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# Relationship of obsessive compulsive symptoms/disorder with clozapine: A retrospective study from a multispeciality tertiary care centre

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ABSTRACT

*Objective:* To study the prevalence, phenomenology and course of OCS/OCD in patients receiving clozapine.
*Methodology:* Case records of 220 patients who received clozapine for at least 3 months were reviewed.
*Results:* One fifth ($N = 42$; 19.1%) of patients had OCS/OCD, of which majority (13.2%) had onset of OCS/OCD prior to starting of clozapine and remaining 5.9% developed OCS/OCD after starting of clozapine. About one fourth of the patients with pre-existing OCS/OCD had worsening with clozapine while the remaining maintained at the same level (55.17%) or improved (20.7%). Majority of the patients who developed de novo OCS/OCD on clozapine were females and OCS/OCD emerged within 12 months (69.2%) of starting of clozapine. In those who developed OCS/OCD with clozapine, among obsessions, pathological doubts were most common, followed by obsessions with sexual content; among compulsions repetitive checking was the most common. SSRIs were required for management in half the patients, while the remaining improved spontaneously or with reduction in clozapine dose.
*Conclusion:* Clozapine can lead to aggravation or de novo presentation of OCS/OCD but these can be managed with reduction in dose or addition of SSRIs.



## 1. Introduction

Schizophrenia is known to be associated with obsessive compulsive symptoms (OCS) and obsessive compulsive disorder (OCD) with prevalence ranging from 10% to 64% for OCS (Bottas et al., 2005; Nolfe et al., 2010) and 7.8% to 29.8% for OCD (Bottas et al., 2005; Nolfe et al., 2010). However there are also reports of OCS/OCD starting de novo with use of second generation antipsychotics (SGAs) (Lykouras et al., 2003; Scheltema-Beduin et al., 2012). Due to this some authors suggest that high prevalence of OCS/OCD in patients of schizophrenia could also be due to use of SGAs (Bottas et al., 2005; Nolfe al., 2010; Schirmbeck and Zink, 2012).

Among the various SGAs, OCS/OCD has been reported to be linked mostly to clozapine. Studies which have compared the prevalence of OCS in patients receiving various SGAs have also reported significantly higher prevalence of OCS with clozapine compared to those receiving olanzapine, risperidone and no antipsychotic (Scheltema-Beduin et al., 2012).

A review of the topic suggested existence of 30 case reports linking this association (Lykouras et al., 2003). However, many retrospective and prospective studies have also evaluated this association. The sample sizes of these studies have varied from 41 to 200 and these studies suggest that 0–28.4% of patients have new symptoms of OCS/OCD while receiving clozapine (Ertugrul et al., 2005; de Haan et al., 1999, 2004; Ghaemi et al., 1995; Baker et al., 1992; Mahendran et al., 2007; Lin et al., 2006; Mukhopadhaya et al., 2009; Sa et al., 2009; Bleakley et al., 2011; Doyle et al., 2014). Some studies suggest that presence of OCS/OCD may be related to the severity of primary illness, higher doses of clozapine administered and the longer duration of clozapine use (Lin et al., 2006; Schirmbeck et al., 2011; Schirmbeck and Zink, 2013); however, others have reported no such association (Ertugrul et al., 2005; Kim et al., 2012). Some studies suggest that development of OCS/OCD may be related to plasma concentration of clozapine (Lin et al., 2006) and motoric impairment (Mukhopadhaya et al., 2009). The time to development of OCS/OCD in these studies also vary considerably with some studies reporting onset of symptoms as early as 1 month and as late as 5 years (Lykouras et al., 2003; Lin et al., 2006). With regards to the course of OCS/OCD some evidence suggest spontaneous resolution of OCS

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(Lykouras et al., 2003), while others suggest reduction in symptoms with reduction in doses of clozapine (Rocha and Hara, 2006; Zink et al., 2006; Englisch et al., 2009). Studies have also reported beneficial effect of aripiprazole (Englisch et al., 2009) and selective serotonin reuptake inhibitors (SSRIs) (de Haan et al., 1999; Lykouras et al., 2003).

Studies have also reported worsening of OCS/OCD in a small proportion (1.4–20.6%) of patients receiving clozapine (Ghaemi et al., 1995; de Haan et al., 1999; Baker et al., 1992; Lin et al., 2006). Some of the studies have not given breakup of de novo OCS/OCD with clozapine and preexisting OCS/OCD, but have reported these features in 76.9% of their sample (Schirmbeck et al., 2011). Occasional reports also suggest improvement in OCS with clozapine in a subgroup of patients (Reznik et al., 2004).

Recently some of the studies have also focused on the phenomenology of OCS induced by antipsychotics. Many studies have evaluated phenomenology of OCS associated with clozapine and have tried to compare the same with patients with OCD. However there is no consensus as to whether the phenomenology OCS/OCD induced by clozapine differ from that seen in patients of schizophrenia or that of OCD (Doyle et al., 2014; Kim et al., 2012). The commonly reported de novo OCS include obsessive doubts (Doyle et al., 2014), forbidden thoughts of aggressive or sexual content, contamination and hoarding (Kim et al., 2012). Some of the studies have suggested that phenomenology of de novo OCS associated with clozapine is similar to that seen in patients with OCD alone (Kim et al., 2012). Other studies have shown that phenomenology of de novo OCS associated with clozapine differ from those with OCD, with obsessive doubts being more common in clozapine induced OCD (Doyle et al., 2014).

