The dynamics of cannabis use and dependence
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As cannabis is the most frequently used illicit substance worldwide, it is a much-discussed topic, especially in times of a growing addiction treatment demand and an increasing THC concentration of cannabis [2-7]. This thesis aimed to add nuance to ongoing public and politic debates by providing a better understanding of the dynamics of frequent cannabis use and dependence and of the facilitators and barriers of treatment seeking behaviour. It described results from the so-called “CanDep” study (chapter 2): a three-year prospective cohort of 600 young adult (18-30 years) frequent (≥3 days per week for 12 months) cannabis users in the Netherlands. With particular focus on mental health and details of cannabis use, the central question was “which frequent cannabis users are/become/stay dependent, and seek treatment, and which do not?”

The rationale behind our central question consists of four aspects. First, what we know about the differences between frequent cannabis users who are and are not dependent is quite limited and mostly based on studies either in the general population or in treatment seeking populations. Whereas general population studies often include only few frequent and dependent cannabis users (thus low power), studies in treatment seeking cannabis users typically include only severe cases of cannabis dependence (Berkson’s bias [8]). The current study attempted to fill the gap between these two types of studies with an investigation of a large sample of frequent cannabis users with and without a DSM-IV dependence diagnosis, recruited from the general population. These two groups were compared cross-sectionally with a general population sample of non-(frequent) users (chapter 3). In addition, the cannabis dependent subjects were compared with a group of treatment seeking cannabis dependent patients (chapter 6). Second, epidemiological prevalence estimates suggest that (frequent) cannabis use and dependence often discontinue eventually [9-11]. However, longitudinal data that is required to understand the course of frequent cannabis use and dependence is almost non-existent. We therefore followed the cohort of frequent cannabis users for three years. To offer information needed to develop targeted (indicated) cannabis dependence prevention strategies, we examined risk factors for the onset (chapter 4) and persistence (chapter 5) of cannabis dependence. Third, the difference between the estimated numbers of cannabis dependent users in the community and the number in addiction treatment is referred to as the “treatment gap”. To improve understanding of this gap, dependent cannabis users who did and did not seek treatment were compared (chapter 6). In addition, the current study can be important to improve treatment participation by identifying facilitators and barriers to seek treatment for
cannabis dependence (chapter 6). Fourth, the current study aimed to provide a better picture of the role of cannabis exposure in frequent cannabis users. Specifically, we investigated whether detailed assessment of (self-reported) cannabis use predicted the presence/onset/persistence of cannabis dependence (chapter 4 and chapter 5), and validated these self-reports with objective measurements (chapter 7). Moreover, we used smoking topography data to look at the relationship between THC concentration and smoking behaviour (i.e. “titration”) and as risk indicator of dependence (chapter 8). Finally, data are presented on the reliability and validity of a screening questionnaire for the detection of cannabis dependence in frequent cannabis users (chapter 9). This concluding chapter integrates our findings around these four topics, and discusses practical implications for prevention, treatment and policy.

FREQUENT VERSUS DEPENDENT CANNABIS USE Chapter 3

By differentiating frequent cannabis users with and without dependence, and comparing them with non-(frequent) users and patients in treatment, the association between cannabis use and mental health problems was examined.

Cannabis use

One of the most striking and unexpected results of this study was that, on average, cannabis use of dependent frequent users barely differed from non-dependent frequent users at baseline. Both groups had roughly used cannabis for seven years and one third used cannabis daily. On a typical cannabis using day, on average, both groups consumed three joints containing a third of a gram cannabis, and were “stoned” for about six hours. In both groups, most subjects preferred herbal cannabis and used at home. The only cannabis use characteristics that differed between the two groups were not related to cannabis exposure itself, but to the context in which cannabis was used; i.e. more frequent solitary use and coping motives for cannabis use (e.g. to forget one’s problems) in the dependent compared to the non-dependent group. These last variables could help identify frequent users with dependence for targeted prevention or treatment. It should be noted, however, that cross-sectional differences do not necessarily represent risk factors for future dependence and they do not necessarily play a causal role in the onset or persistence of dependence. It should also be noted that patients in treatment used twice as much cannabis as dependent cannabis users in the community (chapter 6). Thus, while cannabis exposure did not seem to differentiate between frequent cannabis users with and without dependence in the community, very intensive cannabis use as seen in the treatment sample (on average 177 joints per month) is a marker and possibly a risk factor for future problematic cannabis use or dependence.

