

Contrasting Clozapine Prescribing Patterns in the East and West ?

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Abstract

Introduction: Polypharmacy is common in the treatment of schizophrenia and it may be especially common in the East. In this survey, we compared the effect of clozapine, an atypical neuroleptic, on polypharmacy in two groups of patients with schizophrenia in two different settings. **Materials and Methods:** The medical charts of patients on stable doses of clozapine from a Canadian psychiatric centre and that of a Southeast Asian centre were analysed to evaluate the daily dose requirement and the concomitant medications prescribed. The beliefs of the Asian psychiatrists on the concomitant use of another neuroleptic were also examined. **Results:** The mean daily dose of clozapine was 408 mg/day for the Canadian subjects and 169 mg/day for the Asian sample. Of the Canadian sample, none were prescribed another neuroleptic, 45% were on a benzodiazepine, and 10% were receiving an anticholinergic agent. The Singapore sample indicated 28% of the subjects on another neuroleptic, with 36% taking an anticholinergic agent and 28% on a benzodiazepine. The Asian psychiatrists prescribed a second neuroleptic in the belief that it would reduce cost and enhance the antipsychotic effect. **Conclusions:** This study suggests that there are regional differences in the prescription patterns and daily dose requirements of clozapine.

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Introduction

Schizophrenia is a severe mental illness which causes enormous suffering, impaired social and occupational functioning, as well as higher mortality among the sufferers.¹ The mainstay of treatment is neuroleptics which are largely effective for certain symptoms of this illness. However, only 36% of patients with schizophrenia have a favourable outcome² and it is therefore not unusual for clinicians to resort to polypharmacy (defined as the use of two or more psychotropic drugs) to optimise response.

For the past four decades, there were no significant advances in the pharmacotherapy of schizophrenia until the advent of clozapine. Early open studies in Europe had demonstrated its efficacy in patients with schizophrenia but in 1974, 8 patients in Finland died after developing agranulocytosis which led to the withdrawal of clozapine from widespread clinical use although some limited usage was permitted under strict monitoring.³ The publication in 1988 of a landmark study in America showed clozapine to be more effective than the older antipsychotic medications

in a group of treatment-resistant schizophrenia.⁴ This led to its licensed use in America, United Kingdom, and other countries including Singapore albeit with mandatory haematological monitoring.

While clozapine is reported to be effective in 30% to 60% of schizophrenic patients who do not respond to the older neuroleptics,⁵ there remains a substantial percentage who have a less than optimal response. This study compared the clozapine prescribing patterns with regards to dose and concomitant medications of psychiatrists in a North American psychiatric facility with their counterparts in a Southeast Asian facility. We also examined the beliefs of the Asian psychiatrists about adding a second neuroleptic to clozapine.

Materials and Method

The North American study was conducted at the Schizophrenia Division of the Clarke Institute of Psychiatry in Toronto, Canada which is an academic and research unit. The Southeast Asian study was undertaken within an

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outpatient facility of the state mental institute in Singapore. In both centres, clozapine was used to treat patients who had not been able to tolerate or had shown poor response to conventional neuroleptics. A list of all outpatients who were on clozapine at both centres was compiled from computerised pharmacy databases and the records of the haematological monitoring systems. All subjects had a DSM-IV diagnosis of schizophrenia and were receiving stable doses of clozapine (i.e. unchanged for at least one month). The following information was extracted from the case records: age, gender, duration of illness, duration and daily dose of clozapine treatment, and concomitant medications at the time of the study.

In addition, all the psychiatrists at the centre in Singapore who were prescribing clozapine were asked to complete a questionnaire on their opinion of using a second neuroleptic with clozapine. This semi-structured questionnaire which gave the psychiatrists a number of specific choices including increased antipsychotic efficacy, cost containment and reduction of side-effect of clozapine, also allowed each psychiatrist to give any other reason for using this strategy.

Results

Forty-two patients from the Clarke Institute were identified. There were 36 Caucasians, 2 African-Americans, 1 South Indian, 2 Vietnamese and 1 Korean. Ten (23.8%) were females and 32 (76.2%) were males. The sample from Singapore comprised 45 patients (43 Chinese, 1 Malay and 1 South Indian), with 28 (62.2%) females and 17 (37.8%) males. Table I shows the clinical characteristics of these two samples. There were more females than males among the patients in Singapore ($\chi^2 = 12.9$, $df = 1$, $P < 0.01$). Clozapine is used in both centres to treat patients with treatment refractory schizophrenia and so the patients were similar to each other in this aspect.

Of the 14 Canadian psychiatrists who had prescribed clozapine, none added a second neuroleptic to clozapine. Twelve (26.7%) patients in the Singapore sample were prescribed another neuroleptic (Table II). The second most common concomitant medication prescribed for this sample

was an anticholinergic agent in 16 (35.6%) patients and, of these, 6 were also receiving a typical neuroleptic. Among the Canadian patients, the most common concomitant agent was a benzodiazepine.

A total of 21 Asian psychiatrists completed the questionnaire. Eight did not subscribe to adding another neuroleptic. Of the 13 who so prescribed, the most frequently nominated reason was an attempt at cost containment ($n = 10$), while 7 indicated that it may improve antipsychotic efficacy.

