five percent of the sample (N = 11) met 2 or more of the inclusion criteria. Table 1 contains the demographic information on the entire sample.

This open-label study consisted of 3 phases. Phase 1 was a screening period lasting 2 to 9 days in which a physical examination, laboratory analyses, and electrocardiographic data were obtained. In phase 2, patients were seen at weekly intervals during the cross-titration of olanzapine and clozapine. Here, patients received flexible dosing of olanzapine (5–20 mg/day) guided by symptom control, while clozapine dose was decreased 25 mg every other day. Weekly or biweekly complete blood counts (CBCs) were collected as indicated. At the initiation of phase 2, the patient remained on his or her current clozapine dosage, and 5 mg of olanzapine was added. After 7 days of olanzapine treatment, the downward titration of clozapine was begun at a rate of 25 mg every other day. After another 7 days, olanzapine was increased to 10 mg/day, while clozapine discontinuation continued at 25 mg every other day. During phase 2, the protocol allowed for the olanzapine to be increased to a maximum of 20 mg/day or decreased to a minimum of 5 mg/day at any time based on level of psychopathology and side effects. If patients demonstrated poor clinical response to olanzapine, 20 mg/day, the dosage could be increased to 25 mg/day after clozapine discontinuation. However, an increase was permitted only if the patient received olanzapine, 20 mg/day, for at least 7 days. The time of treatment during phase 2 was variable according to the amount of clozapine at study start. The final phase consisted of 2 monthly follow-up visits after the complete discontinuation of clozapine and 1 follow-up visit 6 months after study endpoint. Patients continued to have CBCs monitored for 4 weeks after the final dose of clozapine. Treatment with concomitant psychoactive agents (including antipsychotics) was not permitted with the exception of benztropine for extrapyramidal symptoms or a benzodiazepine for agitation.

Table 1. Patient Demographics at Study Entry

Characteristic	Value
Gender	
Female, N (%)	3 (15)
Male, N (%)	17 (85)
Age at study entry, mean (SD), y	36.6 (7.7)
Length of illness, mean (SD), y	14.58 (6.42)
No. of previous hospitalizations, mean (SD)	3.83 (2.21)
Length of clozapine treatment, mean (SD), y	5.25 (2.52)
Clozapine dosage, mean (SD), mg	363.5 (160.4)
Tobacco users, N (%)	12 (60)
Employment status (at enrollment)	
Full-time competitive work, N (%)	2 (10)
Part-time competitive work, N (%)	4 (20)

RESULTS

Eighteen patients completed the study, and 2 patients requested clozapine reinitiation after symptom exacerbation (LOCF). The mean ± SD dose of olanzapine at the end of the study was 21.7 ± 3.3 mg (range, 15–25 mg). A t test of YMRS and PANSS scores for nonindependent samples ($\alpha = .05$) was used to evaluate the significance of

Table 2. Positive and Negative Syndrome Scale and Young Mania Rating Scale Scores at Baseline and Endpoint

Scale and Range of Possible Scores[a]	Baseline		End of Study		Statistic		
	Mean	SD	Mean	SD	t[b]	F[c]	p Value
Positive and Negative Syndrome Scale[d]							
Positive symptoms (7–49)	20.42	7.82	14.92	4.56	2.622	…	.012
Negative symptoms (7–49)	18.50	9.04	16.50	7.56	0.652	…	.264
General symptoms (16–112)	40.92	17.14	31.08	8.25	2.181	…	.026
Total symptoms (30–210)	79.84	32.43	62.50	11.92	2.042	…	.033
Young Mania Rating Scale (0–60)[d]	4.33	4.79	4.58	5.93	…	0.013	.911

[a]Lower scores indicate better functioning.
[b]Paired 2-sample t test for means, df = 19.
[c]One-way analysis of variance, df = 1,38.
[d]Last observation carried forward.

change in symptomatology. Analysis of PANSS data noted within-group improvement in negative symptoms that fell short of statistical significance. However, a statistically significant reduction in positive and general symptoms between baseline and end of study was observed (Table 2).

An analysis of YMRS data using analysis of variance ($\alpha = .05$) found no significant increase in mood elevation during the study period. Follow-up data collected monthly for 2 months and once at 6 months poststudy revealed no significant change in psychopathology, with mean total PANSS scores of 62.56 at 1 month, 61.23 at 2 months, and 63.14 at 6 months.

Most patients saw improvement in relation to the inclusion criteria upon which they entered the study. As expected, all patients reported satisfaction with the decrease in blood monitoring. Additionally, nocturnal enuresis and sialorrhea resolved in all patients who had previously reported them. Sedation was improved in 75% of the patients (N = 15), unchanged in 15% (N = 3), and worsened in 10% (N = 2). No significant change was noted in those patients entering under the excessive weight gain criterion.

Employment status for the group improved with the switch to olanzapine. At baseline, 30% of the patients (N = 6) were employed competitively, either full- or part-time. By study end, 30% of the patients (N = 6) were employed full-time, 15% (N = 3) were employed part-time, and 5% (N = 1) had a volunteer position.

The most significant overall finding was that 18 (90%) of the 20 patients safely converted to olanzapine without rehospitalization or suicidal behavior.

DISCUSSION

If clozapine discontinuation symptoms can be adequately managed, then the issue of switching from clozapine to olanzapine rests upon its effectiveness in the treatment-resistant population. Curiously, research with olanzapine in this population has yielded mixed results. In a 6-week open-label study with 24 patients that included an optional 26-week extension, Martín and colleagues[12] reported a significant decrease in positive and negative symptoms. Thirteen patients from the sample completed the extension phase and reported further reduction of symptoms. Conversely, in a 12-week open-label trial with 16 treatment-refractory inpatients, Sanders and Mossman[13] reported that only 2 patients responded favorably to olanzapine. The authors noted that the sample may have been prone to agitated behavior, and the patients may have benefited from higher dosing with rapid titration. Additionally, a longer treatment duration might have been helpful. Finally, Buezen and colleagues[14] compared olanzapine with clozapine in a double-blind, randomized design for 18 weeks (N = 180). Mean change from baseline to endpoint found olanzapine to be at least as effective as clozapine, with additional reduction in negative symptoms.

Our study investigated a method of slow cross-titration to olanzapine among patients determined to be clozapine responsive. Several methodological limitations warrant attention. Although no rehospitalizations or suicidal behavior was noted, the absence of a control group and the small number of patients limit the generalizability of these results. Additionally, olanzapine was not assessed as a monotherapeutic strategy, since 9 patients were receiving benzodiazepines at end of study. Consequently, the use of benzodiazepines may have contributed to the results. Future studies with a larger sample and increased extension phase may provide different results. Also needed are studies that investigate the role of patients' subjective attitude toward medication conversion to determine the impact of subjective attitude on illness behavior and treatment outcome.

This study does, however, provide additional information regarding the cross-titration of clozapine-responsive patients to another atypical antipsychotic. Despite methodological flaws, our data are consistent with those studies that found olanzapine to be at least as effective as clozapine in some patients.[13,14] Additionally, our results support those of Sanders and Mossman,[13] who suggest that higher doses of olanzapine and longer treatment duration may be essential for improved treatment outcome. Overall, this method of prolonged cross-titration was determined to be a safe procedure.

Drug names: benztropine (Cogentin and others), clozapine (Clozaril and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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