

Efficacy of clozapine in patients with chronic schizophrenia

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Background

Clozapine is the most effective treatment for refractory schizophrenia. There is evidence that clozapine improves social and occupational functioning and patients' quality of life.

Aims

To evaluate the presence of psychopathology and level of functioning in a cohort of patients treated with clozapine.

Methods

Sixty seven patients attending a clozapine clinic during a two month period were enrolled. Socio-demographic characteristics, duration of treatment and dose of clozapine were recorded. Symptom severity was measured using a psychopathology scale. Level of functioning was assessed using the "Psycho Social Functioning Scale".

Results

Of the sample 53.7% were males. Majority were aged 20-39 years. In the sample 7.4% were treated with clozapine for two years or less, 38.8% for 3-5 years and 40.3% for 6-10 years. Of the sample 43.3% were on 225-400 mg/day. In the self care sub scale 61 (95.3%) scored 13-15 from a maximum of 15. In the daily function sub scale 42 patients (65.7%) scored more than 10 from maximum 15 points. Thirteen males (36.1%) and 8 females (25.8%) were engaged in full time paid employment. Three males and 2 females were full time students. Another 6 (19.4%) females did full time household work.

Conclusions

Patients on long term treatment with clozapine showed low levels of psychopathology. In the majority self care and other daily functions were adequate. Many patients treated with clozapine were engaged in full time employment.

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Introduction

About 25% to 33% of patients with schizophrenia have illnesses that are treatment-resistant (1). Clozapine is the most effective treatment of refractory schizophrenia (2, 3). There is evidence that clozapine improves social and occupational functioning and patients' quality of life, decreases the rate and length of hospitalization and reduces affective symptoms, secondary negative symptoms, and tardive dyskinesia (4). A Cochrane review of 42 randomized trials found no significant difference in the effects of clozapine and typical neuroleptic drugs for broad outcomes such as mortality, ability to work or suitability for discharge (1). Other studies have found clozapine to be superior to other antipsychotics in the treatment of acute symptoms (1, 3, 4). The superiority is more for residual positive symptoms but it is also more effective than first generation antipsychotics in the treatment of negative symptoms (1). Clozapine is also more effective than first generation antipsychotics in non treatment resistant patients (5).

There is evidence that clozapine is more effective than second generation antipsychotics. The National Institute of Mental Health (NIMH) sponsored Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) reports that for patients with schizophrenia who failed to improve with an atypical antipsychotic, clozapine is more effective than switching to another newer atypical antipsychotic (6). However a randomized trial comparing high-dose olanzapine (25-45 mg/day)

and clozapine (300-900 mg/day) in patients with schizophrenia or schizoaffective disorder who had failed to respond adequately to prior treatment with other antipsychotic drugs, found both drugs to be equally effective in reducing psychopathology and improving cognitive functions (7). Most studies on effectiveness of clozapine considered reduction in symptoms as the primary outcome measure. However restoring psychosocial functioning is a main goal of recovery from mental illness. Ability to look after oneself, role functioning, quality of life and being a productive member of society are now increasingly used as outcome measures in schizophrenia.

Cognitive functions are impaired in patients with schizophrenia. There is evidence that cognitive impairment is a better predictor of work and social function in schizophrenia than are positive and negative symptoms (8).

Data from a prospective longitudinal study in 59 treatment-resistant schizophrenia or schizoaffective disorder patients found 47 of 59 (79.7%) patients were unemployed at baseline (8). Over a 12 month period, 23 (48.9%) additional patients were able to gain paid or volunteer jobs, or attend school. Another study reporting long term outcome of patients on clozapine found that 85% of 96 patients with schizophrenia who were hospitalized could be discharged from hospital after one year. Of the 62 patients who were still on clozapine after 2 years, 18% had full time and 21% half-time employment (9).

Because there is little data on effectiveness of clozapine in treating psychopathology and improving psychosocial functioning among patients in developing countries, we carried out a cross sectional study on a cohort of patients attending the specialized clozapine monitoring clinic at the University Psychiatry Unit, Colombo.

