Obsessive-Compulsive Symptoms in Patients With Schizophrenia: A Naturalistic Cross-Sectional Study Comparing Treatment With Clozapine, Olanzapine, Risperidone, and No Antipsychotics in 543 Patients

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ABSTRACT

Objective: To compare the prevalence of obsessive-compulsive symptoms (OCS) in a population of patients with schizophrenia taking clozapine, olanzapine, or risperidone or taking no antipsychotic medication.

Method: Baseline data of the Genetic Risk and Outcome of Psychosis study were collected between April 2005 and October 2008. We conducted a naturalistic cross-sectional study of 543 patients with schizophrenia and related disorders, who were recruited from multiple mental health centers, including inpatient and outpatient clinics, across The Netherlands. The patients met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition criteria and were taking no antipsychotic medication or taking clozapine, olanzapine, or risperidone. OCS severity was measured with the Yale-Brown Obsessive Compulsive Scale. We compared patients to a sample of 575 healthy controls.

Results: Prevalence of OCS in patients was significantly higher than in the control sample, 23.4% versus 4.9% ($\chi^2 = 73.8$, $P < .001$). Patients taking clozapine reported OCS significantly more often during the last week (38.9%), when compared to patients taking olanzapine (20.1%, $\chi^2 = 10.02$, $P = .002$) or risperidone (23.2%, $\chi^2 = 5.96$, $P = .015$) and patients taking no antipsychotics (19.6%, $\chi^2 = 8.20$, $P = .004$). Patients taking clozapine for 6 months or longer reported OCS significantly more often than patients taking clozapine for less than 6 months, 47.3% versus 11.8% ($\chi^2 = 6.89$, $P = .009$).

Conclusions: Treatment with clozapine in patients with schizophrenia is associated with a higher prevalence of OCS, especially when patients have been taking clozapine for 6 months or longer. We cannot rule out the possibility that this association is related to illness characteristics. Patients treated with risperidone or olanzapine or without treatment with antipsychotic medication had comparable prevalence of OCS, all significantly higher than the control sample.

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A substantial proportion of patients with schizophrenia have comorbid obsessive-compulsive symptoms (OCS) or obsessive-compulsive disorder (OCD).[1] The prevalence of OCS and OCD in patients with schizophrenia is estimated, respectively, to be 25% to 64%[2–4] and 7.8% to 30%.[4–9] In a recent meta-analysis, Swets et al found pooled prevalence rates of 30.0% and 12.3% for OCS and OCD, respectively (M.S., et al, unpublished data, 2012). This is remarkably higher than expected, considering the lifetime prevalence of OCS (21%–25%) and OCD (0.3%–3%) in the general population.[10,11] Moreover, recent studies report a worse outcome in patients with schizophrenia and OCS or OCD compared to schizophrenia patients without OCS or OCD.[2,12,13]

There is an ongoing debate regarding the reasons for these high comorbidity rates. Some postulate the existence of a distinct schizo-obsessive subtype of schizophrenia,[14–17] but conclusive proof is lacking. Several authors suggest that a substantial part of the OCS comorbidity is related to the use of specific atypical antipsychotics.[18–21] The emergence or deterioration of OCS has predominantly been reported during use of clozapine[22–36] and risperidone[37–43] and has been associated with use of olanzapine,[44–47] as well. Clozapine is thought to have the highest propensity for the emergence or deterioration of OCS on the basis of its antiserotonergic properties.[23,26,48,49] This hypothesis is supported by the efficacy of selective serotonin reuptake inhibitors (SSRIs) in the treatment of clozapine-induced OCS.[22,24,25,27–29,33,36]

On the other hand, atypical antipsychotics represent an effective treatment of OCD patients and, in some psychotic patients with comorbid OCS, they are reported to alleviate the OCS symptoms.[21,50]

Duration of treatment with antipsychotics is possibly a contributing factor in the emergence or deterioration of OCS, with a longer duration of treatment associated with more OCS.[44,51]

The best way to study the hypothesis that specific antipsychotics induce or worsen OCS is to compare the effects of these compounds in a double-blind, randomized, controlled design. Only 2 such studies are available. One study reports that olanzapine did not cause OCS when compared to placebo.[52] A more recent double-blind, randomized, controlled study compared olanzapine to risperidone in 122 patients with early psychosis. A significant decrease in OCS after 6 weeks of treatment favoring olanzapine was found. However, illustrating the response complexity, after 6 weeks of treatment in 2 patients taking olanzapine and 8 patients taking risperidone de novo OCS occurred.[51] We are not aware of double-blind randomized studies on the effect of clozapine on OCS.

