Brief Communication

Effect of Olanzapine and Risperidone on Subjective Well-Being and Craving for Cannabis in Patients With Schizophrenia or Related Disorders: A Double-Blind Randomized Controlled Trial

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Objective: 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, the Obsessive–Compulsive Drug Use Scale, the Drug Desire Questionnaire, and the cannabis use self-report. An analysis of covariance 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 comorbid 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 dosages leading to comparable dopamine D2 occupancy.

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Clinical Implications
• Both olanzapine and risperidone are associated with improvements in subjective well-being in adolescent patients with first psychosis.
• There is no preference for olanzapine or risperidone regarding improvement of subjective well-being.
• There is no preference for olanzapine or risperidone regarding craving for cannabis.

Limitations
• Other antipsychotics might show similar results when prescribed in dosages with comparable dopamine D2 receptor occupancy.
• The sample size of patients that used cannabis was small.
• Olanzapine and risperidone might have had a differential impact on craving for other substances of abuse.
Effect of Olanzapine and Risperidone on Subjective Well-Being and Craving for Cannabis in Patients With Schizophrenia or Related Disorders

Key Words: schizophrenia, olanzapine, risperidone, subjective well-being, cannabis

An estimated 50% of psychotic patients are noncompliant with antipsychotic medication, and nonadherence is strongly associated with psychotic relapse. Initial dysphoric responses to antipsychotic medication and cannabis use are powerful predictors of nonadherence.

As subjective experiences are correlated with occupancy of dopamine D2 receptors by the antipsychotic compound, and as olanzapine dissociates faster from the dopamine D2 receptor than risperidone, olanzapine is hypothesized to induce less negative subjective experiences. Using the SWN, patients receiving olanzapine treatment reported higher levels of subjective well-being than patients treated with either clozapine or risperidone.

The use of cannabis (12% to 50%) is associated with low treatment adherence in schizophrenia, leading to more positive symptoms and psychotic episodes, and higher rehospitalization rates, but also with a reduction of negative symptoms, anxiety, and depression. Typical antipsychotic medications are thought to be associated with the induction of negative subjective experiences, and craving by antagonizing striatal dopaminergic D2 receptors, whereas atypical antipsychotics are suggested to reduce smoking and substance use.

The results concerning olanzapine and risperidone are inconsistent and reductions, increases, and no change in craving have been reported.

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

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

Method

Subjects

Male and female in- and outpatients aged 18 to 30 years were eligible for this 6-week, multicentre, double-blind RCT. 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. Exclusion criteria were: the concomitant use of any other antipsychotic drug (not olanzapine or risperidone), depot antipsychotic medications in the 3 months prior to inclusion, and current use of other psychotropic medications other than oxazepam or biperiden.

The study was approved by each centre’s ethics committee and written informed consent was obtained.

Patients were recruited from 4 mental health centres 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 6 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/day) or risperidone (1.25, 2.5, 3.75, or 5 mg/day) in identical-looking capsules. The dosage ratio of 1:4 is estimated according to our goal to reach comparable dopamine D2 receptor occupancy. In the first week, treating physicians could adjust the daily dosage, to a fixed dosage for the following 5 weeks. All patients (similar in both groups) were treated with disease and stress management programs, including psychoeducation about psychoses, substance abuse, and social skills training.

Assessments

All patients were assessed with the SWN, short version, a 20-item, 6-point, Likert-type self-rating scale measuring the subjective experience in the past 7 days, with robust psychometric qualities. All patients rated the cannabis use self-report—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, 2 craving questionnaires were obtained. The OCDUS, a self-rating scale consisting of 11 items with a 5-point, Likert-type rating measuring drug craving in the past 7 days, and the DDQ, a self-rating scale measuring instantaneous craving.

Baseline characteristics were compared between treatments with a chi-square test, or an independent t test. An ITT analysis of covariance was used to test between-group differences outcome variables, including treatment, site, and baseline...
score of the outcome parameter as factors. All tests were 2-sided and were performed at the 5% significance level.

Results
Among the 201 eligible patients, 128 (64%) received at least one 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), with no significant differences in patients that refused participation, compared with 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 3 patients (2%) were lost to follow-up. There were no significant differences between the 2 treatment groups about age (25 years), sex (80% male), or diagnosis. Among 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 patients using cannabis in the 2 treatment conditions, except for the olanzapine group using cannabis and 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 at 2 weeks, 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 2 groups.

After adjusting for SWN scores at baseline, there was no significant treatment by centre interaction effect (F3,119 = 1.5, P = 0.22), and also none of the main effects were statistically significant (centre: F3,119 = 1.35, P = 0.26; treatment: F1,119 = 0.037, P = 0.85). These results suggest there was no difference between centres and treatment conditions. The largest increase in SWN took place within the first week of the trial (Table 1).

Within the group of patients using cannabis, after adjusting for baseline scores, there were no significant group by centre interaction effects on the OCDUS (F2,33 = 0.28, P = 0.76) and the DDQ (F2,32 = 1.67, P = 0.21), and none of the main effects were statistically significant for the OCDUS (centre: F2,33 = 1.50, P = 0.23; treatment: F1,33 = 0.76, P = 0.39) and the DDQ (centre: F2,32 = 1.50, P = 0.23; treatment: F1,32 = 0.93, P = 0.34). These results suggest there was no difference in effect on craving between centres 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), compared with the risperidone group (mean 4.3, SD 6.5), P = 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 SWN or in reduction of craving for cannabis (OCDUS, DDQ), or in use of cannabis. As 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 with 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. Whether receiving olanzapine or risperidone, patients 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.

