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What is This?

Differences in craving for cannabis between schizophrenia patients using risperidone, olanzapine or clozapine

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Abstract

Substance abuse and psychotic disorders have a high rate of comorbidity. Both disorders are associated with changes in the dopaminergic transmission in the mesocorticolimbic pathways of the brain. Since antipsychotic medications interact with the dopamine receptors in these pathways, these medications could affect craving for substances. In the current study, the effect of clozapine ($n = 27$, mean dosage 350 mg), risperidone ($n = 54$, mean dosage 3.46 mg) and olanzapine ($n = 60$, mean dosage 13.78 mg) on subjective craving for cannabis was compared in 123 patients with cannabis dependence and psychotic disorder. Patients treated with risperidone reported significantly more craving compared with patients treated with clozapine ($Z = -3.19$, $p = .001$) or olanzapine ($Z = -2.24$, $p = .025$). No significant differences in craving between clozapine and olanzapine were found. These results are in concordance with findings in the literature on this subject and could be explained by differences in three dopamine mediated mechanisms of these compounds: 1) occupancy rate of dopamine D_2 receptors, 2) dissociation rate of dopamine D_2 receptors, 3) D_1/D_2 occupancy ratio. Risperidone and clozapine show a maximal difference in D_2 receptor occupancy rate, dissociation rate and D_1/D_2 ratio. Olanzapine is intermediate between risperidone and clozapine in these characteristics.

Keywords

Antipsychotics, cannabis, clozapine, craving, OCDUS, olanzapine, psychosis, risperidone, schizophrenia

Introduction

Substance abuse is a major problem in patients with psychotic disorders (Dixon, 1999; Linszen et al., 1994; Regier et al., 1990). Several theories have been proposed to explain the association between substance abuse and psychosis (Lubman et al., 2010). The 'self-medication' theory states that patients use substances to relieve (pre-)psychotic symptoms or side effects of antipsychotic medication (Khantzian, 1985). However, studies testing this theory have not been conclusive so far (Potvin et al., 2006; Schaub et al., 2008). The theory of 'common causes' proposes that the high comorbidity rate between psychotic disorders and substance use disorders could be caused by common underlying biological, personality or environmental factors (Lubman et al., 2010). Since substance abuse and psychotic disorders are both associated with changes in the dopaminergic transmission in the mesocorticolimbic pathways of the brain, this could be one of the possible explanations for the high comorbidity rate (Green, 2005). Antipsychotic medications influence the dopaminergic neurotransmission in these pathways and could therefore influence the severity of substance abuse in patients. Blum et al. (2000) described the reward deficiency hypothesis in which they state that patients with a relatively low level of dopaminergic transmission in the mesocorticolimbic system are more vulnerable to substance abuse. Substance use results in a strong increase in the release of dopamine in the mesocorticolimbic system (Volkow et al., 2004), which is associated with a feeling of pleasure/reward. Chronic substance abuse, on the other hand, decreases the

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level of dopamine in the orbitofrontal cortex (Volkow and Fowler, 2000), which could result in insensitivity to natural rewards (anhedonia). This may enhance the tendency of patients to use the substance of abuse. The psychological urge to administer a drug is called craving, which is regarded to be a central phenomenon in substance abuse (Franken, 2003; Robinson and Berridge, 1993). Most first generation antipsychotics have a strong antagonistic effect on dopamine transmission and could worsen craving and substance abuse (McEvoy et al., 1995; Siris, 1990). Second generation antipsychotics with a weaker antagonistic effect on dopaminergic transmission have been found to attenuate craving and substance abuse (Smelson et al., 2008; Wobrock and Soyka, 2008). Since second generation antipsychotics mutually differ in their antagonistic effect on dopamine, differences in effect on substance abuse and craving between these medications can be expected. Some studies suggest a superior effect of clozapine in the treatment of co-morbidity of substance use disorders and psychotic disorders (Machielsen and de Haan, 2009; Smelson et al., 2008; Wobrock and Soyka, 2008). Differences between antipsychotic medications in efficacy of treating substance use disorders (i.e. craving) may be explained by three possible dopamine mediated mechanisms: 1) differences in occupancy rate of dopamine D_2 receptors, 2) differences in dissociation rate of dopamine D_2 receptors, 3) differences in D_1/D_2 ratio (Machielsen and de Haan, 2009). In a study on occupancy rates of different antipsychotics to the dopamine D_2 receptors, Kuroki et al. (2008) found that clozapine had a low affinity to the dopamine D_2 receptor (7.0 pKi) while olanzapine had a higher affinity (7.8 pKi) and risperidone had an affinity to the dopamine D_2 receptor (8.9 pKi) comparable to that of haloperidol (9.0 pKi). Dissociation rates of the different antipsychotics were investigated by Seeman (2002). They found that clozapine showed a fast dissociation of the dopamine D_2 receptor, while olanzapine had a medium and risperidone and haloperidol had a slow dissociation rate. In a comparative study on the differences in ratio of dopamine D_1 and D_2 receptor occupancies, Tauscher et al. (2004) found that the ratio of striatal D_1/D_2 occupancy was significantly higher for clozapine (0.88) relative to olanzapine (0.54), quetiapine (0.41), or risperidone (0.31).