Placebo-controlled trials to ascertain whether OCS occurs more often during treatment with antipsychotic medication than without are not feasible on ethical grounds. Furthermore, patients who are able and willing to be included in a randomized double-blind medication study

Clinical Points

- Schizophrenia patients taking either olanzapine or risperidone do not have different occurrence of obsessive-compulsive symptoms (OCS) compared to schizophrenia patients not taking antipsychotic medication.
- Chronic clozapine treatment may result in a higher risk for developing OCS.

may not be representative of the general patient population. Therefore, other research strategies will have to contribute to our knowledge on the relation between antipsychotic treatment and OCS in patients with psychotic disorders.

In the present study, we aimed to compare the prevalence of OCS in a large population of patients with schizophrenia taking no antipsychotic medication or taking clozapine, olanzapine, or risperidone. We chose to compare these atypical antipsychotics because these agents have been associated with the emergence or deterioration of OCS in several publications.[22–47]

We hypothesized that patients treated with the atypical antipsychotics clozapine, olanzapine, and risperidone would have a higher prevalence of comorbid OCS compared to patients not taking antipsychotic medication. Because of its specific dopaminergic and serotonergic profile, we expected clozapine to be associated with the highest prevalence of OCS. We expected patients not treated with antipsychotics to have a higher prevalence of OCS than healthy controls. We expected that a longer duration of treatment would be associated with a higher prevalence of OCS.

METHOD

Participants

The study sample was taken from the baseline data of 1,120 patients who were examined within the Genetic Risk and Outcome of Psychosis (GROUP) study. Data were collected between April 2005 and October 2008. In summary, the GROUP study is a multisite, longitudinal, naturalistic cohort study examining the 6-year course of patients with nonaffective psychotic disorders and their siblings. Patients were recruited from mental health centers covering more than 75% of the mental health institutions of The Netherlands, including both inpatient and outpatient clinics. Eligible patients for the GROUP project had to fulfill the following criteria: (1) aged 16 to 50 years; (2) meeting *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) criteria for a nonaffective psychotic disorder (schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, psychotic disorder not otherwise specified); (3) fluent in Dutch; and (4) able and willing to give written informed consent. Persons identified as potentially eligible were given a detailed explanation of the study procedures and were asked for informed consent for detailed assessment and for contacting their first-degree family members (brothers, sisters, parents).

Inclusion criteria for siblings were the following: (1) aged 16 to 50 years, (2) fluent in Dutch, and (3) able and willing to give written informed consent. Comorbidity in patients, siblings, and parents was not an exclusion criterion. When siblings or parents appeared to have a lifetime psychotic disorder, they were included in the patient group.

Controls were selected through a system of random mailings to addresses in the catchment areas of the cases. Inclusion criteria for healthy controls were the following: (1) aged 16 to 50 years, (2) having no lifetime psychotic disorder, (3) having no first-degree family member with a lifetime psychotic disorder, (4) fluent in Dutch, and (5) able and willing to give written informed consent.

The study protocol was approved centrally by the Ethical Review Board of the University Medical Centre Utrecht and subsequently by local review boards of each participating institute. After full verbal and written information about the study, informed consent was obtained from all participants before the start of the first assessment. Healthy volunteers were recruited by advertisements and by mailings. (For more detailed information about the GROUP project see Korver et al.[53])

For the current report, we included patients with schizophrenia or related disorders for whom data on OCS (assessed with the Yale-Brown Obsessive Compulsive Scale [YBOCS]) were available. We compared patients treated with clozapine, olanzapine, or risperidone or taking no antipsychotic medication to a sample of siblings and a sample of healthy controls. We excluded patients who used more than 1 type of antipsychotic medication.