TABLE II: CONCOMITANT MEDICATIONS PRESCRIBED WITH CLOZAPINE

Drugs prescribed with clozapine	Canadian patients		Singaporean patients	
	n	%	n	%
Typical neuroleptics	0	0.0	12	26.7
Anticholinergic agents	4	9.9	16	35.6
Benzodiazepines	19	45.2	12	26.7
Selective serotonin reuptake inhibitors	8	19.0	1	2.2
Tricyclic antidepressants	2	4.8	5	11.1
Sodium valproate	11	26.2	5	11.1
Lithium	0	0.0	2	4.5

Discussion

Fleischhacker et al⁶ reported that the mean clozapine dose of the studies done in Europe was 284 mg/day, while a higher daily dose of 444 mg/day was found in the North American studies. The mean daily dose of the Canadian patients was 408 mg/day closely paralleling other North American studies, while that of the Asian patients was much lower (169 mg/day). The low daily clozapine dose among the Asian patients could be due to a number of reasons. One of which may be the different demographics of the two groups. The Asian sample, predominantly Chinese, had more females than males. It has been suggested that most patients will respond to clozapine with blood levels of 200 to 400 ng/ml,⁷ and while blood levels were not

TABLE I: CHARACTERISTICS OF PATIENTS ON CLOZAPINE

Variables	Patients from Clarke Institute, Toronto (n = 42)				Patients from Woodbridge Hospital, Singapore (n = 45)				Mann-Whitney U test
	Mean	Standard deviation	Median	Range	Mean	Standard deviation	Median	Range	P
Age (y)	34.4	8.2	33.0	21-55	34.7	9.2	34.0	21-53	0.95
Duration of illness (y)	13	7.8	10.5	3-36	12.4	7.1	10.0	3-28	0.91
Duration of clozapine (mo)	30.6	18.1	30.4	4-68	36.1	18.7	34.0	11-71	0.19
Daily dose of clozapine (mg/day)	408.3	155.0	400.0	75-900	169.1	106.5	150.0	25-425	<0.001

examined here, studies have reported that higher plasma levels are attained in females^{8,9} and in Chinese patients,¹⁰ two factors of possible relevance. Another reason may be the deliberate strategy of the Asian psychiatrists to combine another neuroleptic to augment the antipsychotic efficacy of clozapine as well as to contain cost, thereby reducing the daily dose of clozapine. The practice of using another antipsychotic does not appear to be unique to Asian psychiatrists. Naber et al,¹¹ in a chart review of 480 inpatients in Germany, reported that 19% were being treated concomitantly with typical neuroleptics. A survey in Denmark¹² reported that 35% of 656 patients treated with clozapine also received typical neuroleptics. Peacock and Gerlach¹² suggested that typical neuroleptics may be added to counter certain side-effects of clozapine; to ensure compliance through the addition of depot preparation; and, to increase antipsychotic efficacy. The potential of an augmented antipsychotic effect has also been suggested in some reports.^{13,14} However, the addition of a typical antipsychotic medication would expose the patients to extrapyramidal side-effects. This might have led to the greater use of anticholinergic agents among the Asian than Canadian patients. It could also be possible that the Asian patients are generally more prone to developing hypersalivation which is then treated with anticholinergic agents.

The use of concomitant benzodiazepines was common in both samples. Despite reports of severe cardiorespiratory collapse with clozapine-benzodiazepine combinations,¹⁵ other studies have also reported that the concomitant use of benzodiazepines and clozapine in clinical practice is not uncommon. For example, Frankenburg and Baldessarini¹⁶ reported a third of 200 patients treated with clozapine were also taking benzodiazepines, with no increase in side-effects. Again, Peacock and Gerlach¹² reported that 28% of 656 patients treated with clozapine were also receiving benzodiazepines.

Our study suggests that polypharmacy still occurs commonly for patients on clozapine, with apparent differences among Canadian and Asian psychiatrists in their attitude towards adding a second neuroleptic, as well as prescription of lower doses for Asian patients. Polypharmacy in the management of patients with schizophrenia has been suggested to be particularly common among Asian psychiatrists.¹⁷⁻¹⁹ Some of the reasons suggested include the "unproven" belief of the physicians that a combination of drugs is more effective¹⁹ and the beliefs of patients that the more drugs prescribed, the better the effect.¹⁷ It has further been suggested that polypharmacy in the East is related to the Oriental traditional medicine in which the best prescriptions include a mixture of various ingredients.¹⁸

As with all cross-sectional surveys, this study has the

inherent limitations of just collecting prescription data and with what treatment is prescribed, and not why the treatment is being prescribed or determining any differences in the response of patients with clozapine monotherapy and those with concomitant neuroleptics.

As the study involved single outpatient facilities in each region (albeit the Singapore one being the state mental facility and the Canadian one being an academic centre), differences may reflect Eastern versus Western patterns of practice or merely be idiosyncratic to each facility. The fact that such differences have been identified, though, argues for an international overview of this issue, particularly to evaluate other regional differences and possible determinants.

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