



Cannabis with high cannabidiol content is associated with fewer psychotic experiences

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ABSTRACT

Objective: Cannabis is associated with psychotic outcomes in numerous studies, an effect that is commonly attributed to Δ^9 -tetrahydrocannabinol (Δ^9 -THC). An increasing number of authors identify cannabidiol, another component of the cannabis plant, as an antipsychotic agent. The objective of the current study is to investigate the role of cannabidiol content in the association between cannabis use and psychiatric symptoms in a large non-clinical population of cannabis users.

Methods: In a web-based cross-sectional study we obtained detailed information about cannabis use and subclinical psychiatric experiences using the Community Assessment of Psychic Experiences (CAPE). Different types of cannabis (i.e. marijuana, hashish etc.) have distinctive proportions of Δ^9 -THC and cannabidiol. Since average concentrations of Δ^9 -THC and cannabidiol in the most popular types of cannabis sold on the Dutch market are annually measured, we were able to estimate exposure to Δ^9 -THC and cannabidiol.

Results: We included 1877 subjects (mean age 23, SD 6.0) who used the same type of cannabis in the majority of the occasions (in >60% of occasions). We found a significant inverse relationship ($F(1,1877): 14.577, p < 0.001$) between cannabidiol content and self-reported positive symptoms, but not with negative symptoms or depression. The estimated effect size of cannabidiol content was small.

Conclusion: Although the observed effects are subtle, using high cannabidiol content cannabis was associated with significantly lower degrees of psychotic symptoms providing further support for the antipsychotic potential of cannabidiol.

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1. Introduction

The association between cannabis use and psychotic outcomes is reported consistently, (Arseneault et al., 2004; Schubart et al., 2010; Moore et al., 2007; Skinner et al., 2010) although the causality of this association is difficult to assess and still under debate (Macleod et al., 2004; DeLisi, 2008). However, as cannabis is the most widely used illicit drug in the world (United Nations Office on Drugs and Crime, 2009), clarifying mental health sequelae of cannabis use is of great importance. A possible explanation of the heterogeneous nature of the findings in this field, is that exposure to cannabis is not uniformly defined and that several factors might influence biological exposure to cannabis. A number of effect modifying factors have already been identified. With an odds ratio of 2.09, a recent meta-analysis reported frequent use to be associated with psychotic outcome in general (Moore et al., 2007), moreover continued cannabis use might increase

the risk on persistence of symptoms and therefore a psychotic disorder (Kuepper et al., 2011). Likewise, subjects who start to use cannabis early in life might also be more at risk to develop psychotic symptoms (McGrath et al., 2010; Schubart et al., 2010; Konings et al., 2008). Commonly, Δ^9 -tetrahydrocannabinol (Δ^9 -THC) is denoted as the main psychoactive ingredient of cannabis products such as marijuana and hashish (Mechoulam and Gaoni, 1965) and the concentration or content of Δ^9 -THC is traditionally considered as the main measure of cannabis potency (McLaren et al., 2008). However, cannabis plants contain more than 70 different cannabinoids that are also found in the cannabis products on the market (Elsobly and Slade, 2005). Cannabidiol is one of these cannabinoids and a number of studies suggest that cannabidiol has antipsychotic properties and could therefore modify the mental health sequelae of cannabis use. (Morgan and Curran, 2008; Leweke et al., 2000; Zuardi et al., 1995, 2006b). Di Forti et al. found that the use of cannabis containing a high Δ^9 -THC- and a low cannabidiol (CBD) concentration was retrospectively associated with a higher risk of a first psychotic episode (Di Forti et al., 2009). Similarly, a number of authors hypothesize that cannabidiol possibly antagonizes the effects of Δ^9 -THC (King, 2008; Smith, 2005; McLaren et al., 2008); i.e. that it has protective properties against psychosis.

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Concentrations of cannabidiol and Δ 9-THC differ greatly between various types of cannabis products such as marijuana (weed) and hashish (resin), year and by place of origin (Potter et al., 2008; Trimbos, 2008, 2009; Mehmedic et al., 2010). For instance, in 2008 marijuana produced in The Netherlands contained virtually no cannabidiol and had a mean Δ 9-THC concentration of 16%, whereas hashish imported from countries as Nepal, Afghanistan or Morocco, contained a similar concentration of Δ 9-THC (17%) but also contained 9% of cannabidiol (Trimbos, 2009). Given the hypothesized antipsychotic potential of cannabidiol, the variation in concentrations of cannabidiol could be reflected in a moderation of the association between cannabis use and psychotic symptoms. Further exploring the role of cannabidiol in the association between cannabis and psychosis symptoms could be of value in the debate on the impact of cannabis on population mental health. Moreover, evidence on the associated risks of particular cannabis products could improve the quality of psychoeducation on the risks of cannabis use.

This study aims to investigate the influence of the Δ 9-THC/cannabidiol ratio in different cannabis products on the association between cannabis use and psychiatric symptoms in a large non-clinical population of young adult cannabis users.

