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Research report

Cannabis use and expression of mania in the general population

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Abstract

Background: Cannabis use is common in patients with bipolar disorder, however little is known about cannabis as a risk factor for mania. In order to investigate the association between exposure to cannabis and subsequent development of manic symptoms whilst controlling for psychotic symptoms, a longitudinal population-based study was carried out.
Methods: 4815 individuals aged 18 to 64 years were interviewed using the Composite International Diagnostic Interview at baseline, 1 year follow up and 3 year follow up, including assessment of substance use, manic symptoms and psychotic symptoms.
Results: Use of cannabis at baseline increased the risk for manic symptoms during follow-up (adjusted OR 2.70, 95% CI: 1.54, 4.75), adjusted for age, sex, educational level, ethnicity, single marital status, neuroticism, use of other drugs, use of alcohol, depressive symptoms and manic symptoms at baseline. The association between cannabis use and mania was independent of the prevalence and the incidence of psychotic symptoms. There was no evidence for reverse causality, as manic symptoms at baseline did not predict the onset of cannabis use during follow-up (OR = 0.35, 95% CI: 0.03, 3.49).
Limitations: As 3 years is a relative short period of follow-up, long-term effects of cannabis use on mania outcomes could not be detected.
Conclusion: The results suggest that cannabis use may affect population expression of manic symptoms (and subsequent risk to develop bipolar disorder [Regeer, E.J., Krabbendam, L., R, DE Graaf, Ten Have, M., Nolen, W.A., Van Os, J., 2006. A prospective study of the transition rates of subthreshold (hypo)mania and depression in the general population. Psychol Med, 1-9.]). These findings may not be due to the emergence of psychotic symptoms or the effects of self-medication.

Keywords: Tetrahydrocannabinol; Bipolar disorder; Psychosis; General population; Cohort study

1. Introduction

Manic symptoms are common in patients diagnosed with schizophrenia and, conversely, psychotic symptoms often occur in those with bipolar disorder. The two co-morbid but separable symptom dimensions of mania and psychosis (McGorry et al., 1998; Peralta and Cuesta, 1999) also display a degree of overlap in genetic and non-genetic aetiological influences (Murray et al., 2004; Walker et al.,

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2002). Increased risk for schizophrenia has been reported in relatives of patients with bipolar illness characterised by a high familial loading (Valles et al., 2000) and twin studies suggest overlap in the genes contributing to schizophrenia, schizo-affective and mania syndromes (Cardno et al., 2002). High rates of mental illness among minority groups are not specific to schizophrenia and have been described in mania as well (van Os et al., 1996). Furthermore, neuroticism has been associated with the development of both schizophrenia (van Os and Jones, 2001)/psychotic symptoms (Krabbendam et al., 2002) and bipolar disorder (Angst et al., 2003a,b). Other risk factors however, such as obstetric complications (Browne et al., 2000) and urbanicity (Mortensen et al., 2003) have been associated with schizophrenia/psychotic symptoms, but not with bipolar disorder.

