

## AN OPEN CLINICAL TRIAL WITH CLOZAPINE IN TREATMENT-RESISTANT SCHIZOPHRENICS

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### ABSTRACT

*In an open trial, drug-resistant schizophrenics were treated with clozapine for sixteen weeks. The patients were rated on BPRS, PANSS, Side effects scale and Global Impression Scale at weeks 0, 9 and 16. A battery of base-line investigations were done, and hemogram was repeated at weekly intervals. Of the total 29 patients included, 25 completed the trial. The patients showed significant improvement on both BPRS and PANSS, although the improvement was more in initial weeks than between 9 and 16 weeks. The most common side effects observed were sedation, hypersalivation and tachycardia. Issues of response of clozapine on negative symptoms and a longer duration of the drug therapy are discussed.*

*Key Words:* clozapine, open trial, treatment-resistant schizophrenia

Clozapine is an atypical antipsychotic with superior efficacy in severely ill, treatment-resistant schizophrenics. It is a noncateptogenic agent (Coward et al., 1990) with high affinity for D<sub>1</sub> and D<sub>2</sub> receptors (Van Tol et al., 1991), besides having action on 5TH<sub>1</sub> (Altar et al., 1988) and 5TH<sub>2A</sub> sites (Cannon et al., 1990).

Its efficacy in schizophrenia was clearly demonstrated in earlier studies (Elholm & Haggerstrom, 1974; Singer & Law, 1974; Fischer Cornelissen & Ferner, 1976), but it was withdrawn from the market following reports of associated agranulocytosis (Idanpana-Heikkilä et al., 1977), a potentially life-threatening side-effect.

It was not until late eighties, that Kane et al. (1988) demonstrated the usefulness of clozapine in severely ill treatment resistant schizophrenics. This led to rejuvenation of interest in the drug, and many studies, both of controlled (Pickar et al., 1992); and descriptive type (Meltzer et al., 1990; Davies et al., 1991; Wilson, 1992) were published. These studies gave clozapine a solid standing in the treatment of schizophrenic patients who were resistant to conventional neuroleptics.

With clozapine being prescribed more frequently, although not regularly to every schizophrenic patient, further issues opened up. One such

point of debate was its ability to ameliorate negative symptoms. The drug was seen to have an unequivocal effective response on positive symptoms, and some studies also reported improvement in the negative symptoms. But what was not clear in these studies was that whether it were the primary or secondary negative symptoms that responded. As these studies also reported diminution in positive and extrapyramidal symptoms, this possibly could have led to a secondary improvement in the negative symptoms, rather than being a direct action of the drug. Addressing this issue, Brier et al. (1994) in a double blind study of clozapine and haloperidol concluded that the former drug was comparatively superior in treating negative symptom, although this effect was relatively minor. However, as haloperidol itself is known to have propensity for producing extrapyramidal symptoms, this conclusion does not seem to be very convincing. Other studies that support its efficacy in ameliorating the negative symptoms have also been published (Meltzer et al., 1989; Pickar et al., 1992; Clozapine Study Group, 1993; Miller et al., 1994) while others have refuted this finding (Brier et al., 1994; Conley et al., 1994). Carpenter et al. (1995) "... are profoundly committed to the idea that the deficit state is enduring and that no treatment yet available can provide effective relief." (cited in Meltzer, 1995).

Thus the present study was undertaken to evaluate the efficacy of clozapine in an open trial in schizophrenic patients who were non-responsive to the classical antipsychotics.

## MATERIAL AND METHOD

In an open, non-comparative and non-cross-over study schizophrenics were taken up for a 16 week trial. The cases selected were either chronic schizophrenics, acutely relapsed schizophrenics, or chronic schizophrenics with exacerbation. The diagnosis of schizophrenia was made according to ICD-10 (WHO, 1992). All the patients had already been treated in vain with at least two neuroleptics chosen from chlorpromazine (1000 mg/day or more), haloperidol or trifluoperazine in dose equivalents of 1000 mg/day or more of chlorpromazine. These drugs had already been tried for a period of at least six weeks in the past.

