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The dynamics of cannabis use and dependence

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GENERAL INTRODUCTION
Cannabis use can spiral from a first experimental puff, into a habit, dependence, and on occasion, the need for treatment. Although this escalation is not the norm for the vast majority who inhale cannabis for the first time, it can happen to some. To understand why frequent cannabis use escalates to severe sustained problems for some but not for others, this thesis investigates the dynamics of cannabis use and dependence.

BACKGROUND

It takes approximately 15 minutes after the inhalation of smoke from a cannabis “joint” for the intoxicating effects of the main psychoactive ingredient Δ9-tetrahydrocannabinol (THC) to take effect which will last for approximately 2-3 hours. This experience is usually described as pleasant and relaxing, and is often accompanied by laughter, talkativeness, a sense of enhanced well-being, and/or an enhanced sensory appeal of foods or sleepiness [1]. However, dysphoric reactions may also occur and occasionally unpleasant feelings such as anxiety may escalate to panic. Moreover, acute THC intoxication impairs learning and memory functions and adversely affects psychomotor and cognitive performance [2]. Such adverse acute effects as well as concerns of permanent long-term effects [3;4], and the fact that cannabis is the most frequently used illicit drug worldwide, contribute to cannabis use sometimes being portrayed as very problematic.

According to the UNODC World Drug Report 2013, the worldwide last-year prevalence of cannabis use is 3.9%: 180.6 million people of the world population between 15 and 64 years [5]. This is just a fraction of the number of people who have ever used cannabis, as for the vast majority of these people cannabis use is a transient phenomenon limited to adolescence and early adulthood [6]. Only a small minority continues using cannabis and runs the risk to become dependent [7]. Particularly frequent cannabis users are at risk of developing dependence, but even among (near) daily users “only” 20-50% are dependent (defined in Table 1) [8;9]. Thus, cannabis dependence is a potential but by no means imperative consequence of cannabis use. Still, such loss of control over the cannabis use and its interference with family life, career, school and social functioning can have a considerably negative effect on a person’s life: a recent global estimate attributed roughly 2 million years lived with disability due to cannabis dependence [10].

Prevention of the onset of cannabis dependence will therefore help to avoid human suffering and reduce societal damage, including loss of productivity. As people who have never used a substance will not become dependent on it, much attention has been devoted to the prevention of the onset of cannabis use. However, the effectiveness of universal prevention of cannabis use is very limited [11]. Therefore, rather than aiming prevention at a large, unselected population unlikely to develop dependence, prevention may be more efficiently targeted at the relatively small group of frequent users, who are at an increased risk of further escalation and the development of dependence due to additional risk factors predictive of the transition into dependence (i.e. selective and indicated prevention). Unfortunately, there is little evidence of why some frequent
cannabis users become dependent while others do not. Therefore, the main topic of this thesis is the difference between frequent cannabis users who are, become, and stay dependent; and those who are or do not become dependent. We portray the dynamics of a Dutch community sample of 600 frequent cannabis users (≥3 days use per week for > 12 months), with specific consideration for mental health and cannabis exposure.

Among frequent cannabis users, there are both non-dependent users, and dependent users with substantial impairment or distress [14-16]. However, the distinction is often neglected when investigating “adverse outcomes” of cannabis use. Outcomes of physical harm such as motor vehicle accidents, respiratory and cardiovascular disease aside, these adverse outcomes are mainly mental disorders [17].

Investigation of adverse mental health outcomes of cannabis use mostly draw upon general population samples, and indicate that these problems are almost exclusively associated with frequent and dependent cannabis use. However, these studies generally included relatively low numbers of heavy users and therefore, only investigated the association between mental disorders and either dependent cannabis use or frequent use including dependent use. As a consequence, the group of frequent non-dependent cannabis users has been largely ignored, which may have led to an overestimation of the mental health risks of non-dependent frequent cannabis use.

Δ9-tetrahydrocannabinol (THC) exposure. A dose-response relationship between cannabis exposure and adverse consequences is presumed because frequent cannabis users are more often dependent and at higher risk of mental disorders than less frequent users. Yet, cannabis research has given little consideration to the actual level

