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van Nimwegen, L.J.M.

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Chapter 1.2

Effect of olanzapine and risperidone on subjective well-being and craving for cannabis in patients with schizophrenia or related disorders: a double blind randomized trial

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Lonneke van Nimwegen, Lieuwe de Haan, Nico van Beveren, Mischa van der Helm, Wim van den Brink, Don Linszen.
Abstract

**Objective** The aim of this study was to examine whether subjective well-being and craving for cannabis were different in patients with schizophrenia or related disorders treated with either olanzapine or risperidone.

**Method** A 6-week, double blind, randomized trial of olanzapine and risperidone was carried out in 128 young adults with recent onset schizophrenia or related disorders. Primary efficacy measures were the mean baseline-to-endpoint change in total scores on the Subjective Well-being under Neuroleptics Scale (SWN), the Obsessive Compulsive Drug Use Scale (OCDUS), the Drug Desire Questionnaire (DDQ) and the Cannabis Use Self Report (CUSR). Analysis of covariance (ANCOVA) was used to test between-group differences.

**Results** Estimated D₂ receptor occupancy did not differ between olanzapine (n=63) and risperidone (n=65). Similar improvements in subjective well-being were found in both groups. In the co-morbid cannabis-using group (n=41, 32%), a similar decrease in craving for cannabis was found in both treatment conditions.

**Conclusions** Both, olanzapine and risperidone were associated with improved subjective well-being. No evidence was found for a differential effect of olanzapine or risperidone on subjective experience or on craving for cannabis in doses leading to comparable dopamine D₂ occupancy.
Introduction


Since subjective experiences are correlated with occupancy of dopamine D₂ receptors by the antipsychotic compound (de Haan et al 2000, 2003, Kapur and Seeman 2001) and since olanzapine dissociates faster from the dopamine D₂ receptor than risperidone, olanzapine is hypothesized to induce less negative subjective experiences (Kapur and Seeman 2001). Using the Subjective Well-being under Neuroleptics (SWN), patients receiving olanzapine treatment reported higher levels of subjective well-being than patients treated with either clozapine or risperidone (Naber et al 2001).

The use of cannabis (12-50%) is also associated with low treatment adherence in schizophrenia (Fowler et al 1998, Mueser et al 1990, Regier et al 1990, Soyka et al 1993), leading to more positive symptoms and psychotic episodes, and higher rehospitalization rates (Cleghorn et al 1991, Linszen et al 1994, Negrete et al 1986), but also with a reduction of negative symptoms, anxiety and depression (Dixon et al 1990, Peralta and Cuesta 1992). Typical antipsychotic medications are thought to be associated with the induction of negative subjective experiences and craving by antagonizing striatal dopaminergic D₂ receptors (Brown et al 2003, de Haan et al 2006, McEvoy et al 1995), whereas atypical antipsychotics are suggested to reduce smoking and substance use (Green et al 1999, McEvoy et al 1995). The results with regard to olanzapine and risperidone are inconsistent and both reductions (Hutchison et al 2003, 2004), increases (Kampman et al 2003, Sayers et al 2005, Smelson et al 2002), and no change in craving (Smelson et al 2004) have been reported.

We hypothesized that olanzapine (because of faster dissociation) would have a more favorable effect on subjective well-being and craving for cannabis than risperidone. This hypothesis can only be tested when doses of antipsychotic medication are compared that lead to similar dopamine D₂ receptor occupancy.

This first double-blind randomized trial in young adults with recent onset schizophrenia and related disorders was designed to examine whether olanzapine and risperidone have a differential effect on 1. subjective experiences, 2. craving for cannabis and on 3. continued use of cannabis.
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Methods

Subjects

Eligible for this 6-week, multicenter, double-blind, randomized controlled trial were male and female in- and outpatients age 18 to 30. They had to meet DSM-IV-R criteria for schizophrenia, schizoaffective disorder or schizophreniform disorder based on the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, patient version (SCID-P). Patients with concomitant use of any other antipsychotic drug than olanzapine or risperidone, depot antipsychotic medications in the three months prior to inclusion, current use of other psychotropic medications other than oxazepam or biperiden were excluded. Each center’s ethics committee approved the study and written informed consent was obtained.

Patients were recruited from four mental health centers in the Netherlands (Academic Medical Centre in Amsterdam; Erasmus Medical Centre in Rotterdam; Parnassia Psychomedical Centre in the Hague and Mediant in Enschede). Assessments took place at baseline just before randomization, after one week of treatment and at the end of the six weeks treatment or when the patient discontinued randomized therapy (last-observation-carried-forward approach).

