ORIGINAL RESEARCH PAPER

Psychiatry

CLOZAPINE IN CHILDHOOD ONSET RESISTANT BIPOLAR DISORDER

KEY WORDS:

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ABSTRACT

Recurrent episodes of bipolar disorder and consequent repeated hospitalizations can negatively impact the overall functioning and treatment compliance of bipolar patients. In all 7170 files were individually screened, patients included in the study had received clozapine for at least 6 weeks Nineteen patients were included in the final evaluation. Response to clozapine was assessed according to a four-point scale both in acute and maintenance phase. Those who continued their treatment maintained in remission and relapses were seen only on discontinuation of treatment. The results show clozapine is relatively well tolerated and efficacious in the childhood onset resistant bipolar disorder in terms of long periods of remission, fewer hospital visits, and hospitalization.

INTRODUCTION

Bipolar disorders are chronic disorders that tend to cause severe dysfunction and social incompetence as severe as schizophrenia (Ertugrul & Meltzer, 2003). Bipolar disorder has also been reported to cause significantly more rehospita lizations than nonpsychotic or psychotic depressions in a long-term prospective follow-up study (Goldberg & Harrow, 2004). The recurrent episodes of bipolar disorder and consequent rehospitalizations can negatively impact the overall functioning and treatment compliance of bipolar patients (Joyce, 1985).

Bipolar disorders are also common among adolescent populations with lifetime prevalence of 1 percent of adolescents 14 to 18 years of age (Lewinsohn et al, 1995). The clinical picture of childhood mania is characterized by predominant irritable mood, mania mixed with major depression, and chronic course, as opposed to euphoric, biphasic and episodic course seen in adult onset (Geller and Luby, 1997).

Clozapine, an atypical antipsychotic that has been widely used for chronic schizophrenia, (Kane *et al*, 1988; Wahlbeck *et al*, 1999) is regarded as a very effective agent for schizophrenic patients showing treatment resistance, suicidality, or intolerable extrapyramidal symptoms as seen with other antipsychotics (Wagstaff *et al,* 2003; Conley *et al*, 1999; Gerlach *et al*, 1996). Studies have shown that clozapine is effective in treating affective disorders not responding to conventional treatment (Zarate *et al*., 1995). Further, clozapine has also been used for clinically difficult cases such as lithium-resistant rapid-cycling episodes or dysphoric mania (Masi *et al*, 2002; Barbini *et al*, 1997; Calabrese *et al*, 1996). In fact, along with other atypical antipsychotics, clozapine is now considered as one of the effective treatment alternatives for bipolar patients resistant to lithium or anticonvulsant treatment (Brambilla *et al*, 2003).

Child and adolescent onset bipolar disorder are known to be resistant to treatment and have poor long term outcome. However, only few studies address the effectiveness of clozapine in bipolar disorder that have not responded to previous trials of conventional mood stabilizers. The current study therefore has been conceived to address these aspects.

AIM, OBJECTIVE AND HYPOTHESIS

To assess the efficacy of clozapine in treatment resistant bipolar disorders in children and adolescent in acute and maintenance phase. To assess the safety and tolerability of clozapine. There will be no change in 'scale for response to clozapine' at point of initiating clozapine therapy as compared to the last follow up.

MATERIAL AND METHODS

SAMPLE

This study was a retrospective chart review conducted at Central Institute of Psychiatry, Ranchi, India. The study was approved by ethical committee of our Institute. Study sample comprised of patients seen between 1st January 2000 to 31st December 2006 with a diagnosis of bipolar affective disorder according to ICD-10 Diagnostic Criteria for Research (WHO, 1993), under the age 18 at the time of first consultation and resistant to at least two conventional mood stabilizers (lithium, sodium valproate and carbamazepine) and were on clozapine therapy for at least six weeks. Those with organic brain disorder or who received ECT in past three months were excluded from the study.

TOOLS FOR ASSESSMENT

A pro-forma specially designed for the study was used to collect socio-demographic and clinical details. To assess improvement in psychopathology and socio-occupational functioning from the clinical records of patients treated with clozapine, Scale for Response to Clozapine (McElroy et al., 1987) was used. It is a four point scale, with score 0 for no response, 1 for minimal improvement, 2 for moderate improvement and 3 for marked improvement. To assess side effects of clozapine, a checklist developed by Kutcher (1997) was used.

PROCEDURE

Clinical data from case record files of all patients who attended out-patient or in-patient department of Child and Adolescent Psychiatry Unit from 1st January 2000 to 31st

December 2006 were reviewed (N=7170). Of these, 29 fulfilled diagnosis of bipolar affective disorder who had failed trial of two conventional mood stabilizers prior to the date of assessment, and were started on clozapine therapy. Ten patients were excluded, as the duration of clozapine therapy was less than six weeks or it was discontinued. In the remaining sample (N=19), socio-demographic and clinical data, Scale for Response to Clozapine (McElroy et al., 1987) and clozapine side effects checklist (Kutcher, 1997) was administered.