Although evidence is accumulating that cannabis is a risk factor for schizophrenia/psychotic symptoms (Andreasson et al., 1987; van Os et al., 2002), little is known about cannabis as a shared risk factor for both mania and psychosis. In studies of psychotic outcomes, there is evidence that exposure to cannabis plays a role not only in the expression of psychotic disorder, but also in the emergence of psychotic experiences at lower levels of severity in non-clinical samples (Henquet et al., 2005; van Os et al., 2002; Verdoux et al., 2003). Results from population-based studies furthermore suggest that cannabis use interacts synergistically with pre-existing liability to psychosis, indicating that the risk-enhancing effect of cannabis is much stronger in individuals with prior evidence of psychosis diathesis (Caspi et al., 2005; Henquet et al., 2005; van Os et al., 2002). Patients with bipolar disorder have elevated levels of substance use (Regier et al., 1990; Strakowski and DelBello, 2000), including cannabis (Sherwood Brown et al., 2001). There is also evidence that substance use in these patients is associated with poor treatment response and poorer clinical outcome (Sonne et al., 1994; Tohen et al., 1990). There are no data shedding light on whether associations between cannabis use and mania may be causal (Strakowski and DelBello, 2000). Clinical data, however, suggest that in many patients the use of substances precedes the onset of bipolar disorder (Strakowski et al., 1998). Several case studies, on the other hand, report that patients may start using cannabis to moderate their manic symptoms (Grinspoon and Bakalar, 1998; Khantzian, 1997; Strakowski and DelBello, 2000). Prospective studies, however, have not provided evidence to support the self-medication hypothesis, as patients with prior histories of substance use often did not resume their substance use after onset of the disease (Strakowski and DelBello, 2000; Strakowski et al., 1998). Only few population-based studies have actually investigated the temporal sequence of substance use and bipolar disorder (Escamilla et al., 2002). To our knowledge, no prospective study to date has investigated the hypothesis of cannabis as a risk factor for mania outcomes, disentangling co-morbidity with psychotic symptoms, potential confounding variables (such as use of other drugs), and reverse causality (i.e. the self-medication hypothesis).

The aims of the current study, therefore, were to investigate prospectively (i) if baseline cannabis use increases the risk for development of manic symptoms, (ii) if the association between cannabis and mania is independent of the emergence of psychotic symptoms, and (iii) if baseline mania predicts cannabis use at follow-up (the self-medication hypothesis).

2. Methods

2.1. Sample

The Netherlands Mental Health Survey and Incidence Study (NEMESIS), is a prospective study with three measurement points over a period of 3 years (Bijl et al., 1998a,b). A multistage, stratified, random sampling procedure was used to first select 90 municipalities, then a sample of private households, and finally a Dutch-speaking individual aged 18–64 years within each household. Selected households were sent an introductory letter by the Minister of Health, inviting them to participate. A total of 7076 individuals provided informed consent and was interviewed at baseline, representing a response rate of 69.7%. At T_1, 5618 subjects participated at the first follow-up and at T_2, 4848 subjects participated at the second follow-up; 4815 individuals had completed the mania section of the CIDI at both follow ups. The sample was found to be representative of the Dutch population in terms of gender, marital status and level of urbanisation (Bijl et al., 1998b), with the exception of a slight under-representation of individuals in the age group 18–24 years.

2.2. Measures

Subjects were interviewed at home using the Composite International Diagnostic Interview (CIDI) version 1.1 (Smeets and Dingemans, 1993). The CIDI was designed for trained interviewers who are not clinicians and has been found to have high inter-rater reliability (Cottler et al., 1991; Wittchen et al., 1991) and high test–retest reliability (Wittchen, 1994). Ninety interviewers experienced in systematic data collection collected the data, having received a 3-day training course in recruiting and interviewing, followed by a 4-day course at the

WHO-CIDI training centre in Amsterdam. Extensive monitoring and quality checks took place throughout the entire data collection period (Bijl et al., 1998b). CIDI assessment at baseline yielded lifetime ratings, assessment during follow up referred to the period between baseline and T_1 and between T_1 and T_2.

2.3. Drug use assessment

Cannabis use was assessed using the CIDI-L section, which includes a variety of substances. Two types of cannabis use at baseline were constructed: (1) lifetime any use (hereafter: baseline cannabis use and (2) lifetime frequency of use (hereafter: baseline frequency of cannabis use). Baseline frequency of cannabis use referred to the period of heaviest use on a 1 to 5 scale (less than once a month; 1–3 days/month; 1–2 days/week; 3–4 days/week; nearly every day). Similarly, cannabis use at either T_1 or at T_2 was combined into a single variable 'cannabis use during follow up' (i.e. use of cannabis from baseline to T_1 and/or use of cannabis from T_1 to T_2). Lifetime use of psychostimulants, cocaine, phencyclidine (PCP) and psychedelics at baseline, was combined into one variable 'use of other drugs'. Alcohol use at baseline was analysed as frequency of use during the past twelve months (no use; less than once a month; 1–3 days/month; 1–2 days/week; 3–4 days/week; nearly every day).