Instruments

Comprehensive Assessment of Symptoms and History/ Schedules for Clinical Assessment for Neuropsychiatry. To establish a *DSM-IV* diagnosis of psychotic disorder, the Comprehensive Assessment of Symptoms and History (CASH)[54] or the Schedules for Clinical Assessment for Neuropsychiatry (SCAN 2.1)[55] was used.

YBOCS. First, the presence of obsessive and compulsive symptoms during the week before assessment was evaluated, defined according to the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders, Research Version, Patient Edition (SCID-I/P), as persistent, repetitive, intrusive, and distressful thoughts (obsessions) not related to the patient's delusions, or repetitive goal-directed rituals (compulsions) clinically distinguishable from schizophrenic mannerisms or posturing. To measure the severity of obsessive and compulsive symptoms the YBOCS was used.[56,57] The scale measures 5 obsessive-compulsive aspects (duration, interference, distress, resistance, and control) as reported by the subject and is divided into obsessions and compulsions subscales. Previous research has found the YBOCS suitable for assessing severity of OCS in patients with schizophrenia.[58,59] When the YBOCS score was positive, the presence of OCS was established.

Table 1. Demographic and Disease Characteristics of Patients, Siblings, and Controls

Characteristic	Patients (n = 543)	Siblings (n = 979)	Test Statistic	*P* Value	Controls (n = 575)	Test Statistic	*P* Value
Age, mean (SD), y	27.6 (7.59)	27.8 (8.33)	$z = -0.07$	.95	30.4 (10.63)	$z = -3.02$	.003
Sex, male, %	79.0	46.1	$\chi^2 = 155.4$	< .001	45.4	$\chi^2 = 133.6$	< .001
Ethnicity, white, %	78.3	82.9	$\chi^2 = 5.01$	.03	90.3	$\chi^2 = 30.53$	< .001
OCS during last week, %	23.4	7.8	$\chi^2 = 73.8$	< .001	4.9	$\chi^2 = 80.2$	< .001

Abbreviations: OCS = obsessive-compulsive symptoms, SD = standard deviation.

Table 2. Demographic and Disease Characteristics of Patients Treated With Clozapine, Olanzapine, Risperidone, or No Antipsychotic Medication, With and Without Obsessive-Compulsive Symptoms (OCS) During the Last Week

Characteristic	Patients With OCS During the Last Week (n = 135, 24.9%)	Patients Without OCS During the Last Week (n = 408, 75.1%)	Test Statistic	*P* Value
Age, mean (SD), y	27.2 (7.23)	27.8 (7.70)	$z = -0.377$	.706
Sex, male, %	81.1	78.4	$\chi^2 = 0.439$	.507
Ethnicity, white, %	74.8	78.3	$\chi^2 = 1.2$	.179
Age at onset of first psychosis, mean (SD), y	21.1 (7.17)	23.3 (6.89)	$z = -3.07$	.002
Duration of illness, mean (SD), y	5.59 (5.25)	3.94 (3.94)	$z = -4.00$	< .001

Abbreviation: SD = standard deviation.

The Positive and Negative Syndrome Scale. The Positive and Negative Syndrome Scale (PANSS) is currently the most widely used scale to assess a variety of symptoms in patients with schizophrenia.[60] It consists of 30 items, each item ranging on a 7-point scale of severity from 1 (absent) to 7 (extreme). Originally, the PANSS consisted of 3 subscales: positive syndrome scale (items P1–P7), a negative syndrome scale (items N1–N7), and a general psychopathology scale (items G1–G16). Peralta and Cuesta[61] showed that the positive and negative subscale can be better conceptualized as composed of 3 factors instead of 2 factors: positive, disorganized, and negative.

Statistical Analysis

Statistical analyses were performed using SPSS 18.0.2 software (IBM, Armonk, New York).

Demographic and disease characteristics were compared between patients and controls using Pearson χ^2 tests, and when assumption of normal distribution was violated, Mann-Whitney *U* tests were used. Of the patients with OCS, demographic and disease characteristics were compared in the different medication groups using Pearson χ^2 tests and, when the assumption of normal distribution was violated, Kruskal-Wallis tests. YBOCS scores were compared between the different medication groups using 1-way analysis of variance (ANOVA). Logistic regression was used to compare groups, controlling for confounding variables.