Patients received flexible dosing of either olanzapine (5, 10, 15 or 20 mg/d) or risperidone (1.25, 2.5, 3.75 or 5 mg/d) in identical-looking capsules. The dose ratio of 1:4 is estimated according to our goal to reach comparable dopamine D_2 receptor occupancy (Kapur and Seeman 2001). In the first week, treating physicians could adjust the daily dose, to a fixed dose for the following 5 weeks. All patients (similar in both groups) were treated with disease and stress management programme, including psycho-education about psychoses and substance abuse and social-skills-training.

Assessments

All patients were assessed with the Subjective Well-being under Neuroleptics Scale short version (SWN/sv), a 20 item six point Likert type self rating scale measuring the subjective experience in the past seven days, with robust psychometric qualities (de Haan et al 2002, Naber et al 1995, 2001). All patients also rated the Cannabis Use Self Report (CUSR), measuring cannabis use in the past month. Self reported data were affirmed by Recent Drug Use Urine analysis. From the patients with self-reported cannabis use at baseline, two craving questionnaires were obtained. The Obsessive Compulsive Drug Use Scale (OCDUS), a self rating scale consisting
of 11 items with a five point Likert type rating measuring drug craving in the past seven days, and the Drug Desire Questionnaire (DDQ) (Franken et al 2002), a self rating scale measuring instantaneous craving.

Baseline characteristics were compared between treatments with a Chi² test, or an independent T test. An intention-to-treat (ITT) analysis of covariance (ANCOVA) was used to test between-group differences outcome variables, including treatment, site, and baseline score of the outcome parameter as factors. All tests were two-sided and were performed at the 5% significance level.

Results

Hundred-twenty-eight of 201 eligible patients (64%) received at least 1 dose of olanzapine (n= 63) or risperidone (n= 65), had at least one follow up assessment and were included in the ITT analysis (Figure 1.2.1), with no significant differences in patients that refused participation compared to those who were randomized.

Thirty-one patients (22%) discontinued treatment because of adverse events (n=9), lack of efficacy (n=8), patient decisions (n=10) or a combination of factors (n=4), and three patients (2%) were lost to follow-up. There were no significant differences between the two treatment groups with respect to age (25 years), gender (80% male) or diagnosis. Of the 128 randomized patients, 41 (32%) were using cannabis at baseline: 20 (49%) in the olanzapine and 21 (51%) in the risperidone group (p=0.95). There were no significant differences in baseline characteristics between the cannabis using patients in the two treatment conditions, except for the cannabis using olanzapine group having a significantly lower OCDUS score (mean 19.3, SD 6.5) than the cannabis using risperidone group (mean 26.7, SD 10.3), p=0.01.

Patients received a mean dosage of 9.8 mg olanzapine and 2.5 mg risperidone after 1 week and 11.1 mg olanzapine and 3.0 mg risperidone at 6 weeks. There was no significant difference in estimated D₂ receptor occupancy between the two groups.

After adjusting for SWN scores at baseline, there was no significant treatment by center interaction effect \[F (3, 119) =1.5, p=0.22\], and also none of the main effects were statistically significant [center: \(F (3,119) = 1.35, p=0.26\); treatment: \(F (1,119) =0.037, p=0.85\)]. These results suggest that there was no difference between centers and treatment conditions. The largest increase in SWN took place within the first week of the trial (Table 1.2.1).

Within the group of cannabis using patients, after adjusting for baseline scores, there were no significant group by center interaction effects on the OCDUS \(F (2, 33) =0.28, p=0.76\) and the DDQ \(F (2, 32) =1.67, p=0.21\), and none of the
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Figure 1.2.1 Flowchart of a Randomized 6-Week Double Blind Trial Comparing Olanzapine, 5-20 mg/day, to Risperidone in Adolescents with Recent Onset Schizophrenia or Related Disorders.

Main effects were statistically significant for the OCDUS [center: \( F(3, 33) = 1.50, \ p=0.23 \); treatment: \( F(1, 33) = 0.76, \ p=0.39 \)] and the DDQ [center: \( F(3, 32) = 1.50, \ p=0.23 \); treatment: \( F(1, 32)=0.93, \ p=0.34 \)]. These results suggest that there was no difference in effect on craving between centers or between treatments. Within the group of cannabis users, the reduction in the mean number of joints per week was not significantly different for olanzapine (mean = 4.7, SD 9.8) versus the risperidone group (mean = 4.3, SD 6.5) \( p=0.16 \).
In this first randomized, double blind comparison of olanzapine and risperidone with subjective well-being and craving for cannabis as primary outcome measures, there were no significant differences in subjective well-being (SWN) or reduction of craving for cannabis (OCDUS, DDQ) or in use of cannabis. Since most of the changes in SWN and OCDUS scores took place within the first week of the trial, it seems unlikely that differences would have been found if the trial had been extended beyond 6 weeks.

