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Drug side effects of adolescent patients with remitted bipolar affective disorder on treatment with clozapine VS mood stabilizer: A comparative study

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Abstract
This study was an attempt to see the level of drug side effects of adolescent patients with remitted bipolar affective disorder on treatment with clozapine and mood stabilizer. The present study was conducted at the Child and Adolescent Psychiatric Unit of Central Institute of Psychiatry (CIP), Ranchi. The present study was a cross sectional hospital based study and used purposive sampling technique. The present study sample consisted of 40 adolescents, among which 20 were adolescent patients with bipolar affective disorder on treatment with clozapine and 20 were adolescent patients with bipolar affective disorder on treatment with mood stabilizer. The following tools were used for the current study: Socio-demographic data sheet and self-prepared questionnaire for assessing drug side effects. The study result indicates that clozapine may be a better alternative to mood stabilizers when medication related adverse drug effects are considered in adolescent patients with bipolar affective disorder.

Keywords: Adolescents, bipolar affective disorder, side effects, clozapine, mood stabilizers

1. Introduction

In recent days a silent revolution has been occurred in the field of psychopharmacology through the arrival of various molecules which have shown very efficiency in dealing with psychopathologies which were previously held to be refractory. Advancement in the field of psychopharmacology has been found to be a boon to persons with severe psychiatric illness like Bipolar Affective Disorder. Administration of newer molecules has ensured prompt recovery as well as revival of the socio-occupational performances of the affected individuals. Several randomized, placebo-controlled trials have shown pharmacotherapeutic agents like atypical and conventional antipsychotics (Yatham, 2004) [9] and conventional mood stabilizers, i.e. Lithium (Goodwin *et al.*, 1969; Stokes *et al.*, 1971) [10, 11] carbamazepine (Ballenger & Post, 1978; Ketter, & Kalali, 2004; Weisler *et al.*, 2004, 2005) [12, 13, 14, 15] and valproate (MacRitchie *et al.*, 2000; Muller-Oerlinghausen *et al.*, 2000) [16, 17] are considered to be the first line of treatment in acute mania. As the risk of recurrence is highly associated with bipolar disorder so often the pharmacotherapy is given for longer time. Often patients with BPAD are given combinational medications, i.e. antipsychotics, mood-stabilizers, antipsychotics and other medications to control adverse effects of first line drugs. Atypical antipsychotic like clozapine opened a new vista to the people with recalcitrant psychotic symptoms. Clozapine is recognized as 'atypical antipsychotic medication' which is very much effective in eliminating refractory symptoms of psychosis and often it has been regarded as the last option in the treatment of psychosis. The introduction of clozapine, an atypical antipsychotic, for the treatment of poorly responsive schizophrenic patients has fostered widespread hope among patients, their families, and caregivers. For the first time in over 30 years, a treatment is available that appears to be more effective than the standard or typical neuroleptics for many such treatment-resistant schizophrenic patients (Green *et al.*, 2000) [20]. Retrospective studies by a number of groups suggest that clozapine may be particularly effective in the treatment of psychotic affective disorder, perhaps even more effective than it is for schizophrenia (Owen *et al.*, 1989; McElroy *et al.*, 1991; Suppes *et al.*, 1992) [19, 18]. Many bipolar disorder patients with psychotic mania respond well to traditional medication (including mood stabilizers and antipsychotics), a substantial portion do not respond to traditional medication, in those cases clozapine can be used as it was found to be very much effective in dealing with refractory psychosis (Green *et al.*, 2000) [20].

2. Materials and Methods

The present study was conducted at the Child and Adolescent Psychiatric Unit of Central Institute of Psychiatry (CIP), Ranchi. The present study was a cross sectional hospital based study and used purposive sampling technique. The present study sample consisted of 40 adolescents, among which 20 were adolescents with bipolar affective disorder on treatment with clozapine and 20 matched adolescent patients with bipolar affective disorder on treatment with mood stabilizer. The following tools were used for the current study: Socio-demographic data sheet and self-prepared questionnaire for assessing drug side effects.