All the patients were rated on the following instruments by one of the authors (MS)

1. Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962) at weeks 0, 9, and 16.
2. Positive and Negative Syndrome Scale (PANSS) (Kay *et al.*, 1988) at weeks 0, 9, and 16.
3. Global Impression Scale at the beginning and end of the trial.
4. Side-effects scale-weekly.
5. Blood cell counts (Hb, TLC, DLC) - once weekly during the trial period and until 4 weeks later.
6. Blood pressure, pulse and temperature were recorded at weekly intervals.

All the patients were given a washout period of one week who were on oral neuroleptics, and four weeks for depot preparations. The patients who were not receiving any neuroleptics at the time of intake in the trial were initiated on clozapine right away after baseline investigations were completed. The initial dose was 50 mg/day which was increased to 100 mg/day by the end of the first week. Increments were made in the dose as 100 mg/week to achieve a daily dose of 300 mg by the end of the fourth week. From fifth to sixteenth week the dose range was 300-450 mg/day depending upon the therapeutic response and/or the presence of side ef-

fects.

The permitted concomitant medication was oral trihexyphenidyl for extrapyramidal symptoms, and nitrazepam for sleep.

Baseline investigations comprised of SGOT, SGPT, ECG, serum creatinine, chest X-ray, complete hemogram and urine analysis.

A total leucocyte count below 3500/cmm or granulocyte count below 1500/cmm warranted cessation of clozapine therapy.

The total scores of BPRS and subscales of PANSS were compared at 9 and 16 weeks from the baseline. Paired 't' test was employed to compare these ratings. The side-effect scores were calculated as the total percentage of patients exhibiting them.

## RESULTS

A total of 29 patients, between the ages 18-40 years, were included in the study, of which 4 dropped out for various reasons (seizures - 1, GIT disturbance - 1, pyrexia -1 and intercurrent illness-1). Thus 25 patients (18 males and 7 females) completed the study. The mean age of the patients and the duration of illness were  $28.8 \pm 5.2$  years and  $7.3 \pm 4.2$  years respectively.

**TABLE I**  
**BPRS TOTAL SCORES**

	MEAN	S.D
Week 0	40.76	12.50
Week 9	27.72	7.74*
Week 16	23.20	5.11**

\*Paired t-value = 17.53, d.f. = 24, ( $p < .001$ )

\*\*Paired t-value = 22.30, d.f. = 24, ( $p < .001$ )

The BPRS scores (Table I), when compared from week 0 ( $40.8 \pm 12.5$ ) showed improvement both at week 9 ( $27.7 \pm 7.7$ ) and week 16 ( $23.2 \pm 5.1$ ), which was highly significant statistically.

The improvement on BPRS total scores is further illustrated by the observation that by the end of 9th week, of the 25 patients, 17(68%) had shown improvement upto 25%. By the end of trial i.e. 16 weeks, the number had changed to 19(76%) in the 26-50% group and 6(24%) in the 0-25% group. None

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**TABLE 2**  
PERCENTAGE IMPROVEMENT FROM  
BASELINE TOTAL SCORES

PERCENTAGE IMPROVEMENT	9TH WEEK	16TH WEEK
0-25	8 (32%)	6 (24%)
26-50	17 (68%)	19 (76%)
Above 50	Nil	Nil

of the patients had improved beyond 50% as compared to the baseline (Table 2).

The PANSS scores also showed similar improvement, but the results were more variegated. When compared from the baseline, at week 9 the scores for the positive and negative syndromes, and general psychopathology showed moderately significant improvement ( $p < .05$ ) (Table 3), while for

**TABLE 3**  
SCORES ON PANSS SUBSCALES

MEASURES	WEEK 0 MEAN (S.D.)	WEEK 9 MEAN (S.D.)	WEEK 16 MEAN (S.D.)
Positive Syndrome	19.08 (6.82)	13.68(4.80)*	10.38 (3.87)
Negative Syndrome	20.08 (5.91)	13.80 (5.77)*	12.36 (6.01)
Composite Index	-0.28 (5.38)	0.08(5.72)	-2.24 (4.87)
General Psychopathology	36.2(10.1)	25.64 (8.30)	22.28 (5.97)*