In the present study, craving for cannabis is compared in patients using risperidone, olanzapine or clozapine. We chose to compare these medications because risperidone and clozapine show a maximal difference in D_2 receptor occupancy rate, dissociation rate and D_1/D_2 ratio. Olanzapine is intermediate between risperidone and clozapine in these three characteristics.

We intended to test the hypothesis that treatment with risperidone was associated with more severe craving for cannabis compared with treatment with clozapine. We hypothesize that levels of craving for cannabis during treatment with olanzapine would be intermediate between those associated with risperidone or clozapine.

Methods

Participants

The study sample was taken from 1120 patients who were examined within the Genetic Risk and Outcome of Psychosis (GROUP) study. In summary, GROUP is a multi-site, longitudinal, naturalistic cohort study examining the six-year course of patients with non-affective psychotic disorders and their siblings. Patients were recruited from mental health centres covering more than 75% of the mental health institutions of The Netherlands, including both inpatient and outpatient clinics. Eligible patients for the GROUP project had to fulfil the following criteria: 1) age between 16 and 50 years, 2) meet Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM IV) (American Psychiatric Association, 1994) criteria for a non-affective psychotic disorder (schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, psychotic disorder NOS), 3) fluent in Dutch, and 4) able and willing to give written informed consent. Persons identified as potentially eligible were given a detailed explanation of the study procedures and were asked for informed consent for assessment. The study protocol was approved centrally by the Ethical Review Board of the University Medical Centre Utrecht and subsequently by local review boards of each participating institute. After full verbal and written information about the study, informed consent was obtained from all participants before the start of the first assessment. (For more detailed information about the GROUP project see Korver et al., 2012.)

For this study we included patients using risperidone, olanzapine or clozapine with a diagnosis of cannabis dependence of which data on craving (assessed with the Obsessive Compulsive Drug Use Scale (OCDUS)) were available. We excluded patients who used more than one type of antipsychotic medication.

Instruments

Cash/Scan. To establish DSM IV (American Psychiatric Association, 1994) diagnosis of psychotic disorder, the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992) or the SCAN Schedules for Clinical Assessment for Neuropsychiatry (SCAN 2.1) (Wing et al., 1990) were used.

CIDI Substance Abuse Module. A special Substance Abuse Module of the Composite International Diagnostic Interview (CIDI) (Robins et al., 1988) was used to assess tobacco, alcohol, and other drug abuse in considerable detail, allowing the assessment of the quality and severity of dependence and its course. This questionnaire was used as a diagnostic tool to establish DSM IV diagnosis of lifetime cannabis abuse and dependence. Nicotine use was defined as daily use of cigarettes for at least one month in the past 12 months. Alcohol use in the past year was defined as having consumed more than 12 alcoholic drinks in the past 12 months. Illicit substance use (other than cannabis) in the past year was defined as having used any hard drug (speed, amphetamines, hallucinogens, opiates, cocaine or ecstasy) in the past year.

OCDUS. The Obsessive Compulsive Drug Use Scale (OCDUS) is a self-rating scale consisting of 12 items with a

five-point Likert type rating measuring drug craving in the past seven days. For this study the OCDUS-CAN was used, which is a cannabis-specific version of the OCDUS. The OCDUS was based on the Obsessive Compulsive Drinking Scale (OCDS) (Anton et al., 1996), which contains two underlying factors, namely obsession and compulsions (Anton et al., 1996). The OCDUS also can be divided into two comparable factors, namely items 1–6 on thoughts, and items 7–12 on craving. The OCDUS has been validated for patients using opiates by Franken et al. (2002). Recently Dekker et al. (submitted) found evidence supporting the reliability and validity of the Obsessive Compulsive Drug Use Scale for cannabis (OCDUS-CAN) in patients with recent onset non-affective psychotic disorder, their non-affected siblings, and healthy controls who all used cannabis in the past year. In a psychometric analysis three underlying factors (subscales) were found: craving/urge, resistance and impact. For more details see Dekker et al. (submitted).