Mental health

Similar to the differences in the level of cannabis use, we expected a gradient in the prevalence of mental disorders with increasing levels of psychiatric comorbidity, from the general population, through non-dependent frequent users and dependent
frequent users, to cannabis dependent patients in treatment. This pattern was confirmed for externalising disorders (attention-deficit/hyperactivity disorder (ADHD) and conduct disorder (CD)) but not for internalising disorders (mood and anxiety disorders) (chapter 6). Given their early age of onset, externalising disorders are more likely to be predictors rather than consequences of frequent cannabis use or dependence [12;13]. Hence, targeting prevention at young people with externalising disorders may help prevent cannabis dependence. This is highlighted by the prevalence of childhood externalising disorders, which was as high as 58% among dependent frequent cannabis users in the community (and 63% among those in treatment), compared to “only” 9% in the general population. In line with these results, a recent study suggests that particularly (early onset and persistent) conduct disorder predicts problem cannabis use [14]. In contrast, the presence of a gradient in the prevalence of internalising disorders was only partly confirmed. Regarding mood and anxiety disorders, non-dependent frequent users were in fact mostly comparable with the general population, whereas the prevalence in dependent users in the community was roughly twice as high, and again twice more in treatment settings.

Regarding internalising disorders, we found that the mental health of non-dependent frequent users was rather similar to non-users in the general population and better than in dependent frequent users. This is an important nuance of findings from general population studies [15-17]. As these studies had usually limited numbers of frequent cannabis users, dependent and non-dependent frequent use could not be differentiated. Thus, frequent non-dependent cannabis users had been largely ignored as mental health problems were linked to either cannabis dependence or frequent cannabis use (including dependent users). Our findings suggest that based on findings from studies of all frequent users, including dependent use, the mental health problems of frequent non-dependent cannabis users may be overestimated. General population studies linked other illicit drug use or childhood vulnerability with both mental health problems and cannabis dependence [18;19] (the association with frequent non-dependent use has not been examined). It could therefore be suggested that the observed difference in mental health between dependent and non-dependent frequent users is explained by these confounding risk indicators. However, we observed that other illicit substance use and childhood vulnerability were equally elevated in both dependent and non-dependent frequent cannabis users compared with the general population. This suggests that these factors are associated with frequent cannabis use in general rather than just dependence. As a result, these factors do not offer an explanation for the mental health differences between dependent and non-dependent frequent cannabis users. Moreover, as we also observed that the level of cannabis use was also comparable for frequent users with and without dependence, mental disorders seem mostly associated with dependence and not with frequent cannabis use per se. This also suggests that for the differentiation between frequent users with and without dependence, the presence of comorbid disorders seem to play a more prominent role than the level of cannabis use. Correspondingly, treatment seeking
cannabis dependent patients reported more comorbidity compared to non-treatment seeking dependent frequent cannabis users (chapter 6). This further emphasises the importance of comorbidity, which was also recently highlighted in a study that compared treatment seeking patients with different primary substances of abuse: co-occurring disorders were more important than the substance of abuse for the overall severity [20]. Nonetheless, it cannot be precluded that very high levels of cannabis use have a role in the development of cannabis dependence, as the treatment seeking cannabis dependent patients also reported twice the amount of cannabis use (joints per month) compared to non-treatment seeking dependent frequent cannabis users (chapter 6). Although these cross-sectional designs do not provide decisive evidence about the specific roles of cannabis use and mental disorders in the development of cannabis dependence, our findings emphasise that when community prevalence estimates are coloured with the brush of clinical samples, this would overestimate problems related to dependence by roughly twofold.

DYNAMICS OF CANNABIS USE AND DEPENDENCE  Chapter 4&5

The longitudinal design of CanDep enabled us to study the dynamic course of frequent cannabis use, the onset and persistence of dependence, and predictors of an unfavourable course.

Course of cannabis use

There was a general decline in the frequency and quantity of cannabis use over the three years of follow-up in both dependent and non-dependent frequent cannabis users (intermezzo). This suggests that young adult frequent cannabis users (with and without dependence) generally reduce their cannabis consumption over time. This finding partly corroborates population studies showing that desistence of cannabis use in peoples’ twenties is normative [9] and might be linked to family and educational role transitions [21], a process often referred to as “maturing out” [22-29]. Yet, after three years, only 12% of the participants were abstinent and 66% were still a frequent user. Thus, while cannabis use overall decreased, abstinence was rare after three years. Yet desistance could still occur later on, given the relatively young baseline mean age of 22 in our cohort.