2. Materials and methods

2.1. Participants

Participants were recruited using a project website launched in 2008 (www.cannabisquest.nl). Individuals were directed to the website via different media; advertisements distributed on more than 100 different collaborating colleges and universities using intranet, posters and flyers. The chance to win an Apple iPod® or an Nintendo Wii® was used as an incentive. The website targeted mainly Dutch speaking young adults and adolescents (18–25 years). Besides personal information as age, educational level and contact details, all participants filled out the Community Assessment of Psychic Experiences (CAPE) (Stefanis et al., 2002; Konings et al., 2006) and the Cannabis Use Inventory (CUI) (described below). Only subjects who indicated to use cannabis were included in the analyses. Participants who indicated having an inconsistent pattern of cannabis use (<60% consistent preference) or were not aware of the type of cannabis they used, were excluded from the analyses. Verification questions were used to protect against random answers and internet bots that run automated tasks. To increase the homogeneity of the sample participants who indicated to be younger than 10 years or older than 60 years of age were excluded.

This study was approved by the UMC Utrecht medical ethical commission and all participants gave online informed consent.

2.2. Assessment of psychiatric symptoms

The CAPE is a 42-item, self-rating instrument and measures experiences from three symptom dimensions: positive-, negative- and depressive symptoms with discriminative validity in individuals from the general population (Stefanis et al., 2002; Konings et al., 2006).

2.3. Cannabis quantity measure

To assess detailed information on cannabis use the Cannabis Use Inventory (CUI) questionnaire was developed. The CUI offers a retrospective comprehensive inventory of life time cannabis exposure. Participants are asked to indicate at which age they started to use cannabis and in which frequency. Thereafter subjects are asked to indicate if, and if so at what age, their consumption frequency had changed significantly and how long this period lasted. In total,

participants can indicate five different periods of distinct cannabis use frequency, covering the period since first use until present day. Based on information from the CUI, the population sample was arbitrarily divided in nine categories on quantity of cannabis use in the last year: 1) Once a year or less, 2) Over once a year but not monthly, 3) Once a month, 4) Weekly for 0 to 5 euros a week, 5) Weekly for 5 to 10 euros a week, 6) Weekly for 10 to 25 euros a week, 7) Weekly for 25 to 50 euros a week, 8) Weekly for 50 to 100 euros a week, 9) Weekly for more than 100 euros a week. Outliers in amount of use (more than two standard deviation from the mean equalling) were excluded from analysis.

2.4. Annual reports on Δ 9-THC and cannabidiol content

The Netherlands Institute of Mental Health and Addiction (Trimbos Institute) is a Dutch centre of expertise and conducts research on mental health, mental resilience and addiction. Since 1999, the Trimbos Institute annually visits a random selection of 50 Dutch Coffeeshops (establishments where the distribution of small quantities of cannabis for personal use is legal under Dutch law), for reference, approximately 700 Coffeeshops existed in The Netherlands in 2007 (Bieleman et al., 2008). The researchers measured the concentrations of Δ 9-THC, cannabidiol and cannabinol in the following five cannabis products: i) Dutch marijuana, ii) imported marijuana, iii) Dutch hashish, iv) imported hashish and v) the strongest marijuana sold in the Coffeeshop (Trimbos, 2009). Since all subjects in the current analysis had indicated the type of cannabis product they commonly use, the average measurements mentioned in the annual Trimbos reports, were used as a by proxy estimate of exposure to these cannabinoids.

2.5. Cannabis type

Following the categorization of the annual Trimbos Institute measurements as described above, we asked participants which of the following types of cannabis they usually consumed; 1) Dutch marijuana, 2) imported marijuana, 3) Dutch hashish, 4) imported hashish, 5) the strongest type in my Coffeeshop. To increase the validity of our classification, participants could also give the following answers 6) hashish of unknown origin, 7) marijuana of unknown origin, 8) the most popular type in my Coffeeshop, 9) variation between two types 10) different every time, and finally 11) unknown. Only those participants were selected for further analysis who indicated using one of the cannabis types that are represented in the annual Trimbos Institute report (types 1,2,3,4 and 5). Finally, participants were asked how often they used the selected type of cannabis. We excluded subjects if they indicated using the selected type in less than 60% of the occasions where they used cannabis. Combining information from the Trimbos Institute annual reports on cannabinoid concentrations and the individual cannabis use patterns in our dataset, we were able to estimate the exposure to Δ 9-THC and cannabidiol. A Δ 9-THC/cannabidiol ratio was calculated for each participant.

As a result of different THC and cannabidiol concentrations in the five cannabis products in the years 2008 and 2009, ten (5×2) levels THC/cannabidiol concentrations were calculated within the sample (THC/cannabidiol concentrations: 2.0, 3.6, 8.8, 16.0, 24.8, 29.6, 45.8, 55.3, 75.0, 81.5).

To avoid analyses of small groups and in order to conserve power we applied a median split to dichotomize the THC/cannabidiol ratio given that these cannabidiol concentrations broadly fall into two categories (high and low THC/cannabidiol ratio). Median split was at 55.3 effectively defining a high cannabidiol content group and a low cannabidiol group that were used in the final analyses.

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