Obsessive-Compulsive Symptoms During Treatment With Olanzapine and Risperidone: A Prospective Study of 113 Patients With Recent-Onset Schizophrenia or Related Disorders

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Objective: To determine whether severity of obsessive-compulsive symptoms (OCS) differs during treatment with olanzapine or risperidone and to establish whether duration of antipsychotic treatment is related to severity of OCS.

Method: We conducted a prospective study of consecutively hospitalized young patients (mean age = 22.4 years) with DSM-IV schizophrenia or related disorders (N = 113) who were treated with olanzapine or risperidone. Olanzapine or risperidone was randomly prescribed for patients who were drug-naive or were treated with typical antipsychotics before admission (N = 36). Patients who had started olanzapine (N = 39) or risperidone treatment (N = 23) prior to admission continued with that medication if they showed initial clinical response. Patients who prior to admission started olanzapine (N = 6) or risperidone (N = 9) but showed no response or suffered from adverse effects switched at admission to risperidone or olanzapine, respectively. Medical records, parents, and patients revealed information on duration of treatment and compliance with olanzapine or risperidone prior to admission. The Yale-Brown Obsessive Compulsive Scale (YBOCS) was administered at admission and 6 weeks thereafter.

Results: At baseline and 6-week assessments, OCS were found in about 30% of 106 evaluable cases and 15% met DSM-IV criteria for obsessive-compulsive disorder. No differences in OCS were found in the patients randomly assigned to olanzapine or risperidone. The 35 subjects treated with olanzapine at both assessments had significantly ($p = .01$) more severe OCS at week 6 than the 20 subjects treated with risperidone at both assessments. Duration of treatment with olanzapine was significantly ($p < .01$) related to severity of OCS.

Conclusion: There are no differences in the short-term propensity of olanzapine or risperidone to induce or exacerbate OCS. However, severity of OCS was associated with duration of treatment with olanzapine.

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The prevalence of obsessive-compulsive disorder (OCD) is estimated to be 14% in patients with first-episode schizophrenia.[1] Obsessive-compulsive symptoms (OCS) probably occur more frequently than OCD in patients with schizophrenia.[2] Retrospective studies and case reports suggest that some antipsychotic drugs may induce or exacerbate OCS in patients with schizophrenia. Most reports concern clozapine.[3–5] Case reports mention the occurrence of OCS in olanzapine-treated patients.[6,7] Tibbo and Warneke[3] reviewed 4 case reports with regard to the relation between risperidone and OCS that showed contradictory results. The retrospective and cross-sectional methodology and the focus on chronically ill patients limit the conclusions that can be drawn from these reports. Baker et al.[8] conducted a prospective study of the propensity of olanzapine to induce or exacerbate OCS. In a 6-week double-blind design, 7 patients received placebo, 11 received olanzapine, 1 mg/day, and 7 received olanzapine, 10 mg/day. No significant differences in OCS were found between these groups. The small sample size and low dose of olanzapine limit the conclusions to be drawn from this study also.

In the present prospective longitudinal study, we attempted to determine if the prevalence and severity of OCS differ during treatment with olanzapine or risperidone. We also examined the relationship between duration of treatment with olanzapine or risperidone and severity of OCS.

METHOD

Consecutively admitted patients (N = 113) participating in a prospective study of recent-onset schizophrenia and related disorders were included. Patients were diagnosed at admission according to DSM-IV criteria and were treated at a specialized unit in the Academic Medical Center, Amsterdam, The Netherlands. The intensive treatment program was aimed at decreasing psychotic symptoms, preventing psychotic relapse, and improving quality of life. The reasons for admission to the treatment program were that clinical treatment was considered necessary to enable stabilization, psychoeducation, and rehabilitation. Discharge diagnoses according to DSM-IV criteria were based on longitudinal, clinical, and heteroanamnestic assessment (Longitudinal Expert Assessment of Diagnosis procedure[9]). Exclusion criteria were neurologic or endocrine disease and mental retardation. After a complete description of the study was given to the subjects, written informed consent was obtained from all.