3. Results

Table 1: Comparison of socio-demographic profile of adolescents with bipolar affective disorder in remission with clozapine and mood stabilizers

Variables		Clozapine Group n=20 (Mean/n±SD/ %)	Mood stabilizer group n=20 (Mean/n±SD/ %)	χ2/t	df	P
Age(in years)		16.05± .94	15.70±1.34	0.954	38	0.064
Education	Illiterate	1 (2.5%)	0(0%)	1.059	2	0.589
	Primary	8 (20%)	9 (22.5%)			
	Secondary & above	11(27.5%)	11(27.5%)			
Sex	Male	11(27.5%)	14(35%)	0.960	1	0.327
	Female	9(22.5%)	6(15%)			
Occupation	Employed	1(2.5%)	0(0%)	1.026	1	0.311
	Unemployed	19(47.5%)	20(50.0%)			
Socioeconomic status	Lower	15(37.5%)	14(35.0%)	0.617	1	0.432
	Middle/upper	5(12.5%)	6(15%)			
Marital status	Married	2(5%)	1(2.5%)	0.360	1	0.548
	Unmarried	18(45.0%)	19(47.5%)			
Habitat	Rural	18(45.0%)	15(37.5%)	1.55 8	1	0.212
	Urban	2(5%)	5(12.5%)			
Family type	Nuclear	14(35.0%)	15(37.5%)	0.125	1	0.723
	Joint	6(15%)	5(12.5%)			

p=not significant

Table (1) shows comparison of socio-demographic variables of adolescents with bipolar affective disorder treated with clozapine and mood stabilizers. There were no significant difference in socio-demographic variables i.e. age, sex, occupation, socio-economic status, marital status, habitat and family type between two groups.

Table 2: Comparison of clinical variables of adolescents with bipolar affective disorder in remission across clozapine and mood stabilisers group

Variables		Clozapine Group n=20 (Mean/n±SD/ %)	Mood stabilizer group n=20 (Mean/n±SD/ %)	t	df	P
Duration of illness (in years)		2.00±0.79	1.95±0.82	.195	38	0.846
Duration of treatment (in years)		1.50±.7609	1.30 ±0.47	1.00	38	0.324
Family history	Present	11(27.5%)	11(27.5%)	.000	1	1.00
	Absent	9(22.5%)	9(22.5%)			

P=not significant

Table (2) shows comparison of clinical variables of adolescents with bipolar affective disorder currently in remission on treatment with clozapine and mood stabilizers. There was no significant difference in clinical variables i.e. duration of illness, family history and duration of illness between clozapine and mood stabilizer group.

Table 3: Comparison of side effects in adolescents with bipolar affective disorder currently treated with clozapine and mood stabilizers

Side effects		Clozapine group n=20 n (%)	Mood stabilizer group n=20 n (%)	χ2	df	P
Gastric irritation	Present	0(0)%	9(21.5%)	11.613	1	0.001**
	Absent	20(50%)	11(28.5%)			
Diarrhoea	Present	0(0%)	4(10%)	4.444	1	0.035*
	Absent	20(50%)	16(40%)			
Hair loss	Present	1(2.5%)	4(10%)	2.057	1	0.151
	Absent	19(47.5%)	16(40%)			
Increased salivation	Present	13(32.3%)	0(0%)	19.259	1	0.000**
	Absent	7(17.5%)	20(50%)			
Tremor	Present	0(0%)	8(20%)	10.00	1	0.002**
	Absent	20(50%)	12(30%)			
Constipation	Present	1(2.5%)	0(0%)	1.026	1	0.311
	Absent	19(47.5%)	20(50%)			
Fever	Present	1(2.5%)	2(5%)	.360	1	0.548
	Absent	19(47.5%)	18(45%)			
Memory impairment	Present	1(2.5%)	0(0%)	1.026	1	0.311
	Absent	19(47.5%)	20(50)			

* Significant at p<0.05 level (2-tailed)
**Significant at p<0.01 level (2-tailed)

Table (3) shows comparison of side effects in adolescents with bipolar affective disorder treated with clozapine and mood stabilizer. There was significant different in side effects profile i.e. Increased salivation was more common in clozapine group while mood stabilizer group showed significantly more side effects in the domains of gastric irritation, tremors and diarrhoea. However there was no significant difference in others side effects between clozapine and mood stabilizer group.