Onset of cannabis dependence

The incidence of cannabis dependence in our sample of frequent cannabis users was rather low (37%), meaning that 63% of the baseline never-dependent frequent cannabis users remained non-dependent during three years follow-up. Although most young adult frequent cannabis users who are not dependent will not develop dependence within a three-year period, a substantial minority will. To reach the minority of frequent users likely to develop dependence, thus those who would benefit most from preventive interventions, it is not sufficient to focus on high frequency of use alone. Identification of more specific risk indicators is needed to target prevention to those at substantial risk, as proposed in Chapter 1. The next paragraph therefore discusses predictors of the onset of dependence.
The transition from non-dependent frequent cannabis use to dependence was independently predicted by baseline factors describing the current (living) situation: living alone, using cannabis to cope with problems, and the number and type of negative life events in the past year (especially financial problems). Baseline lifetime cannabis use disorder (CUD) symptoms were also important: both the number of symptoms and the “impaired control over use” symptom were predictors of dependence onset. These predictors contributed independently to the probability of the onset of dependence after adjusting for the effect of other covariates. As usual when examined individually, the list of bivariate predictors was longer; also including a diagnosis of cannabis abuse at baseline, daytime cannabis use, rarely pause while smoking a joint, childhood abuse and impulsivity. These predictors, relating both to context of cannabis use and “stable vulnerability”, may mediate the effect of the independent “current” situation predictors [30], or reflect strong underlying associations. Nonetheless, they could still help identify users at increased transition risk from frequent cannabis use to dependence.

In our study among frequent cannabis users we found a different set of risk factors for the development of cannabis dependence than the ones identified in traditional general population studies [e.g. 9;31]. Most of the traditional risk factors had no predictive value in our sample of frequent cannabis users (e.g. socio-demographics, other substance use, mental disorders) suggesting that predictors established in general population studies seem to predict progression from incidental to frequent cannabis use rather than the onset of cannabis dependence. Instead, the current study showed a number of new predictors for the transition from frequent non-dependent to frequent dependent cannabis use (e.g. coping motives, negative life events, and number and type [impaired control over use] of CUD symptoms). However, the total amount of explained variance using McFadden’s pseudo $R^2$ was quite modest (although the c-index produced a more favourable estimate, see footnote 1). This means that these factors contributed only very little to the prediction of the onset of dependence, suggesting that other factors (e.g. genetic vulnerability, endophenotypic characteristics, and time dependent variables) are also of great importance. One needs to realise that this model had to predict a complex multi-factorial disorder over a considerable period of time and only included baseline variables, some of which may have changed over time (see future research). In addition, as we investigated the first onset of dependence, we excluded baseline lifetime dependent cannabis users. Thus, it should be considered that youngsters who developed cannabis dependence before baseline assessment (i.e. before the age 18) may have a different risk profile.

1 Predictive power of a model can also be quantified with the c-index: a measure of concordance between the predicted and the observed outcome. The c-index equals the models’ area under the receiver operating characteristic curve [65]. For our final multivariable prediction model of the onset of dependence among frequent non-dependent cannabis users, the c-index was 0.81 (0.77 in Model 2 excluding baseline CUD variables as predictors). As values of 0.50 represent prediction no better than chance and values of 1.0 represent perfect prediction, 0.81 is considerable. In a similar recent study predicting CUD among lifetime cannabis users it was even concluded that the model, with a c-index of 0.84, had good predictive power [30].
Persistence of cannabis dependence

Only 28% of the dependent frequent cannabis users at baseline also met criteria for dependence at both follow-ups, whereas 41% was non-dependent at both follow-ups (early stable remitters). Notably, addiction treatment was uncommon: even of the “persisters” only 15% sought treatment during follow-up. Thus, the course of dependence in this community sample was characterised by a high rate of spontaneous remission (although 13.5% relapsed), rather than the chronic, progressive course that is seen so often in clinical samples [i.e. 32]. A persistent course of dependence was associated with more functional impairments and cannabis consumption. Nevertheless, most remitted persons also continued their (heavy) cannabis use and a third still had cannabis related problems and relapse could still occur later on.

