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Chapter 1.4

Effect of early dysphoric response and cannabis use on discontinuation of olanzapine and risperidone in young adults with recent onset schizophrenia and related disorders

Submitted

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Abstract

**Objective** To examine whether early (relatively) dysphoric response to olanzapine or risperidone and cannabis use were related to discontinuation of antipsychotic medication in young adults with recent onset schizophrenia or related disorders.

**Methods** In a 6-week, double blind randomized controlled trial comparing olanzapine (n=63) and risperidone (n=65), we assessed early (relatively) dysphoric response using the Subjective Well-being under Neuroleptics Scale (SWN) and the presence of cannabis use. Time to the discontinuation of treatment was measured in the following 1-year open extension period; survival analyses for patients treated with olanzapine and risperidone, (relatively) early dysphoric and non-dysphoric responders, cannabis users and non-users were performed.

**Results** After one-year follow up, 75 of 113 patients (66%) had discontinued the treatment. Mean time to discontinuation was 5.8 (SD 4.9) months, with no significant difference between olanzapine (5.6 months, SD 4.9) and risperidone (5.9 months, SD 4.9). However, patients with an early (relatively) dysphoric response discontinued medication (mean 4.1 months, SD 4.4) significantly earlier than those with no early (relatively) dysphoric response (mean 7.3 months, SD 4.8; log-rank chi squared=13.3, d.f.=1, $P =0.0003$). In addition, patients using cannabis discontinued medication significantly earlier (mean 4.3 months, SD 4.2) compared to the non-users (mean 6.4 months, SD 5.0; log-rank chi squared= 4.98, d.f. =1, $P =0.03$). No significant interaction effects for early dysphoric response or cannabis use and medication were observed.

**Conclusions** Initial (relatively) dysphoric response to antipsychotic medication and cannabis use are associated with early discontinuation of medication in patients with recent onset psychosis.
Effect of early dysphoric response and cannabis use on discontinuation

Introduction

While long-term antipsychotic medication remains the cornerstone of treatment in schizophrenia, only a minority of the patients take these drugs for longer periods of time. A recent landmark study showed that as many as 80% of patients with chronic schizophrenia discontinued their medication at 18 months (Lieberman et al 2005). Specific reasons for discontinuation of antipsychotic medication are lack of motivation, substance abuse, ineffectiveness, and intolerability due to side effects such as weight gain, extrapyramidal signs or sedation (Lieberman et al 2005). Discontinuation often is a direct result of patients’ subjective complaints (Naber et al 1998, 2001, van Putten et al 1978) and is a leading cause of relapse (Fenton et al 1998) and rehospitalisation (Gitlin et al 2001). Subjective experience under neuroleptics is strongly correlated with occupancy of dopamine D2 receptors (de Haan et al 2000, 2003, Mizrahi et al 2007). It has been suggested that antipsychotic drugs with fast dissociation from the receptor modulate the dopamine system in a manner that allows for more appropriate dopaminergic functioning and fewer dysphoric reactions (Kapur and Seeman 2001). Olanzapine showed faster dissociation from the dopamine D2 receptor than risperidone; therefore olanzapine was hypothesized to be effective without inducing negative subjective experience (Kapur and Seeman 2001), with higher initial subjective well-being and longer time to discontinuation than risperidone. Indeed, olanzapine treatment was continued longer than haloperidol, risperidone, ziprasidone, or quetiapine treatment in a previous study (Beasley et al 2007).

Discontinuation of medication in patients with schizophrenia is also associated with substance abuse (Haro et al 2007). Moreover, olanzapine and risperidone may have a differential effect by decreasing as well as increasing craving and abuse of substances (Hutchison et al 2003, 2004, Sayers et al 2005, Smelson et al 2002, 2004).

