Well-being and co-morbidity in recent onset schizophrenia
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Citation for published version (APA):
van Nimwegen, L. J. M. (2008). Well-being and co-morbidity in recent onset schizophrenia

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Chapter 2.1

Obsessive-compulsive symptoms in a randomized double blind study with olanzapine or risperidone in young patients with early psychoses


Lonneke van Nimwegen, Lieuwe de Haan, Nico van Beveren, Winfried Laan, Wim van den Brink, Don Linszen.
Abstract

**Background** The prevalence of obsessive-compulsive symptoms (OCS) in patients with schizophrenia is relatively high. Antipsychotics have been found to influence OCS.

**Objective** To determine whether induction or severity of OCS differ during treatment with olanzapine or risperidone in young patients with early psychoses.

**Material and Methods** One hundred and twenty-two patients with a DSM-IV diagnosis of schizophrenia, schizoaffective disorder or schizophreniform disorder were randomized in a double-blind design to groups 6 weeks treatment with olanzapine (n = 59) or risperidone (n = 63), with a mean dose of 11.3 mg olanzapine and 3.0 mg risperidone at 6 weeks. Primary outcome measures were the mean baseline-to-endpoint change in total score on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS).

**Results** Treatment with olanzapine was associated with greater decreases in Y-BOCS total score than treatment with risperidone in total group (n = 122: -2.2 versus -0.3, z = -2.651, p < 0.01), in patients with baseline Y-BOCS total score > 0 (n=58: -5.1 versus -0.4, z = -2.717, p < 0.01), and in patients with baseline Y-BOCS total score > 10 (n=29: -7.1 versus -0.6, z = -2.138, p = 0.032).

**Conclusion** In this randomized 6 weeks double blind trial we found a significant and clinically relevant difference in decrease in Y-BOCS scores favouring olanzapine compared to risperidone.
Introduction

The prevalence of obsessive-compulsive symptoms (OCS) (Berman et al 1998) and obsessive-compulsive disorder (OCD) (Bottas et al 2005, Poyurovsky et al 1999) in patients with schizophrenia is relatively high (25-45%) and may predict a poor prognosis (Berman et al 1995, Fenton et al 1986). Several reports mention the emergence or exacerbation of OCS during treatment with atypical antipsychotic medication, which has been related to the serotonin and dopamine interactions of these compounds, particularly the 5-HT₂/dopamine antagonistic ratios (Tibbo et al 1999). Most reports on the emergence or exacerbated OCS during treatment with antipsychotic medication involve clozapine (Eales and Layeni 1994, de Haan et al 1999, 2004). However also reductions of OCS during clozapine treatment have been described (de Haan et al 2004). Case reports mention induction or an increase of OCS during treatment with olanzapine (al-Mulhim et al 1998, Lykouras et al 2000, Morrison et al 1998, Mottard et al 1999, Ramasubbu et al 2000) and during treatment with risperidone (Alevizos et al 2002, Alzaid and Jones 1997, Andrade et al 1998, Diler et al 2003, Dodt et al 1997, Dryden-Edwards and Reiss 1996, Ke et al 2004, Kopala et al 1994, Levy et al 2003, Mahendran 1998, 1999, Remington et al 1994, Sinha et al 2000). However decrease of OCS during treatment with risperidone has also been reported (Veznedaroglu et al 2003). In a randomized open study, no differences were found in the short-term propensity of olanzapine or risperidone to induce or exacerbate OCS, although longer treatment with olanzapine was associated with higher OCS-scores (de Haan et al 2002). In order to overcome methodological limitations of previous studies, the present randomized trial had a double blind design and examined whether there was difference in the prevalence and severity of OCS and OCD in a trial comparing olanzapine with risperidone.