2.4. Manic symptom scores

The CIDI mania section (section F) consists of two probe items asking about the presence of experiences during a period of at least 2 days of (1) feeling so happy or excited that it caused the individual to get into trouble or family or friends to be worried about it, or a doctor saying the subject was manic or (2) being unusually irritable so that the subject complained, started arguments or shouted at or hit people. A positive rating on at least one of these probe items, subsequently directed to further mania items (9 items), to explore the specific nature of the manic symptoms. All of these 9 items can be rated either "yes" (1) or "no" (2). At baseline, the mania outcome was defined as having at least one positive rating on any of the 11 items of the CIDI core mania section (F) (hereafter: baseline mania). Similar mania scores were constructed during follow-up, and a single follow-up mania outcome was constructed consisting of a positive rating on at least one of the mania items at T_1 or at T_2 (hereafter: follow-up mania). These measures of isolated manic symptoms were validated, in terms of risk of transition to bipolar disorder, in a previous study (Regeer et al., 2006).

2.5. Psychotic symptom scores

Baseline lifetime ratings from the 17 CIDI core psychosis sections on delusions (13 items) and hallucinations (four items) were used (items G1–G13, G15, G16, G20, G21). These concern classic psychotic symptoms involving, for example, persecution, thought interference, auditory hallucinations and passivity phenomena. All these items can be rated in six ways: "1"—No symptom, "2"—Symptom present but not clinically relevant (not bothered by it and not seeking help for it), "3"—Symptom result of ingestion of drugs, "4"—Symptom result of somatic disease, "5"—Symptom present, bothered by it/seeking help for it, "6"—Symptom may not really be a symptom because there appears to be some plausible explanation for it.

Individuals with at least one positive rating on any of the CIDI psychosis items at baseline, irrespective of the qualitative symptom score of to "2" to "6", were considered as having psychotic symptoms at baseline (hereafter: baseline psychosis). The justification for this broad rating was derived from a previous study, where it was shown that the five qualitative ratings of "2" to "6" on the CIDI psychosis items were in fact strongly associated with each other (van Os et al., 2000). In addition, the five qualitative ratings independently showed a similar pattern of associations with known risk factors for psychosis (van Os et al., 2000, 2001).

At T_1 and T_2, the same 17 CIDI psychosis items were used in the interviews (covering the time intervals between interviews), yielding T_1 and T_2 measures of psychosis defined similarly as the baseline measure described above. A single follow-up psychosis measure was constructed similar to the single follow-up mania measure, by combining the T_1 and T_2 psychosis measure into one item (hereafter: follow-up psychosis).

2.6. Statistical analyses

2.6.1. Associations between cannabis and mania outcome

Associations between baseline cannabis use and follow-up mania were expressed as odds ratios using logistic regression analyses in the STATA statistical software program (Stata Corporation, 2003). All analyses were a priori adjusted for age (five groups), sex (Escamilla et al., 2002), educational level (four levels), ethnicity (van Os et al., 1996) (0, subject and both parents born in the Netherlands; and 1, other), single marital status, neuroticism (Angst et al., 2003b), lifetime use of other drugs, alcohol use during the past twelve months, baseline depression (total score on the CIDI-section E)(Stefanis et