The few studies that have investigated subjective well-being, substance abuse and treatment continuation until now, differ in methodology and are difficult to compare (Lambert et al 2003). In a retrospective study among patients with schizophrenia or schizoaffective disorder and co-morbid substance dependence, patients taking risperidone stayed longer in treatment than patients taking olanzapine (Stuyt et al 2006). Randomized controlled trials comparing the effect of olanzapine and risperidone on subjective well-being, craving for cannabis and treatment discontinuation are lacking.

In this study in adolescent and young adult patients with recent onset schizophrenia or related disorders, we examined whether early dysphoric response to
olanzapine or risperidone and baseline cannabis use predicted discontinuation of antipsychotic medication.

Methods

Subjects

Eligible for the study were male and female inpatients and outpatients age 18-30, meeting criteria for a diagnosis of schizophrenia, schizoaffective disorder or schizophrreniform disorder based on the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, patient version (SCID-P; Spitzer et al 1995). Exclusion criteria were (1) pregnancy, (2) lactating women, (3) women without adequate contraception, (4) known hypersensitivity to any ingredient of olanzapine or risperidone, (5) use of depot antipsychotics in the 3 months prior to inclusion, (6) current use of clozapine, (7) use of other psychotropic medication other than oxazepam or biperiden, (8) narrow angle glaucoma, and (9) known neurological or endocrine disease. A total of 201 patients were eligible for the study and 131 patients received the allocated intervention, with no significant differences in terms of used antipsychotic medication between patients that refused participation compared to those that were randomized: 106 patients (81%) were male and 25 (19%) female; 64 received olanzapine, and 67 received risperidone (Figure 1.4.1).

The vast majority (118 = 90%) was diagnosed with schizophrenia, 5 (4%) with schizophrreniform disorder and 8 (6%) with schizoaffective disorder. The frequencies of patients enrolled per site were 41 (31.3%) in the AMC, 54 (41.2%) in the EMC, 28 (21.4%) in PPC and 8 (6.1%) in Mediant.

Three patients (2%) were lost to follow-up in the first phase. This means that 128 received at least one dose of olanzapine (n = 63) or risperidone (n = 65) and had at least one follow up assessment.

One year follow-up data were not available for 5 patients taking olanzapine and 10 patients taking risperidone. Thus, the one-year analyses included 113 (88%) patients, 58 of whom were initially treated with olanzapine and 55 with risperidone (Figure 1.4.1). There were no significant differences concerning subjective well-being, cannabis use or treatment assignment at baseline, between groups that were lost to follow-up (n=15) or that were not lost to follow-up (n=113).

Each site's review board or ethics committee approved this multicenter study. The benefits and risks of study participation were fully explained to each subject, and written informed consent was obtained.
Earlier publications of this study concerned the initial effect of olanzapine and risperidone on subjective well-being and craving for cannabis (van Nimwegen et al 2008) and obsessive compulsive symptoms in young patients with first psychoses (van Nimwegen et al 2008).

**Study Design**

Consecutively admitted and contacted patients were recruited from inpatient and outpatient settings at 4 treatment centres in the Netherlands: Academic Medical Centre in Amsterdam (AMC), Erasmus Medical Centre in Rotterdam (EMC), Parnas-sia Psychomedical Centre in The Hague (PPC), and Mediant in Enschede from July
Effect of early dysphoric response and cannabis use on discontinuation

1st, 2003 through July 1st, 2005. All patients were treated with a disease, medication and stress management program, including psycho-education about psychoses and substance abuse and social-skills-training. Patients meeting enrolment criteria were randomly assigned to either olanzapine or risperidone by a computer block-randomization list using last month cannabis use as a pre-stratification factor.

Medications

Patients received flexible dosing of either olanzapine (5 mg/capsule) or risperidone (1.25 mg/capsule) in identical-appearing capsules for 6 weeks (phase 1). The dose of the medication ranged from one to four capsules a day, based on the treating physician’s judgment. The above mentioned dose ratio of 1:4 was estimated according to dopamine D2 receptor occupancy (Kapur and Seeman 2001) and the clinical available and advised dose range of both antipsychotic drugs in patients with recent onset schizophrenia. Following unblinding of the study medication after 6 weeks, an open extension phase started with the study medication that was prescribed in the first 6 weeks in the dose given at the end of week 6. Patients were followed for a period of 12 months (phase 2).