RESULTS

The GROUP sample consisted of 1,120 patients, 1,057 siblings, and 590 healthy controls. Of the patients, data on OCS prevalence and severity were available for 107 patients not taking antipsychotics and 431 patients taking clozapine (n = 71), olanzapine (n = 196), or risperidone (n = 149). Data on OCS prevalence and severity were available for 979 siblings and for 575 controls.

Prevalence of OCS in the sample of 543 patients (23.4%) was significantly higher than in the group of 979 siblings (7.8%, $\chi^2 = 73.8$, $P < .001$) and 575 healthy controls (4.9%, $\chi^2 = 80.2$, $P < .001$; Table 1). The difference in the prevalence of OCS between siblings and controls, 7.8% versus 4.9%, respectively ($\chi^2 = 4.9$, $P = .028$), was much smaller but significant. The control sample was significantly different from the patient sample concerning sex, age, and ethnicity. The sibling sample differed significantly from the patient sample when sex was considered (see Table 1). Differences in prevalence between controls and patients remained highly significant, even after controlling for sex, age, and ethnicity using logistic regression analysis, with an unadjusted odds ratio (OR) of 5.96 (95% confidence interval [CI], 3.89–9.16) and an adjusted OR of 5.74 (95% CI, 3.70–8.95), with none of the possible confounders reaching statistical significance.

Comparing patients with and without OCS, no differences were found in sex, age, and ethnicity. Patients with OCS had a significantly earlier age at onset of psychosis ($Z = -3.07$, $P = .002$) and had a significantly longer duration of illness ($Z = -4.00$, $P < .001$) (Table 2).

Comparing the prevalence of OCS between the different medication groups revealed a significant difference ($\chi^2 = 11.77$, $P = .008$). Post hoc tests showed that patients taking clozapine reported significantly more OCS during the last week (38.9%), when compared to patients taking olanzapine (20.1%, $\chi^2 = 10.02$, $P = .002$) or risperidone (23.2%, $\chi^2 = 5.96$, $P = .015$) and patients not taking antipsychotics (19.6%, $\chi^2 = 8.20$, $P = .004$). Comparing diagnoses between patients taking antipsychotics versus patients not taking antipsychotics, no significant difference was found. Of patients taking antipsychotics, 77.7% were diagnosed with schizophrenia versus 67.0% of those not taking antipsychotics ($\chi^2 = 6.73$, $P = .150$). The remaining diagnoses of patients taking antipsychotics versus patients not taking antipsychotics were, respectively, schizoaffective disorder, 9.0% versus 11.6%; brief psychotic disorder or psychosis not otherwise specified,

Table 3. Demographic and Disease Characteristics of Patients Treated With Clozapine, Olanzapine, Risperidone or No Antipsychotic Medication, With Obsessive-Compulsive Symptoms During the Last Week

Characteristic	Clozapine (n = 28, 22.0%)	Olanzapine (n = 41, 32.3%)	Risperidone (n = 36, 28.3%)	No Antipsychotics (n = 22, 17.3%)	χ^2	*P* Value
Age, mean (SD), y	27.4 (3.81)	25.9 (6.08)	27.5 (8.63)	29.1 (9.65)	3.90	.273
Sex, male, %	89.3	80.5	86.1	63.6	6.20	.102
Ethnicity, white, %	67.9	82.9	75.0	68.2	2.67	.446
Age at onset of first psychosis, mean (SD), y	19.3 (4.55)	21.1 (5.53)	21.1 (7.89)	23.5 (10.50)	2.34	.506
Duration of illness, mean (SD), y	7.69 (3.45)	4.24 (3.90)	5.87 (7.42)	5.01 (4.42)	17.91	< .001
Daily dose of antipsychotic, mean (SD), mg	357.1 (160.85)	14.2 (5.83)	5.4 (9.45)	NA	NA	NA

Abbreviations: NA = not applicable, SD = standard deviation.

