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Brief original

Obsessive–compulsive symptoms and disorder in clozapine-treated schizophrenia

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ABSTRACT

Background: Obsessive–compulsive symptoms (OCS) and obsessive–compulsive disorder (OCD) are commonly reported in patients with schizophrenia. Furthermore, the use of clozapine in treatment-resistant schizophrenia has been thought to induce or aggravate these disorders. To date, there is a paucity of research regarding the prevalence and associated factors. Hence, this study aims to report the prevalence of OCS and OCD, and examine potential risk factors, in clozapine-treated schizophrenia.
Methods: This is a cross-sectional study conducted in the only tertiary hospital for psychiatric patients in Singapore. In total, 162 patients on a stable dose of clozapine were recruited for this study; 159 patients with a diagnosis of schizophrenia or schizoaffective disorder were included in the current analysis. Sociodemographic, clinical and treatment factors were analysed to identify factors associated with OCS and OCD.
Results: The prevalence of OCS and OCD is 21.4% and 12.6% respectively. Factors associated with OCS include younger age (OR:0.96, $p = 0.033$) and younger age of onset of psychosis (OR:0.92, $p = 0.017$). There were no significant factors associated with OCD. However, in an analysis of both OCS and/or OCD, factors associated include younger age (OR:0.96, $p = 0.027$) and younger age of onset of psychosis (OR:0.91, $p = 0.016$). Severity of psychotic illness and Clozapine dose were not associated with OCS or OCD in clozapine-treated schizophrenia.
Discussion & conclusions: Our results suggest a high prevalence of OCS and OCD in clozapine-treated schizophrenia which clinicians should routinely screen for. Further research is warranted to establish the link between the factors identified in this study and OCS/OCD in clozapine-treated schizophrenia.

Introduction

Schizophrenia is commonly associated with obsessive compulsive symptoms (OCS) and obsessive compulsive disorder (OCD) with prevalence rates of 30.3% and 13.6% respectively.[1] The presence of comorbid OCS in schizophrenia is linked to poorer prognostic outcomes such as more severe psychotic and depressive symptoms, greater suicidality, lower functioning and quality-of-life.[2,3]

The onset of OCS has been described to occur at different stages during schizophrenia, mainly, (a) before the onset of psychosis, (b) simultaneously with the first manifestation of psychotic illness, (c) during schizophrenia and d) after the initiation of antipsychotic treatment (i.e., de novo OCS).[4]

To date, clozapine is the most effective antipsychotic medication for treatment-resistant schizophrenia.[5] However, compared to other antipsychotics, clozapine is known to induce or aggravate OCS in patients with schizophrenia.[6,7] A recent study found the prevalence of OCS and/or OCD in clozapine-treated patients to be 47%,[8] which is three times higher than those schizophrenia patients who are not on clozapine.[1] This study aimed to identify the prevalence of OCS and OCD in a cohort of clozapine-treated

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Table 1
Characteristics of study participants.

Variable	OCS		OCD		OCS/OCD		Statistic*	p value*
	Present	Absent	Present	Absent	Present	Absent		
n	34 (21.4%)	125 (78.6%)	20 (12.6%)	139 (87.4%)	35 (22.0%)	124 (78.0%)	–	–
Male	23 (67.6%)	79 (63.2%)	13 (65.0%)	89 (64.0%)	23 (65.7%)	79 (63.7%)	$\chi^2(1) = 0.0003545$	0.985
Smoker	4 (11.8%)	18 (14.4%)	2 (10.0%)	20 (14.4%)	4 (11.4%)	18 (14.5%)	$\chi^2(1) = 0.03610$	0.849
Employed	14 (41.2%)	50 (40.0%)	9 (45.0%)	55 (39.6%)	15 (42.9%)	49 (39.5%)	$\chi^2(1) = 0.02585$	0.872
Hypertension	1 (2.9%)	18 (14.4%)	0	19 (13.7%)	1 (2.9%)	18 (14.5%)	$\chi^2(1) = 2.505$	0.114
Diabetes	5 (14.7%)	20 (16.0%)	1 (5.0%)	24 (17.3%)	5 (14.3%)	20 (16.1%)	$\chi^2(1) = 2.734e\text{-}06$	0.999
Dyslipidaemia	8 (23.5%)	54 (43.2%)	5 (25.0%)	57 (41.0%)	8 (22.9%)	54 (43.5%)	$\chi^2(1) = 4.081$	**0.043***
Clozapine only antipsychotic	25 (73.5%)	76 (60.8%)	14 (70.0%)	87 (62.6%)	25 (74.3%)	75 (60.5%)	$\chi^2(1) = 1.688$	0.194
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
Age (years)	36.4 (10.0)	41.0 (11.0)	36.8 (8.7)	40.4 (11.1)	36.3 (9.9)	41.0 (11.0)	$W = 1636.5$	**0.027***
Age of onset (years)	21.4 (4.6)	24.5 (7.0)	21.3 (4.9)	24.2 (6.8)	21.3 (4.5)	24.6 (7.0)	$W = 1550$	**0.016***
BMI (kg/m²)	24.2 (4.5)	24.9 (4.8)	24.4 (4.6)	24.8 (4.8)	24.2 (4.4)	24.9 (4.8)	$W = 1986$	0.446
CGI-SCH	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
Positive	3.06 (1.20)	2.75 (1.43)	2.95 (1.10)	2.80 (1.43)	3.03 (1.20)	2.76 (1.44)	$W = 1904$	0.260
Negative	2.32 (0.81)	2.60 (1.14)	2.30 (0.67)	2.58 (1.12)	2.31 (0.80)	2.60 (1.14)	$W = 2459$	0.210
Depressive	1.65 (0.88)	1.48 (0.88)	1.60 (0.82)	1.50 (0.89)	1.66 (0.87)	1.48 (0.88)	$W = 1876.5$	0.150
Cognitive	1.97 (0.94)	2.05 (1.06)	2.10 (0.97)	2.02 (1.05)	1.97 (0.92)	2.05 (1.07)	$W = 2203.5$	0.885
Overall	3.18 (1.17)	3.12 (1.25)	3.10 (1.07)	3.14 (1.26)	3.14 (1.17)	3.13 (1.26)	$W = 2147.5$	0.925
SOFAS	60.24 (10.80)	59.05 (13.99)	59.80 (11.44)	59.23 (13.64)	60.77 (11.10)	58.89 (13.93)	$W = 2038$	0.582
Current daily CLZ dose (mg)	337.5 (165.3)	298.9 (140.9)	325.0 (148.5)	304.7 (147.0)	336.4 (163.0)	298.9 (141.5)	$W = 2446.5$	0.249
Plasma CLZ (ng/ml)	915.2 (522.8)	844.8 (520.3)	880.6 (459.1)	857.0 (529.7)	915.4 (515.1)	844.2 (522.4)	$W = 2379$	0.344
Duration of CLZ use (days)	1645 (1824)	1686 (1840)	1771 (1638)	1663 (1863)	1683 (1811)	1675 (1844)	$W = 2206.5$	0.707