Assessments

Clinical characteristics

Subjects were evaluated for study entry by an experienced psychiatrist and a Structured Clinical Interview for DSM IV Axis I disorders (SCID-P, Spitzer et al 1995) was performed, including the sections on DSM IV schizophrenia, schizoaffective and schizophreniform disorder. Study visits in phase 1 took place at baseline, after one week and at the end of double-blind treatment (after 6 weeks or when the patient discontinued randomized therapy), and after one-year follow-up (phase 2).

Outcome measure

The outcome measure was the time to discontinuation of study medication. The moment of discontinuation in the first phase was measured at 6 weeks treatment, whereas the moment of discontinuation in the second phase was retrospectively measured after one year, when patients were interviewed with the Life Chart Schedule (LCS). The LCS is a semi structured instrument, collecting information in a patient interview and also from all other available sources including the family, medical records, and treating physicians. The LCS rates symptoms, treatment and
use of medication and nicotine, alcohol, cannabis and other drugs for the follow-up period. The LCS has been found to yield reliable ratings of the long-term course of schizophrenia in the clinical research setting (Susser et al 200). We also assessed reasons for discontinuation of treatment.

**Predictors of antipsychotic medication discontinuation**

**Subjective well-being under neuroleptics**

Difference in subjective well-being between study entry and after six weeks treatment with study medication was assessed with the short version of Subjective Well-being under Neuroleptics Scale (SWN/sc); a 20 items and 6 point Likert type self rating scale referring to the subjective experience in the past 7 days. It consists of five subscales: emotional regulation, self-control, mental functioning, social integration and physical functioning. Internal consistency and good construct validity of this instrument have been shown in several studies (Garavan et al 1998, Naber et al 1995) and psychometric qualities of the SWN in patients with recent onset schizophrenia during treatment with olanzapine and risperidone were affirmed by our group (de Haan et al 2002). Items are clearly formulated and easy to understand so that even cognitively disturbed patients are able to fill out the questionnaire within 10–15 min. Patients were asked to fill out the questionnaire without discussing any of the items with others in order to avoid suggestive external manipulation.

Patients were divided in a group with a relatively 'early non-dysphoric reaction' and a group with a relatively 'early dysphoric reaction'. The first group was defined as having a difference in SWN-scores between baseline and 6 weeks treatment larger than the median, whereas the second group had an SWN difference score less than the median.

**Cannabis use**

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. Patients with self-reported cannabis use at baseline, filled out two craving questionnaires; the Obsessive Compulsive Drug Use Scale (OCDUS, Franken et al 2002), 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. Cannabis use and craving questionnaires were rated at baseline and 6 weeks treatment.
Effect of early dysphoric response and cannabis use on discontinuation

**Statistical Analysis**

The hypothesis whether an early (relatively) dysphoric reaction and cannabis use at baseline negatively affected continuation of antipsychotic medication, was tested (two-sided) at the 5% significance level. The time to discontinuation was measured with a survival curve in months after the start of the trial; an event occurred when a patient discontinued the medication. Three different survival curves were executed; 1) in patients using olanzapine vs. risperidone; 2) in patients with an 'early (relatively) dysphoric reaction' vs. a group with an 'early (relatively) non-dysphoric reaction'; and 3) in patients using cannabis at the start of the trial vs. patients that did not use cannabis at the start of the trial. Differences between groups were tested with a log rank test. Multiple logistic regression analysis was executed to demonstrate the most important predictors of medication discontinuation and interaction effects between groups and predictors.

