Patients' perspectives. Subjective experiences and attitudes of patients with recent onset schizophrenia

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Citation for published version (APA):
de Haan, L. (2002). Patients' perspectives. Subjective experiences and attitudes of patients with recent onset schizophrenia

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Chapter 4.3.

Obsessive-compulsive symptoms during treatment with olanzapine and risperidone, a prospective study of 113 patients with recent onset schizophrenia or related disorders

In press The Journal of Clinical Psychiatry

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Summary

Background: 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: Prospective study of consecutively hospitalized young patients with DSM-IV schizophrenia or related disorders (n=113), 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 with olanzapine (n=39) or risperidone (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. The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was administered at admission and 6 weeks thereafter.

Results: OCS were found in about 30% of all cases at both assessments and 15% met DSM-IV criteria for Obsessive-Compulsive Disorder (OCD). No differences in OCS were found in the patients randomly assigned to olanzapine or risperidone. Subjects treated with olanzapine at both assessments had significantly more severe OCS than subjects treated with risperidone at both assessments. Duration of treatment with olanzapine was significantly 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.
4.3.1. Introduction

The prevalence of Obsessive-Compulsive Disorder (OCD) is estimated to be 14% in patients with first-episode schizophrenia. Obsessive-Compulsive Symptoms (OCS) probably occur more frequently in patients with schizophrenia. Retrospective studies and case-reports suggest that some antipsychotic drugs may induce or exacerbate OCS in patients with schizophrenia. Most reports concern clozapine. Case-reports mention OCS as occurring in olanzapine-treated patients. Tibbo et al. reviewed four 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. 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 daily, and 7 received olanzapine, 10 mg daily. No significant differences 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 differs during treatment with olanzapine or risperidone. We also examined the relationship between duration of treatment with olanzapine or risperidone and severity of OCS.

4.3.2. Method

Consecutively admitted patients (n=113) participating in a prospective study of recent-onset schizophrenia and related disorders were included. Patients 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. Reasons for admission to the treatment program were: clinical treatment was considered necessary to enable stabilization, psycho-education and rehabilitation. Discharge diagnoses according to DSM-IV criteria were based on longitudinal, clinical and, heteroanamnestic assessment (Longitudinal Expert Assessment of Diagnosis procedure). Exclusion criteria were: neurological or endocrine disease and mental retardation. After a complete description of the study 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 or risperidone prior to admission continued with that medication if they showed initial clinical
response (olanzapine, \( n=39 \); risperidone, \( n=23 \)). Patients who showed no response or adverse effects of olanzapine (\( n=6 \)) or risperidone (\( n=9 \)) at admission were switched to risperidone or olanzapine.

Excluded from analyses were three patients because of medication non-compliance (two patients were treated with olanzapine at admission, one patient was treated with risperidone), and four patients because of crossover to typical antipsychotics 6 weeks after first assessment (two olanzapine-treated subjects, two risperidone-treated subjects). Analyses of differences in OCS of these small groups were deemed not to be appropriate.

The presence of OCS was defined according to the 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 \(^{11}\) (Y-BOCS) was administered at admission and 6 weeks later by two trained psychiatric residents (N.B., B.H.) who rated the patients twice and were not blind to medication. Inter-rater agreement for Y-BOCS total score in four categories was good (weighted \( \kappa = 0.73 \)).

The cut-off point of clinically significant OCD is a Y-BOCS score of 7 in non-psychotic populations. However, we chose a cut-off score of 10 for clinically significant comorbid OCD in these patients with schizophrenia and related disorders, since a patient with a Y-BOCS score of 10 or less could have no more than mild OCS. We think that it is appropriate to increase the threshold for clinical significant co-morbidity of OCD in this severe 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.

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

**4.3.3. Results**

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

At admission 33 (29.2%) patients had OCS, (mean Y-BOCS total score=3.6, SD=6.8). Six weeks later 36 (31.9%) patients had OCS, (mean Y-BOCS total score=3.1, SD=5.9).

Seventeen (15%) patients had a Y-BOCS total score of 10 or higher and fulfilled DSM-IV criteria for OCD at both assessments (mean Y-BOCS total
score at admission=17.5, SD=7.0; mean Y-BOCS total score 6 weeks after admission=17.8, SD=5.8).