Statistical analysis

Prevalence rates of cannabis dependence in the different medication groups were calculated. To compare the patients with cannabis dependence with those without cannabis dependence on demographics and substance use characteristics, chi-square tests and Mann–Whitney U tests were used. Of the patients with cannabis dependence, demographic and substance use characteristics were also compared in the different medication groups. Estimations of D_2 receptor occupancy rates were made of patients treated with risperidone or olanzapine using the dose-occupancy function as described by Lataster et al. (2011). D_2 receptor occupancy rates of olanzapine and risperidone were compared with a t-test.

Because the assumption of normal distribution was violated for the OCDUS scores, we used the Kruskal–Wallis test to compare the OCDUS scores of all patients with cannabis dependence for which OCDUS data were available. We made comparisons for the OCDUS total score, for the 'original' subdivision of thoughts and craving items and for the more recent subdivision of craving/urge, resistance and impact as described before. Post hoc comparisons were made using Mann–Whitney U tests.

Results

Sociodemographic characteristics and prevalence rates of cannabis dependence

Sample characteristics are shown in Table 1. Our study population covered 503 patients using risperidone, olanzapine or clozapine. In the group of patients with cannabis dependence significantly more patients were male ($n = 141$; 90.8% males) compared with the patients without cannabis dependence ($n = 362$; 78.2% males). No differences were found in age and ethnicity between these two groups. The abuse of nicotine, alcohol and other illicit substances was significantly higher among patients with cannabis dependence (Table 1). Of all 503 patients, 187 patients used risperidone, 234 used olanzapine and 82 used clozapine at the time of the interview, of which, respectively, 54, 60 and 27 patients were also diagnosed with cannabis dependence. Of these patients, OCDUS data were available for, respectively, 48, 52 and 23 patients. No differences were found in age, gender, ethnicity and the abuse of alcohol or other substances between the different medication groups among the patients with cannabis dependence (see Table 2). Of the patients using clozapine, significantly fewer patients smoked cigarettes compared with patients using olanzapine or risperidone (Table 2). The mean dosage of risperidone was 3.46 mg (SD 1.62), of olanzapine 13.78 mg (SD 6.725) and of clozapine 350 mg (SD 166.58) in the group of patients with cannabis dependence. The mean estimated D_2 receptor occupancy according to Lataster et al. (2011) of risperidone (66.3%) was significantly higher ($t = 2.18$, $p = .003$) compared with olanzapine (61.2%).

OCDUS scores in cannabis-dependent patients using risperidone, olanzapine or clozapine

Using the Kruskal–Wallis test, significant differences between the three medication groups were found in OCDUS total score ($Z = 5.02$, $p = .005$) (see Table 3). In the original subdivision of OCDUS thoughts and craving subscales, significant differences between the medication groups were found in OCDUS thoughts ($Z = 4.37$, $p = .017$) and craving ($Z = 3.93$, $p = .007$) items (Table 3). Separate Mann–Whitney U tests showed significant differences in the

Table 1. Demographic and substance use characteristics of patients with and without cannabis dependence

		Patients with cannabis dependence ($n = 141$)	Patients without cannabis dependence ($n = 362$)	x^2 or Z	p-value
Gender	Male (%)	90.8	78.2	9.959	0.002
Age	Mean (SD)	26.5 (5.9)	27.3 (7.7)	−.331	0.740
Ethnicity	Caucasian (%)	74.5	80.3	2.03	0.154
Nicotine use in past year	Yes (%)	89.4	57.7	45.6	<0.001
Alcohol use in past year	Yes (%)	85.1	68.8	13.7	<0.001
Other illicit substance use in past year[a]	Yes (%)	28.4	8.3	17.0	<0.001

[a]Other illicit substances: stimulants (speed, amphetamines), hallucinogens, opiates, cocaine, ecstasy.

