Clozapine-Related Constipation: A Retrospective Study

To the Editor,

As per the Rome III Expert Consensus, functional constipation is considered to be present if the patient experiences change in bowel movements, with an inability to pass stools less than three times per week despite adequate intake.[1] The prevalence of constipation in patients who are on clozapine is three times that of patients taking other antipsychotics.[2] A recent meta-analysis suggests that constipation is one of the most common side-effects (prevalence rate: 31.2%; CI: 25.6–37.4) of clozapine and that the prevalence of clozapine-associated constipation is influenced by factors like whether the constipation was assessed as a primary, secondary, or a nonspecific outcome of the study, with higher rates reported in studies which evaluated the same as a primary or secondary outcome.[2] Available evidence also suggests that constipation is related to the dose of clozapine, with doses higher than 300 mg/day being more frequently associated with constipation.[2]

There is limited data on the association of clozapine with constipation from India and other Asian countries. If one looks at the dietary pattern, it is expected that patients from Indian subcontinent should have a low prevalence of constipation. However, when one looks at the cultural aspect, with respect to preoccupation with bowel movements, it can be said that Indians get very much distressed about alteration in bowel movements and possibly report the same early.[3-5] If one goes by a strict definition of constipation, in many of these cases, a patient may not fulfill the standard definition of constipation, but may still be distressed.[2] One recent study from India investigated the prevalence and predictors of clozapine-related constipation and reported a prevalence of 56%, with the median time to onset of constipation as 60 days and the median dose of clozapine to develop constipation to be 300 mg/day.[6] Keeping this in mind, this retrospective study evaluated the data of inpatients who were started on clozapine during the period of 2010 to 2016, with the aim to evaluate the dose of clozapine-associated with the development of constipation and time to the development of constipation. The study was approved by the Ethics Committee of the Institute.

In our set up (a tertiary health care centre in North India), we maintain a clozapine registry for all patients started on clozapine. Besides the relevant socio-demographic and clinical data, data with respect to the efficacy of clozapine and various side effects of clozapine is also maintained. When the patient is started on clozapine, especially in the inpatient setting, doses at which each side effect develop is captured.

For this study, data of 53 patients with treatment-resistant schizophrenia who were started on clozapine as inpatients was extracted. The mean age of the patients was 33.3 (SD: 12.26) years with two third (66%) of them being males. The mean duration of illness at starting clozapine was 10.96 (SD: 7.70) years.

In terms of the dose of clozapine associated with the development of constipation, the mean dose was 147.87 (SD: 66.94) mg/day, with a median dose of 150 mg/day and a range of 25-300 mg/day. The mean duration to onset of constipation was 19.56 (SD: 9.45) days, with a median of 20 days and a range of 6-38 days.

The most common strategy utilized to manage clozapine-associated constipation included the use of high fiber diet (N = 36; 67.9%), followed by use of bulk laxatives (Isabgul husk –N = 8; 15.1%) and a combination of liquid paraffin and magnesium hydroxide (Cremaffin- N = 6; 11.3%). Using these strategies, constipation could be effectively managed, and the dose of clozapine could be increased further in all the cases to the level required for a therapeutic response.

The findings of the present study suggest that our patients who received clozapine developed constipation on much lower doses than that reported in some of the earlier studies[7-11] and this side effect is often encountered during the initial phase of the treatment. Our findings are not in concurrence with the previous Indian study, which reported constipation with a median dose of 300 mg/day, and the time to onset of constipation being 60 days.[5] Although the previous study from India used rating scales to define constipation, which was not done in the present study, the findings of the earlier studies do not fit into the clinical experience with day to day encounter with patients from India.

Our findings must be understood in the background of the fact that Indians are very much pre-occupied with their bowel functions and get very distressed if they experience constipation. In view of this, some of the researchers and clinicians have proposed different median normal stool frequency and stool form to define constipation in Indian population[3,4,12,13] when compared with Western population. This suggests that, in the Indian context, constipation as a side effect of clozapine should not be defined as per the standard Western definitions. Accordingly, there is a need to relook at the prevalence of constipation and its association with the dose of clozapine by using a definition of constipation which has been accepted and standardized in the Indian context.

The present study has limitations in the form of small sample size, retrospective study design, not evaluating the information on stool consistency, and inclusion of inpatients only. The study was limited to patients for whom data was available in terms of the dose of clozapine at which constipation developed and the time of development of constipation. Accordingly, this study does not provide information on the prevalence of constipation with clozapine. Further, this study did not specifically evaluate the effectiveness of interventions carried out for the management of constipation.

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Conflicts of interest
There are no conflicts of interest.

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