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Prescription practices and attitude of psychiatrists towards clozapine: A survey of psychiatrists from India

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ABSTRACT

Aim: To assess the attitude of psychiatrists towards clozapine and also to evaluate the prescription practices of psychiatrists for clozapine.
Methodology: An email survey was sent to 3381 psychiatrists from India, of whom 548 (16.2%) responded.
Results: Mean number of years in clinical practice was 12.59 (SD—10.1) for participating psychiatrists. Majority of the participants rated their knowledge about clozapine to be good (61.5%)/very good (34.5%). The primary indication for use of clozapine for almost all the participants was treatment resistance and most of the psychiatrists initiated clozapine either in the dose of 25 mg OD (44.3%) or 12.5 mg OD (37%). Half (51.8%) of the psychiatrists preferred to use clozapine as BD dosing schedule, and median doses required to stabilize the patients ranged from 137.5 to 400 mg/day. Once the clozapine dose had been stabilized, about half (51%) of the psychiatrists advised blood monitoring at monthly intervals. Almost all psychiatrists rated effectiveness of clozapine to be better than other antipsychotics. In terms of tolerability, 45.3% of the psychiatrists rated it as 'same as other antipsychotics' and 15.9% rated it as better than other antipsychotics. Most common patient and therapist related factors associated with reluctance to start clozapine were history of poor medication compliance and need for monitoring, respectively. Upon reviewing the prescription of other psychiatrists, participating psychiatrists reported that in about 28.46% of patients clozapine was not prescribed though indicated.
Conclusions: This survey suggests that clozapine is underused in India, although psychiatrists have adequate knowledge about the drug but many psychiatrists have negative attitude towards clozapine.

1. Introduction

Clozapine is an atypical antipsychotic medication which has been found to be more efficacious than other antipsychotics. However, due to its side effect profile, its use is usually limited to patients with treatment resistant schizophrenia (TRS). It is possibly the only antipsychotic medication which has been shown to be superior to other medications in patients of schizophrenia who are partially or non-responsive to treatment, and is the only evidence-based medication for TRS (Kane and Correll, 2010). The CATIE trial suggested that time to discontinuation for clozapine is longer than other atypical antipsychotics, and it is more effective than quetiapine in management of depressive symptoms in patients with chronic schizophrenia (McEvoy et al., 2006; Meltzer et al., 2003; Nakajima et al., 2015). Clozapine has also been shown to reduce the incidence of suicide (Krakowski et al., 2006), aggression (Krakowski et al., 2006), risk of relapse of substance abuse (Brunette et al., 2006), rate of rehospitalization (Tiihonen et al., 2006) and is associated with lowest risk of premature mortality even after controlling for clinical monitoring and other potential confounders (Tiihonen et al., 2009; Hayes et al., 2015).

Clozapine is often under-used (Nielsen et al., 2010) and its initiation is often delayed (Howes et al., 2012; Grover et al., 2015a). Data from Australia demonstrate that only 8.4% of individuals with refractory schizophrenia are prescribed clozapine (Vella and Pai, 2012). Similarly, data from the United Kingdom shows that only 30% of the patients who actually require clozapine are prescribed the same (Downs and Zinkler, 2007). According to a study, significant proportions of psychiatrists (64%) prefer to combine two antipsychotics rather than use clozapine (Nielsen et al., 2010).

In contrast, the evidence suggests that patients receiving clozapine are happier and more satisfied with the medication but are less happy with regard to the blood test than estimated by the

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clinicians (Hodge and Jespersen, 2008). The Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) trial also demonstrated that treatment with clozapine is associated with better subjective rating of mental health compared to other atypical antipsychotics, i.e., risperidone, olanzapine, quetiapine and amisulpiride (Lewis et al., 2006). Other researchers who have evaluated patients' perceptions about clozapine also affirm that for majority of patients advantages of clozapine outweigh its disadvantages (Taylor et al., 2000).

Despite all this evidence, because of the possible side effects like agranulocytosis, seizures, myocarditis etc., its use is dreaded by the psychiatrists. Psychiatrists often have negative attitude towards using clozapine (Nielsen et al., 2010). A recent survey of clinical staff reported that patients concerns about tolerability and patients' refusal to adhere to blood test monitoring are the common barriers to clozapine prescription (Gee et al., 2014).

In India, where almost all antipsychotic medications are available, olanzapine and risperidone have been reported to be the most commonly prescribed antipsychotic medications (Grover et al., 2014), and clozapine forms only a small proportion of the total prescriptions of antipsychotic (Grover and Avasthi, 2010). A recent study from our tertiary care centre, found an average of 1.5 years of delay in initiation of clozapine (Grover et al., 2015a). There is no data from India with respect to the attitude of psychiatrists towards clozapine. In this background, this survey aimed to assess the attitude of the psychiatrists towards clozapine and also to evaluate the prescription practices of the psychiatrists for clozapine.