Material and Methods

Design

We conducted a 6-week, randomized, double blind, multi-center study comparing olanzapine and risperidone in adolescents and young adults with recent onset schizophrenia or related disorders.
**Study population**

Eligible for the study were male and female in- and outpatients 18 to 30 years old, meeting criteria for a DSM-IV diagnosis of schizophrenia, schizoaffective disorder or schizophreniform disorder based on the Structured Clinical Interview for the DSM-IV, patient version (SCID-P). Each site’s institutional review board or ethics committee approved the study and written informed consent was obtained. Patients were recruited from in- and outpatient settings at 4 centres in the Netherlands: the Academic Medical Centre in Amsterdam (AMC), Erasmus Medical Centre in Rotterdam (EMC), Parnassia Psychomedical Centre in the Hague and Mediant in Enschede from July 1, 2003 through July 1, 2005. All patients (similar in both groups) were treated with a disease and stress management programme, including psycho-education about psychosis and substance abuse and social-skills-training.

**Treatment conditions**

Patients received flexible doses of either olanzapine (5, 10, 15 or 20 mg/d) or risperidone (1.25, 2.5, 3.75 or 5 mg) in identical-looking capsules. The above mentioned dose ratio of 1:4 reflects comparable dopamine D₂ receptor occupancy for these compounds (Kapur et al 1999, Kapur and Seeman 2001). In the first week, treating physicians could adjust the daily dose upward or downward, to a fixed dose the following 5 weeks.

**Assessments**

The primary outcome measure was the Y-BOCS total score, which was assessed at baseline and at 6 weeks or at treatment discontinuation (last observation carried forward). In the Y-BOCS scoring, Obsessive Compulsive Symptoms were defined according to the SCID-P, i.e. as (a) persistent, repetitive, intrusive, and distressful thoughts not related to the patient’s delusions (obsessions) or (b) repetitive goal directed rituals that were clinically distinguishable from schizophrenic mannerisms or posturing (compulsions). The Y-BOCS consists of 10 items (five concerning obsessions and five concerning compulsions) with scores ranging from 0 (no symptoms) to 4 (severe symptoms) and one item with a score ranging from 0 (no symptoms) to 6 (extreme severe symptoms) in which the severity of the OCS is judged by the interviewer. The Y-BOCS has showed good internal consistency and good inter-rater reliability in patients with recent onset schizophrenia (de Haan et al 2006). Secondary outcome measures were the Positive and Negative Syndrome Scale (PANSS), to measure severity of psychopathology and the Calgary Depression
Scale for Schizophrenia (CDSS; http://www.ucalgary.ca/cdss/) to measure severity of depressive symptoms in schizophrenia.

Statistical analysis

Depending on distribution characteristics, treatment comparisons were performed using Chi-square, Student T or Mann-Whitney tests for significance. All tests (two-sided) were performed at the 5% significance level using an intent-to-treat (ITT) analysis and last observation carried forward (LOCF) for missing endpoints. The Reliability Change Index (RCI) was calculated in order to demonstrate clinical relevance in cases of statistical significance (Hagemann and Arrindell 1993, Jacobson and Truax 1991).

Results

Sample characteristics

Of the 201 patients that were eligible for this study, 131 received at least 1 dose of the study medication (64 olanzapine, and 67 risperidone). At 6 weeks data were available from 59 patients with olanzapine (92%) and from 63 patients taking risperidone (94%). Therefore 122 (93%) patients were included in the analysis. There were no notable imbalances between treatment conditions in age (mean of total group: 24.6 years), sex (91.3% male), diagnostic subgroups (90% schizophrenia, 6% schizophreniform disorder, 4% schizaffective disorder), or baseline Y-BOCS-score (mean total group 5.3 ± 8.1). Also PANSS-scores (62.9 ± 18.8 in olanzapine vs 65.8 ± 20.2 in risperidone) and CDSS scores (3.1 ± 5.8 in olanzapine vs 2.8 ± 12.3 in risperidone) were not significantly different between groups at baseline. The mean dosage received by the patients was 9.9 ± 4.8 mg olanzapine and 2.5 ± 1.1 mg risperidone at one week and 11.3 ± 4.6 mg olanzapine and 3.0 ± 1.1 mg risperidone at 6 weeks. Percentage of patients using at least two capsules per day was not significantly different in the treatment conditions: risperidone 57/63 = 90.5% and olanzapine 47/59 = 79.7%. Altogether, there was no significant difference in the estimated D2 receptor occupancy between the two groups (de Haan et al 2002, Kapur and Seeman 2001).
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**Treatment effect**