Olanzapine or risperidone was randomly prescribed for patients who were drug-naive or were being treated with typical antipsychotics at admission (N = 36). Patients who had started with olanzapine (N = 39) or risperidone (N = 23) prior to admission continued with that medication if they showed initial clinical response. Patients who showed no response or adverse effects to olanzapine (N = 6) or risperidone (N = 9) at admission were switched to risperidone or olanzapine, respectively.

Excluded from analyses were 3 patients because of medication noncompliance (2 patients were treated with olanzapine at admission, 1 patient was treated with risperidone) and 4 patients because of crossover to typical antipsychotics 6 weeks after first assessment (2 olanzapine-treated subjects, 2 risperidone-treated subjects). Analyses of differences in OCS for these small groups were deemed inappropriate.

The presence of OCS was defined according to the Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-P)[10] 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. The Yale-Brown Obsessive Compulsive Scale[11] (YBOCS) was administered at admission and 6 weeks later by 2 trained psychiatric residents (N.B., B.H.) who rated the patients twice and were not blind to medication. Interrater agreement for YBOCS total score in 4 categories was good (weighted $\kappa = 0.73$).

The cutoff point of clinically significant OCD is a YBOCS score of 7 in nonpsychotic populations. However, we chose a cutoff score of 10 for clinically significant comorbid OCD in these patients with schizophrenia and related disorders, since a patient with a YBOCS score of 10 or less could have no more than mild OCS. We think that it is appropriate to increase the threshold for clinically significant comorbidity of OCD in this severely disabled group, since it is difficult to disentangle interference with social or occupational activities caused by OCS from symptoms of a schizophrenic disorder.

Determination of the duration of antipsychotic treatment with olanzapine or risperidone was based on the clinical research file. Sources of information on duration of treatment and compliance with olanzapine or risperidone prior to admission were medical records, parents, and patients.

The Mann-Whitney statistic was used to determine grouping effects, and the Pearson statistic was used for correlations (both 2-tailed).

RESULTS

One hundred thirteen patients (92 men and 21 women) were included; 97 had schizophrenia, 7 had a schizophreniform disorder, and 9 had a schizoaffective disorder. The mean ± SD age at admission was 22.4 ± 3.2 years. The mean dose of olanzapine at both assessments was 14.2 ± 5.4 mg; the mean dose of risperidone at both assessments was 4.1 ± 1.7 mg.

At admission, 33 patients (29%) had OCS (mean ± SD YBOCS total score = 3.6 ± 6.8). Six weeks later, 36 patients (32%) had OCS (mean ± SD YBOCS total score = 3.1 ± 5.9). Seventeen patients (15%) had a YBOCS total score of 10 or higher and fulfilled DSM-IV criteria for OCD at both assessments (mean YBOCS total score at admission = 17.5 ± 7.0; mean YBOCS total score 6 weeks after admission = 17.8 ± 5.8).

In the randomly allocated group, we found no differences 6 weeks after admission in YBOCS total scores between patients assigned to the olanzapine or risperidone treatment condition. In the groups starting with olanzapine or risperidone prior to admission and taking olanzapine (N = 35) or risperidone (N = 20) at both assessments, the YBOCS total score tended to be higher in the olanzapine group at admission (Mann-Whitney test, p = .08) and was significantly higher in the olanzapine group 6 weeks later (Mann-Whitney test, p = .01). The mean ± SD total score for compulsions was significantly higher in the olanzapine group (2.4 ± 4.6 vs. 0.5 ± 2.2; Mann-Whitney test, p = .04). There were no significant differences in mean YBOCS total score at admission and 6 weeks later in the 6 patients who switched from olanzapine to risperidone, nor in the 9 patients who switched from risperidone to olanzapine (Table 1).

Twelve (19%) of 63 patients who took olanzapine 6 weeks after admission fulfilled DSM-IV criteria for OCD; 4 (9%) of 43 patients who took risperidone 6 weeks after admission fulfilled DSM-IV criteria for OCD (Table 1).