The mechanism of clozapine induced and aggravation of OC is considered to be related to its anti serotonergic action and antagonism at 5-HT1C, 5-HT2A and 5HT2C receptors (Kang and Simpson, 2010; Meltzer and Huang, 2008). This theory is in line with the therapeutic effects of SSRI action as anti-obsessive medication. Additional mechanisms of action recently considered include reciprocal interactions of clozapine with serotonergic receptors leading to altered glutamatergic neurotransmission (Lopez-Gil et al., 2010).

As the literature is limited to few studies, there is a need to study the relationship of OCS/OCD with clozapine further. Pharmacogenomic studies have reported that the pharmacokinetics and pharmacodynamics of various psychotropics vary across various ethnic groups (Silva, 2013) and as there is some evidence of OCS/OCD to be linked to the dose and duration of clozapine use, there is a need to evaluate this relationship in all the ethnicities. There is a limited data from Asian countries (Kim et al., 2012) and there is no study from India which has evaluated this relationship. Accordingly, the aim of this study was to (1) to study the prevalence of OCS/OCD in patients with schizophrenia/affective disorder receiving clozapine; (2) to study the course of OCS and treatment used for management of OCS/OCD in patients; (3) to study the emergence of OCS/OCD associated with clozapine; (4) to study the phenomenology of OCS/OCD associated with clozapine.

## 2. Methodology

This study was done in a multispeciality tertiary care hospital in North India. The study was approved by the Institute Ethics Committee. This study followed a retrospective study design. In our setting clozapine is usually considered for patients who have treatment resistant schizophrenia or are not able to tolerate other antipsychotics. In most cases clozapine is started in the inpatient setting after detailed evaluation. The detailed evaluation involves taking a detailed history with regards to the type of symptoms and course of illness, both from the patient and reliable informants, response to various medications, medical history and physical examination. Whenever the patients are found to have OCS/OCD, these are documented in detail in terms of the phenomenology. Diagnosis of OCD is based on ICD-10 criteria. Patients who are started on clozapine usually remain in the inpatient setting for a duration of 1–3 months. Once a patient is discharged, she/he is followed up regularly in the outpatient setting and her/his progress is regularly documented in the same treatment file, which is used during the inpatient setting.

For this study, inpatient register was reviewed and all the patients who were on clozapine at the time of admission or were started on clozapine during the period of Jan 2007–April 2014 were identified. Data was also obtained from the consultants about the patients who were started on clozapine after detailed evaluation from the outpatient services. Treatment records of these patients were reviewed. To be included in the study, follow-up data of at least 3 months was required. Patients who were receiving clozapine prior to the specified admission period, but were admitted again during the evaluation period were also included.

## 3. Results

Treatment records of 220 patients who were prescribed clozapine were reviewed. Follow-up data for at least 3 months after starting clozapine was available for all the patients, with longest follow-up data available for 18 years. Most of the patients ($N = 165$; 75%) were still on active follow-up and maximum follow-up duration of 18 years. For 87.7% ($N = 193$) of cases follow-up information for more than 1 year was available, for 5.5% ($N = 12$) follow-up information was available for a duration of more than 6 months but less than 1 year and for 6.8% ($N = 15$) follow-up information was for less than 6 months period.

Majority of the patients were males (65%) and the mean age of the study sample was 33.5 (SD 11.2) with age range of 15–67 years. About two-third of them were single (65%) and more than half were unemployed (56.4%). About three-fourth of them were from nuclear families, from urban background and had income more than 6000 rupees per month.

The mean age of onset of psychiatric illness was 23.0 (SD 9.5) years and the mean duration of illness was 110.4 (SD 93.9) months. Most of the patients were suffering from schizophrenia with paranoid schizophrenia ($N = 107$; 48.6%) and undifferentiated schizophrenia ($N = 78$; 35.5%) contributing to more than 80% of the study population. Other less common diagnosis included schizoaffective disorder ($N = 10$; 4.54%), psychosis NOS ($N = 7$; 3.18%), catatonic schizophrenia ($N = 3$; 1.36%), hebephrenic schizophrenia ($N = 1$; 0.45%), residual schizophrenia ($N = 1$; 0.45%), post-schizophrenic depression ($N = 2$; 0.91%), persistent delusional disorder ($N = 3$; 1.36%), bipolar disorder ($N = 5$; 2.27%) and recurrent depressive disorder with tardive dyskinesias ($N = 3$; 1.36%).

The mean dose of clozapine used in the patients was 276.8 (SD 102.7; median 250) mg/day with a range of 75–700 mg, with majority ($N = 152$; 69.1%) of the patients receiving a dose between 200 and 350 mg/day. When started on clozapine, only other change in treatment which was done was stoppage of unnecessary psychotropics (which involved stoppage of medications like trihexiphenidyl and mood stabilizers in few cases) or continuing antipsychotic to which patient had not responded.

Out of the 220 patients, review of treatment records revealed that 42 (19.1%) patients had OCS/OCD, of whom 29 (13.2%) had OCS/OCD prior to starting of clozapine. Of the 29 patients, with OCS/OCD prior to starting of clozapine, 16 (7.28%) had OCD and 13 (5.9%) had OCS. When the relationship of OCS/OCD with clozapine was evaluated in patients having OCS/OCD prior to starting of