Table 2. Demographic and substance use characteristics of patients with cannabis dependence

		Risperidone ($n = 48$)	Olanzapine ($n = 52$)	Clozapine ($n = 23$)	χ^2 or Z	p-value
Gender	Male (%)	89.6	92.3	91.3	0.230	0.892
Age	Mean (SD)	26.7 (6.9)	26.8 (5.7)	26.4 (4.0)	0.458	0.795
Ethnicity	Caucasian (%)	75.0	80.8	60.9	3.35	0.187
Dosage in mg	Mean (SD)	3.46 (1.62)	13.78 (6.73)	350 (166.6)		
Nicotine use in past year	Yes (%)	93.8	92.3	73.9	7.26	0.003
Alcohol use in past year	Yes (%)	87.5	88.5	73.9	3.00	0.224
Other illicit substance use in past year[a]	Yes (%)	25.0	36.5	17.4	3.62	0.164

[a]Other illicit substances: stimulants (speed, amphetamines), hallucinogens, opiates, cocaine, ecstasy.

Table 3. OCDUS scores of patients with cannabis dependence using risperidone, olanzapine or clozapine

	Risperidone ($n = 48$) Median	Olanzapine ($n = 52$) Median	Clozapine ($n = 23$) Median	Z	p-value
OCDUS total	1.83	1.54	1.33	10.7	0.005
Subscales*					
Thoughts	1.83	1.67	1.5	8.19	0.017
Craving	1.83	1.50	1.17	10.0	0.007
Subscales**					
Craving/urge	2.00	1.60	1.20	5.19	0.075
Resistance	3.00	1.50	1.00	18.1	<0.001
Impact	1.50	1.20	1.20	5.22	0.075

*Subscales according to Anton et al. (1996). **Subscales according to Dekker et al. (submitted).

OCDUS total score between risperidone and clozapine ($Z = -3.19$, $p = .001$) and risperidone and olanzapine ($Z = -2.24$, $p = .025$); in the OCDUS thoughts items, between risperidone and clozapine ($Z = -2.73$, p = .006) and risperidone and olanzapine ($Z = -2.09$, $p = .036$); and in the OCDUS craving items, between risperidone and clozapine ($Z = -3.16$, $p = .002$) and risperidone and olanzapine ($Z = -1.98$, $p = .047$). No significant differences were found between olanzapine and clozapine. All differences between risperidone and clozapine were still significant after Bonferroni correction for multiple testing.

In the subscales craving/urge, resistance and impact a significant difference was found between the medications in the resistance items ($Z = 18.1$, $p = <.001$) and trends for differences were found in craving/urge items and impact items (Table 3). When the different medications were compared using Mann–Whitney U tests, significant differences were found in the resistance items between risperidone and olanzapine ($Z = -3.46$, $p = .001$) and risperidone and clozapine ($Z = -3.58$, $p = <.001$). No significant differences in craving scores were found between olanzapine and clozapine.

A Mann–Whitney U test revealed no difference in OCDUS total scores between male and female patients with cannabis dependence ($Z = -1.09$, $p = .275$). A comparison of OCDUS total score was also made between patients with solitary cannabis dependence and patients with both cannabis dependence and abuse of other substances (nicotine, alcohol or other illicit substances). These comparisons also revealed no significant difference for nicotine ($Z = -1.85$, $p = .065$),

alcohol ($Z = -.575$, $p = .565$) and other illicit substances ($Z = -1.44$, $p = .15$).

Discussion

Sociodemographic characteristics and prevalence rates of cannabis dependence

In the present study population a larger proportion of males was found among the patients with cannabis dependence compared with the patients without cannabis dependence. This is often described in the literature (Cantwell et al., 1999; Machielsen et al., 2010) and supports the notion that men have a higher propensity to use substances of abuse.

A higher percentage of patients using cannabis also abused nicotine, alcohol and other substances. This is in concordance with the pattern of substance abuse in the general population and supports the hypothesis that the abuse of different substances has a common cause (Blum et al., 2000).

OCDUS scores in patients using risperidone, olanzapine or clozapine

We found more severe craving for cannabis in cannabis-dependent patients treated with risperidone compared with patients treated with clozapine or olanzapine. This is in concordance with our hypothesis. We are not aware of studies comparing craving for cannabis in schizophrenia patients

using risperidone, clozapine and olanzapine in one study. However, some studies compared the effect on craving of two of these medications. van Nimwegen et al. (2008) compared the effect of risperidone and olanzapine on subjective craving in a double blind randomized controlled trial. They concluded that there was no difference in decrease of subjective craving for cannabis between these two medications. A limitation of this study was the small proportion of patients with cannabis abuse (van Nimwegen et al., 2008). In an eight-week follow up study, Kim et al. (2010) found an increase in both craving and dependence on nicotine in patients with schizophrenia treated with risperidone. No change was found in craving for nicotine in patients using olanzapine. In a double blind study, Akerele and Levin (2007) found that patients with schizophrenia and cocaine dependence who used risperidone reported more craving compared with patients using olanzapine. Green et al. (2003) showed in a retrospective assessment of patients with schizophrenia and cannabis and/or alcohol use disorder that patients treated with clozapine had a significantly higher rate of abstinence compared with those treated with risperidone.

