

Olanzapine Discontinuation Emergent Recurrence in Bipolar Disorder

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ABSTRACT

Objective: The efficacy of atypical antipsychotics including olanzapine in acute treatment of manic episode has been established, whereas its role in maintenance treatment is not clear. **Materials and Methods:** Thirteen patients of bipolar disorder who were on regular treatment with mood stabilizer and subsequently relapsed into mania or depressive episode after discontinuation of olanzapine were studied for various socio-demographic and clinical factors using retrospective chart review. **Results:** There was no correlation found between the period of tapering olanzapine, time to recurrence of episode after discontinuation, and the dosage of olanzapine at the time of discontinuation. The predominant early signs of relapse after discontinuation of olanzapine included sleep disturbance (72.7%), lack of insight for change in behavior (72.7%), irritability (54.5%), and elevated mood (45.5%). **Conclusion:** Mood stabilizer alone as a maintenance therapy of bipolar disorder may be inadequate for long-term management. A low dose of olanzapine along with mood stabilizers might be useful for prevention of recurrence in bipolar disorder.

Key words: Bipolar disorder, depression, mania, olanzapine, recurrence

INTRODUCTION

The aims of long-term prophylaxis in bipolar affective disorder are to decrease mortality, to reduce the rate of relapse, to shorten illness duration, and minimize the risk of suicide. The mainstay of maintenance therapy in bipolar disorder has been lithium. Lithium is effective both in the treatment of acute manic symptoms and for long-term maintenance therapy and is the most extensively studied mood stabilizer.^[1] Meta-analyses have demonstrated it to be superior to placebo for the prevention of relapse, reducing the risk of relapse

3.6-fold.^[2] Nevertheless, lithium monotherapy is associated with relapse-free outcomes in only a proportion of compliant individuals.^[3]

Pharmacotherapy of bipolar disorder has increasingly involved combination therapy, typically consisting of a combination of lithium and another psychotropic agent such as an antipsychotic. The use of typical antipsychotics has been associated with risk of tardive dyskinesia^[4] and depression.^[5] Atypical antipsychotics avoid the drawbacks of the conventional antipsychotics, but there have been very few studies of atypical anti-psychotics in the prophylactic treatment of bipolar disorder.

Olanzapine is the most widely studied of all atypical anti-psychotics for the treatment of bipolar disorder and evidence of its mood-stabilizing properties exists. Olanzapine in a dosage of 5-20 mg/day was found significantly superior to placebo in the treatment of acute mania.^[6] In patients not responding to

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monotherapy with lithium or divalproex, combination treatment with olanzapine proved more efficacious than lithium or divalproex alone in the prevention of manic relapse.^[7] Olanzapine was also found to be useful in treatment-resistant bipolar disorder in an open-label study.^[8]

Evidence for efficacy of olanzapine in prophylaxis of bipolar disorder comes from a 52-week placebo-controlled study.^[9] Compared with placebo, olanzapine significantly prolonged time to relapse to any affective episode, and the relapse rate of olanzapine patients was significantly lower than that for placebo patients (46.7% versus 80.1%, respectively). In another study by Tohen, *et al.*,^[10] olanzapine and lithium were compared during a 52-week double-blind trial in 431 patients who had achieved symptomatic remission after receiving open-label combination therapy of olanzapine and lithium for 6 to 12 weeks. Although the two agents were equally effective in preventing patients relapsing into a depressive episode, olanzapine was significantly better than lithium in avoiding a manic relapse. In all the above studies, olanzapine was found to be well tolerated.

We conducted a chart review of bipolar disorder patients who relapsed after discontinuation of olanzapine but with continued use of mood stabilizer and studied the socio-demographic and clinical factors associated with relapse.