Given the high rates of spontaneous remission, and significant worse outcomes related with persistent dependence, treatment may be more efficiently targeted at dependent users at risk for a persistent course. This highlights the need to identify more specific risk indicators other than fulfilling criteria for cannabis dependence. Again, the lifetime number of CUD symptoms at baseline independently predicted persistence of dependence. However, in contrast with the onset of dependence in which impaired control over use was the most important symptom, problems related to the use of cannabis (role impairment, use despite problems) were the most important predictive symptoms for the prediction of persistence of dependence. This suggests that different CUD symptoms predict different transitions in the onset and course of cannabis use disorders, with loss of control being more prominent in the early phase of developing dependence, and functional impairments more in the persistence of dependence. This is consistent with the (even) more severe impairments seen in patients seeking treatment, which was an important self-reported reason to seek treatment.

Other variables that predicted cannabis dependence persistence but did not survive multivariate analyses with lifetime CUD symptoms in the model included coping motives to use cannabis, lifetime anxiety disorders and lifetime psychosis symptoms. Of these, coping motive to use cannabis also differentiated dependent from non-dependent frequent cannabis users cross-sectionally and predicted the onset of dependence. Given the lack of knowledge about cannabis dependence persistency, these factors may still be useful as a marker to identify individual dependent users at risk for a persistent course.

Internalising disorders

It seems contradictory that the prevalence of internalising disorders was the most important cross-sectional difference between dependent and non-dependent frequent cannabis users, but that lifetime presence of these disorders predicted neither the onset nor the persistence of dependence, except the bivariate prediction of persistence by lifetime anxiety disorder. There are generally three explanations for cross-sectional associations. First, there is no direct relationship between the two, and the observed association is explained by shared risk factors that increase the risk of both disorders. Although it can never be precluded that other unmeasured factors explain the
observed association (residual confounding), the cross-sectional associations between internalising disorders and dependence were robust for statistical adjustment for several important factors: socio-demographics, childhood adversity factors, other substance use, and cannabis use factors (chapter 3). The other two explanations suggest causality. Internalising disorders may be a contributory cause of cannabis dependence: e.g. self-medication to improve mood or reduce anxiety. Conversely, cannabis dependence may be a contributory cause of internalising disorders: e.g. cannabis dependence precipitates internalising disorders. An important component of causality is temporality, which is why we followed-up the cohort for three years. We did not find support for mood disorders preceding the onset or persistence of cannabis dependence, like other studies among less frequent users [33;34]. However, the finding that lifetime anxiety disorder (bivariately) predicted a persistent course may indicate that cannabis self-medication of an anxiety disorder can maintain cannabis dependence. The opposite causal direction was outside the scope of this thesis, but CanDep has data to study this in the future. Already, a recent prospective study found no evidence of cannabis dependence predicting mood disorders, and some evidence for anxiety disorders, despite cross-sectional associations [35]. Taken together, current evidence is not decisive about the nature or the direction of the association between cannabis dependence and internalising disorders [36], yet associations seem stronger for anxiety than for mood disorders.

TREATMENT

As mentioned before, only a minority of dependent cannabis users seek treatment (chapter 5), and patients in treatment for cannabis dependence reported approximately twice as much cannabis use, comorbid mental disorders and functional impairments compared to non-treatment seeking dependent frequent cannabis users in the community. They also had more CUD symptoms, perceived a greater lack of social support and more pressure to seek treatment, had more previous treatments, and a more positive attitude to treatment. Importantly, the strongest reason to seek treatment reported by patients was self-reported functional impairment, especially related to mental health problems associated with cannabis use.

In addition to these facilitators for treatment seeking, we also investigated barriers to identify potential cues to increase participation in targeted prevention and treatment. We asked the non-treatment seeking dependent cannabis users in the community sample whether they would seek treatment “if they would need it”. One-third (34%) said they would (probably) seek treatment when needed. This suggests that they experienced their “objective” treatment need (i.e. cannabis dependence) as non-problematic or not sufficiently problematic to require treatment. However, the majority (66%) thought they would not seek addiction treatment for cannabis problems. The main reasons for not seeking treatment in these subjects were the absence of a perceived need for treatment, the desire for self-reliance, and the preference for informal help. In total, 12% thought they needed treatment, but did not
seek it. For them, the perceived ineffectiveness of currently available treatments and avoiding stigma were important barriers.