4. Discussion

The comparison of socio-demographic data of adolescent remitted BPAD patients treated with clozapine and mood stabilizers showed no statistically significant difference with respect to age, sex, occupation, socioeconomic status, marital status, habitat and family type between the two groups. This finding is consistent with the finding of previous study done by Lewinsohn *et al.* (2002) [3] where the authors mentioned that there had been no significant difference in sociodemographic parameters in remitted adolescent BPAD patients within group but when compared to normal controls they found marked impairment in social (67%), family (56%), and academic/school related (83%) functioning. In our study only remitted BPAD adolescent patients were taken, hence no significant difference was observed on sociodemographic variables. This finding was consistent with previous studies (Lewinsohn *et al.*, 2002) [3]. Similarly no significant difference was observed in variables like duration of illness and duration of treatment between clozapine group and mood stabilaizers. Although no difference was found in family history, the number of patients having family history of mood disorder has been 22 out of 40 patients. This observation was also consisted with various findings of previous studies e.g., Nurnberger and Gershon (1992) [7]. These authors indicated that in bipolar disorder genetic loading is an important issue.

Comparison between Side Effect Profile of Clozapine and Mood Stabilizer Group

In our study, we found significant difference in side effect profile of adolescent population receiving either clozapine or mood stabilizers. The side effects which differ significantly between two groups include gastric irritation, diarrhea, tremor and increased salivation. Gastric irritation (21.5%), diarrhoea (10%) and tremor (20%) were significantly higher in adolescent patients receiving mood stabilizer where as these side effects were absent in patients receiving clozapine. Unlike First Generation Antipsychotics, clozapine is relatively free from certain motor side effects, such as Parkinsonism, akathisia, and tardive dyskinesia. In fact, there is some evidence that clozapine treatment may improve these conditions (Spivak *et al.*, 1997) [8]. Various studies have reported an incidence of gastrointestinal side effects such as heart burn, gastric irritation, in subjects receiving clozapine in the range of 1-10 % (Iqbal *et al.*, 2003; Miller, 2000; NPC, 2003) [2, 6]. Also constipationis more commonly observed in patients receiving clozapine due to its strong anticholinergic effect. These side effects are commonly seen in patients receiving mood stabilizers. Hypersalivation was observed in significantly more subject receiving clozapine (32.3%) when compared to mood stabilizer group where none of the subjects reported increased salivation. Unlike most antimuscarinic drugs that cause dry mouth, clozapine frequently causes hypersalivation. This is due to fact that clozapine is an antagonist at M3 and M5 receptors and an agonist at M4 receptors. The M4-agonist properties have been associated with clozapine-induced hypersalivation (de Leon *et al.*, 2003) [1]. Other authors have hypothesized that blocking of alpha-receptors may be a contributing factor (Marder & Wirshing, 2004) [4]. This side effect was more troublesome during sleep hours which are generally observed in patients receiving clozapine. Thus our study has correctly reflected the side effect profiles as observed by other authors in their studies.

5. Conclusion

Thus this study concludes that clozapine may be a better alternative to mood stabilizers when medication related adverse drug effects are considered in adolescent patients with bipolar affective disorder.