**Results**

Sample Baseline demographic and clinical characteristics of all 128 patients who received the allocated intervention and had at least one set of follow-up data are previously described (van Nimwegen et al 2008). There were no notable imbalances between treatment groups in the distribution of diagnoses (schizophrenia, schizophreniform or schizoaffective disorder), age or gender. At baseline 42 of the 128 (33%) patients had used cannabis in the last month. After one-year follow-up, only 24 of 113 (21%) patients used cannabis. There were no significant differences between olanzapine and risperidone in the use of cannabis at baseline or at 1-year follow-up. The mean doses of study medication were 9.8 mg per day for olanzapine and 2.5 mg per day for risperidone in the first week, and 11.0 mg per day for olanzapine and 3.0 mg per day for risperidone at the end of phase 1.

**Reasons for discontinuation**

The reasons of treatment discontinuation are listed in Table 1.4.1. Reasons for discontinuation did not differ significantly by treatment condition.

**Early subjective response**

Mean SWN scores increased in both groups in phase 1; for the olanzapine group from 82.2 (SD 14.9) at baseline to 84.2 (SD 14.3) after six weeks, and for risperidone
Effect of early dysphoric response and cannabis use on discontinuation

Chapter 1.4

from 79.2 (SD 17.7) to 82.5 (SD 15.7). Thirty-two (25%) patients with olanzapine and 28 (22%) with risperidone showed an early dysphoric reaction ($P=0.49$).

**Time to discontinuation**

After one year follow up, 75 of the 113 patients (66%) with follow-up data had discontinued the treatment. Of the 58 patients using olanzapine 39 (67%) discontinued treatment with olanzapine within a year and 36 of the 55 patients (65%) stopped taking risperidone ($P=0.84$) The mean time to the discontinuation of treatment for any reason was 5.8 (SD 4.9) months for the total group with no statistical difference ($P =0.68$) between olanzapine (mean 5.6 months, SD 4.9, range 11.9) and risperidone (mean 5.9 months, SD 4.9, range 11.9) (Figure 1.4.2).

Time to discontinuation due to any reason was significantly longer for the group with an early (relatively) non-dysphoric response (7.3 months, SD 4.8) compared to the group with an early (relatively) dysphoric response (4.1 months, SD 4.4) (log-rank chi squared=13.3, d.f. =1, $P =0.0003$) (Figure 1.4.3).

**Table 1.4.1 Reasons for Discontinuation of Treatment [no (%)]**

<table>
<thead>
<tr>
<th>Reasons for Discontinuation</th>
<th>Olanzapine (n=58)</th>
<th>Risperidone (n=55)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inefficacy</td>
<td>19 (33%)</td>
<td>14 (27%)</td>
<td>0.64</td>
</tr>
<tr>
<td>Weight gain</td>
<td>5 (9%)</td>
<td>1 (2%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Extrapyramidal Sx</td>
<td>2 (3%)</td>
<td>5 (10%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Sedation</td>
<td>6 (10%)</td>
<td>9 (17%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Other</td>
<td>7 (13%)</td>
<td>7 (13%)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

**Figure 1.4.2. Survival Curve in the One-year Follow-up Phase of Continued Antipsychotic Medication in Patients that used Olanzapine and Risperidone**

Time to Discontinuation for Any Cause (mo)
Effect of early dysphoric response and cannabis use on discontinuation

**Figure 1.4.3.** Survival Curve in the One-year Follow-up Phase of Months of Study Medication in Patients with an Initial (relatively) Dysphoric Response and an Initial (relatively) Non-dysphoric Response

Patients that did not use cannabis at baseline had a significant longer mean time on the study medication (mean 6.4 months, SD 5.0) compared to cannabis users at baseline (4.3 months, SD 4.2) (log-rank chi squared= 4.98, d.f. =1, P =0.03) (Figure 1.4.4).

Using logistic regression analysis, (relatively) dysphoric early response (B=-1.39, S.E. 0.45, Wald= 9.8, df =1, P=0.002), as well as cannabis use (B= 1.18, S.E.