**THC**

Self-reported cannabis exposure (frequency of cannabis use, joints per day, dose per joint) varied widely between users, but it was unrelated to the baseline status of dependence (chapter 3), the onset of cannabis dependence among frequent users, and the persistence of dependence (chapter 4 and chapter 5). These results were found despite our efforts to obtain more accurate estimates of cannabis and THC exposure than most other studies: we included self-report measures of cannabis dose and potency in addition to the number of days using cannabis and joints per day. However, this does not necessarily mean that the level of cannabis exposure played no role at all.

First, self-reported measures of dose were, unfortunately, rather imprecise. We were the first to investigate the reliability and validity of several self-reported measures of both dose and potency in an ecological study. Participants used their own cannabis to prepare a joint in their habitual manner, and the dose and potency were determined objectively. We found that the prompt card self-report method to assess amount of cannabis put in a joint seriously underestimated the actual cannabis dose. Moreover, underestimation was larger among dependent than non-dependent users, which would lead to biased results. Instead, the average dose per joint based on “number of joints made from one gram of cannabis” was an accurate estimate of the average dose per joint at a group level (no indication of differential accuracy for subjects with and without cannabis dependence), and was therefore applied in the analyses included in this thesis. THC concentration in cannabis correlated with subjective (self-reported) potency and with cannabis price, but in contrast with previous studies [37] not with the subjective level of intoxication. Therefore, while we added detail to our assessment of cannabis exposure, the imprecision of these measures may have weakened or obscured small differences in self-reported exposure between groups.

Second, and more important, data from the naturalistic cannabis exposure experiment showed that the estimated monthly THC dose was cross-sectionally associated with cannabis dependence severity, and predicted dependence severity at follow-up. This experimental assessment provides a refined approximation of the number of grams of THC that users monthly put in their joints. However, it only considers the “external” exposure, whereas the distribution of THC into the body (i.e. “internal” THC dose) may also depend on inhalation behaviour. Indeed, the experiment showed that cannabis users “titrate” by inhaling lower volumes when smoking strong joints, but this did not fully compensate for the higher cannabis doses per joint when using strong cannabis. Thus while “external” THC exposure differences may be more prominent than “internal” THC exposure differences, users of more (potent) cannabis are generally exposed to more THC. One may argue that these results with more precise experimental measurements contradict our findings based on self-reports. However, monthly THC exposure did not add to the prediction of future cannabis
dependence severity over and above (i.e. adjusted for) baseline cannabis dependence severity, thus matching well with the observed limited role of self-reported cannabis exposure in the prediction of incidence and persistence of cannabis dependence in the full CanDep cohort (chapter 4 and chapter 5). Moreover, smoking behaviour did predict cannabis dependence severity independent of monthly THC dose. Yet, given the limited role of “external” THC exposure, this is unlikely caused by the effect of inhalation on “internal” THC exposure but rather marks compulsive use.

Finally, in recent years cannabidiol (CBD), the other most abundant cannabinoid in cannabis, has gained scientific attention for its psychotropic effects that oppose (at least some of) the THC effects [26]. The type of cannabis that is used was thought to be important because, unlike cannabis resin, the more popular Dutch herbal cannabis contains nearly no CBD. However, we did not find the type of cannabis to be statistically significantly different in young adult frequent cannabis users with and without dependence, and it was no predictor for the onset or persistent course of cannabis dependence. Still, there was a consistent small (non-statistically significant) difference: baseline dependent, as well as the incident dependent, and the persistently dependent groups more often reported a preference for herbal cannabis over resin. Thus overall, a role for cannabis type (or cannabidiol content) is plausible; yet again this is unlikely to be a dominant factor.

METHODOLOGICAL CONSIDERATIONS

CanDep is the first study in its kind worldwide: a large longitudinal cohort of dependent and non-dependent frequent cannabis users from the community. Although it is not a probability sample from the general population, we used a probability general population sample as a reference. The number of frequent and dependent cannabis users that we included in the CanDep study are comparable to the number in large-scale US general population studies (e.g. NESARC: 133/43,093 participants were cannabis users with 12-month cannabis dependence [38]), but with much more detailed assessment of cannabis use characteristics. Another important merit of the CanDep study is its three-year follow-up, with quite impressive retention rate (overall 78%). For young adults, three years is a considerable time with many social, educational, and professional developments. As more than half of cannabis abusers develop dependence within two years [39], three years seems sufficient to examine transitions from frequent cannabis use to dependence in relation with cannabis use and mental health, and to shed light on the course of frequent cannabis use and dependence. Nonetheless, given the relatively young age of our cohort, the majority (94%) had not yet finished their twenties within the three-year follow-up. A longer follow-up period would further improve our understanding of the course of frequent cannabis use and dependence, and the process of “maturing out” (desistence) in peoples’ late twenties or early thirties.

