SUMMARY
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Part I Introduction

Chapter 1 General introduction. In chapter 1, we reviewed the literature showing that while most cannabis use remains occasional and temporary, some people continue their use and run the risk to become dependent. Young adults who often smoke cannabis are at higher risk of dependence, but still most do not become dependent. Furthermore, it seems that most dependent users do not apply for treatment at addiction care services. To advance targeted prevention and treatment, this thesis investigated the dynamics of frequent cannabis use and dependence. The central question in Part II was: "which frequent cannabis users are/become/stay dependent, and seek treatment, and which do not?" In this search for predictors, we focused on mental health problems and cannabis use characteristics with special attention to the role of potent (Dutch) cannabis. Part III addressed measurement issues and provided more detailed information on the role of cannabis potency in developing and maintaining cannabis dependence. Part IV (chapter 10) integrated and discussed findings of part II and III (i.e. chapters 2 to 9).

Part II Cannabis dependence: predictors, course, and treatment seeking

Chapter 2 Study design. Chapter two showed how little is known about the transition from frequent to dependent cannabis use (and vice versa) and how this is investigated in the "Cannabis Dependence" (CanDep) study. In the CanDep study, we included 600 young adults (18-30 years) who used cannabis on three or more days per week for at least a year. They were recruited directly from coffee shops and through the social network of these coffee shop visitors.

• Two cohorts were distinguished: dependent frequent users (N=252) and non-dependent frequent users (N=348). Differences were assessed between both cohorts regarding cannabis use, childhood adversities, life events, and mental health, and put in perspective by comparing both groups with 1,027 non-users/infrequent users from the general population. Reasons to (not) seek treatment were investigated by comparing the 241 dependent users who had not been seeking treatment with 70 people in treatment for cannabis dependence. Next, the course of cannabis use and dependence, and predictors for the onset and persistence of dependence were examined in follow-up assessments (after 1.5 and 3 years) in the two cohorts of non-dependent and dependent frequent cannabis users, respectively. (Part II)

• In a naturalistic experiment with a subpopulation of the cohorts, the ability of users to estimate the dose used per joint and the potency of their cannabis was assessed. It was also investigated whether people "titrate" their THC exposure (i.e. whether people smoking stronger cannabis use less cannabis in their joint or inhale less smoke) and whether smoking behaviour characteristics predict dependence. Finally, the validity of a screening questionnaire for cannabis dependence was tested in the cohort of frequent cannabis users. (Part III)
Chapter 3 (Dependent) heavy cannabis use and mental health. Strikingly, the results of this study showed that the average cannabis use of dependent frequent users was very similar to that of non-dependent frequent users at baseline. However, while dependent frequent cannabis users more often had mental disorders in comparison with both non-dependent frequent cannabis users and non-(frequent) using peers, the mental health of the two latter groups was mostly comparable (Figure 1). Although non-dependent users had more often externalising disorders than non-(frequent) users, these typically developed before cannabis use onset. Therefore, they are regarded to be a risk factor for early and frequent cannabis use, rather than a consequent of frequent cannabis use. Since childhood adversities, self-reported cannabis use patterns and cannabis use habits were very similar in frequent users with and without dependence, these factors did not explain the observed mental health differences.

Chapter 4 Onset of cannabis dependence. During the three-year follow-up, 37% of the (lifetime) non-dependent frequent cannabis users had their first onset of cannabis dependence. Previously reported vulnerability factors and cannabis use patterns did not predict dependence onset in this group of frequent cannabis users. However, the onset was predicted by variables related to the current situation of the users: living alone, coping motives for cannabis use, number and type of recent negative life events (major financial problems), and number and type of baseline cannabis use disorder symptoms (impaired control over use).

Chapter 5 Persistence of cannabis dependence. The course of dependence appeared to be dynamic but there was a general tendency towards spontaneous (temporary) remission. Only 28% of the dependent frequent cannabis users at baseline were also dependent at both follow-ups. Such persistent course of dependence was associated with more functional impairment and (higher levels of) cannabis consumption.