The better efficacy of clozapine and olanzapine as compared with risperidone in treating substance abuse could be explained by the lower occupancy rate of the D_2 receptor, the higher dissociation rate of the D_2 receptor and the higher D_1/D_2 receptor occupancy rate of these medications as compared with risperidone (Kuroki et al., 2008; Seeman, 2002; Tauscher et al., 2004). de Haan et al. (2000, 2003) and Mizrahi et al. (2007) found a significant correlation between D_2 blockade and reduced subjective wellbeing of patients with schizophrenia. It can be hypothesized that high craving is correlated to reduced subjective wellbeing. In a former study made by our group an association was found between number of cigarettes smoked and a higher occupancy of dopamine D2 receptors in the ventral striatum in patients using haloperidol, risperidone or olanzapine (de Haan et al., 2006). In the current study the D_2 receptor occupancy rates of olanzapine and risperidone were estimated as described by Lataster et al. (2010). We found a significant difference in estimated D_2 receptor occupancy between olanzapine and risperidone, although the absolute mean difference was not large. We propose that it is unlikely that the difference in craving between olanzapine and risperidone is exclusively explained by dose dependent differences in D_2 receptor occupancy rate, because the difference is not substantial. Olanzapine and risperidone also differ in dissociation rate and this could be a more likely explanation for the difference in craving (Lataster et al., 2011). However, the difference in D_2 receptor occupancy rate may partly explain our results. Future studies could compare different antipsychotic medication at comparable D_2 receptor occupancy. As we mentioned earlier the difference in craving could also be based on differences in D_1/D_2 receptor occupancy rate. No reliable estimation of D_2 receptor occupancy could be made for clozapine. In the literature no evidence was found to support a relation between D_2 receptor occupancy and clinical response for clozapine (Pickar et al., 1996; Seeman, 2002).

Some studies suggest a superior effect of clozapine compared with all other antipsychotics in the treatment of substance use disorders in patients with dual diagnosis (Machielsen and de Haan, 2009; Smelson et al., 2008; Wobrock and Soyka, 2008); however, in the current study no significant difference in craving was found between olanzapine and clozapine.

Some limitations of the current study should be mentioned. First, although our findings are relatively robust and concur with former findings, our study was designed as a naturalistic cross-sectional study, and therefore our findings should be interpreted cautiously. A randomized controlled longitudinal study concerning differences between second generation antipsychotics in efficacy on craving and substance abuse would provide more definitive answers. Because of the naturalistic nature of the design a selection bias regarding antipsychotics cannot be ruled out. Where risperidone and olanzapine are agents that can be started during the entire course of treatment, clozapine is an antipsychotic that is indicated for patients who have a treatment refractory illness and are therefore ill for a longer period of time, usually with a more severe course of illness. However, since clozapine was superior to risperidone and equal to olanzapine regarding efficacy in treatment of substance abuse, it is not likely that the superior effect on craving is associated with treatment resistance or illness duration.

Second, a significant difference in gender and abuse of substances other than cannabis was found between patients with cannabis dependence and those without cannabis dependence. However, separate analysis to compare craving between male and female patients within the group of patients with cannabis dependence revealed no differences between these groups. Further, we found no significant differences in craving between the group of patients with solitary cannabis dependence and the group of patients with cannabis dependence and abuse of other substances. A third limitation is that significantly fewer patients using clozapine smoked cigarettes compared with patients using olanzapine or risperidone. This could interfere with the results since craving for cannabis could be related to craving for cigarettes. However, no differences in craving were found between patients with solitary cannabis dependence and patients with both cannabis dependence and nicotine abuse. The finding that fewer patients using clozapine smoked cigarettes may also be important on its own, since former studies also found that patients using clozapine tend to smoke less (McEvoy et al., 1999). This could be explained by differences in the three dopamine-related factors we discussed above and is in line with our hypothesis.

Despite above-mentioned limitations, the results of the current study give support for the hypothesis of differential impact of antipsychotic medication (specially between clozapine and risperidone) on craving for cannabis in patients with both psychotic disorders and substance use disorders.

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Conflict of interest

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