At baseline, mean total Y-BOCS scores between groups did not differ significantly (Table 2.1.1). At baseline 74 patients had a zero Y-BOCS score (36 olanzapine vs. 38 risperidone, P=0.94). In 10 of them (2 olanzapine and 8 risperidone, P=0.11) OCS (YBOCS >0) emerged after 6 weeks. In the total group (n=122) and in the group with Y-BOCS scores > 0 (n=58), decreases in Y-BOCS scores were significantly larger in the olanzapine than in the risperidone group (Table 2.1.1). Also in patients with clinically significant co morbid OCD (Veznedaroglu et al 2002) (Y-BOCS score > 10; n=29), mean reductions in Y-BOCS-scores were significantly larger in the olanzapine than in the risperidone group (Table 2.1.1). No significant differences in the reduction of OCS between groups were found in groups with Y-BOCS score > 16 (n=18, moderate OCD) (Byerly et al 2005) (Table 2.1.1). A very similar pattern of findings was observed using the percentage of patients with Reliability Change (RCI) (Table 2.1.2), indicating that the statistical significant finding between treatment conditions were also clinically relevant. Total PANSS scores at baseline did not

<p>| Table 2.1.1. Y-BOCS Scores at Admission and at 6 Weeks in Adolescents with First-Episode Psychosis, Randomly Assigned Double Blind Treatment with Either Olanzapine or Risperidone |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Y-BOCS Score</th>
<th>Olanzapine</th>
<th>Risperidone</th>
<th>Mann-Whitney U</th>
<th>P</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (N=59) (N=63)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>5.0 (7.3)</td>
<td>5.5 (8.9)</td>
<td>-0.035</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td>After 6 weeks</td>
<td>2.8 (5.4)</td>
<td>5.3 (8.1)</td>
<td>-1.956</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Δ YBOCS</td>
<td>-2.2 (4.9)</td>
<td>-0.3 (5.7)</td>
<td>-2.651</td>
<td>0.008 d=0.36</td>
<td></td>
</tr>
<tr>
<td>Patients with Y-BOCS &gt; 0 (N=25) (N=33)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>11.7 (6.7)</td>
<td>10.5 (9.9)</td>
<td>-1.167</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>After 6 weeks</td>
<td>6.6 (6.7)</td>
<td>10.1 (8.8)</td>
<td>-1.56</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Δ YBOCS</td>
<td>-5.1 (6.5)</td>
<td>-0.4 (7.9)</td>
<td>-2.717</td>
<td>0.007 d=0.65</td>
<td></td>
</tr>
<tr>
<td>Patients with Y-BOCS &gt; 10 (N=13) (N=16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>16.8 (4.3)</td>
<td>17.1 (10.1)</td>
<td>-0.066</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>After 6 weeks</td>
<td>9.7 (7.3)</td>
<td>16.5 (7.9)</td>
<td>-2.360</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Δ YBOCS</td>
<td>-7.1 (6.0)</td>
<td>-6.0 (10.1)</td>
<td>-2.138</td>
<td>0.03 d=0.81</td>
<td></td>
</tr>
<tr>
<td>Patients with Y-BOCS &gt; 16 (N=7) (N=11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>19.7 (3.4)</td>
<td>20.7 (9.7)</td>
<td>-0.502</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>After 6 weeks</td>
<td>11.7 (9.1)</td>
<td>19.5 (7.0)</td>
<td>-1.686</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Δ YBOCS</td>
<td>-8.0 (7.6)</td>
<td>-2.0 (10.7)</td>
<td>-1.5</td>
<td>0.13 d=0.66</td>
<td></td>
</tr>
</tbody>
</table>
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differ between groups: 62.9 ± 18.8 olanzapine group and 65.8 ± 20.2 risperidone group (P=0.43). Also CDSS scores at baseline did not differ between groups: 3.3 ± 5.8 olanzapine group and 2.8 ± 12.3 risperidone group (P=0.84). Y-BOCS scores at baseline and at 6 weeks were significantly correlated with CDSS scores after 6 weeks: r=0.39 (P=0.003) and r=0.38 (P=0.004) respectively. Y-BOCS-scores were not significantly correlated with PANSS scores.