Figure 1 Unadjusted prevalence of 12-month mental disorders in this thesis’ four populations. N: General population of non-users and non-frequent users (N=1,072). D- Non-dependent frequent cannabis users (N=348). D+ Dependent frequent cannabis users (N=252). P: Treatment seeking cannabis dependent users (N= 70). All 18-30 years.
Nevertheless, most persons with remitted dependence continued their (heavy) cannabis use and a third still had cannabis related problems. Yet, even among those with persistent dependence, treatment rates were low (15%). Although persistency was predicted by coping motives to use cannabis, lifetime anxiety disorder and any psychosis symptoms, only the number and type of life-time cannabis use disorder symptoms (role impairment, use despite problems) were independent predictors.

Chapter 6 Treatment seeking for cannabis dependence. For dependent cannabis users, barriers to seek treatment were the desire for self-reliance, preference for informal help, and absence of a perceived need for treatment. Those who thought they needed treatment, but did not seek it, mainly expressed a desire for self-reliance, felt that treatment is not effective and tried to avoid stigma. People in treatment were roughly twice as likely to have a mental disorder (Figure 1) and used twice as much cannabis compared to non-treatment seeking dependent users, and reported that mental health problems and functional impairment were important reasons to seek treatment.

Part III Assessment issues

Chapter 7 Self-reported dose and potency. In the naturalistic study, users’ ability to estimate their cannabis dose per joint and potency was validated against objective measures. Self-reported dose was based on a prompt card and the average number of joints made from one gram of cannabis. Potency was self-reported as level of intoxication, subjective estimate of cannabis potency and price per gram of cannabis. The observed tenfold difference between the lowest and highest objectively measured cannabis dose, and the wide range of the THC concentration (1.1–24.7%) in samples of the respondents’ most commonly used cannabis, highlight the importance of these factors when assessing THC exposure. Unfortunately, self-report measures were only weakly associated with objective measures. However, the self-reported number of joints per gram, cannabis price and subjective potency had at least some validity.

Chapter 8 Cannabis potency, titration and dependence. This study investigated whether consumers of stronger cannabis use less cannabis per joint or inhale less smoke than those using less potent cannabis, and whether these factors predict cannabis dependence severity. We found that users of more potent cannabis in fact used larger doses, yet inhaled less smoke when smoking strong joints. Hence, they partly titrated their THC intake, but were generally exposed to more THC. However, inhalation behaviour appeared to be a stronger predictor for cannabis dependence severity than monthly THC exposure.

Chapter 9 Severity of Dependence Scale validation. The Severity of Dependence Scale (SDS) is a short scale to measure the degree of psychological dependence, potentially useful for clinical practice and prevention, to differentiate between frequent cannabis users with and without dependence. However, the results of this study showed that the SDS had a low criterion validity against the CIDI diagnosis cannabis dependence (AUC=.68). Thus its use as a screener is not recommended within populations of young adult frequent cannabis users.
Part IV Discussion

Chapter 10 General discussion. CanDep is a unique study in combining data from a large longitudinal community cohort of high-risk frequent cannabis users, a general population sample and a treatment seeking patient sample, and in combining observational studies with naturalistic experiments. Figure 2 provides an overview of the results. The three-year course of cannabis use and dependence was dynamic, yet mostly “favourable”: overall, frequency and quantity of cannabis use decreased, “only” 37% of the initially non-dependent frequent users developed dependence and “only” 28% of the initially dependent frequent users remained dependent. An extended follow-up period is needed to improve our understanding of the process of “maturing out”, because at the three-year follow-up assessment (mean age 25), 66% of the users still used cannabis (nearly) daily.

In our population of young adult frequent cannabis users, the role of THC exposure (frequency, quantity, potency) as a predictor of onset or persistence of cannabis dependence seemed to be relatively small. In contrast, current (mental health) problems and previous cannabis abuse/dependence symptoms were important predictors of onset and course of cannabis dependence. Therefore, on a societal scale, the incidence of cannabis dependence and treatment demand are unlikely to be reduced by a decrease of the THC concentration in cannabis; selective (low threshold) prevention seems more promising.