In the randomly allocated group we found no differences in Y-BOCS total scores between patients assigned to the olanzapine or risperidone treatment condition. In the groups starting with olanzapine or risperidone prior to admission and using olanzapine (n=35) or risperidone (n=20) at both assessments the Y-BOCS total score tended to be higher in the olanzapine group at admission (Mann-Whitney test p=0.08), and was significantly higher in the olanzapine group 6 weeks later (Mann-Whitney test p=0.01). The mean total score of compulsions was significantly higher in the olanzapine group (mean=2.4, SD=4.6, versus mean=0.5, SD=2.2; Mann-Whitney test p=0.04) There were no significant differences in mean Y-BOCS total score at admission and 6 weeks later in the six patients who switched from olanzapine to risperidone, nor in the nine patients who switched from risperidone to olanzapine. Twelve out of 63 patients (19%) who used olanzapine 6 weeks after admission fulfilled DSM-IV criteria for OCD, four out of 43 patients (9%) who used risperidone 6 weeks after admission fulfilled DSM-IV criteria for OCD.

### Table 1. Y-BOCS score at admission and 6 weeks later

<table>
<thead>
<tr>
<th>Medication at admission and 6 weeks later</th>
<th>Patients with OCD (Y-BOCS score&gt;10)</th>
<th>Mean Y-BOCS score (SD)</th>
<th>6 At admission</th>
<th>6 weeks later</th>
<th>6 At admission</th>
<th>6 weeks later</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomly allocated to:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine (n=19)</td>
<td></td>
<td>2.4 (5.3)</td>
<td>1.9 (4.2)</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Risperidone (n=17)</td>
<td></td>
<td>2.4 (5.4)</td>
<td>2.2 (5.0)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Started before admission:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine (n=35)</td>
<td></td>
<td>4.9 (7.8)</td>
<td>4.5 (6.7)</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Risperidone (n=20)</td>
<td></td>
<td>1.9 (8.8)</td>
<td>2.2 (7.1)</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Switched from: Olanzapine to Risperidone (n=6)</td>
<td></td>
<td>5.8 (7.0)</td>
<td>4.7 (3.1)</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Risperidone to Olanzapine (n=9)</td>
<td></td>
<td>3.5 (4.9)</td>
<td>4.0 (5.6)</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

*a Abbreviations: Y-BOCS = Yale-Brown Obsessive Compulsive Scale, SD = standard deviation

Duration of treatment with olanzapine correlated with Y-BOCS total score (r=0.33, p<0.01). The correlation between duration of treatment with olanzapine and Y-BOCS total score was r=0.51 (p<0.01) for patients who had a positive Y-BOCS total score. Patients who were treated 12 weeks or longer with olanzapine had a significantly higher Y-BOCS total score than patients who used olanzapine for less than 12 weeks (mean=7.3, SD=9.7
versus mean=2.7, SD=4.9; Mann-Whitney test p<0.05). Duration of treatment with risperidone was not related to Y-BOCS total score (r=-0.12, p=0.23). Mean duration of treatment with olanzapine 6 weeks after admission was 53.6 days (SD=50.4 days). Mean duration of treatment with risperidone 6 weeks after admission was 71.3 days (SD=73.0 days).

4.3.4. Discussion

The comorbidity rate of OCD in our patient’s sample (15%) was similar to the 14% reported by Poyurovsky et al. About another 15% of our patients had not 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 olanzapine treatment duration 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 clinical relevant OCS in a subset of patients with recent-onset schizophrenia. Although most patients had low scores on the Y-BOCS, and mean scores slightly decreased from admission to 6 weeks later, almost one fifth of the patients using 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, retrospective chart review studies and prospective open label studies 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 and olanzapine may be efficacious in alleviation of both psychotic symptoms and OCS. However, treatment with clozapine was associated with improvement of OCS in only five of nine cases described. 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. We only assessed the presence of OCS 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. 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 two sources. Those schizophrenic patients in whom obsessive delusions grew out of pre-existing simple obsessions, of which they lost insight, would respond to adjunctive anti-obessional 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. 16 may have been partially attributable to the clozapine discontinuation in two of their three patients. However there may be a great interindividual variability in response concerning OCS to treatment with olanzapine. The abovementioned 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 in contradiction with open reports and studies which suggest that olanzapine augmentation may benefit some patients with treatment refractory OCD 17,18,19,20. However, risperidone showed a more robust response in patients with treatment-refractory OCD 21,22,23,24,25,26. 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-HT2A receptor gene are associated with clinical response to clozapine 27 and obsessive-compulsive disorder 28, 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 homogenous group of patients with recent-onset schizophrenia studied, are strengths of our study. Limitations are the unknown reliability and validity of the DSM-IV OCD diagnosis or Y-BOCS 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 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, with a potential negative effect on maintenance treatment compliance. Also, if differences in long-term propensity of olanzapine and risperidone to induce or exacerbate OCS are replicated, this may contribute to our understanding of mechanisms associated with occurrence of OCS.
References