Methods

Our objectives were to assess the efficacy and level of functioning in a cohort of patients treated with clozapine.

Sixty seven patients attending the specialized clozapine monitoring clinic during a two month period at the University Psychiatry Unit, Colombo were enrolled in the study. Socio-demographic characteristics, duration of treatment and dose of clozapine were recorded. Symptom severity was measured using the "Psychopathology Measurement Scale" a scale similar to the Positive and Negative Syndrome Scale (PANSS) (10). The scale was scored by a medical officer trained in the use of the scale after interviewing the patient. The Psychopathology Measurement Scale measured key areas of positive symptoms, negative symptoms and other psychopathology. The positive symptom sub scale measured the severity of seven positive symptoms. The negative symptom sub scale measured the severity of seven negative symptoms. The general psychopathology sub scale measured 16 symptoms which included anxiety and mood symptoms. The positive and negative symptom sub scale scores ranged from 0-42 and other psychopathology sub scale score ranged from 0-96 giving a total score range of 0-180. Severity of each item was measured on a scale of 0 (absent) to 6 (extreme).

Level of functioning was assessed using the "Psycho Social Functioning Scale" which was developed for use in the clozapine clinic. In developing the scale we first identified behaviours which are impaired in patients with chronic schizophrenia. The scale comprised of two sub scales "self care" and "daily functions". The five item "self care" sub scale assessed the behaviours of bathing, dressing, oral care, toileting and eating. The "daily functions" sub scale assessed shopping, household work, driving or using public transport, managing medication and managing finances. These items were then scored on a scale of 0-3 based on

Table 1- Characteristics of the sample	
Demographic and treatment details	Frequency (%) n=67
Gender	
Female	31(46.3)
Male	36 (53.7)
Age group	
12-19 years	1 (1.5)
20-29 years	23 (34.3)
30-39 years	31 (46.3)
40-49 years	9 (13.4)
50-59 years	3 (4.5)
Education	
Grade 1-5	1 (1.5)
Grade 6-10	10 (14.9)
GCE O' Level	27 (40.3)
GCE A' Level	20 (29.9)
Degree or higher	6 (9.0)
Not recorded	3 (4.5)
Duration of clozapine treatment	
0-2 years	5 (7.4)
3-5 years	26 (38.8)
6-10 years	27 (40.3)
>10 years	9 (13.4)
Clozapine dose	
0-200 mg/day	17 (25.4)
225-400mg/day	29 (43.3)
425-600mg/day	18(26.9)
>600mg/day	3 (4.5)

the ability of the patient to carry out each behaviour. Scores were given as follows. "Carries out function independently"-3, "needs verbal prompting" -2, "needs help from others"-1, "does not carry out behavior at all"-0. Assessment was done by medical officers after interviewing the patient and a carer. The two sub scales were scored separately. Each sub scale gave a total score ranging from 0-15.

Ethical clearance for the study was obtained from the National Hospital of Sri Lanka Ethics Committee.

Results

The description of the sample is given in table 1. Of the sample 53.7% were males. Majority were young aged

Table 2- Distribution of psychopathology				
Score	Positive scale range 0-42 n (%)	Negative scale range 0-42 n (%)	Other symptoms scale range 0-96 n (%)	Total score range 0-180 n (%)
0	35 (52.2)	22 (32.8)	16 (23.9)	11 (16.4)
1-10	28 (41.8)	25 (37.3)	28(41.8)	23 (34.3)
11-20	4 (6.0)	11(16.4)	14 (20.9)	8 (11.9)
21-30	0	7 (10.4)	7 (10.4)	9 (13.4)
31-40	0	1 (1.5)	2 (3.0)	4 (6.0)
40-60	0	1(1.5)	0	10 (14.9)
>60	Not relevant	Not relevant	0	2 (3.0)

20-39 years. Because adolescents were registered in another clinic there was only one patient aged less than 19 years in the sample. Most patients had achieved a reasonable educational attainment with 40.3% passing GCE O' Level and 29.9% passing GCE A' Level.