Table 4. Demographic Characteristics of Patients Treated With Clozapine for 6 Months or Longer or Less Than 6 Months

Characteristic	Clozapine < 6 months (n = 17, 23.6%)	Clozapine ≥ 6 months (n = 55, 76.4%)	Test Statistic	*P* Value
Age, mean (SD), y	29.3 (6.71)	26.0 (4.06)	$z = -1.56$	.118
Sex, male, %	100	85.5	$\chi^2 = 2.78$	.095
Ethnicity, white, %	82.4	60.0	$\chi^2 = 2.86$	.091
Age at onset of first psychosis, mean (SD), y	25.0 (6.37)	18.8 (3.84)	$z = -3.73$	< .001
Duration of illness, mean (SD), y	3.81 (3.18)	6.73 (3.07)	$t = -3.24$	.001
Daily dose of antipsychotic, mean (SD), mg	341.2 (199.2)	304.1 (146.2)	$\chi^2 = -0.882$	.378
OCS during last week, %	11.8	47.3	$\chi^2 = 6.89$	.009

Abbreviations: OCS = obsessive-compulsive symptoms, SD = standard deviation.

Table 5. Prevalence of OCS in Odds Ratios (ORs) Comparing Patients Using No Antipsychotics, Risperidone, Olanzapine, Clozapine < 6 Months, and Clozapine ≥ 6 months

Variable	Unadjusted Model OR (95% CI)	Fully Adjusted Model OR (95% CI)
No antipsychotic use (n = 107)	Reference	Reference
Risperidone (n = 149)	1.3 (0.7–2.3)	1.3 (0.7–2.4)
Olanzapine (n = 196)	1.1 (0.6–2.0)	1.2 (0.6–2.1)
Clozapine < 6 months (n = 16)	0.3 (0.03–2.2)	0.2 (0.03–1.9)
Clozapine ≥ 6 months (n = 55)	3.7 (1.8–7.5)*	2.8 (1.3–5.9)**
Sex		1.0 (0.6–1.7)
Age		0.8 (0.4–1.6)
Ethnicity		1.0 (0.6–1.6)
Age at onset of first psychosis		1.3 (0.6–2.7)
Duration of illness		1.4 (0.7–2.9)
Severity of psychosis measured with PANSS positive symptom scale		1.6 (1.2–2.1)

*$P < .001$; **$P = .007$.
Abbreviations: CI = confidence interval, OCS = obsessive-compulsive symptoms, PANSS = Positive and Negative Syndrome Scale.

10.0% versus 15.2%; delusional disorder, 1.9% versus 2.7%; and other psychotic disorders, 1.4% versus 3.6%.

Within the group of patients with OCS, the mean dosage of clozapine was 357.14 mg (standard deviation [SD] = 160.9); of olanzapine, 14.2 mg (SD = 5.83); and of risperidone, 5.4 mg (SD = 9.45).

No differences were found in sex, age, ethnicity, and age at onset of first psychosis between the different medication groups. The patients taking clozapine had a significantly longer duration of illness ($\chi^2 = 18.9$, $P \leq .001$) (Table 3).

Within the group of patients with schizophrenia, we compared patients taking clozapine for 6 months or longer (n = 55) to patients taking clozapine for less than 6 months (n = 17). No differences were found in sex, age, ethnicity, and daily dose of clozapine between these groups. Patients taking clozapine for 6 or more months were significantly younger when they developed schizophrenia ($Z = -3.73$, $P < .001$) and had a significantly longer duration of illness ($Z = -3.24$, $P = .001$). Furthermore, the prevalence of OCS was significantly higher in patients taking clozapine for 6 months or longer versus patients taking clozapine for less than 6 months, 47.3% versus 11.8% ($\chi^2 = 6.89$, $P = .009$) (Table 4).

No significant differences were found in OCS prevalence, age at onset, or duration of illness between patients taking olanzapine or risperidone for 6 months or longer or less than 6 months.

Since OCS is associated with more psychotic psychopathology and clozapine is used by patients with more severe psychotic illness, severity of the psychotic illness should be controlled for. Comparing the prevalence of OCS between all 5 medication groups (no antipsychotics, risperidone, olanzapine, clozapine < 6 months, clozapine ≥ 6 months) in logistic regression controlling for age, sex, ethnicity, age at onset of first psychosis, duration of illness, and score on the PANSS positive symptom scale showed a significantly higher prevalence of OCS in the clozapine ≥ 6 months group (Table 5). The group not taking antipsychotics was used as reference group. None of the potential confounders proved significant.