IN THE ACUTE PHASE

- rating of symptom severity with the above scale was done for the point of admission(Baseline) and at discharge.
- dose and duration of treatment was noted.
- use of additional drugs with doses were noted.
- In the maintenance phase
- ratings was done for subsequent follow ups at 1, 3, 6, 12, 18, 24, months and also at the last follow up if the patient had come after 24 month period.
- scores were compared for the above mentioned periods.
- time to remission was noted (side effects noted from the case record files)
- duration of remission.
- number of relapses and their severity.
- recurrences with causes.
- The safety and tolerability profile of the drug was assessed by using a checklist for side effects of clozapine.
- other side effects mentioned in the case record file.

ANALYSIS OF DATA

Analysis done by using Statistical Package of Social sciences-version 10.0(SPSS 10). Descriptive Statistics was used to calculate mean, percentage and standard deviation of the sample. Correlation was done to find the significance of the study.

RESULTS

Sixty-nine patients treated with clozapine at Central Institute of Psychiatry between January 2000 and December 2006 for various disorders twenty nine patients had at least a six month working diagnosis of bipolar disorder. All had a history of well-documented treatment resistance marked by recurrent episodes of illness or incomplete response of symptoms to lithium, anticonvulsant mood stabilizers, standard neuroleptics, antidepressants alone or in combination. The mood stabilizers and antipsychotics were used up to their maximum effective dose (with adequate therapeutic serum levels of the drugs) and the duration of trial with these drugs were also adequate. Nineteen patients were finally included in the study as six patients had a trial of clozapine for less than 6 weeks, one patient had an organic condition, one patient was noted to have EEG abnormalities, one patient developed clinical seizures, and one patient did not turn up for follow up.

Table 1 shows the clinical characteristics of the study population. The final assessment included 16 males (84.2%) and 3 females 15.8 %. The mean age of onset was 13.84 with SD of 2.34 (range 7 to 17 years) and the age at the time of consultation was 14.95 years with a SD of 1.96 (range 10-17 years). Mean duration of illness before starting clozapine had been 24.11 months and SD of 18.87 (range 2-70 months). Majority of patients belonged to the lower SES (52.63%, n=10), Middle 26.31% patients were from middle SES (n=5) and 21.05 % were from the upper SES. Co-morbidity was found in five patients. Family history of mood disorder was found in a significant number (n=7, 36.84%). Eleven (57.9%) out of 19 patients had their first episode as mania and 8 (42.1 %) patients their first episode as depression.

Mean dose of clozapine at 1 month 210.53 mg (Range 50-500mg), at 6 months mean dose was 214.47 (Range 0-500mg), at 1 year the mean dose was 192.19 (range 75- 400mg). The mean overall dose of clozapine was 205.84 milligrams **(Table 2).** Clinical improvement assessed by using the McElroy scale. Four (21.05 %) patients showed maximum possible improvement (ie. Score of 3) within the first month of treatment, 10 (52.63%) showed moderate improvement (score 2) in the first month and 5 (26.32%) showed minimal improvement. At six months into treatment 12 (63.156%) patients attained the score of 3, 6 (31.58%) patients the score of 2 and 1 (5.26%) the score of 1. All patients had shown at least some improvement. At 12 months sixteen patients were available for assessment. Clozapine was stopped in 2 patients because of EEG abnormality and one patient did not turn up for follow up. Nine (56.25%) patients had a score of 3, 6 patients had score 2 (37.5 %), 1 patient had a score of 1 (6.25%). Kaplan-Meyer survival analysis shows time to improvement **(Figure 1)** shows survival time of 3.5 with standard deviation of 1.04.

Clozapine was relatively well tolerated by most patients. Most common side effect was sedation seen in 15 (78.9 %) followed by salivation in 13 (68.4 %) patients. Tremors were seen 8 (42.1 %), weight gain was seen in 6 (31.6 %) and bradykinesia in 4 (21.1%) patients. Menstrual irregularities were seen in 2 out of the three female children. Eoisnophilia was seen in 9(47.4%) patients. EEG abnormality was seen in two patients. However aggranulocytosis was not seen in any patient at any point of time **(Table 3)**.

Table 1: Sample characteristics (N=19) shows the sociode mographic and clinical details of the patient.