<table>
<thead>
<tr>
<th>Table 1 Definition of cannabis dependence according to DSM-IV.</th>
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<td>A maladaptive pattern of cannabis use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:</td>
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<tr>
<td>1. Tolerance, as defined by either or all of the following: (a) a need for markedly increased amounts of cannabis to achieve intoxication or desired effect, (b) markedly diminished effect with continued use of the same amount of the substance.</td>
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<td>2. Withdrawal, as manifested by either of the following: (a) the characteristic withdrawal syndrome (not specified for cannabis), (b) the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms.</td>
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<td>3. Cannabis is often taken in larger amounts or over a longer period than was intended.</td>
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<td>4. There is a persistent desire or unsuccessful efforts to cut down or control cannabis use.</td>
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<td>5. A great deal of time is spent in activities necessary to obtain cannabis, use cannabis, or recover from its effects.</td>
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<td>6. Important social, occupational or recreational activities are given up or reduced because of cannabis use.</td>
</tr>
<tr>
<td>7. Cannabis use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by cannabis [54].</td>
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FREQUENT CANNABIS USE WITH AND WITHOUT DEPENDENCE

Among frequent cannabis users, there are both non-dependent users, and dependent users with substantial impairment or distress [14-16]. However, the distinction is often neglected when investigating “adverse outcomes” of cannabis use. Outcomes of physical harm such as motor vehicle accidents, respiratory and cardiovascular disease aside, these adverse outcomes are mainly mental disorders [17].

Mental health. Investigation of adverse mental health outcomes of cannabis use mostly draw upon general population samples, and indicate that these problems are almost exclusively associated with frequent and dependent cannabis use. However, these studies generally included relatively low numbers of heavy users and therefore, only investigated the association between mental disorders and either dependent cannabis use or frequent use including dependent use. As a consequence, the group of frequent non-dependent cannabis users has been largely ignored, which may have led to an overestimation of the mental health risks of non-dependent frequent cannabis use.
The Netherlands
Although the Netherlands is internationally known for its legal tolerance regarding small scale production and sale of small amounts of cannabis in “coffee shops”, the Dutch prevalence of cannabis use has been roughly stable and similar to the European average for the past decade [12]. About one in four Dutch adults ever used cannabis, one in twenty-five used it in the past month, of whom approximately a third used cannabis daily or nearly daily (Figure 1). There are an estimated 29.3 thousand (0.3%) adult dependent cannabis users in the Netherlands and 10.2 thousand people who annually seek treatment for cannabis-related problems on a total population of 16.8 million inhabitants [13].

Of THC exposure, as most studies only measure frequency of cannabis use, occasionally complemented with the quantity that is used (e.g. number of joints) per day. However, particularly in the instance of (nearly) daily cannabis use: the exposure to THC can vary widely with differences in the number of joints per day, dose per joint, cannabis type, cannabis potency (THC-concentration) and smoking behaviour [16]. More precise cannabis (THC) exposure measures could help explain why some frequent cannabis users are, become and stay dependent and others are not/do not. In particular, it has been suggested that the worldwide increase of the THC concentration in cannabis [18-20] directly leads to higher THC-exposure, more cannabis dependence and an increase in the need for treatment [21]. However, people smoking cannabis with a high THC concentration may reduce the amount of cannabis that they use or adapt their smoking behaviour to “titrate” their THC exposure, i.e. smoke until a satisfactory effect is reached [22-25]. Finally, the type of cannabis that is used may also be important: unlike cannabis resin, Dutch herbal cannabis contains nearly no cannabidiol (CBD). CBD is the other most abundant cannabinoid in cannabis and has psychotropic effects that oppose the THC effects [26].

**Figure 1** Prevalence of cannabis use, cannabis dependence and cannabis dependence treatment in the Dutch population. Population estimates NPO (aged 15-65), dependence estimate NEMESIS (aged 18-65), Treatment LADIS (>15 years).
WHO BECOMES DEPENDENT?

To target prevention specifically at frequent users with a substantial risk to become dependent (selective prevention), factors predicting the transition from non-dependent frequent use to dependence require preliminary identification. This should necessarily involve longitudinal research. However, most prospective studies have focussed on the identification of risk factors for cannabis use onset, while “only” one in ten people who have ever used cannabis will develop dependence [7]. The few available longitudinal studies on escalation from cannabis use to dependence identified the following risk factors: younger age, early onset of cannabis use, other substance use, early parental death, deprived socio-economic status, poor financial situation, and the presence of an anxiety disorder [6;7;27-29]. However, these studies included too few frequent cannabis users to specifically investigate the transition from frequent cannabis use to dependence. This renders secondary prevention impossible, because secondary prevention is targeted at high risk populations of frequent cannabis users who also have additional risk factors predictive of the transition into dependence. Primarily, factors that differentiated dependent from non-dependent cannabis users in cross-sectional studies can be used as candidate predictors for the transition to dependence. These factors include: mental disorders [7;30-37], personality traits [38-42], life events [43-45], level of cannabis exposure, setting in which the cannabis use takes place [16;46;47] and motives to use cannabis [40;48]. What is still lacking are prospective studies examining predictors of cannabis dependence in a large population of non-dependent frequent cannabis users. The current study intends to fill this gap in our knowledge.