**Figure 1.4.4.** Survival Curve in the One-year Follow-up Phase of Continued Antipsychotic Medication in Patients that used Cannabis and Patients that did not use Cannabis

![Graph showing survival curves for patients with and without cannabis use](image-url)
Effect of early dysphoric response and cannabis use on discontinuation

0.51, Wald = 5.38, df =1, P=0.02) was a significant predictor of discontinuation of medication; type of medication was not (B= 0.08, S.E. 0.43, Wald= 0.031, df =1, P=0.86). Nagelkerke R Square was 0.174. The interaction effects for early dysphoric response and medication [F(1,118)=0.95, p=0.83] or cannabis use and medication [F(1,118)=0.75, p=0.39] were not significant, neither were the interaction effects for early (relatively) dysphoric response and cannabis use [F(1,118)=1.5, p=0.23].

Discussion

The aim of this study was to determine whether early subjective responses to antipsychotic medication and cannabis use are predictors of time to discontinuation on antipsychotic medication in the following year, and whether olanzapine and risperidone would differ in this respect. To our knowledge this is the first prospective study on this issue.

We found no significant differences in discontinuation rates or time to discontinuation between olanzapine and risperidone, and both groups reported a comparable increase in subjective well-being in the early phase. However, we did find that early (relatively) dysphoric response and cannabis use are associated with earlier discontinuation of antipsychotic medication.

In our study, patients discontinued medication at rates that were comparable to those found in the CATIE study (Lieberman et al 2005), but higher compared to the recent SOHO-study (Haro et al 2007). In the CATIE study, the time to discontinuation of treatment for any cause was longer in the olanzapine group than in the risperidone group. Moreover, treatment with olanzapine was associated with a significant higher rate of weight gain than risperidone (Lieberman et al 2005). We could replicate neither of these findings. Differences in population (the CATIE study was performed in a population of patients with chronic schizophrenia) or dosage of medication (in the CATIE study doses of medication were higher; mean modal doses were 20.1 mg olanzapine per day and 3.9 mg risperidone per day) may account for these differences in findings.

Most studies concerning (early) dysphoric response on antipsychotic medication focus on the relationship with adherence. In the current study we focused on the impact of (early) dysphoric response on the time until discontinuation.

Most AP studies found a negative relationship between (early) dysphoric response and adherence (Garavan et al 1998, Naber et al 2001, de Millas et al 2006, Karow et al 2007). Early subjective response and adherence were earlier described to be more favorable in olanzapine-treated patients compared to patients treated with
risperidone and haloperidol (Garcia-Cabeza et al 2001). However, the median doses (both initially and overall) used in that study were 10 mg per day for olanzapine, 6 mg per day for risperidone, and 10 mg per day for haloperidol. The doses of the latter two antipsychotics in first episode psychosis are considered quite high, with incomparable D₂ receptor occupancy (Zipursky et al 2005). High attrition rates are common in patients with first episode psychosis; previous reports describe that adolescents and young adults are more susceptible to the side effects of antipsychotic medication than adults, and that they are also more likely to be sensitive to the negative impact of side effects on appearance, body image, and self-esteem (Arango et al 2004). We found that 17% of the variance of discontinuation of medication was explained by dysphoric response and cannabis use.

Strengths of our study are the randomized double blind design, and the relatively high number of patients included, meaning that outcomes regarding discontinuation of olanzapine and risperidone are quite certain. The dysphoric reaction and cannabis use seem to be predictors of early discontinuation, however, since the study was not randomized for these variables, others factors such as selection bias or confounding cannot be excluded. Still, the interaction effects for early dysphoric response and cannabis use were not significant.

In conclusion: time on medication was associated with early dysphoric response and baseline use of cannabis, whereas no significant difference in treatment duration was found between olanzapine and risperidone. Improving the subjective response on medication by adjusting dose or type of medication may increase time on medication.
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Effect of early dysphoric response and cannabis use on discontinuation


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Effect of early dysphoric response and cannabis use on discontinuation