Duration of treatment with olanzapine correlated with YBOCS total score (r = 0.33, p < .01). The correla-

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Table 1. YBOCS Scores and Number of Patients With OCD at Admission and at 6 Weeks[a]

	YBOCS Score				Patients With OCD (YBOCS score > 10)	
	At Admission		At 6 Weeks		At	At
Treatment Group	Mean	SD	Mean	SD	Admission	6 Weeks
Randomly allocated to:						
Olanzapine (N = 19)	2.4	(5.3)	1.9	(4.2)	2	2
Risperidone (N = 17)	2.4	(5.4)	2.2	(5.0)	1	1
Started before admission on:						
Olanzapine (N = 35)	4.9	(7.8)	4.5	(6.7)	7	8
Risperidone (N = 20)	2.9	(8.8)	2.2	(7.1)	2	2
Switched from:						
Olanzapine to risperidone (N = 6)	5.8	(7.0)	4.7	(3.1)	2	1
Risperidone to olanzapine (N = 9)	3.5	(4.9)	4.0	(5.6)	2	2

[a]Abbreviations: OCD = obsessive-compulsive disorder, YBOCS = Yale-Brown Obsessive Compulsive Scale, SD = standard deviation.

tion between duration of treatment with olanzapine and YBOCS total score was r = 0.51 ($p < .01$) for patients who had a positive YBOCS total score. Patients who were treated 12 weeks or longer with olanzapine (N = 22 of the group who took olanzapine at 6 weeks) had a significantly higher YBOCS total score than patients who took olanzapine for less than 12 weeks (N = 41 of the group who took olanzapine at 6 weeks) (mean ± SD = 7.3 ± 9.7 vs. mean ± SD = 2.7 ± 4.9; Mann-Whitney test, $p < .05$). Duration of treatment with risperidone was not related to YBOCS total score (N = 24 ≥ 12 weeks; N = 19 < 12 weeks) (r = 0.12, p = .23). The mean duration of treatment with olanzapine 6 weeks after admission was 53.6 ± 50.4 days. The mean duration of treatment with risperidone 6 weeks after admission was 71.3 ± 73.0 days.

DISCUSSION

The comorbidity rate of OCD in our patient sample (15%) was similar to the 14% reported by Poyurovsky et al.[1] About another 15% of our patients lacked severe enough OCS to fulfill DSM-IV criteria for OCD, underscoring the importance of a dimensional view on the co-occurrence of OCS and schizophrenia.

We found no differences in the short-term propensity of olanzapine versus risperidone to induce or exacerbate OCS. However, the findings of our study give a preliminary indication that the duration of treatment with olanzapine is related to severity of OCS, whereas duration of treatment with risperidone is not related to severity of OCS. Olanzapine may be associated with a delayed expression of clinically relevant OCS in a subset of patients with recent-onset schizophrenia. Although most patients had low scores on the YBOCS, and mean scores slightly decreased from admission to 6 weeks later, almost one fifth of the patients taking olanzapine had clinically significant OCS.

Our findings should be cautiously interpreted because of the response complexity of patients with both schizophrenia and OCS to atypical antipsychotics. A number of case reports and retrospective chart review studies[5,12] link clozapine, olanzapine, and risperidone to worsening or precipitating obsessions and compulsions in individuals with schizophrenia. There are also preliminary reports indicating that in some individuals clozapine[13–16] and olanzapine[17] may be efficacious in alleviation of both psychotic symptoms and OCS. However, treatment with clozapine was associated with improvement of OCS in only 5 of 9 cases described.[13] Moreover, it is worth mentioning the differences in the definition of OCS between our study and that in the case reports described by Bermanzohn et al.[13] We assessed the presence of OCS only if patients had 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. Bermanzohn et al.[13] included OCS related to delusions. In fact, psychotic and obsessive symptoms were intertwined and were referred to as "obsessive delusions." Therefore, the improvement of obsessive delusions in some patients reported by Bermanzohn et al. could be accounted for by the effectivity of clozapine on neuroleptic-refractory psychotic symptoms. Bermanzohn et al. have suggested that obsessive delusions in schizophrenic patients may originate from 2 sources. Those schizophrenic patients in whom obsessive delusions grew out of preexisting simple obsessions, of which they lost insight, would respond to adjunctive antiobsessional agents, whereas those in whom obsessive delusions grew out of "obsessive preoccupation with schizophrenic delusions" would be responsive to atypical antipsychotics. Although we agree that obsessions and delusions are not necessarily mutually exclusive, we took a different stand in our study because we wanted to disentangle psychotic symptoms and OCS as much as possible. The improvement of OCS during treatment with olanzapine described by Poyurovsky et al.[17] may have been partially attributable to clozapine discontinuation in 2 of their 3 patients. However there may be a great interindividual variability in OCS response to treatment with olanzapine. The above-mentioned complexity of response of patients with both schizophrenia and OCS to atypical antipsychotics underscores the need for further investigation in larger controlled studies.