Table 1
Patterns of baseline cannabis use and follow-up manic symptoms

Cannabis exposure at baseline	Any manic symptom at follow-up in whole risk set		Any manic symptom at follow-up in risk set with no manic symptoms at baseline		Any manic symptom at follow-up in risk set with no manic or psychotic symptoms at baseline	
	N outcome− (*n*=4679)	*N* outcome+ (*n*=118)	N outcome− (*n*=4560)	*N* outcome+ (*n*=63)	*N* outcome− (*n*=3924)	*N* outcome+ (*n*=34)
No use	4284 (98.2%)	78 (1.8%)	4174 (99.1%)	40 (0.9%)	3641 (99.4%)	23 (0.6%)
Any use	413 (91.2%)	40 (8.8%)	386 (94.4%)	23 (5.6%)	283 (96.3%))	11 (3.7%)

al., 2002) and baseline mania. To examine whether the effect of baseline cannabis use on follow-up mania was independent of psychotic symptoms, associations between baseline cannabis use and follow-up mania were additionally adjusted for both baseline and follow-up psychosis. In order to examine whether any association with follow-up mania was due to recent intoxication rather than the long-term effects of cannabis exposure, baseline cannabis use and cannabis use during follow-up were entered jointly in the adjusted model.

Reverse causality (i.e. the self-mediation hypothesis) was investigated by assessing the association between baseline mania and cannabis use during follow-up. Odds ratios were adjusted for the a priori selected confounders, but not for follow-up mania, nor for baseline and follow-up psychosis.

2.6.2. Risk sets and sensitivity analyses

All analyses were conducted in the group of individuals who successfully completed the mania items of the CIDI interview at T_2 (n=4815). Analyses were repeated for a risk set of individuals who at baseline had a score of lifetime absence on all the individual items of the CIDI mania section (n=4623), in order to ensure that the use of cannabis preceded the incidence of manic symptoms. In addition, analyses were restricted to individuals who at baseline had a score of lifetime absence on all the individual items on both the CIDI mania section and the CIDI psychosis section (n=3958), in order to investigate whether the use of cannabis was specifically associated with the mania outcome and independent of baseline prevalence of psychotic symptoms. The analysis to investigate reverse causality was repeated for the individuals who were lifetime cannabis-naive at baseline.

Sensitivity analyses were conducted to examine whether differential attrition in the sample as a whole (7076 at baseline, 4815 at follow-up) could have biased the findings. This was done by multiple imputation of missing values of CIDI follow-up mania using the HOTDECK command in STATA. The HOTDECK procedure is used several times within a multiple imputation sequence since missing data are imputed stochastically rather than deterministically. One thousand imputation sequences were run, yielding 1000 data sets in which the average odds ratio of the cannabis mania association was estimated within the HOTDECK procedure. Imputation of missing values was stratified by known correlates of mania, namely age, sex, educational

Table 2
Associations between baseline cannabis use and follow-up manic symptoms

Cannabis exposure	Any manic symptom at follow-up in whole risk set OR [a] (95% Confidence Interval)	Any manic symptom at follow-up in whole risk rest, adjusted [b] for *a priori* covariates OR [a] (95% Confidence Interval)
Baseline any use	5.32 (3.59–7.89)	2.70 (1.54–4.75)
Cumulative frequency		
No use [c]	1	1
<once a month	1.09 (0.27–4.51)	0.90 (0.20–4.11)
1–3 days per month	4.48 (2.01–10.00)	2.23 (0.82–6.07)
1–2 days per week	5.23 (2.54–10.73)	3.78 (1.59–8.97)
3–4 days per week	13.52 (5.39–33.90)	6.94 (2.00–24.06)
Nearly every day	9.01 (5.07–16.01)	3.43 (1.42–8.26)
Linear trend [d]	1.62 (1.47–1.79)	1.37 (1.17–1.59)

[a] OR, odds ratio.
[b] Adjusted for age, sex, educational level, ethnicity, single marital status, neuroticism, lifetime use of other drugs, alcohol use, baseline depression and baseline mania.
[c] Reference category, those subjects who did not use cannabis at baseline.
[d] The increase in risk with one unit change in cannabis frequency.

level, ethnicity, single marital status, neuroticism, lifetime use of other drugs, alcohol, baseline depression and baseline mania. The HOTDECK procedure replaces missing values in the relevant variables by values randomly sampled from complete lines in the same stratum.