For all values d.f. = 24; \* $p < 0.001$

**TABLE 4**  
SCORES ON PANSS MEASURES

MEASURES	WEEK 0 MEAN (S.D.)	WEEK 9 MEAN (S.D.)	WEEK 16 MEAN (S.D.)
Anergia	10.8 (8.34)	6.52 (2.21)***	6.16(2.57)***
Thought Disturbance	11.8 (3.57)	8.84 (3.39)***	6.64 (3.34)***
Activation	4.92 (2.17)	3.88(1.42)*	3.64(1.26)**
Paranoid/Belligerence	9.00 (3.76)	5.8 (2.49)***	4.2 (1.49)***
Depression	7.36 (4.13)	5.60 (2.28)**	4.92(1.83)*

for all values d.f.=24

\* $p > 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$

**TABLE 5**  
SIDE EFFECTS AT END OF WEEKS 1,9,16 IN  
PATIENTS WHO COMPLETED STUDY (N=25)

SIDE EFFECTS	WEEK1 N(%)	WEEK9 N(%)	WEEK16 N(%)
1. Mild sedation	5 (20)	8(32)	14 (56)
2. Moderate sedation	10 (40)	3(12)	7(28)
3. Severe sedation	4(16)	2(8)	1(4)
4. Mild hypersalivation	10(40)	12(48)	7(28)
5. Moderate hypersalivation	4(16)	1(4)	1(4)
6. Severe hypersalivation	1(4)	1(4)	--
7. Tachycardia	17(68)	12(48)	15(60)
8. Weight gain	1(4)	1(4)	3(12)
9. Constipation	3(12)	5(20)	4(16)
10. Tremors	--	1(4)	4(16)
11. Hyperthermia	1(4)	2(8)	--
12. Dizziness	2(8)	--	--
13. Hypotension	--	--	3(12)

anergia, thought disturbance and paranoid/belligerence showed highly significant improvement ( $p < 0.001$ ) (Table 4); for the rest of the subscales, the scores were significant at  $p < 0.01$  level.

At week 16, the trend for improvement on PANSS continued, but with little variation. Compared to that at week 9, for the positive syndrome, negative syndrome, general psychopathology, anergia, thought disturbance and paranoid/belligerence the improvement was similar, but that in activation was much more ( $p < 0.01$ ), and for depression much less ( $p < 0.05$ ), as compared to the other variables.

The side-effect profile (Table 5) shows that the most frequently observed side-effect was tachycardia throughout the period of the trial (68% at week 1, 48% at week 9, and 60% at week 16), followed by mild hypersalivation (40%, 48% and 28% respectively). Although a general trend seen was in diminution in the frequency of the observed side-effects, but sedation (mild) showed an acclivity with the progression of the trial. Moderate sedation was maximally observed in the initial week, and severe

sedation, although present initially in only a few patients (16% at week 1), gradually diminished in frequency (8% and 4% at weeks 9 and 16 respectively).

A significant finding was that among the 4 dropouts, none were due to hematological side-effect.

## DISCUSSION

Ours was an open study in which the efficacy of clozapine was evaluated in patients of schizophrenia who had been labeled previously as chronic/resistant or were intolerant to conventional neuroleptics.

In our study the initial BPRS scores were quite high, and showed a steady diminution over the duration of the trial. The improvement rated between weeks 9 and 16 was much more than that in the initial nine weeks. However, as the trial was terminated at this point, it cannot be commented whether this improvement would have accrued further or achieved a plateau. Other studies of longer duration have reported that the benefits stabilize in about 3-6 months time, after which no further benefit is seen (Lindstrom, 1988; Meltzer, 1992; Brier *et al.*, 1993). However, this time course of improvement seems not unique to clozapine, as Carpenter and colleagues (1995) have commented that a similar response time course is seen with the standard neuroleptic treatment.

In our study, clozapine was found to be effective against positive and negative symptoms both, as measured on PANSS. The changes in the negative symptoms, when compared from the baseline, were highly significant (Table 4), and the patients showed benefit on all the parameters. Other workers have shown a differential response on negative symptoms.