The Dutch tolerant cannabis legislation and policy created a unique setting for recruitment of participants from coffee shops and for the naturalistic experiments. Recruitment through coffee shops and chain referral was deemed the only possible
way to recruit a large enough sample of non-dependent and dependent frequent cannabis users not in treatment. As a first limitation, however, it is difficult to assay the representativeness of the population recruited through this method, as there is no data available of representative samples of frequent cannabis users. At least, socio-demographic characteristics were comparable to a group of last-month cannabis users recruited through street surveys for a recent Dutch evaluation study [40]. The possible lack of representativeness of the study population is especially important when it comes to the cross-sectional comparisons and to the point estimates with respect to the course of frequent use and dependence. The potential effect of sample characteristics on longitudinal relationships (predictors) is generally thought to be smaller. Although external validity should be considered when interpreting the findings from this specific sample, our field experiences during data collection strengthen our notion that we included a reasonable reflection of frequent young adult cannabis users in the community, i.e. most participants were socially integrated and lived rather conventional lives. However, few marginalised users were also included in this study. Although in our opinion these are exceptions rather than typical frequent cannabis users, probabilistic general population studies relying on postal registers would most likely not reach them at all. The narratives from the qualitative study with a subset of the CanDep respondents also describe rather conventional young adult lives regarding work, school and leisure. Cannabis use was usually restricted to leisure time, at the end of the day after finishing daily tasks [41].

A second limitation of the current study related to our methods is that the elaborate interview detailing mental health and cannabis use may have influenced participants’ cannabis use. Yet, after three years, only 5% reported that participating in the study had changed their cannabis use, suggesting the impact on our results was minimal (though it would be great if it were that simple to change peoples’ behaviour).

Third, the choice for a dichotomous cannabis dependence diagnosis imposes restrictions. It is important for the comparability between studies to use structured interviews, which is why most studies use instruments like the Composite International Diagnostic Interview (CIDI). However, it is inevitable to lose detail when using categorical measures. Specifically, one symptom more or less can make the difference between fulfilling a dependence diagnosis or not. This may oversimplify the complicated and gradual process of the onset, course and remission of cannabis dependence, and largely ignores increases or decreases in the severity of dependence. In this respect, the revised DSM-5 seems an improvement as it distinguishes mild, moderate, and severe dependence. In the current study, part of the participants with a dynamic course of temporary dependence (13% of the non-dependent cohort), and remission and relapse (13% of the dependent cohort) may have gained or lost just one symptom. Moreover, some of the transitions may be due to measurement error, as our latent Markov model estimated a considerable false negative rate (chapter 4). Labelling true dependent cases as non-dependent may have diluted cross-sectional differences and underestimated the onset and persistence of dependence. Nonetheless, the predictors of the onset and course of dependence seem rather unaffected by such measurement
issues. That is illustrated by results of the sensitivity analyses of chapter 5 using extreme groups (comparing persistent dependence DDD with stable non-persisters DNN) and in chapter 8 using both dimensional and dichotomous dependence measures did not change our inferences. Finally, the low validity of the Severity of Dependence Scale to detect dependence also underlines difficulties in the assessment of cannabis use problems among frequent users (chapter 9). Possibly, the Cannabis Abuse Screening Test (CAST) will outperform the SDS, as it includes questions about solitary and daytime cannabis use, which differentiated dependent from non-dependent frequent users (chapter 3) and predicted the onset of dependence (chapter 4), respectively.

**CLINICAL IMPLICATIONS**

**Prevention and treatment priorities**

An old saying goes “prevention is better than cure”. However, should prevention targeted at frequent cannabis users be a public health priority? If so, how should targeted prevention be approached? Another question is whether all dependent cannabis users in the community should be convinced to seek treatment in order to prevent escalation of problems and to prevent chronic dependence? In other words, is there a need to fill the so called “treatment gap”? In order to answer these important questions we look at some of the main findings of the current study.