Discussion

The aim of the study was to investigate the differential effect of olanzapine and risperidone on presence and severity of OCS in patients with recent onset schizophrenia or related disorders. Treatment with olanzapine was associated with a significant and clinically relevant larger decrease of OCS compared to treatment with risperidone. However, Y-BOCS scores only decreased significantly in the subgroup
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with mild OC symptoms (YBOCS >10) and not in the group with moderate OC symptoms (YBOCS>16). The latter might be related to the small sample size of this subgroup (n=18). To our knowledge, this is the first randomized double blind clinical trial that compared the effect of olanzapine and risperidone on the presence and severity of OCS.

Previous reports showed conflicting results regarding the effect of treatment with olanzapine or risperidone on OCS severity (Lykouras et al 2003). However, these reports were based on cases series (Diler et al 2003, Levy et al 2003, Lykouras et al 2003, Ke et al 2004) or single blind studies (Veznedaroglu et al 2003). In a randomized but non-blinded study with 113 patients, no difference in the change in OCS between olanzapine and risperidone occurred, but an association of the severity of OCS and duration of olanzapine treatment was observed (de Haan et al 2002). In the current study we found a decrease instead of an increase in OCS during 6 weeks treatment with olanzapine. A reason may be that the relatively low dose of olanzapine in this group of young patients was related to the decrease of OCS. In most case reports and the randomized non-blinded study mentioned before, doses of $\geq$3 mg risperidone and $\geq$15 mg olanzapine were used. Alevizos et al (2002) described that higher doses of risperidone seemed to induce OCS, while lower doses decreased OCS. However, this is in contrast with the finding that atypicals in higher doses used as augmentation therapy in primary OCD have an ameliorative effect on OCS, though this was an open case series study with only three patients (Ramasubbu et al 2000). It is also in contrast with the hypothesis that the high affinity for serotonin 5HT$_2$ receptors compared to the affinity for dopamine D$_2$ receptors of atypical antipsychotics may induce OCS at low doses due to high 5HT$_2$ antagonism, whereas improvement in OCS is thought to occur at high doses due to high D$_2$ antagonism (Ramasubbu et al 2000). It could be that a critical factor for the difference between olanzapine and risperidone is that at low doses olanzapine blocks 5HT$_2a$ with a lower affinity than risperidone (Marek et al 2003). This is in line with the finding that in primary OCD olanzapine improves OCS in doses of 5 mg (Marek et al 2003). Differences in neurobiology of primary OCD and co-morbid OCS in schizophrenia could explain the varied reactions to antipsychotics (Gao et al 2006).

A limitation of the current study is that treatment lasted only 6 weeks and therefore effects of supersensitivity of the 5HT$_2a$ receptor could not be observed. This factor might be (partially) responsible for different results after short and longer treatments. Another limitation is the small sample sizes of some of the subgroups; only 18 patients had moderate OCD. Also the relatively low doses used in the study may not represent clinical practice where some patients need higher doses. However, the described dose in our study was an average of 122 patients, meaning...
that also patients in need of higher doses (until 20 mg, which is a clinically used dosage at the higher end of the spectrum) were included.

Strengths of the trial are the double blind randomized design, the homogeneous sample of young adult patients with first psychosis and the absence of differences in assumed D₂ receptor occupancy of the doses used.

With regard to further studies, we recommend that OCS assessments should also be done with a longer duration of study medication and with different doses of atypical antipsychotics. This would offer the opportunity to find out whether effect on OCS is related to dosing of antipsychotic medication.

We conclude that a decrease in severity of OCS occurs during treatment with a relatively low dose of olanzapine and not with a relatively low dose of risperidone, and that this difference between these medications is clinically relevant. Therefore, olanzapine may have advantages over risperidone in the treatment of patients with a psychotic disorder and co-morbid obsessive-compulsive symptoms.
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