3. Results

The sample consisted of 4815 subjects. The mean age of the sample at baseline was 41.2 years (S.D. = 11.9) and 2573 (53.4%) were women. The rate of baseline (lifetime) mania was 192 (4.0%) and 118 (2.5%) over the follow-up period (36 months). The rate of baseline psychosis was 784 (16.3%) and of follow-up psychosis 325 (6.8%). Use of cannabis at baseline (lifetime) was admitted to by 453 subjects (9.4 %) of the risk set and by 187 individuals (3.9%) during the follow-up. Subjects with a mania outcome during follow-up had higher rates of cannabis use at baseline (Table 1).

Cannabis use at baseline was associated with follow-up mania (OR = 5.32, 95% CI: 3.59, 7.89). The association was reduced substantially but remained significant after correction for age, sex, educational level, ethnicity, single marital status, neuroticism, use of other drugs, alcohol use and manic symptoms at baseline, with the strongest confounder being depressive symptoms at baseline (OR = 2.70, 95% CI: 1.54, 4.75). After adjustment for baseline and follow-up psychotic symptoms, the association between baseline cannabis use and follow-up mania was reduced slightly (OR = 2.51, 95% CI: 1.38, 4.59). The risk for manic symptoms increased with increased baseline frequency of cannabis use. The effect size of cannabis use was largest in individuals using cannabis 3 to 4 days/week and smaller in those using cannabis less frequently, apart from daily use (Table 2). When entering both distal and recent cannabis use together in the same model, baseline cannabis use remained significantly associated with the mania outcome (OR = 2.11, 95% CI: 1.06, 4.20), whereas cannabis use during follow-up did not display a significant association (OR = 1.64, 95% CI: 0.69, 3.88).

After exclusion of all individuals with baseline mania, baseline cannabis use still predicted incident follow-up mania (OR = 2.86, 95% CI: 1.34, 6.09, adjusted for the a priori selected variables and baseline and follow-up psychosis). Similarly, in the risk set of individuals without both baseline mania and baseline psychosis, the association between baseline cannabis use and follow-up mania remained strong (OR = 3.14, 95% CI: 1.10, 8.98, adjusted for the a priori selected variables).

Manic symptoms at baseline did not predict cannabis use during follow-up (OR = 0.56, 95% CI: 0.28, 1.15 for the whole sample and OR = 0.35, 95% CI: 0.03, 3.49 for the risk set with no cannabis use at baseline, adjusted for the a priori selected variables).

Based on 1000 imputation sequences in which missing values of CIDI follow-up mania in the whole sample were imputed stochastically, the estimated average adjusted association between baseline cannabis exposure and follow-up manic symptoms remained large and statistically significant (OR = 6.07, 95% CI: 3.81, 9.67).

4. Discussion

The results suggest that use of cannabis increases the risk for subsequent manic symptoms. This association remained significant after adjustment for possible confounders, such as use of other drugs and pre-existing symptoms of depression and mania, both by adjustment in the regression equation and by sample restriction. The data were furthermore suggestive of a dose–response relationship between frequency of exposure and mania outcome. The relationship between cannabis and mania was mediated by neither the prevalence nor the incidence of psychotic symptoms. Cannabis use during the follow-up period was not significantly associated with manic symptoms at follow-up, suggesting that the association between cannabis use and the incidence of manic symptoms is not explained by the acute effects of cannabis, but is more likely the result of its longer-term exposure. There was no evidence to support the self-medication hypothesis, as manic symptoms at baseline did not, directionally or statistically, predict the onset of cannabis use during follow-up.