To begin with, the majority of frequent (non-dependent) users did not become dependent within the three-year follow-up period and their mental health situation was generally comparable to the general population (except childhood-onset externalising disorders). At the same time, however, 37% of young adult frequent users fulfilled a diagnosis of dependence at some point during follow-up, and cannabis dependence was associated with comorbid mental disorders. This suggests that indeed a minority of frequent cannabis users would benefit from interventions. Preferably, such interventions target those at elevated risk of dependence, rather than frequent cannabis users in general. For example, prevention of cannabis dependence should be targeted on frequent cannabis users with additional risk factors for the development of dependence, i.e. those who live alone, have coping motives for their cannabis use, experience negative life events, and have certain cannabis use disorder symptoms such as impaired control over use. For intervention at an earlier stage, i.e. before the onset of frequent use, our results in chapter 3 corroborate the findings of previous studies showing that externalising disorders (CD and ADHD) are serious risk indicators for frequent cannabis use and dependence [12;13].

While the “treatment gap” is an important argument to improve treatment participation of cannabis dependent users, our results imply that the treatment gap is much smaller than some epidemiological data seem to suggest [42;43]. Most of those who were dependent at baseline went into remission within a few years without any addiction treatment. In addition, dependent cannabis users in the community (who did not seek treatment) performed much better in terms of their cannabis use, functioning and mental health than treatment seeking dependent subjects at addiction
treatment facilities. However, even among cannabis users who fulfilled a diagnosis of
dependence at all three assessments (persistently dependent users), only 15% sought
treatment. Treatment of dependence may be required only in those dependent users
at an increased risk for a persistent course. However, while this is minority of dependent
users, it was difficult to predict which dependent user awaits a persistent course. For
example, dependent users with many CUD symptoms, specifically role impairment and
cannabis use despite problems, were at greater risk of a persistent course. They are
more likely to benefit from treatment and thus need to be reached through targeted
treatment. In general, monitoring of non-treatment seeking cannabis users fulfilling
criteria for dependence (“watchful waiting”) may be more sensible than treatment.

Important barriers to seek treatment were the preference for self-reliance
and absence of treatment need. It thus seems important to know whether brief
interventions are appropriate for some dependent users in the community.
Specifically, interventions directed at a reduction of cannabis use and improvement
of cannabis-related problems, that have a low-threshold and are non-stigmatising
(e.g. e-health: [44;45] or telephone interventions [46]), may be suitable to prevent
escalation or to slowly engage dependent users in more demanding treatments. The
social network may be another important target, as the preference for informal help
was an important treatment barrier. In addition, they may facilitate treatment seeking
as patients perceived more social pressure to seek treatment, or could benefit from
support dealing with dependent users as patients reported less social support even
though they asked more support from friends/family. Proven effective examples are
the use of Community Reinforcement And Family Training (CRAFT [47]), Adolescent
Community Reinforcement Approach with Assertive Continuing Care (A-CRA/ACC
[48]), and Multidimensional Family Therapy (MDFT [49;50]). Cognitive Behaviour
Therapy (CBT) has also shown to effectively reduce cannabis involvement of adults
[51]. Patient-treatment matching may improve treatment success, as adolescents
showed differential treatment response to MDFT based on age and comorbidity
[52]. While until recently no medications for the treatment of cannabis dependence
proved to be effective, N-acetylcysteine (NAC) is a promising treatment shown to
be effective in cannabis-dependent adolescents [53;54]. Treatment effectiveness may
further increase by polypharmacy or combining pharmacotherapy with psychotherapy
and psychosocial support [55]. The barriers for dependent users with a subjective
treatment need (i.e. perceived treatment ineffectiveness, stigma) (chapter 6) suggest
that treatment participation may improve with a better communication about the nature
and success of these cannabis dependence treatments, and work on destigmatisation.

**THC exposure and cannabis dependence**

Despite wide variations between individual users, the level of cannabis exposure based
on self-reports did not differentiate frequent users with and without dependence, and
had little predictive value for the onset and course of dependence. This does not mean
that the level of cannabis exposure played no role at all. First, treatment seeking cannabis
dependent patients used twice more cannabis than non-treatment seeking dependent
users in the community, so there may be a limit or critical threshold where the level of cannabis exposure becomes an important element (chapter 6). Second, validity of self-reported cannabis dose and potency was modest at best, thus measurement error may have obscured associations (chapter 7). Third, the naturalistic experiment showed that the estimated monthly THC dose did predict cannabis dependence severity at follow-up, although users might partly “titrate” their THC intake with inhalation adaptations (chapter 8). Altogether we conclude that THC exposure may have a role as a predictor of cannabis dependence severity, yet other factors are likely to be much more prominent. These include negative life events, coping motives, certain abuse and dependence symptoms and smoking behaviour (topography). This suggests that the level at which cannabis use has harmful effects largely depends on the presence of other risk factors, especially current problems. 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. It should be repeated though, that the current study only included frequent adult experienced cannabis users and one should be careful to extrapolate the findings to younger or less frequent users.