Severity of OCS did not significantly differ between medication groups (including the group taking no antipsychotic medication): severity of obsessions ($F = 0.610$, $P = .610$), severity of compulsions ($F = 1.69$, $P = .173$), resistance to obsessions and compulsions ($F = 0.300$, $P = .825$), and total

score ($F = 0.146$, $P = .932$). Taking a cutoff point of 16 on the YBOCS, a standard criterion for OCD studies,[62] severe OCS was not significantly differently distributed between the medication groups (including the group taking no antipsychotic medication) ($\chi^2 = 0.567$, $P = .904$).

DISCUSSION

Patients had OCS more frequently (23.4%) than unaffected siblings (7.8%) or controls (4.9%). OCS prevalence in the control sample was relatively low compared to OCS prevalence reported in the general population, 21%–25%.[10] This difference is most likely due to differences in assessment. In community surveys most often the Diagnostic Interview Schedule (DIS) or its successor, the Composite International Diagnostic Interview (CIDI), is used. This instrument is known to considerably overdiagnose OCS/OCD, up to 5-fold.[63] In our study, the presence of OCS was assessed with criteria according to the SCID-I/P, and OCS was considered present only when the severity of OCS resulted in a positive YBOCS score. In consequence, only clinically relevant symptoms were scored, potentially resulting in an underestimation of the prevalence of OCS, compared to an assessment in which minor OCS are also included. Secondly, the DIS or CIDI cover lifetime prevalence or the last 12 months prior to assessment, whereas the YBOCS measures symptoms in the week before assessment, again leading to a stricter but more reliable assessment. It is possible that demographic differences between patient and control groups may have contributed to the difference in prevalence of OCS we found. Compared to patients, the control sample comprised significantly more females, with a significantly higher mean age and significantly more white ethnicity. However, sex ratio of prevalence of OCS is estimated to be 1:1,[64] and logistic regression analysis showed no significant influence of sex, age, or ethnicity on the OCS prevalence.

For patients with schizophrenia, we found significant differences in age at onset of first psychosis and duration of illness between those with and without OCS. It is known that patients with schizophrenia with an earlier age at onset have poorer outcomes[65]; furthermore, several studies have shown the unfavorable effect of comorbid OCS on the course of schizophrenia.[2,12,13] Therefore, a higher prevalence of OCS may be associated with a more severe illness, a younger age at onset of illness, and a longer illness duration.

Significantly more patients taking clozapine for 6 months or longer had OCS during the last week when compared to patients taking clozapine for less than 6 months, olanzapine or risperidone, and patients not taking antipsychotic medication. This finding may be interpreted to support the hypothesis that clozapine contributes to the prevalence of OCS.[22,36] However, clozapine is indicated for patients with treatment resistance. Therefore, the association between OCS and clozapine treatment may be explained by duration of illness, illness severity, or treatment resistance. However, when using logistic regression controlling for these confounders, with the patient group taking no antipsychotics as control group, clozapine use for 6 months or longer was still significantly associated with OCS prevalence.

No significant difference in prevalence of OCS between patients taking olanzapine or risperidone and patients not taking antipsychotic medication was found. Patients taking antipsychotic medication did not differ significantly in clinical characteristics or in diagnosis from patients not taking antipsychotic medication. This finding does not support the second part of our hypothesis, that patients taking atypical antipsychotics have a higher prevalence of OCS compared to patients not taking antipsychotic medication.

Within the group of patients with schizophrenia and OCS, a significant difference in duration of illness was seen between patients taking clozapine on one hand and olanzapine, risperidone, or no antipsychotic medication on the other hand. Again, this finding may possibly be explained by specific indication to take clozapine. No significant difference was found in severity of OCS between the different medication groups and the group not taking antipsychotic medication. This finding may imply that, for most patients, OCS related to treatment with clozapine is not severe and that there is no specific intervention needed.

Patients who were treated with clozapine for 6 months or longer had an earlier age at onset, a longer duration of illness, and more frequently reported OCS in the week before assessment, compared to patients with a shorter treatment period. Maybe the effect of clozapine on OCS develops gradually. This possibility could imply that a substantial proportion of patients without OCS who took clozapine for less than 6 months may develop OCS during continued treatment. De Haan et al[44] found that severity of OCS was associated with duration of treatment with olanzapine. Another possible explanation for this finding is that patients taking clozapine for 6 months or longer are in fact, as mentioned above, the most severely ill patients associated with the most OCS comorbidity, although logistic regression analysis did not support this hypothesis.