4.1. Methodological issues

We studied the broader mania phenotype (i.e. subthreshold manic symptoms in the general population) rather than bipolar disorder, for which the current analyses would be low in statistical power. Similar to subthreshold psychotic symptoms (Johns and van Os, 2001; van Os et al., 2001), research suggests that expressions of mania outside the realm of clinical disorder have a distribution in the general population (Akiskal, 2003; Angst et al., 2003a; Krabbendam et al., 2004). Symptoms are more prevalent than their corresponding DSM-IV disorder-counterparts and therefore may have greater sensitivity to detect subtle changes in mania induced by common risk factors. Studying the general population and not clinical samples has furthermore the advantage of avoiding Berkson's bias, which refers to the phenomenon that patients with comorbid bipolar and substance use disorders are more likely to seek psychiatric treatment than patients with

either condition (Strakowski and DelBello, 2000). Recent findings suggest that subthreshold expressions of mania show continuity with clinical bipolar disorder (Kwapil et al., 2000; Lewinsohn et al., 2003; Thomas, 2004) (Akiskal, 2003; Regeer et al., 2006). The association between cannabis and manic symptoms as described in the current study may thus not only apply to the lower ends of the continuum, but may play a role in the expression of clinical bipolar disorder as well.

4.2. Strengths and weaknesses

Our measure for subthreshold mania required the presence of manic symptoms during at least 2 days. It has been argued that hypomania according to DSM-IV is very difficult to assess in the general population (Akiskal, 2002), suggesting that the criterion of subthreshold mania may have yielded a significant number of false negatives as well. If this were the case however, than this would result in an underestimation rather than an overestimation of the risk associated with use of cannabis. The issue of misclassification may also apply to our assessments of drug use, as these were based on self-report and were not confirmed by urine screens. However, personal use of cannabis is legal in the Netherlands, which makes underreporting unlikely, and any false negatives would also have resulted in an underestimation of the actual association between cannabis and mania.

One could argue that 3 years is a relative short period of follow-up. In the current analyses though, we found that the association between cannabis use and manic symptoms was much stronger for the long-term effects of cannabis exposure than for its proxy effects. The fact that such a strong association was observed after the relatively short period of 3 years suggests that the follow-up period was adequate.

4.3. Co-morbidity between manic and psychotic symptoms

The results indicate that cannabis is a shared, but independent risk factor for psychosis and mania, suggesting that cannabis may play a role in the co-morbidity of both symptom dimensions and clinical disorders. It has been suggested that both disorders may share a genetic vulnerability to dysregulation of the dopaminergic system due to social or pharmacological stress, for example induced by cannabis (Murray et al., 2004). It is generally known that acute symptoms associated with both psychosis and mania can be induced by dopamine-releasing drugs such as cannabis, amphetamine and cocaine. Antipsychotic medication, through dopamine receptor antagonism, is effective in both psychotic and manic disorder. There is some evidence that the catechol-O-methyltransferase gene, which regulates dopamine breakdown, is weakly associated with schizophrenia (Kunugi et al., 1997) and also affects the rate of bipolar disorder (Kirov et al., 1998). The association between cannabis and both bipolar and psychotic disorder may be linked to a process commonly referred to as "sensitisation". Sensitisation, in this case dopamine sensitisation, refers to the process whereby repeated, intermittent stimulant exposure produces a permanent change in dopaminergic responses (Robinson and Becker, 1986; Wolf et al., 1993). A dysregulated, hyperdopaminergic state may consequently lead to stimulus-independent release of dopamine which may take over the normal process of contextually driven salience attribution. This mechanism has been suggested in relation to the development of psychosis (Kapur, 2003; Tsapakis et al., 2003), but may apply to mania as well. Once established, it represents a permanent change in the central nervous system, so that cannabis may be necessary to initiate initial manic or psychotic vulnerability, but once sensitised, the individual will display continuing symptoms without additional substance use (Strakowski and DelBello, 2000). Interactions between genetic vulnerability and other environmental factors may further determine if a person becomes psychotic or manic at one point in his life (Murray et al., 2004). Research focusing on individuals with pre-existing vulnerability to dysregulation of the dopaminergic system in relation to cannabis exposure is needed to further investigate these interactions in the aetiology and co-morbidity of mania and psychosis.

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