* Statistical comparisons for OCS/OCD.
Abbreviations: BMI, body mass index; CGI-SCH, Clinical Global Impression – Schizophrenia scale; SOFAS, Social Occupational Functioning Assessment Scale; CLZ, clozapine.

patients with schizophrenia in Singapore, and to investigate the factors associated with OCS and OCD.

Methods

Participants were recruited from the Institute of Mental Health (IMH) in Singapore, which is the only tertiary psychiatric hospital and sees the majority of patients with schizophrenia in the city-state. IMH provides a comprehensive suite of psychiatric services for people with psychosis and is the only site providing outpatient clozapine clinics to monitor patients. The inclusion criteria for the study included (i) patients with a diagnosis of schizophrenia who are currently prescribed clozapine, and (ii) no changes to current prescription for the past 2 weeks.

Information collected included sociodemographic data such as age, sex, ethnic group, marital status, employment, and smoking. Details of clozapine prescription, including duration of use and current dose were obtained from the medical records. Details on age of onset of psychosis, duration of illness and medical comorbidities were obtained from medical records.

Anthropometric measurements such as weight and height were recorded at the research visit, and body mass index (BMI) was calculated. A venous blood sample was collected from all patients 12 h after the last clozapine dose. The whole blood was centrifuged at 3000 rpm for 10 min for collection of plasma, which was stored at −80 °C. Levels of clozapine in plasma were quantitated using the high-performance liquid chromatography–ultraviolet (HPLC–UV) method with loxapine as an internal standard.

Psychiatric diagnoses were ascertained using the Structured Clinical Interview for DSM-IV-TR (SCID-IV-TR).[9] The Yale-Brown Obsessive–Compulsive Scale – second edition (Y-BOCS-II) was used to evaluate presence and severity of OCS in each participant, where presence of OCS was defined as the combined score of ≥1.[10] Psychopathology was rated using the Clinical Global Impressions –Schizophrenia (CGI-SCH, Severity subscale).[11] Symptom remission was defined by a rating of ≤3 (mildly ill) on all the CGI-SCH subscales. Functioning was assessed using the Social and Occupational Functioning Assessment Scale (SOFAS).[12] Clinical recovery was defined as being in both symptom remission and functional remission (SOFAS ≥ 60).[13]

Statistical analyses were done using R version 4.0.5. The distribution of data was examined and found to be nonparametric. For categorical variables, Pearson Chi-squared test was used. For continuous variables, Mann–Whitney *U* test was performed. The level of significance was kept at $p < 0.05$. Odds ratio and 95% confidence intervals are reported where appropriate.

Results

In this study, 159 participants were enrolled, of which 102 (64.2%) were male and 57 (35.8%) were female. Regarding marital status, 134 (84.3%) participants were single, 15 (9.4%) were married and 10 (6.3%) were separated or divorced. Sixty-four (40.3%) participants were employed and 22 (13.8%) were currently smoking. OCS was detected in 34 (21.4%) participants, whereas comorbid OCD was diagnosed in 20 (12.6%) participants.