Clozapine treatment

All patients were started on clozapine due to resistance to at least two other antipsychotics. Only 7.4% had been on clozapine two years or less, 38.8% had been treated for 3-5 years and 40.3% for 6-10 years. Although a minimum daily dose of 200 mg is recommended for clozapine, 12 patients (17.9%) were on a daily dose of 200 mg/day while 5 were on 150 mg/day. These patients could not tolerate a higher dose of clozapine. Of the sample 43.3% were on 225-400 mg/day. Only 3 patients were on more than 600 mg/day.

Outcome measures

Psychopathology was assessed using a scale which had a positive scale, negative scale and general psychopathology scale similar to the PANSS (10). Distribution of psychopathology in the patients is given in table 2. Majority of the patients (52.2%) did not have any positive symptoms such as delusions, hallucinations or hostility as measured by the positive scale. Only 32.8% did not have any negative symptoms. Significant negative symptoms (score>20) were seen in 9 (13.4%) patients. The total score which is an indication of the overall psychopathology shows that 16 (23.8%) had a score over 30. The mean total score was 18.8 (SD=20.3).

Scores on the scales measuring level of functioning are given in table 3. Scores of the self care sub scale show 95.3% of the patients scored high (13-15) indicating good self care in relation to bathing, dressing, oral care, toileting and eating . In the daily functions sub scale which measured shopping, household work, driving or using public transport, managing medication and managing finances, 42 patients (65.7%) scored more than 10 points indicating reasonable independent functioning.

Table 4 shows employment status of the sample. Thirteen males (36.1%) and 8 females (25.8%) were engaged in full time paid employment. A considerable number functioned as clerks and professionals Three males (8.3%) and 2 (6.4%) females were full time students. Another 6 females (19.4%) were engaged in full time household work.

Score	Self care sub scale frequency (%) n=64	Daily functions sub scale frequency (%) n=64
0-5	0	9 (14.1)
6-9	0	13 (20.3)
10-12	3 (4.7)	20 (31.3)
13-15	61 (95.3)	22 (34.4)

Employment	Female n(%)	Male n(%)	Total n (%)
Student	2 (6.5)	3 (8.3)	5 (7.5)
Full time housework	6 (19.4)	0 (0)	6 (9)
Manual worker	1 (3.2)	2 (5.6)	3 (4.5)
Clerk	4 (12.9)	7 (19.4)	11 (16.4)
Professional	1 (3.2)	2 (5.6)	3 (4.5)
Others	2 (6.5)	2 (5.6)	4 (6)
Unemployed	15 (48.4)	20 (55.6)	35 (52.2)
Total	31	36	67

Discussion

The main findings from our study are that in a population of patients treated with clozapine due to resistance to other antipsychotics, majority experienced little psychopathology. These patients had good self care and reported reasonable independent functioning. More than 30% of the patients were engaged in paid employment.

In the CATIE trial where 49 patients who were resistant to other antipsychotics were treated with clozapine the PANSS mean score reduced by 18.4 from a baseline mean of 90.3 after 6 months of treatment (6). The mean total score in our sample of 18.8 was much lower. One possible explanation is that the CATIE sample was evaluated after six months of treatment whereas our sample had been on treatment for much longer. The lower rate of psychopathology among our sample is corroborated by the high level of functioning in the group.

Few studies have looked at level of functioning and employment status of patients treated with clozapine. Lindstrom reported in a long-term follow up study of 96 patients treated with clozapine for up to 13 years 39% were employable on at least a part-time basis (9).

Other studies report poor outcome in patients with schizophrenia with no more than 30% of schizophrenia patients holding part-time or full-time jobs (11) For example, only 51.8 percent of first-episode schizophrenia patients were reported to recover functionally one year after the onset of psychosis (12). In the USA unemployment rates amongst people with severe mental disorder are estimated at 75–85% while in the UK rates of 61–73% have been reported (13,14). Considering that our sample consisted of patients resistant to at least two other antipsychotics the rate of full time employment and education in our sample was as good as or better than those reported from the West.