MATERIALS AND METHODS

Participants

The study was conducted at the Central Institute of Psychiatry, Ranchi, India, a tertiary referral center in eastern India. The study was approved by Institutional ethics committee. Sample was collected from the mood disorder clinic and out-patient department of adult and child psychiatry. Patients of either sex with the diagnosis of bipolar affective disorder according to ICD-10 Diagnostic Criteria for Research (DCR),^[11] currently symptomatic (mania, depression, and mixed episode), after discontinuation of olanzapine but with continuous use of mood stabilizer, which was confirmed from the informant as well as serum lithium estimation done for the patients on lithium as a mood stabilizer. Only patients with adequate prophylactic level of serum lithium were taken for the study. Patients with organic brain syndrome, any other major psychiatric illness, mental retardation, or who had received electroconvulsive therapy within the previous 6 months were excluded.

Thirteen patients of bipolar disorder who were on regular treatment with mood stabilizer and

subsequently relapsed into mania or depressive episode after discontinuation of olanzapine were identified. The data-gathering included a comprehensive review of all available clinical information from the patient, informants, and case record file. All the patients were assessed for the prodromal symptoms of mania and depression using Young Mania Rating Scale (YMRS)^[12] and Hamilton Depression Rating Scale (HDRS),^[13] respectively, defined as cognitive, behavioral, and affective signs or symptoms that may signal an early stage of an episode.^[14]

Assessment

A semi-structured pro-forma was used for recording demographic details like age, sex, marital status, education, occupation, socio-economic status, and family type, as well as clinical data such as age of onset of illness, duration of illness, number of episodes, history of hospitalization, past history of ECT, family history of medical or psychiatric illness, and premorbid personality. Detailed information about the treatment history including the use of mood stabilizer and antipsychotic, the rate of taper of antipsychotic, and the time to relapse after discontinuation was recorded. YMRS, an 11-item clinician-administered rating instrument, is used to assess the severity of mania.^[12] All the patients were assessed for the prodromal symptoms, defined as the symptoms present before the onset of current episode using YMRS, symptoms being present or absent. HDRS, a 17-item scale, was used to assess the severity of depression.^[13] All the patients who had depression in the current episode were assessed for the prodromal symptoms, defined as the symptoms present before the onset of current episode using HDRS, symptoms being present or absent.

Statistical analysis

Statistical analysis was done using Statistical Package for Social Sciences (SPSS) 10.0. Descriptive statistics was used to describe the sample in terms of socio-demographic and clinical characteristics. Pearson's chi-square test was used to assess for any significant difference in family history and drugs received. Paired 't' test was used to compare mean serum lithium levels in the last and the current episode. Pearson's correlation coefficient was used to assess linear relationship between time taken to taper olanzapine, last dose of olanzapine received, and the time of recurrence of episode after discontinuation of olanzapine.

RESULTS

The sample consisted of 13 bipolar patients with a mean age of 26.76 (SD 12.18) years, of which 10 (76.9%) were males [Table 1]. The mean age of onset of the patients was 17.77 (SD 4.47) years with a mean

duration of illness 107.54 (SD 114.54) months. Five (38.5%) had a family history of mood disorder. Eleven (84.6%) patients had mania in their last episode, rest had depression, of which 76.9% patients had psychosis. After discontinuation of olanzapine, 10 (76.9%) patients had mania, 2 (15.4%) patients had depression, and 1 (7.7%) patient had mixed episode. Among the patients who had manic episode, 6 (46.2%) had euphoric mania. Nine (69.2%) of the patients were on a combination of lithium and olanzapine; rest received either valproate (23.1%) or carbamazepine (7.7%) along with olanzapine. Average serum lithium level in the previous episode was 0.85 (SD 0.12) meq/L as compared to 0.84 (SD 0.10) meq/L in the current episode; no significant difference was found between the two levels. Mean time taken to taper olanzapine was 10.23 (SD 5.29) months. Mean dose of olanzapine at the time of discontinuation was 2.50 (SD 0.88) mg, and the time to relapse after discontinuation of olanzapine was 2.78 (SD 2.61) months. The predominant early signs of relapse after discontinuation of olanzapine included sleep disturbance (72.7%), lack of insight for change in behavior (72.7%), irritability (54.5%), and elevated mood (45.5%) [Table 2]. There was no correlation found between the period of tapering olanzapine, time to recurrence of episode after discontinuation, and the dosage of olanzapine at the time of discontinuation.