FUTURE STUDIES
We here propose some ideas for future research. First, we showed that the course of frequent cannabis use and dependence is dynamic, and for the majority favourable with an overall decrease in cannabis use and the tendency towards non-dependence. However, desistance of use was uncommon within the three-year follow-up. Another (e.g. six-year) follow-up would enable further investigation of desistance of frequent cannabis use (“maturing out”) in peoples’ late twenties and early thirties. Second, as we have shown the necessity and difficulty of THC exposure measurement, more valid and reliable exposure measures need to be developed. Although there may be a limited role for THC exposure for frequent users, this may be different for younger or less frequent users. Third, future studies will apply the revised DSM-5 definition of cannabis use disorder with three severity levels: mild, moderate and severe. Particularly a focus on severe cases, with six or more out of eleven CUD symptoms may lead to the identification of cases with a more consistent course, as the number of CUD symptoms was an important predictor for the onset and persistence of dependence. Fourth, although we included a wide array of potential predictors, only few strong predictors were identified, especially for the persistence of dependence and the explained variance of this set of predictors was rather low. However, our predictors were all static and measured at baseline, whereas changes in risk factors may be more predictive than baseline values. Future studies should therefore include dynamic risk factors and use time dependent analyses or a life course approach instead of only static baseline predictors and regression models. This is supported by the qualitative study among a subsample of CanDep: according to the users themselves, changes in cannabis use such as (temporary) increases or decreases are associated with life events, leisure time activities, and social relationships [21;41]. The authors observed similar associations with transitions in cannabis dependence status.
In addition, prediction of (the course of) dependence may improve with consideration of risk factors from other domains, including genetic vulnerability, gene-environment interactions, gene expression, and endophenotypic characteristics [56-58]. For example, a study from the neurobiological field regarding endophenotypic predictors showed, analogous to our results, that primarily problem severity -not amount of cannabis use- was associated with activity in reward-related brain areas in response to visual cannabis cues among frequent users [59].

Fifth, patients in treatment reported functional impairment (especially associated with mental health problems) as strongest reason to seek treatment, whereas one of the main reasons not to seek treatment for cannabis dependent community subjects was the absence of treatment need. This suggests that, rather than fulfilment of the criteria for cannabis dependence, the decision whether or not to seek treatment is in fact a valid judgement of the objective need for treatment. To test this hypothesis, it is important to prospectively assess whether dependent users correctly self-select into treatment. Especially because Grella and Stein (2013) suggest that substance dependent users enrol themselves in treatment when impairment reaches a critical threshold [60], and less severe cannabis dependent users (with lower levels of impairment and less comorbidity) show high natural remission [61;62]. At the same time, it would be important to know whether short, low-threshold and non-stigmatising interventions are appropriate for some of the dependent people who do not seek treatment, to prevent escalation or to slowly engage them in more demanding treatments. For cannabis dependent users presenting for treatment, the high prevalence of comorbid mental disorders accentuate the importance of (the evidence base of) screening, diagnostics, and (concurrent) treatment of dual diagnoses [63;64].

Finally, our future CanDep endeavours will proceed with the examination of time dependent variables and the inverse longitudinal relation between frequent/dependent cannabis use and the onset or persistence of mental disorders. However, if anything, our results illustrate the complex multi-factorial nature of dependence.

IN CONCLUSION

- For young adult frequent cannabis users (with and without cannabis dependence) the three-year course of cannabis use and dependence was dynamic, yet for the majority “favourable”. Overall, cannabis use decreased; “only” 37% of frequent users developed dependence; and “only” 28% of dependent users remained dependent.

- Among frequent cannabis users fulfilling criteria for cannabis dependence, the actual need for treatment is often questionable, given high remission rates without treatment, absence of a perceived need for treatment, and better functioning, mental health and less cannabis use than patients in treatment.

- For the presence, onset and persistence of cannabis dependence, the role of THC exposure (frequency, quantity, potency) seemed small. Instead, current (mental health) problems and previous cannabis abuse/dependence symptoms were more important factors.
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