6. References

1. De Leon J, Diaz FJ, Rogers TJ, *et al.* A pilot study of plasma caffeine concentrations in a US sample of smokers and non-smokers volunteers. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2003; 27:165-171.
2. Iqbal MI, Rahman A, Husain Z, *et al.* Clozapine: A clinical review of adverse effects and management. Annals of Clinical Psychiatry. 2003; 15:33-48.
3. Lewinsohn PM, Seeley JR, Buckley ME, *et al.* Bipolar disorder in adolescence and young adulthood. Child and Adolescent Psychiatric Clinic of North America, 2002; 11:461-475.
4. Marder SR, Wirshing DA. Clozapine. In CB. Schatzberg, & Nemeroff CB (Eds.), The Americanpsychiatric publishing textbook of psychopharmacology, 2004, 443-456.
5. Washington DC. American Psychiatric Publishing.
6. Miller DD. Review and management of clozapine side effects. Journal of Clinical Psychiatry; 2000; 61:14-19.
7. Nurnberger, Gershaon. Genetics. In: Handbook of Affective disorder, (Eds.) Paykel ES. Edenburg: Churchill Livingstone, 1992, 131-148.
8. Spivak B, Mester R, Abesgaus J, *et al.* Clozapine treatment for neuroleptic-induced tardive dyskinesia, parkinsonism and chronic akasthisia in schizophrenic patients.Journal of Clinical Psychiatry, 1997; 58:318-322.
9. Yatham LN, Lecrubier Y, Fieve RR, et al, Quality of life in patients with bipolar I depression: data from 920 patients, Bipolar disorders, 2004; 6:379-385.
10. Goodwin FK, Murphy DL, *et al.* Lithium-carbonate treatment in depression and mania. A longitudinal double-blind study. *Archives of General Psychiatry,* 1969; 21(4):486-496.
11. Stokes PE, Shamoian CA, *et al.* Efficacy of lithium as acute treatment of manic-depressive illness. *Lancet*, 1971; 1(7713):1319-1325.
12. Ballenger & Post A randomized controlled trial of risperidone in the reatment of aggression in hospitalized adolescents with subaveragecognitive abilities: Journal of Clinical Psychiatry. 1978; 62:239-248.
13. Ketter TA, Kalali AH. A 6-month, multicenter, open-label evaluation of beaded, extended-release carbamazepine capsule monotherapy in bipolar disorder patients with manic or mixed episodes. *Journal of Clinical Psychiatry*,

2004; 65:668-673.
14. Weisler RH, Kalali AH, Keck PE, *et al.* A multicenter, randomized, double-blind, placebo-controlled trial of extended-release carbamazepine capsules as monotherapy for bipolar disorder patients with manic or mixed episodes. *Journal of Clinical Psychiatry*, 2004; 65:478-484.
15. Weisler RH, Keck PE, Swann AC, *et al*. Extended-release carbamazepine capsules as monotherapy for acute mania in bipolar disorder: a multicenter, randomized, double-blind, placebo-controlled trial. *Journal of Clinical Psychiatry*, 2005; 66:323-330.
16. MacRitchie K, Geddes JR, Scott J, *et al.* Valproic acid, valproate and divalproex for acute mood episodes in bipolar disorder. Cochrane Library, 2000, 4-4.
17. Muller-Oerlinghausen B, Retzow A, *et al.* Valproate as an adjunct to neuroleptic medication for the treatment of acute episodes of mania: a prospective, randomized, double-blind, placebo-controlled, multicenter study. Journal of Clinical Psychopharmacology, 2000; 20:195-203.
18. McElroy SL, Dessain EC, Pope HG, *et al.* Clozapine in the treatment of psychotic mood disorders, schizoaffective disorder, and schizophrenia. *Journal of Clinical Psychiatry*, 1991; 52:411-414.
19. Owen RR, Jr Beake BJ, Marby D, *et al.* Response to clozapine in chronic psychotic patients. *Psychopharmacological Bulletin*, 1989; 25:253-256.
20. Green A, Tohen M, Patel JK, *et al.* Clozapine in the treatment of refractory psychotic mania. *American Journal of Psychiatry*, 2000; 157:982-986.