DISCUSSION

In this study, all the patients had received a combination of mood stabilizer and olanzapine for the previous episode, as the episodes were severe and most of them required hospitalization. A combination of a mood stabilizer and an antipsychotic is preferred for severe manic episodes, including psychosis, whereas monotherapy with mood stabilizers may be appropriate for less severe episodes.^[1]

In all the patients, olanzapine was tapered off gradually over a mean duration of 10.23 (SD 5.29) months, and the mean dose at discontinuation was 2.5 (SD 0.88) mg. Abrupt discontinuation of mood stabilizer such as lithium has been associated with significantly lesser time to relapse compared to gradual tapering.^[15] No significant correlation between the period of tapering olanzapine, time to recurrence of episode after discontinuation, and the dosage of olanzapine at the time of discontinuation indicates that even a dose of olanzapine as low as 1.25 mg may have a significant role in preventing recurrence, and it is not the rate of taper of olanzapine but discontinuation, which plays a role. In 85% of the patients, the mean time to relapse was 1.9 (SD 1.28) months after olanzapine discontinuation, suggesting a prophylactic role of low

Table 1: Sample characteristics (n=13)

Age, Mean (SD)		26.76 (12.18)
Male gender, n (%)		10 (76.9)
Age of onset in years, Mean (SD)		17.77 (4.47)
Duration of illness in months, Mean (SD)		107.54 (114.54)
Number of episodes, Mean (SD)		4.46 (3.97)
Number of hospitalization, Mean (SD)		2.23 (2.20)
Last episode, n (%)	Mania	11 (84.6)
	Depression	2 (15.4)
Drugs in addition to olanzapine, n (%)	Lithium	9 (69.2)
	Valproate	3 (23.1)
	Carbamazepine	1 (7.7)
Mode of onset of current episode, n (%)	Abrupt	2 (15.4)
	Acute	9 (69.2)
	Insidious	2 (15.4)
Current episode, n (%)	Mania	10 (76.9)
	Depression	2 (15.4)
	Mixed	1 (7.7)
Time to taper olanzapine in months, Mean (SD)		10.23 (5.29)
Last dose of olanzapine, Mean (SD)		2.50 (0.88)
Time to recurrence after discontinuation of olanzapine, Mean (SD)		2.78 (2.61)

Table 2: Prodromal symptoms (n=13)

YMRS items	n	%
Elevated mood	5	45.5
Increased motor activity-energy	3	27.3
Sexual interest	2	18.2
Sleep	8	72.7
Irritability	6	54.5
Speech (rate and amount)	5	45.5
Language-thought disorder	2	18.2
Thought content	2	18.2
Disruptive-aggressive behavior	2	18.2
Appearance	1	9.1
Insight	8	72.7

dose of olanzapine. Suppes *et al.*^[16] had found use of low dose of clozapine for mood stabilization compared to the antipsychotic dose. There is no study, which has examined the minimum dosage of olanzapine required for the prophylaxis of bipolar disorder, and there is no consensus on the ideal way to discontinue olanzapine.

Most of the patients had recurrence of the manic episode after discontinuation of olanzapine, which is in agreement with other studies^[9,10] that have found prophylactic role of olanzapine against manic rather than depressive episode. Onset of manic episode is usually rapid, occurring within days. In our study, acute or abrupt onset of manic episode after olanzapine discontinuation was noted in 85% patients.

Sleep disturbance was the most common prodromal sign of relapse after discontinuation of olanzapine; other signs were irritability, absence of insight for behavior change, changes in speech, and elevated mood.

A retrospective study by Molnar *et al.*^[17] found sleep disturbance and mood change as common prodromal symptoms. Similar prodromal signs of relapse, using YMRS, were found in a recent study in patients on lithium after discontinuation of olanzapine.^[18]

The sample size was small, for generalization of the findings. A well-designed prospective study is required to explore the recurrence of affective episode after olanzapine discontinuation and to establish the minimum required dose for prophylaxis.

Mood stabilizer alone as a maintenance therapy of bipolar disorder may be inadequate for long-term management in some patients. In addition to its acute antimanic effect, a low dose of olanzapine along with mood stabilizers might be useful for prevention of recurrence in bipolar disorder.

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