COURSE OF CANNABIS DEPENDENCE

Studies among patients in addiction treatment suggest that the course of cannabis dependence tends to be persistent or will chronically relapse. However, people seeking treatment for their cannabis problem are usually more severely affected than those not seeking treatment [49]. Therefore, studies in treatment seeking populations are likely to overestimate the persistence of cannabis dependence. However, little is known about the course of cannabis dependence in people not in treatment. The few prospective community studies on the course of dependence show an average annual remission rate of 17% [50]. As diagnostic remission from dependence does not necessarily equate to cessation of cannabis use or cannabis-related problems, it is firstly important to assess differences in the course of dependence in more detail. Next, given the high “natural” remission rates, it is crucial to identify predictors of persistence allowing us to target treatments to those unlikely to remit “naturally” and to avoid exhausting the limited intervention budgets on those likely to recover spontaneously.

TREATMENT

Less than a third of those dependent on cannabis seek professional treatment [35;51;52]. The reasons why some people seek treatment for cannabis dependency while others
do not is largely unknown. An increased and improved understanding of these reasons may help to develop treatments that improve treatment participation. In addition, it may augment our understanding of the recent increase in treatment demand for (primary) cannabis problems, seen internationally [53]. This increase was fivefold in the Netherlands from 2,659 in 1996 to 10,971 in 2010 [13]. Although this may reflect improved accessibility of addiction care and/or a greater readiness to seek treatment, some argue that the increased treatment demand marks an increase in problematic cannabis use due to the increased THC concentration in the cannabis that is currently on the market [21].

AIMS AND OUTLINE OF THIS THESIS

This chapter (Part I) introduced a crucial question for drug policy, targeted prevention and treatment strategies that has been hardly addressed so far and can be summarised as: “Which frequent cannabis users are/become/stay dependent, and seek treatment, and which do not? To address this question, this thesis aims to provide a clearer picture of frequent cannabis users with and without dependence, particularly regarding their mental health and the specifics of their cannabis use. In addition, the transition from non-dependent to dependence and the persistence of dependence are investigated taking into account levels of THC exposure and other possible predictors.

Part II describes the design and the main results of a unique longitudinal cohort study, known as the CanDep study. This part begins with a detailed description of the design and an overview of the study population (chapter 2). In brief, a large sample of 600 frequent cannabis users (≥3 days per week for 12 months, aged 18-30 years), often considered to be difficult to reach for scientific research, was recruited from coffee shops and through chain referral. The main design aspects are shown in Figure 2. After the study design, the main results of the CanDep study are presented. First, mental health indicators of dependent frequent cannabis users (N=252) and non-dependent frequent cannabis users (N=348) are compared with 1,072 young adult non-users and non-frequent cannabis users participating in a Dutch representative general population survey, the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2) (chapter 3). Second, the cohort of frequent users was re-interviewed after 1.5 and 3 years to assess the incidence and predictors of the onset (chapter 4) and persistence (chapter 5) of cannabis dependence.

Figure 2 Study outline. Δ= cross-sectional comparisons, arrows = prospective comparisons. Numbers refer to the chapters of this thesis.
Third, barriers and facilitators to seek treatment are investigated by comparing the
dependent users who did not seek treatment with an additional sample of 70 patients in
specialised treatment for cannabis dependence (chapter 6).

Throughout Part II, the role of cannabis exposure and setting of cannabis use are
addressed. In order to better understand the role of these factors in the development of
cannabis dependence, a naturalistic “experimental” study is presented in Part III using
a subsample of 106 frequent cannabis users from the CanDep cohort. First, we address
the reliability and validity of self-reported cannabis consumption using the data from
the naturalistic study (chapter 7). Second, the study investigates whether consumers of
stronger cannabis (with a higher THC concentration) use less cannabis per joint and/
or inhale less smoke than those using less potent cannabis, i.e. whether they titrate
their total THC exposure, and whether total THC exposure and smoking behaviours
(topography) are associated with concurrent and future cannabis dependence severity
(chapter 8). Another methodological issue addressed in Part II is the validity of the
Severity of Dependence Scale, a screener for cannabis use problems (chapter 9).

Finally, the results and implications of these studies are summarised and discussed in
Part IV (chapter 10).

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