Moreover, the finding that long-term treatment with olanzapine may induce or exacerbate OCS in a subgroup of patients with schizophrenia or related disorders seems to be in contradiction to open reports and studies that suggest that olanzapine augmentation may benefit some

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patients with treatment-refractory OCD.[18–21] However, risperidone showed a more robust response in patients with treatment-refractory OCD.[22–27] Our findings are therefore compatible with a difference between risperidone and olanzapine in terms of effectiveness for treatment-resistant OCD, although double-blind controlled comparisons are needed to establish the differences between olanzapine and risperidone in this respect.

Perhaps the increase in OCS in a subgroup of patients with schizophrenia during treatment with olanzapine, and the decrease in OCS in other patients during treatment with olanzapine, is related to genetic diversity. It has been suggested that polymorphisms in the 5-HT_{2A} receptor gene are associated with clinical response to clozapine[28] and OCD,[29] and such polymorphisms might also be associated with the differential effects of olanzapine in different groups of patients.

The number of patients studied, the prospective longitudinal design, and the relatively homogeneous group of patients with recent-onset schizophrenia are strengths of our study. Limitations are the unknown reliability and validity of the DSM-IV OCD diagnosis or the YBOCS in patients with schizophrenia and the open-label character of our study.

With regard to further studies, we recommend that OCS assessments should also be done a considerable time (for instance, about 12 weeks) after the start of treatment with olanzapine. Replication of the presented findings may raise clinicians' awareness of the possible occurrence or exacerbation of OCS in a subset of patients during long-term treatment with olanzapine that could have a potential negative effect on compliance with maintenance treatment. Also, if differences in long-term propensity of olanzapine and risperidone to induce or exacerbate OCS are replicated, our understanding of mechanisms associated with occurrence of OCS may be enhanced.