2. Methodology

This survey was carried out in the month of December 2014 by using Survey Monkey electronic platform. The survey comprised 40 questions covering various aspects of clozapine use by the clinicians. The invitation and the link for the survey was sent by email to 3930 psychiatrists in India. This was sent to all the psychiatrists twice during the weekends for 4 consecutive weekends. The e-mail explained the purpose of survey, clearly mentioned that the survey has not received ethical clearance from Institutional Ethics Committee and that the participation is voluntary. Besides the survey link, the mail also contained a link, by using which the recipient of the mail could opt out of the survey. Those who responded to the survey or opted out were sent subsequent reminders.

The data obtained was analysed by using SPSS-14. Frequency and percentages were calculated for the categorical variables and mean and standard deviations were calculated for continuous variables. Additionally medians were also calculated for the continuous variables. Comparisons were done by using Chi-square test, *t*-test, Mann–Whitney *U* test, Fischer exact test, ANOVA as per the requirements. Associations between different variables were studied by using Pearson's correlation coefficient or Spearman's rank correlation.

3. Results

3.1. Profile of the participating psychiatrists

The survey was sent to 3930 psychiatrists. Of these, emails of 491 bounced back and 58 opted out of the survey. Of the remaining 3381 psychiatrists, 548 (16.2%) responded to the survey. At the time of responding to the survey, majority ($N = 534$; 97.4%) were practicing in India and very few ($N = 14$; 2.6%) were practicing abroad. The mean age of the participants was 38.9 (SD—10.74) with a median of 36 years and a range of 24–75 years. Majority of the participants were in the age range of 30–39 years ($N = 240$; 43.8%), followed by those aged less than 30 years ($N = 106$; 19.3%), and those aged between 40 and 49 years ($N = 103$; 18.8%). Majority of the participants were male ($N = 453$; 82.7%).

The mean number of years in clinical practice (including the number of years of training) was 12.59 (SD—10.1) with a median of 9 years and range of 6 months to 49 years. A quarter ($N = 143$; 26.1%) of those who responded were holding a faculty position in government run institutes or medical colleges and another one-fourth ($N = 123$; 22.4%) of the respondents were into full time private practice. One-fifth ($N = 114$; 20.8%) of the participants while on the faculty of a teaching institute were at the same time were also into private practice. Another one-fifth ($N = 103$; 18.8%) were working as Senior Resident (equivalent to a registrar). A very small number of participants ($N = 37$; 6.8%) were working as a teaching faculty in a privately-run institute and a small proportion ($N = 28$; 5.1%) of them were trainee residents.

The mean number of patients with schizophrenia seen in a month by these clinicians was 96.78 (SD 140.31) with a median of 50 and range of 0–1500.

3.2. Practice pattern for use of clozapine

The details of clozapine use pattern are given in Table 1. Only few ($N = 37$; 6.8%) participants had a dedicated clozapine clinic at their work place. Majority of the participants rated their knowledge about clozapine to be good (61.5%) or very good (34.5%). The mean number of patients started on clozapine by the participants was 432.92 (SD 4415.52) with a median of 65 patients. The primary indication for use of clozapine for almost all participants was patients with treatment resistance and most psychiatrists initiated clozapine either in the dose of 25 mg once daily (44.3%) or 12.5 mg once daily (37%). More than half (51.8%) of the psychiatrists preferred to use it in twice daily dosing schedule, and rest (46.9%) preferred to use it in once daily dosing schedule. Only occasional psychiatrists preferred to use it in three or four divided doses per day. In terms of blood monitoring, once the clozapine dose had been stabilized, about half (51%) of the psychiatrists advised it at monthly intervals. About one-fifth of the psychiatrists monitored the heamogram at 3 monthly intervals and 8.2% did so at 2 monthly intervals. The participating psychiatrists reported that they used clozapine in 11.26% of their patients with psychosis and 3.49% of their affective disorder patients. The median dose range which was required by the patients to stabilize was 137.5 to 400 mg/day. Nearly half of the participants (49.6%) reported lower limit of the dose of Clozapine to be 100 mg or less and only 15.7% reported it to be 200 mg/day or higher. Similarly, 73% reported the higher limit of the dose range to be up to 400 mg/day and only 2.6% reported it more than 600 mg/day.

3.3. Side effects encountered

As shown in Table 2, sedation and hypersalivation were the two most common side effects encountered by most of the psychiatrists. Other commonly encountered side effects were weight gain, constipation, raised blood sugar levels, hypotension, enuresis and obsessive compulsive symptoms. Among the intolerable side effects reported by patients, again the most common were sedation and hypersalivation. Other common intolerable side effects included weight gain and constipation.

3.4. Management of side effects

The preferred strategies for management of hypersalivation included use of glycopyrrolate (53.8%), waiting for some time for tolerance to develop (45.6%), use of amitriptyline (37%) or trihexiphenidyl (36.8%) and reduction in dose of clozapine