Finally, epidemiological data suggest there are many (frequent) cannabis users in the general population with a DSM-IV diagnosis for cannabis dependence, who are not in treatment. While some stress the importance of filling this so-called “treatment gap”, our results suggest that many dependent users are not in need for treatment, because they showed high spontaneous remission rates, absence of a perceived need for treatment, and better functioning, mental health and less cannabis use than the patients that were in specialized addiction treatment. Thus, although a minority would benefit from being convinced to seek treatment to prevent escalation of problems and chronic dependence, the “treatment gap” may be less problematic than previously assumed.
SUMMARY

General population

Frequent non-dependent users

Frequent dependent users

Treatment seeking dependent users

4 Incidence: 37%

Dependent users more internalising and externalising disorders, coping motive, solitary use, XTC/cocaine use. No difference in cannabis exposure and setting, alcohol and tobacco use, childhood vulnerability.

Patients more cannabis use, dependence severity, internalising and externalising disorders, functional impairment, social pressure, history, attitude), less social support. No difference in cannabis use age of onset, alcohol problems, other substance use.

5 Persistence: 28%

5 Persistence of dependence is (independently) predicted by: lifetime nr CUD (role impairment, use despite problems), coping motive, lifetime anxiety, psychosis symptoms. Not by cannabis exposure and setting, childhood vulnerability, internalising and externalising disorders, life events, lack of social support, other substance use.

6 Barriers for frequent dependent users: absence of perceived treatment need, desire for self-reliance, preference for informal help, perceived ineffectiveness and avoiding stigma.

Facilitators for treatment seeking patients: self-reported functional impairment, mental health problems.

7-8 THC Self-reported cannabis exposure was unrelated to dependence status/onset/persistence, but rather imprecise. While experimentally assessed THC exposure was associated with dependence, previous dependency problems and inhalation behaviour were more important predictors. Cannabis users "titrate" their THC intake by inhaling lower volumes of smoke when smoking strong joints, but this does not fully compensate for the higher cannabis doses per joint when using strong cannabis.

Onset of dependence is (independently) predicted by: living alone, last year abuse, lifetime nr CUD (impaired control), daytime use, continual smoking, coping motive, childhood trauma, impulsivity, negative life events (financial problems), lack of social support. Not by cannabis exposure and setting, other childhood vulnerability, internalising and externalising disorders, other substance use.

Persistence of dependence is (independently) predicted by: lifetime nr CUD (role impairment, use despite problems), coping motive, lifetime anxiety, psychosis symptoms. Not by cannabis exposure and setting, childhood vulnerability, internalising and externalising disorders, life events, lack of social support, other substance use.

4 Onset of dependence is (independently) predicted by:

- living alone
- last year abuse
- lifetime nr CUD (impaired control)
- daytime use
- continual smoking
- coping motive
- childhood trauma
- impulsivity
- negative life events (financial problems)
- lack of social support

Not by cannabis exposure and setting, other childhood vulnerability, internalising and externalising disorders, other substance use.

5 Persistence of dependence is (independently) predicted by:

- lifetime nr CUD (role impairment, use despite problems)
- coping motive
- lifetime anxiety
- psychosis symptoms

Not by cannabis exposure and setting, childhood vulnerability, internalising and externalising disorders, life events, lack of social support, other substance use.

6 Barriers for frequent dependent users:

- absence of perceived treatment need
- desire for self-reliance
- preference for informal help
- perceived ineffectiveness
- avoiding stigma

Facilitators for treatment seeking patients:

- self-reported functional impairment
- mental health problems

7-8 THC Self-reported cannabis exposure was unrelated to dependence status/onset/persistence, but rather imprecise. While experimentally assessed THC exposure was associated with dependence, previous dependency problems and inhalation behaviour were more important predictors. Cannabis users "titrate" their THC intake by inhaling lower volumes of smoke when smoking strong joints, but this does not fully compensate for the higher cannabis doses per joint when using strong cannabis.

Figure 2 Overview of the study results. Numbers refer to the chapters of this thesis. Δ = cross-sectional comparisons, arrows = prospective comparisons. CUD: cannabis use disorder (i.e. abuse or dependence).
Aanleiding
Jongvolwassenen die vaak cannabis roken, hebben een verhoogd risico verslaafd te raken. Toch is lang niet iedere (bijna) dagelijkse gebruiker (chronisch) verslaafd. Een belangrijke vraag is daarom: “Waarom is/wordt/blieft de ene frequente gebruiker wel verslaafd en de andere niet?” Deze centrale vraag in het “CanDep” onderzoek is belangrijk voor gerichte preventie en behandeling. De antwoorden kunnen ook meer inzicht geven in de rol van de sterke Nederwiet in de sterk toegenomen vraag naar behandeling.