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

REFERENCES

1. Poyurovsky M, Fuchs C, Weizman A. Obsessive-compulsive disorder in patients with first-episode schizophrenia. Am J Psychiatry 1999;156: 1998–2000
2. Berman I, Merson A, Viegner B, et al. Obsessions and compulsions as a distinct cluster of symptoms in schizophrenia: a neuropsychological study. J Nerv Ment Dis 1998;186:150–156
3. Tibbo P, Warneke L. Obsessive-compulsive disorder in schizophrenia: epidemiologic and biologic overlap. J Psychiatry Neurosci 1999;24:15–24
4. Eales MJ, Layeni AO. Exacerbation of obsessive-compulsive symptoms associated with clozapine. Br J Psychiatry 1994;164:687–688
5. de Haan L, Linszen DH, Gorsira, R. Clozapine and obsessions in patients with recent-onset schizophrenic disorders. J Clin Psychiatry 1999;60: 364–365
6. Morrison D, Clark D, Goldfarb E. Worsening of obsessive-compulsive symptoms following treatment with olanzapine [letter]. Am J Psychiatry 1998;155:855
7. Mottard JP, De la Sablonniere JF. Olanzapine-induced obsessive-compulsive disorder. Am J Psychiatry 1999;156:799–800
8. Baker RW, Ames D, Umbricht DSG, et al. Obsessive-compulsive symptoms in schizophrenia: a comparison of olanzapine and placebo. Psychopharmacol Bull 1996;32:89–93
9. Spitzer RL, Williams JBW. Classification of mental disorders. In: Kaplan HJ, Sadock BJ, eds. Comprehensive Textbook of Psychiatry. 4th ed. Baltimore, Md: Williams & Wilkins; 1985
10. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-I/P, Version 2.0). New York, NY: Biometric Research, New York State Psychiatric Institute; 1995
11. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale, 2: validity. Arch Gen Psychiatry 1989;46:1012–1016
12. Ghaemi SN, Zarate CA, Popli AP, et al. Is there a relationship between clozapine and obsessive-compulsive disorder? a retrospective chart review. Compr Psychiatry 1995;36;267–270
13. Bermanzohn PC, Porto L, Arlow PB, et al. Are some neuroleptic-refractory symptoms of schizophrenia really obsessions? CNS Spectrums 1997;2: 51–57
14. Bürgy M. Clozapine and obsessive-compulsive symptoms in schizophrenia: a case history of one patient. Nervenarzt 1999;70:64–67
15. LaPorta LD. More on obsessive-compulsive symptoms and clozapine [letter with reply]. J Clin Psychiatry 1994;55:312
16. Tibbo P, Gendemann K. Improvement of obsessions and compulsions with clozapine in an individual with schizophrenia. Can J Psychiatry 1999;44: 1049–1050
17. Poyurovsky M, Dorman-Etrog P, Hermesh H, et al. Beneficial effect of olanzapine in schizophrenic patients with obsessive-compulsive symptoms. Int Clin Psychopharmacol 2000;15:169–173
18. Koran LM, Ringold AL, Elliott MA. Olanzapine augmentation for treatment-resistant obsessive-compulsive disorder. J Clin Psychiatry 2000; 61:514–517
19. Weiss EL, Potenza MN, McDougle CJ, et al. Olanzapine addition in obsessive-compulsive disorder refractory to selective serotonin reuptake inhibitors: an open label case series. J Clin Psychiatry 1999;60:524–527
20. Marazitti D, Pallanti S. Effectiveness of olanzapine treatment for severe obsessive-compulsive disorder [letter]. Am J Psychiatry 1999;156: 1834–1835
21. Potenza MN, Wasylink S, Longhurst JG, et al. Olanzapine augmentation of fluoxetine in the treatment of refractory obsessive-compulsive disorder. J Clin Psychopharmacol 1998;18:423–424
22. Jacobsen FM. Risperidone in the treatment of affective illness and obsessive-compulsive disorder. J Clin Psychiatry 1995;56:423–429
23. McDougle CJ, Fleischmann RL, Epperson CN, et al. Risperidone addition in fluvoxamine-refractory obsessive-compulsive disorder: three cases. J Clin Psychiatry 1995;56:526–528
24. Stein DJ, Bouwer C, Hawkridge S, et al. Risperidone augmentation of serotonin reuptake inhibitors in obsessive-compulsive and related disorders. J Clin Psychiatry 1997;58:119–122
25. Ravizza L, Barzega G, Bellino S, et al. Therapeutic effect and safety of adjunctive risperidone in refractory obsessive-compulsive disorder (OCD). Psychopharmacol Bull 1996;32:677–682
26. Saxena S, Wang G, Bystritsky A, et al. Risperidone augmentation of SRI treatment for refractory obsessive-compulsive disorder. J Clin Psychiatry 1996;57:303–306
27. McDougle CJ, Epperson CN, Pelton GH, et al. A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive-compulsive disorder. Arch Gen Psychiatry 2000;57: 794–801
28. Arranz MJ, Munro J, Sham P, et al. Meta-analysis of studies on genetic variation in 5-HT_{2A} receptors and clozapine response. Schizophr Res 1998; 32:93–99
29. Enoch MA, Kaye WH, Rotondo A, et al. 5-HT_{2A} promotor polymorphism–1438G/A, anorexia nervosa, and obsessive-compulsive disorder [letter]. Lancet 1998;351:1785–1786

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