Evidence suggests that various forms of cognitive impairment, such as verbal learning, memory, executive function, and vigilance, may be of equal or greater importance than positive or negative symptoms in predicting functional outcomes (15). Studies have found that clozapine improves the cognitive domains of verbal fluency, attention, some types of executive

function, verbal learning and memory (15). This could explain why our patients despite long duration of illness had good functional outcome.

There are several limitations in our study. Since there was no evaluation of psychopathology or level of functioning prior to starting clozapine we were unable to evaluate the change in these outcomes due to clozapine. We also did not have a record of pre-illness employment status. The level of functioning was assessed using a simple scale which is useful in clinical practice. Due to the small sample size we did not attempt to identify other factors which would have influenced the functional level in our patients. Since this was a cross sectional study rates of discontinuation and non compliance were also not recorded.

Our findings have several implications. Although the functional level was satisfactory in the majority of patients a sizeable number have ongoing symptoms and poor functional level. This indicates that a parallel psychosocial rehabilitation program must be implemented for patients on clozapine with poor functioning. A cohort of patients evaluated periodically from the onset of starting clozapine treatment will indicate if patients in Sri Lanka treated with clozapine have a better outcome than those in Western countries.

Declaration of interest

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References

1. Essali A, Al-Haj Haasan N, Li C, Rathbone J: Clozapine versus typical neuroleptic medication for schizophrenia. *Cochrane Database Syst Rev* 2009; (1):CD000059.

2. Kane JM: Treatment-resistant schizophrenic patients. *J Clin Psychiatry* 1996;57 Suppl 9:35-40.
3. Safferman A, Lieberman JA, Kane JM, Szymanski S, Kinon B: Update on the clinical efficacy and side effects of clozapine. *Schizophr Bull* 1991; 17(2):247-261.
4. Buchanan RW: Clozapine: efficacy and safety. *Schizophr Bull* 1995; 21(4):579-591.
5. Meltzer HY, Bobo WV, Lee MA, Cola P, Jayathilake K: A randomized trial comparing clozapine and typical neuroleptic drugs in non-treatment-resistant schizophrenia. *Psychiatry Res* 2010; 177(3):286-293.
6. McEvoy JP, Lieberman JA, Stroup TS, Davis SM, Meltzer HY, Rosenheck RA, Swartz MS, Perkins DO, Keefe RS, Davis CE et al: Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry* 2006; 163(4):600-610.
7. Meltzer HY, Bobo WV, Roy A, Jayathilake K, Chen Y, Ertugrul A, Anil Yagcioglu AE, Small JG: A randomized, double-blind comparison of clozapine and high-dose olanzapine in treatment-resistant patients with schizophrenia. *J Clin Psychiatry* 2008; 69(2):274-285.
8. Kaneda Y, Jayathilak K, Meltzer H: Determinants of work outcome in neuroleptic-resistant schizophrenia and schizoaffective disorder: cognitive impairment and clozapine treatment. *Psychiatry Res* 2010; 178(1):57-62.
9. Lindstrom LH: The effect of long-term treatment with clozapine in schizophrenia: a retrospective study in 96 patients treated with clozapine for up to 13 years. *Acta Psychiatr Scand* 1988; 77(5):524-529.
10. Kay SR, Fiszbein A, Opler LA: The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13(2):261-76.
11. Mulhern VM MR: Characteristics of community support programme clients 1980 and 1984. *Hospital and Community Psychiatry* 1989; 40(2):165-172.
12. Renshaw PF, Yurgulen-Todd DA, Tohen M, Gruber S, Cohen BM: Temporal lobe proton magnetic resonance spectroscopy of patients with first-episode psychosis 1995; 152(3): 444-6
13. Marshall M, Almaraz-Sorrano, Creed F et al.: Systematic reviews of the effectiveness of day care for people with severe mental disorders: (1) acute day hospital versus admission; (2) vocational rehabilitation; (3) day hospital versus outpatient care. *Health Technol Assess* 2001; 5(21):1-75.
14. Lehman A: Vocational rehabilitation in schizophrenia. *Schizophrenia Bulletin* 1995; 21:645-656.
15. Meltzer HY, McGurk SR: The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. *Schizophr Bull* 1999; 25(2):233-255.