		Mean	SD
Age		14.95	1.96
Years of formal education		6.63	3.41
Age of onset		13.84	2.34
Duration of illness (months)		24.11	18.87
		N	%
Sex	Male	16	84.2
	Female	3	15.8
SES	Lower	10	52.63
	Middle	5	26.31
	Upper	4	20.05
Residence	Urban	10	52.64
	Rural	9	47.36
Comorbidity	Present	5	26.31
	Absent	14	73.69
Family history of mood disorder	Present	7	36.84
	Absent	12	63.16
Polarity of first episode	Mania	11	57.9
	Depression	8	42.1

Figure 1: Kaplan-Meyer survival analysis showing time to improvement (N=19)

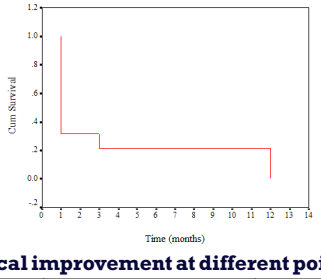

Table 2: Clinical improvement at different point of time

Time of assessment	Dose of clozapine (mean/ SD)	Improvement (No. of Patients)
1 months (n=19)	210.53 (116.469)	Score 3 **(4)**
		Score 2 **(10)**
		Score 1 **(5)**
		Score 0 **(0)**
6 months (n=19)	214.47 (129.45)	Score 3 **(12)**
		Score 2 **(6)**
		Score 1 **(1)**
		Score 0 **(0)**

12 months (n=16)	192.19 (83.53)	Score 3 **(9)**
		Score 2 **(6)**
		Score 1 **(1)**
		Score 0 **(0)**

Table 3: Side effects seen in any point of time during treatment

Side effect	Number	Percentage
Salivation	13	68.4
Sedation	15	78.9
Bradykinesia	4	21.1
Tremors	8	42.1
Urinary side effects	3	15.8
Weight gain	6	31.6
Menstrual irregularities	2	10.5
Seizures	2	10.5
EEG abnormality	2	10.5
Leucocytosis	2	10.5
Neutropenia	1	5.3
Aggranulocytosis	0	0
Eosinophilia	9	47.4

DISCUSSION

This study was conducted at the Central Institute of Psychiatry, Ranchi. Although retrospective in design, this study has the strength in utilizing the record keeping and adequate information about any particular patient. The semi structured interview history-taking and examination sheet ensured proper and reliable data. The chances of recall bias were eliminated. A single rater ensured uniformity in the assessment. Though the scale is a 4 point scale, roughly assesses the condition of the patient, but able to approximately judge the level of dysfunction or the level of functioning.

The age of onset as described by Ritti (1883) reported a paediatric case of circular psychosis (now BPD) starting at age 12. Soukhanoff & Gannouchkine (1903) found an onset before age 15. Recent studies by Lewinsohn *et al* (1995, 2000) retrospectively recalled age at onset was around 12 years. The age of onset does not differ much from the studies around the world and from India. In their study of prepubertal children with mania, Wozniak & coworkers (1995) found a depressive onset in 44%, a manic onset in 19%, and a mixed onset in 37%. In 115 cases of BPD-like disorders diagnosed in adolescence, Lewinsohn & colleagues (1995) reported depression in 61%. Study findings suggest that clozapine may improve the clinical picture in adolescents with treatment-refractory manic or mixed episodes. Required doses for optimal effect in bipolar disorder may be less than for treatment-resistant schizophrenia (Fehr *et al,* ,2005).

Bipolar disorder type I in adolescence is severe disorders that can be refractory to conventional treatments with mood stabilizers (Kafantaris *et al*. 2001; Kowatch *et al*, 2000). Clozapine may rapidly improve the clinical picture of adolescents with severe manic or mixed episodes, on both manic and psychotic aspects. Effects were often evident within the first few weeks of treatment as evidenced by remission in 15 days and were sustained throughout the follow up period. Indeed, patients who continued on clozapine required no further hospitalizations and displayed significant improvement in psychosocial functioning, evidenced by an ability to live in less structured settings, to sustain personal relationships, return to school. Side effects (mainly salivation, sedation, tremors)) were frequent but not so severe as to require reduction of dosage. Of the 2 patients who developed EEG abnormality clinical seizures was seen in 1 patient at 50 mg of clozapine.

LIMITATIONS

The design of the study limits further information that could have been gathered to strengthen findings of the study. The methodological weakness includes the collection of baseline data retrospectively, the lack of comparable comparison groups treated without clozapine. Concomitant medications used in the patients were a confounding factor. The sample size was small as to to generalize these findings to the population at large. More comprehensive scales were needed to give a better assessment of the severity of the episodes of the levels of improvement.

CONCLUSION

There was marked improvement in the socio-occupational functioning of the patients under study. Those who continued their treatment maintained in remission and relapses were seen only on discontinuation of treatment. The side effects noted were not severe enough for discontinuation of medication except in case of seizure disorder. To conclude, clozapine is relatively well tolerated and efficacious in the childhood onset resistant bipolar disorder in terms of long periods of remission, fewer hospital visits and hospitalization.

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