While Kane *et al.* (1988) found that clozapine significantly reduced scores for emotional withdrawal, blunted affect and psychomotor retardation, Meltzer *et al.* (1989) have reported that affective flattening and anhedonia does not respond to the drug. It has also been shown in some studies that the primary negative symptoms do not respond to clozapine (Conley *et al.*, 1994), but the drug is only of use in

ameliorating the secondary negative symptoms. Brier *et al.* (1994) in a controlled study, found that the patients with primary negative symptoms responded poorly to clozapine, although it was beneficial in patients with non-deficit schizophrenia. In our study we did not differentiate between deficit and non-deficit schizophrenia, neither covariates the significance of response in negative symptoms to the positive symptoms.

Clozapine, initially introduced about 3 decades ago, was withdrawn from the market owing to reports of agranulocytosis induced by it. Lieberman *et al.* (1988) have cited a 2% cumulative incidence after 52 weeks of clozapine treatment for agranulocytosis. In our study none of the patients developed even leucopenia sufficient enough to stop the treatment.

The other common side-effects observed in our study were sedation, hypersalivation, tachycardia, postural hypotension and dizziness (Table 5). Fitton & Heel (1990) have observed similar side-effects in as many as 40% of their patients. Brier *et al.* (1994) also found excessive salivation and tachycardia to be most frequently observed adverse effect, which is in close agreement with our findings.

This being one of the first studies in the country, we do not have other data to compare our findings with the patients in this country. This initial study has shown the benefits of clozapine in chronic or treatment-resistant patients which argues favorably for the drug. As it is a new drug for this country, and consequently, there not being much clinical experience with it, the clinicians should be cautious in using it.

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## REFERENCES

- Alter, C.A.; Wasley, A.M.; Neale, R.E. & Stone, G.A. (1988) Typical and atypical antipsychotic occupancy of D<sub>2</sub> and S<sub>2</sub> receptors: an autoradiographic analysis in rat brain. *Brain Research Bulletin*, 16, 517 - 525.