An explanation for the absence of differential effects is that our hypothesis was incorrect. Perhaps 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. Olanzapine showed a decrease and an increase in craving.

More RCTs are needed to establish whether different types of antipsychotics really differ in their effect on craving and drug use behaviour of patients. In conclusion, in this double-blind RCT, we found no evidence for a differential effect of olanzapine and risperidone (in dosages that lead to comparable dopamine D2 occupancy) on subjective well-being or on craving for cannabis.

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Figure 1 Flow chart of a 6-week, double-blind RCT comparing olanzapine, 5 to 20 mg/day, to risperidone in adolescents with recent onset schizophrenia or related disorders

Assessed for eligibility (n = 201)
- Excluded (n = 63)
  - Refused to participate (n = 54)
  - Other reasons (n = 9)

Randomized (n = 138)

Olanzapine
- Allocated to intervention (n = 66)
  - Received allocated intervention (n = 64)
  - Did not receive allocated intervention (n = 2)

Risperidone
- Allocated to intervention (n = 72)
  - Received allocated intervention (n = 67)
  - Did not receive allocated intervention (n = 5)

Allocation

Follow-up

Lost to follow-up (no LOCF possible, no-show) (n = 1)
- Discontinued intervention (n = 17): ineffectiveness (n = 4), side effects (n = 3), withdrew consent (n = 7), combination (n = 3)

Discontinued intervention (n = 14): ineffectiveness (n = 4), side effects (n = 6), withdrew consent (n = 3), combination (n = 1)

Analysis

Olanzapine
- Analyzed (with LOCF, n = 63)
  - Excluded from analyses (n = 1, no LOCF possible, no-show)

Risperidone
- Analyzed (with LOCF, n = 65)
  - Excluded from analyses (n = 2, no LOCF possible, no-show)

LOCF = last observation carried forward
Brief Communication

Table 1 Efficacy results at treatment endpoint for adolescent patients with first-episode psychosis who received double-blind olanzapine or risperidone in a 6-week study

<table>
<thead>
<tr>
<th>Primary efficacy values</th>
<th>Olanzapine</th>
<th>Risperidone</th>
<th>Analysis of change</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Total score of SWN</td>
<td>82.2</td>
<td>14.9</td>
<td>79.2</td>
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<tr>
<td>(n = 128)</td>
<td>Baseline</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>84.2</td>
<td>14.3</td>
<td>82.5</td>
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<tr>
<td></td>
<td>Endpoint</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>2.0</td>
<td>10.4</td>
<td>3.3</td>
</tr>
<tr>
<td>OCDUS scores</td>
<td>19.3</td>
<td>6.5</td>
<td>26.5</td>
</tr>
<tr>
<td>(n = 41)</td>
<td>Baseline</td>
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<td></td>
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<tr>
<td></td>
<td>20.0</td>
<td>7.3</td>
<td>21.3</td>
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<tr>
<td></td>
<td>Endpoint</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>0.7</td>
<td>5.2</td>
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<tr>
<td>DDQ (n = 42)</td>
<td>42.5</td>
<td>16.1</td>
<td>47.8</td>
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<tr>
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<td>33.4</td>
<td>15.1</td>
<td>38.4</td>
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<tr>
<td></td>
<td>Endpoint</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>–9.1</td>
<td>19.0</td>
<td>–9.4</td>
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<tr>
<td>Cannabis use self-report</td>
<td>6.3</td>
<td>9.5</td>
<td>7.8</td>
</tr>
<tr>
<td>scores, joints per week</td>
<td>Baseline</td>
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</tr>
<tr>
<td>(n = 41)</td>
<td>1.6</td>
<td>2.6</td>
<td>3.5</td>
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<tr>
<td></td>
<td>Endpoint</td>
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<tr>
<td></td>
<td>–4.7</td>
<td>9.8</td>
<td>–4.3</td>
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Acknowledgement

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References

Résumé : L’effet de l’olanzapine et de la rispéridone sur le bien-être subjectif et l’état de manque de cannabis chez les patients souffrant de schizophrénie ou de troubles connexes : un essai clinique aléatoire à double insu

Objectif : Examiner si le bien-être subjectif et l’état de manque de cannabis étaient différents chez les patients souffrant de schizophrénie ou de troubles connexes traités à l’olanzapine ou à la rispéridone.

Méthode : Un essai clinique aléatoire à double insu de 6 semaines d’olanzapine et de rispéridone a été mené chez 128 jeunes adultes souffrant de schizophrénie ou de troubles connexes d’apparition récente. Les mesures d’efficacité primaires étaient le changement moyen, de la ligne de départ au point d’arrivée, des scores totaux à l’échelle du bien-être subjectif sous neuroleptique, l’échelle d’utilisation obsessionnelle-compulsive de drogues, le questionnaire sur l’envie de drogues, et l’autodéclaration d’utilisation du cannabis. Une analyse de covariance a servi à vérifier les différences intergroupes.

Résultats : L’occupation du récepteur de dopamine D2 ne différait pas entre l’olanzapine (n = 63) et la rispéridone (n = 65). Des améliorations semblables du bien-être subjectif ont été observées dans les deux groupes. Dans le groupe comorbid utilisant du cannabis (n = 41,32 %), une diminution semblable de l’état de manque de cannabis a été observée dans les deux conditions de traitement.

Conclusions : L’olanzapine et la rispéridone étaient toutes deux associées au bien-être subjectif amélioré. Aucune preuve n’a été constatée d’un effet différentiel de l’olanzapine ou de la rispéridone sur l’expérience subjective ou sur l’état de manque du cannabis dans des dosages menant à une occupation du récepteur de dopamine D2 comparable.