Cannabis use in patients with schizophrenia: motivation for use and relation to clinical variables
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This thesis is about cannabis use in patients with schizophrenia. Schizophrenia is a serious mental illness that is characterized by psychosis, apathy, social withdrawal, and cognitive impairment, causing impaired functioning in everyday living. Cannabis is one of the most commonly used substances in schizophrenia patients, and is more common in people with psychosis than in the general population. Cannabis use has been associated with the development of psychotic disorder and—once it has developed—with a poorer course of the disease.

Studies presented in this thesis were performed in patients with (recent-onset) schizophrenia, who were receiving treatment in outpatient or inpatient clinics. In some studies, data of patients were compared to data of siblings and/or healthy controls.

Self-reported reasons for cannabis use, effects of cannabis use, implicit and explicit associations toward cannabis use, craving for cannabis use, and cessation of cannabis use are described in part I. Cannabis use in relation to other clinical variables such as age at onset of schizophrenia, obsessive compulsive symptoms and cognitive functioning are studied in part II. Adolescent cannabis use in relation to white matter in the brain of patients with schizophrenia is studied in part III.

The following pages give a summary of findings and limitations of the studies described in this thesis.

**Part I**

*Motivation for cannabis use, affective associations toward cannabis use, and craving for cannabis use in recent-onset schizophrenia*

**Chapter 1.1 Reasons for cannabis use and effects of cannabis use as reported by patients with psychotic disorders**

*Findings:*

In this literature review of 14 studies that examined self-reported reasons for cannabis use and self-reported effects of cannabis use in patients with psychotic disorders, it was found that patients commonly report that their reasons for cannabis use are enhancement of positive affect (42.1%), relief of dysphoria (66.3%), and social enhancement (61.7%). Fewer patients report reasons related to relief of psychotic symptoms or relief of side-effects of medication (12.9%). Frequently reported positive effects of cannabis are positive changes in affect and relaxation. Many patients reported that cannabis negatively affected positive symptoms. This review shows that patients suffering from psychotic disorder report using cannabis mainly for affect regulation and socialization, despite awareness that cannabis may have a negative effect on positive symptoms.

*Limitations:*

- A few studies were found with relatively small sample sizes, and most of these studies used interviews and instruments that have not been psychometrically evaluated.
- The retrospective self-report data are prone to recall bias.
Chapter 1.2  Implicit and explicit affective associations toward cannabis use in patients with recent-onset schizophrenia and healthy controls

Findings:
In this study implicit and explicit cannabis associations were compared between individuals with (n=70) and without (n=61) psychotic disorder, with use of three Single-Category Implicit Association Tests (SC-IAT) and a pen and paper questionnaire using the same words as the SC-IAT. There were no differences in implicit associations between patients and controls. However, patients scored significantly higher on explicit negative affect expectancies than controls. Both groups demonstrated strong negative implicit associations toward cannabis use, which might be explained by cannabis users not implicitly liking their cannabis use behaviour. Explicit relaxed expectancies were the strongest predictors of cannabis use and craving. There was a trend for implicit active associations to predict craving. The findings indicate that patients suffering from schizophrenia have associations toward cannabis similar to controls, but they have stronger negative explicit cannabis associations.

Limitations:
- The strong implicit negative associations toward cannabis could partly be due to extra personal associations (like general associations that are present in a culture instead of someone’s personal associations) or saliency effects.
- Different contributions of THC and CBD to explicit and implicit cannabis associations are unknown.
- The study had a cross-sectional nature and many of the observed relationships were relatively weak. A prospective study examining relations between cannabis associations and cannabis use variables at follow-up might overcome these limitations.

Chapter 1.3  Craving for cannabis in patients with psychotic disorder, their non-affected siblings and healthy controls: psychometric analysis of the Obsessive Compulsive Drug Use Scale

Findings:
In this study, Simultaneous Component Analysis (SCA) was used to compare the factor structure of the Obsessive Compulsive Drug Use Scale for cannabis (OCDUS-CAN) in patients with non-affective psychotic disorder, their siblings, and healthy controls who all used cannabis in the past year. A three-component SCA solution explained 74.2 % of the total variance, and consisted of well-interpretable subscales that could be best described as craving/urge, resistance, and impact. Reliability of the subscales was good. The three subscales significantly discriminated between frequent and infrequent cannabis users. Patients scored higher on the craving/urge and impact scale than siblings and controls, which could be related to primary and secondary symptoms of their disorder. This is the first study providing evidence that the OCDUS-CAN is a valid instrument to assess craving for cannabis in clinical and research samples of patients with psychotic disorder, but also in siblings and individuals without a (family) history of psychotic illness.

Limitations:
- The test-retest reliability and the predictive validity of the OCDUS-CAN were not assessed in this study.
Chapter 1.4  Cessation of cannabis use by patients with recent-onset schizophrenia and related disorders

Findings:
In this study, medical records of 206 consecutively admitted patients at the Early Psychosis Department in the AMC were examined for data on cessation of cannabis use. Of all patients that had used cannabis (n=167) in the past, more than half (87) ceased the use of cannabis before they were admitted to our clinic: most of these patients (73%) ceased the use of cannabis after they became psychotic and after their first contact with psychiatric services. A prior psychiatric admittance was reported most frequently as the reason for cessation. No differences in patient characteristics were found between patients that ceased their use of cannabis and patients that continued their use. The results suggest that start of treatment for psychosis is related to the cessation of cannabis use, at least in part of the patients. It may well be, that giving patients psycho-education about the negative effects of cannabis on the course of the illness and therefore motivate them stop the use of cannabis, is effective in a substantial part of cannabis using patients.