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- Brier, A.; Buchmann, R.W. & Kirkpatrick, B. (1994)** Effects of clozapine on positive and negative symptoms in outpatients with schizophrenia. *American Journal of Psychiatry*, 151, 20-26.
- Brier, A.; Buchanan, R. W.; Irish, D. & Carpenter, W. T. Jr. (1993)** Clozapine treatment of outpatients with schizophrenia : outcome and long term response patterns. *Hospital Community Psychiatry*, 44, 1145-1149.
- Canton, H.; Verrielle, L. & Colpaert, F. C. (1990)** Binding of typical and atypical antipsychotics to 5HT<sub>2</sub> sites. Clozapine potentially interacts with 5HT<sub>1c</sub> sites. *European Journal of Pharmacology*, 191, 93-96.
- Carpenter, W.T., Jr.; Conley, R.R.; Buchanan, R. W.; Brier, A. & Tamminga, C. A. (1995)** Patient response and resource management: Another view of clozapine treatment of schizophrenia. *American Journal of Psychiatry*, 152, 827-832.
- Clozapine Study Group (1993)** The safety and efficacy of clozapine in severe treatment resistant schizophrenic patients in the UK. *British Journal of Psychiatry*, 163, 150-154.
- Conley, R.; Gounaris, C. & Tamminga, C. (1994)** Clozapine response varies in deficit versus non-deficit schizophrenic subjects. *Biological Psychiatry*, 35, 746-747.
- Coward, D.M.; Imperata, A.; Urvylef, S. & White, T.G. (1990)** Biochemical and behavioral properties of clozapine. *Psychopharmacology*, 99, 806-812.
- Davies, M.A.; Condely, R.R. & Schulz, S.C. (1991)** One year follow-up of 24 patients in a clinical trial of clozapine. *Hospital Community Psychiatry*, 42, 628-629.
- Elholm, B. & Haggstrom, J.E. (1974)** Clozapine (Leponex) compared with chlorpromazine : a double blind evaluation of pharmacological and clinical properties. *Current Therapeutic Research*, 16, 245-257.
- Fisher Cornelsson, K.A. & Ferner, U.J. (1976)** An example of European multicentre trials : multispectral analysis of clozapine. *Psychopharmacology Bulletin*, 12, 34-39.
- Fitton, A. & Heel, R.C. (1990)** Clozapine. A review of its pharmacological properties, and therapeutic use in schizophrenia. *Drugs*, 40, 5, 722-747.
- Idanpaan-Heikkila, J.; Alhava, E.; Olkioura, M. & Palva, P. (1977)** Agranulocytosis during treatment with clozapine. *European Journal of Clinical Pharmacological*, 11, 193-198.
- Kane, J. ; Honizfeld, G.; Singer, J. & Meltzer, H. (1988)** Clozapine for treatment resistant schizophrenics: a double blind comparison with chlorpromazine. *Archives of General Psychiatry*, 45, 789-796.
- Kay, S.G.; Opier, L.D. & Lindenmayer, J.R. (1988)** Reliability and validity of the Positive and Negative Syndrome Scale for schizophrenia. *Psychiatry Research*, 23, 99-110.
- Lieberman, J.A. ; Johns, C.A.; Kane, J.M.; Rai, K.; Piscotta, A.V.; Saltz, D.L. & Howard, A. (1988)** Clozapine induced agranulocytosis: non cross-reactivity with other psychotropic drugs. *Journal of Clinical Psychiatry*, 50, 329-338.
- Lindstrom, L.H. (1988)** The effect of long term treatment of clozapine in schizophrenia: a retrospective study of 96 patients treated with clozapine for upto 13 years. *Acta Psychiatrica Scandinavica*, 77, 524-529.
- Meltzer, H.Y.; Bastani, B.; Kwan, K.Y.; Ramirez, L.F.; Burnett, S. & Sharpe, J. (1989)** A prospective study of clozapine in treatment-resistant schizophrenic patients. 1: Preliminary report. *Psychopharmacology (Berlin)*, 99 (suppl), 568-572.
- Meltzer, H.Y. ; Burnett, S; Bastani, B. & Ramirez, L.F. (1990)** Effect of six months of clozapine on quality of life of chronic schizophrenic patients. *Hospital Community Psychiatry*, 41, 892-897.
- Meltzer, H.Y. (1992)** Dimensions of outcome with clozapine. *British Journal of Psychiatry*, 160 (Suppl 17), 46-53.
- Meltzer, H.Y. (1995)** Clozapine: Is another view valid? (editorial) *American Journal of Psychiatry*, 152, 821-823.
- Miller, D.D.; Perry, P.J.; Cadorer, R.J. & Andreasen, N.C. (1994)** Clozapine's effect on negative symptoms in treatment refractory schizophrenics. *Comprehensive Psychiatry*, 35, 8-15.

**Overall, J.E. & Gorham, D.R. (1962)** The Brief Psychiatric Rating Scale. *Psychological Report*, 10, 799-812.

**Picker, D.A.; Owen, R.R. & Litman, R.E. (1992)** Clinical and biologic response to clozapine in patients with schizophrenia: crossover comparison with fluphenazine. *Archives of General Psychiatry*, 49, 345-353.

**Singer, K. & Low, S.K. (1974)** A double blind comparison of clozapine (Leponex) and chlorpromazine in schizophrenia of acute symptomatology. *Journal of Internal Medicine Research*, 2, 433-435.

**Van Toi, H.H.M.; Bunzow, J.R.; Guan, H.C. et al. (1991)** Cloning of gene for human D<sub>1</sub> receptor with high affinity for the antipsychotic clozapine. *Nature*, 350, 610-619.

**Wilson, W.H. (1992)** Clinical review of a clozapine treatment in a state hospital. *Hospital Community Psychiatry*, 43, 700-703.

**Wilson W.H. (1992)** Clinical review of a clozapine treatment in a state hospital. *Hospital Community Psychiatry*, 43, 700-703.

**World Health Organization (1992)** International classification of diseases : Clinical descriptions and diagnostic guidelines 10th edition (ICD-10). Geneva : W.H.O.

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