A limitation of the study is that only 41 of the 128 patients were using cannabis at baseline, resulting in limited statistical power for the detection of differences in changes in craving and cannabis use. Another limitation is that only 64% of the eligible patients were willing to participate in the study, possibly limiting the external validity of the study. However, there were no significant differences in patients that refused participation compared to those who were randomized. Similar to many

| Table 1.2.1 Efficacy Results at Treatment Endpoint for Adolescent Patients With First Psychosis Who Received Double Blind Olanzapine or Risperidone in a 6-Week Study Patients Included in Intent-To-Treat Analyses * |  |
|---|---|---|---|---|---|---|---|
| Efficacy Values | Analysis of Change |  |
| Olanzapine | Risperidone |  |
| Mean | SD | Mean | SD | F | DF | P |
| Primary Efficacy Values |  |
| Total score of Subjective Well-being under Neuroleptics (n=128) |  |
| Baseline | 82.2 | 14.9 | 79.2 | 17.7 |  |
| After 1 week | 84.9 | 16.2 | 82.8 | 16.7 |  |
| Endpoint | 84.2 | 14.3 | 82.5 | 15.7 |  |
| Change baseline-endpoint | 2.0 | 10.4 | 3.3 | 12.3 | 0.04 | 1, 119 | 0.85 |
| Obsessive Compulsive Drug Use Scores (n=41) |  |
| Baseline | 19.3 | 6.5 | 26.5 | 10.5 |  |
| Endpoint | 20.0 | 7.3 | 21.3 | 8.4 |  |
| Change baseline-endpoint | 0.7 | 5.2 | - 5.2 | 8.4 | 0.76 | 1, 33 | 0.39 |
| Drug Desire Questionnaire (n=42) |  |
| Baseline | 42.5 | 16.1 | 47.8 | 21.4 |  |
| Endpoint | 33.4 | 15.1 | 38.4 | 17.1 |  |
| Change baseline-endpoint | -9.1 | 19.0 | - 9.4 | 17.2 | 0.93 | 1, 32 | 0.34 |
| Cannabis Use Self Report Scores, joints/ week (n=41) |  |
| Baseline | 6.3 | 9.5 | 7.8 | 8.8 |  |
| Endpoint | 1.6 | 2.6 | 3.5 | 5.8 |  |
| Change baseline-endpoint | -4.7 | 9.8 | - 4.3 | 6.5 | 2.03 | 1, 36 | 0.16 |

Discussion

In this first randomized, double blind comparison of olanzapine and risperidone with subjective well-being and craving for cannabis as primary outcome measures, there were no significant differences in subjective well-being (SWN) or reduction of craving for cannabis (OCDUS, DDQ) or in use of cannabis. Since most of the changes in SWN and OCDUS scores took place within the first week of the trial, it seems unlikely that differences would have been found if the trial had been extended beyond 6 weeks.

A limitation of the study is that only 41 of the 128 patients were using cannabis at baseline, resulting in limited statistical power for the detection of differences in changes in craving and cannabis use. Another limitation is that only 64% of the eligible patients were willing to participate in the study, possibly limiting the external validity of the study. However, there were no significant differences in patients that refused participation compared to those who were randomized. Similar to many
other studies among adolescents and young adults with recent onset schizophrenia, only 70% of the participating patients completed the 6-week treatment. Patients receiving olanzapine and risperidone both reported increased subjective well-being during the 6 week trial. The highest increase of subjective well-being took place in the first week, which is consistent with previous findings (Naber et al 2005).

An explanation for the absence of differential effects is that our hypothesis was incorrect. Maybe the difference in dopamine dissociation between olanzapine and risperidone is too small to generate differences or, differences in dopamine dissociation rate are not related to differences in subjective experience or craving for cannabis. In recent placebo controlled studies, risperidone showed decreases in craving (de la Garza et al 2005, Smelson et al 2002, 2004); olanzapine showed a decrease (Hutchison et al 2001, 2004, Smelson et al 2006) as well as an increase in craving (Kampman et al 2003). More randomized controlled trials are needed to establish whether different types of antipsychotics really differ in their effect on craving and drug use behavior of patients. In conclusion: in this double blind randomized controlled study we found no evidence for a differential effect of olanzapine and risperidone (in doses that lead to comparable dopamine D₂ occupancy) on subjective well-being or on craving for cannabis.
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