The fact that we found no difference in prevalence between patients not taking antipsychotic medication and those taking risperidone, olanzapine, or clozapine for less than 6 months might indicate that the effect of antipsychotic medication is not substantial. The group of patients taking clozapine for 6 months or longer could represent a more severely ill group, with more OCS the result of a virulent psychopathological process instead of the result of treatment with clozapine, even though correcting for illness variables did not change the association between OCS and this patient group. On the other hand, more than 1 factor appears to be associated with OCS in schizophrenia. Many reports are published describing either the appearance of OCS after the start of antipsychotics or the disappearance. The fact that the sum of all the effects shows no significant effect compared to the group of patients not taking antipsychotics does not rule out the possibility that antipsychotic medication does influence OCS on an individual level.

One possible explanation of our findings is the effect of clozapine on the serotonergic system. The serotonergic (5-HT)

and dopaminergic (D) systems have been widely implicated in the pathophysiology of OCD.[66] Theories explaining the role of antipsychotics in emergence or deterioration of OCS mostly address 5-HT neurotransmission.[14,49,67,68] However, in addition to this fact, antipsychotic augmentation is an accepted treatment strategy for refractory OCD.[18,50]

This contradictory effect of atypical antipsychotics can be partially explained by their 5-HT and D_2 receptor occupancy: the emergence or deterioration of OCS is thought to be caused by the antagonism of 5-HT receptors, whereas therapeutic effects are thought to be caused by D_2 receptor blockade. Since positron emission tomography (PET) studies have shown that, compared to typical antipsychotics, olanzapine and risperidone cause high 5-HT_2 receptor occupancy at low doses, whereas relatively high doses are needed to achieve dopamine D_2 receptor occupancy,[69,70] it is possible that higher doses of these atypical antipsychotics might induce less OCS and have a larger treatment effect on OCS.[71] Clozapine has a relatively low D_2 receptor occupancy and a fast dissociation rate. Therefore, one might hypothesize that clozapine does not cause a sufficiently effective D_2 receptor blockade to be therapeutic in OCS and by its high 5-HT_2 receptor occupancy[72] causes more emergence or deterioration of OCS, when compared to other antipsychotics. The pro-obsessional effects of clozapine are reported to be dose-related, with higher doses causing more OCS.[16,73] However, in this study we found no significant difference in mean daily dose of clozapine between the patients with and without OCS.

Another possible explanation for the reported contradictory effect of atypical antipsychotics (improving OCS and worsening OCS) could be that there are subgroups of patients with schizophrenia and OCS who have different 5-HT–related polymorphisms that react differently to administration of antipsychotics in general and clozapine in particular.[48,49,67,68]

Several limitations of the current study should be mentioned. First, although our results are relatively robust and concur with former findings, our study was designed as a naturalistic cross-sectional study; therefore, selection bias cannot be ruled out, and our findings should be interpreted cautiously. We do indeed find that patients taking clozapine have a younger age at onset of first psychosis and a longer duration of illness, so we might have identified a subpopulation with a more severe course of illness, including more OCS comorbidity. Alas, we lack information regarding the onset of OCS in relation to the onset of schizophrenia or start of treatment with antipsychotic medication, which could have given us arguments favoring or opposing the hypothesis that specific atypical antipsychotics induce OCS. In the coming follow-up of the included patients, we will be able to study the association between medication switch or continuation and OCS prevalence and severity.

A randomized controlled, double-blind, longitudinal study of the effect of different second-generation antipsychotics on the emergence or deterioration of OCS in patients with schizophrenia would provide more definite answers.

CONCLUSION

Treatment with clozapine in patients with schizophrenia or related disorders is associated with a higher prevalence of OCS, especially when patients have been taking clozapine for 6 months or longer. We cannot rule out the possibility that this association is related to illness characteristics. Patients treated with risperidone or olanzapine or without treatment with antipsychotic medication had comparable prevalence of OCS, significantly higher than the control sample.

Drug names: clozapine (Clozaril, FazaClo, and others), olanzapine (Zyprexa), risperidone (Risperdal and others).

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