OCS

Participants with OCS were younger (mean age of OCS: 36 years vs. mean age w/o OCS: 41 years, $p = 0.033$) and had a younger age of onset of illness (21 years vs. 23.5 years, $p = 0.017$), but there were no differences in duration of illness when compared to those without OCS. Participants with OCS were prescribed a higher current dose of clozapine (mean dosage of 337.5 mg/day vs 303.5 mg/day, $p = 0.248$) and had higher levels of plasma clozapine, but these were not statistically significant. The presence of OCS was not associated with greater severity on any of the CGI-SCH items (all $p > 0.05$) and functioning ($p = 0.645$).

OCD

OCS was present in 19 out of 20 participants diagnosed with OCD. Findings in participants with OCD were similar to participants

with OCS, but they were not statistically significant (see Table 1). Participants with OCD were younger, had an earlier age of onset of illness, were prescribed higher dose of clozapine and had a higher plasma clozapine level.

OCS and/or OCD

In an analysis of both OCS and/or OCD (see Table 1), factors associated include younger age (OR: 0.96, $p = 0.027$) and younger age of onset of psychosis (OR: 0.91, $p = 0.016$) as well as absence of dyslipidemia (OR: 0.384, $p = 0.043$). Severity of psychotic illness (with reference to CGI-SCH Scale) and clozapine dose was not associated with OCS and/or OCD in clozapine-treated schizophrenia. There were no significant differences in proportions in symptom remission (60.0% vs. 63.7%, $p = 0.688$) or functional remission (a) between the groups with and without OCS/OCD.

Discussion

Our results showed that the prevalence of OCS and OCD were 21.4% and 12.6% respectively. We found that patients with OCS and/or OCD were significantly younger and had a younger age of onset compared to those without OCS and/or OCD. Additionally, patients with OCS and/or OCD were less likely to have dyslipidemia compared to those without OCS and/or OCD. However, clozapine dose, plasma clozapine levels, duration of clozapine use, and severity of psychotic illness were not associated with OCS and/or OCD in clozapine-treated schizophrenia.

The prevalence of OCS and/or OCD in our study is consistent with the results reported by Devi et al.,[14] but much lower than that reported by Fernandez-Egea et al.[8] Devi et al. reported the prevalence of OCS and/or OCD in patients with schizophrenia was 24%.[14] While Fernandez-Egea et al.[8] reported a prevalence of 47% for OCD in clozapine-treated patients.

In this study, we found that patients with OCS and/or OCD were significantly younger and had an earlier age at onset of schizophrenia symptoms compared to non-OCS and/or OCD group. Our finding is in line with the previous study which showed significant earlier onset of schizophrenia in patients with OCS or OCD.[15] The association of absence of dyslipidemia with patients with OCS and/or OCD in this study is possibly due to its association with younger age of patient.

Contrary to the study by Lin et al., we found no significant differences in duration of clozapine treatment between patients with OCS and/or OCD and those without OCS and/or OCD.[16] Additionally, although a study reported that OCS improved after clozapine reduction,[17] our study did not find an association between OCS and/or OCD and clozapine dose. However, our study findings are in line with a study by Kim D.D. et al.[18] which also found that clozapine treatment duration and clozapine dose were not significantly associated with OCS severity.

In addition, we found that the presence of OCS and/or OCD was not associated with severity of symptoms and functioning in schizophrenia. This finding is consistent with Üçok et al.,[15] which reported no relationship in severity of schizophrenia between patients with and without OCS. Contrary to previous studies which reported positive correlation between duration of clozapine use and comorbid OCS,[16] our study did not find duration of clozapine use to be associated with comorbid OCS and/or OCD.

The strengths in this study include a relatively large sample size representing the target population, with the use of a well validated and comprehensive scale such as YBOCS to measure OCS severity, and SCID-IV-TR to establish diagnoses. One of the study limitations was the cross-sectional nature of our study. We were unable to take a longitudinal view to explore causality as there was insufficient data collected to determine if the OCS and OCD were present prior to the diagnosis of schizophrenia or were precipitated by clozapine. Additionally, there was no data on OCD in non-clozapine treated people with schizophrenia in Singapore, which will provide information on relative risk of OCD in clozapine-treated group. Thus, to better evaluate the association of clozapine on OCS and/or OCD, future studies might consider a prospective study design.

In conclusion, we found that a significant proportion of participants with clozapine-treated schizophrenia had OCS and/or OCD. Physicians should monitor for comorbid OCS and OCD when treating patients on clozapine, especially in patients with a young age of onset of psychosis. Future research should consider longitudinal designs to evaluate temporal associations between psychosis and OCD, and study effective treatment modalities for this common comorbid combination.

Conflict of interest

Dr. Jimmy Lee has received honoraria from Sumitomo Pharmaceuticals, Lundbeck Singapore, Otsuka Pharmaceutical and Janssen Pharmaceutical. The rest of the authors have no conflict of interest to declare.

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