Studieopzet
Voor CanDep werden 600 jongvolwassenen (18-30 jaar) geworven die al zeker een jaar minstens drie keer per week blowden. Er werden twee groepen onderscheiden: diegenen die verslaafd (afhankelijk) waren aan cannabis (N=252) en diegenen die dat niet waren (N=348). Daarnaast werden nog twee andere groepen onderzocht: 1027 leeftijdgenoten uit de algemene bevolking die niet of weinig cannabis gebruikten en een groep van 70 mensen die hulp bij de verslavingszorg hadden gezocht wegens hun cannabisverslaving.

- De twee groepen frequente cannabisgebruikers werden onderling vergeleken op basis vanuitgebreide interviews over cannabisgebruik, kwetsbare jeugd, levensgebeurtenissen en psychische gezondheid. De bevindingen werden in perspectief geplaatst door deze groepen te vergelijken met de 1072 leeftijdgenoten uit de algemene bevolking en 70 hulpzoekers. De twee groepen frequent cannabisgebruikers zijn gedurende drie jaar gevolgd om het natuurlijk beloop in kaart te brengen. Ook werden factoren gezocht die (het voortbestaan van de) cannabisverslaving voorspellen.
- In een experiment werd het cannabisgebruik in detail bestudeerd. Hoe goed kunnen gebruikers inschatten hoeveel cannabis en THC ze in een joint stoppen? Passen gebruikers de dosis en wijze van inhaleren aan de sterkte van de cannabis aan?

Resultaten
- Op groepsniveau bleek het verloop van frequent cannabisgebruik en -verslaving dynamisch en relatief “gunstig” gedurende het drijarige onderzoek. Zowel de frequentie van het gebruik als het aantal joints per dag nam af, hoewel na drie jaar tweederde nog steeds stevig blowde. Bij “slechts” 37% van de niet-verslaafden ontstond een verslaving en bij “slechts” 28% van de verslaafden bleef de verslaving aanwezig op alle meetmomenten.
- We zagen geen duidelijk verband tussen de mate (frequentie, aantal joints, dosis, sterkte) van cannabisgebruik en verslaving. Huidige (psychische) problemen, coping motieven voor het gebruik van cannabis en eerdere cannabis verslavingssymptomen kwamen wel vaker voor bij mensen die verslaafd waren, werden, of bleven.
- Het bleek voor individuele gebruikers lastig de cannabisdosis en -sterkte in te schatten, maar het gemiddelde klopte aardig op groepsniveau.
- Vaak ging de verslaving voorbij zonder professionele hulp. Verslaafde gebruikers in de algemene bevolking vonden hulp vaak niet nodig en functioneerden beter en
hadden minder psychische problemen dan patiënten in verslavingszorg. Daarom lijkt professionele verslavingszorg lang niet altijd nodig voor cannabisgebruikers, ook al voldoen ze aan de criteria van verslaving.

**Conclusie**

In onze groep jongvolwassen frequente cannabisgebruikers bleek THC-blootstelling een veel minder belangrijke voorspeller voor het ontstaan en voortduren van een cannabisverslaving dan recente levensgebeurtenissen, de aanwezigheid van (psychische) problemen en eerdere verslavingssymptomen. Het is daarom niet aannemelijk dat cannabisverslaving en de vraag naar behandeling in belangrijke mate het gevolg is van de toename van de THC concentratie in Nederlandse cannabis en het is ook niet te verwachten dat een daling van de THC-concentratie in Nederlandse cannabis zal leiden tot een vermindering van de hulpvraag. Selectieve preventie lijkt een effectievere strategie om escalatie van problemen en chronische verslaving te voorkomen. Gezien het relatief gunstige natuurlijk (driejaars) beloop van een cannabisverslaving in de algemene bevolking, lijkt behandeling slechts nodig voor een deel van de cannabisverslaafden die op dit moment nog geen hulp zoeken. Dat laatste betekent ook dat de veelgenoemde “treatment gap” misschien wel wat overschat is.