Limitations:
- All data were dependent on what medical staff had asked the patients and what they had reported in the records.
- There may have been recall bias by patients.
- Reasons for cessation of cannabis were reported in only 52% of cases.
- Because of the retrospective design of this study, we do not know the course of cannabis use in those patients who had not ceased their use, and we do not know whether patients that had stopped using cannabis were able to sustain this abstinence.

Part II
Cannabis use in relation to clinical variables

Chapter 2.1  Age at onset of non-affective psychotic disorder in relation to cannabis use, other drug use and gender

Findings:
In this cross-sectional study of 785 patients with a non-affective psychotic disorder, we used regression analysis to assess the independent effects of gender, cannabis use, and other drug use on the age at onset of first psychosis. Age at onset was 1.8 years earlier in lifetime cannabis users compared to non-users, irrespective of gender or the use of others drugs. Additional use of other drugs did not have an effect on age at onset. From the Kaplan Meier survival curve, differences in age at onset of psychosis between the cannabis users and non users seem to manifest from the early twenties. Age at onset was 1.3 years earlier in males compared to females, irrespective the use of
cannabis or other drugs. Up to 64% of cannabis using patients had used cannabis most intense before the onset of psychosis.

Limitations:
- The age of first cannabis use was not assessed. A comparison between patients that started cannabis use prior to the onset of psychosis versus non using patients might have provided more robust support about the possible contribution of cannabis use to the onset of psychotic illness.

Chapter 2.2 Substance use in a large sample of patients with schizophrenia or related disorders and co-morbid obsessive-compulsive symptoms

Findings:
In this study we examined the relationship between obsessive compulsive symptoms (OCS) and substance use in patients with a non-affective psychotic disorder. We found no significant differences in substance use variables between patients without co-morbid OCS (n=777), patients with mild OCS (n=143), and patients with more severe OCS (n=85). There was a trend for patients with mild OCS to be more likely to use alcohol heavily and to have a lifetime diagnosis of cannabis use disorder. The results suggest co-morbid OCS is not a protective factor against the use of nicotine and other substances in patients suffering from non-affective psychotic illness.

Limitations:
- Although the Y-BOCS was used as measurement for the severity of OCS, DSM-IV diagnosis of obsessive compulsive disorder was not screened for.
- Subtype of OCS was not included in the analysis. It would be interesting to find out whether there is a relationship between type of OCS and alcohol and cannabis use.

Chapter 2.3 Cannabis and cognitive performance in psychosis: a cross-sectional study in patients with non-affective psychotic illness and their unaffected siblings

Findings:
In chapter 2.3, mixed-model regression analysis was used to assess the effect of cannabis recency (current, lifetime, never), and cannabis frequency (daily, weekly, less) and the interaction between cannabis x status (patient, sibling, control) on cognition in patients with non-affective psychosis (n=956), unaffected siblings (n=953) and controls (n=554). Current cannabis use was associated with worse performance on immediate verbal learning, processing speed and working memory compared to never users. Lifetime cannabis use was associated with better scores on acquired knowledge, affect recognition and face identity compared to never-users. Findings suggest that cannabis using patients have a higher cognitive potential than non-users, while the (sub)acute effects of cannabis may impair cognitive functioning. Lifetime cannabis users perform better on social and general intelligence tasks which may be explained by better pre-morbid (social) functioning, rather than an effect of cannabis itself.

Limitations:
- The cross-sectional design restricts the drawing of causal inferences between cannabis use and cognitive functioning.
Part III  
Cannabis use related to brain white matter

Chapter 3.1  Cannabis use and callosal white matter structure and integrity in recent-onset schizophrenia

Findings:
In this study, high resolution structural and diffusion-tensor brain images were used to compare three groups of patients: patients who started regular use of cannabis before the age of 15 years (n=10), at the age of 17 years or later (n=8), and patients who were cannabis naïve (n=8). To verify patient findings white matter integrity of the three patients groups were also compared to a healthy control group (n=10). Cannabis naïve patients showed reduced white matter density and reduced fractional anisotropy in the splenium of the corpus callosum, compared to patients with early-onset cannabis use. In the same brain area, cannabis naïve patients showed reduced fractional anisotropy compared to healthy controls. Our results suggest that the age of onset of cannabis use is not identifying for white matter abnormalities in schizophrenia patients, however, our results might indicate a more vulnerable brain structure in cannabis naïve schizophrenia patients.

Limitations:
- Only males were included
- The sample size was relatively small.
- The crosssectional study design. It would be of interest to investigate the development of white matter structure and integrity differences in cannabis naïve patients and those who use cannabis.

Chapter 3.2  Reply to Fan and Hart

Chapter 3.2 is a letter to the editor, in which we reply to Fan and Hart (2011) who wrote a letter to the editor referring to our article presented in chapter 3.1. Fan and Hart (2011) put our attention on the fact that the way study results are described or put in certain words can lead to discussion about how they can be (mis)interpreted. Although we did not agree with all their points, we do realize that we have to remain cautious with using some words such as 'brain abnormality'.