Clinical Treatment of Cannabis Use Disorders in Adolescents

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Executive Summary:

There is no unique treatment modality for the treatment of dependence on cannabis. For the most part, research outcomes studies have tested the same treatment methods that have been previously developed for other addictive drugs, including 12-step meetings, psychotherapy, cognitive-behavioral treatments, and motivational interviewing. Youth studies rightly favor approaches that include a strong family component. All appear to produce moderate short-term benefits and significant rates of relapse (best understood as part of the natural history of any addiction treatment). And, although a number of pharmaceuticals have been tested to reduce craving and/or relapse, none have been approved for use in cannabis dependence or withdrawal.

At this time in history, we have more research literature on reasonably effective psychosocial treatment interventions than organized treatment venues for adolescents in California. In the main, adolescents resist treatment for marijuana use, and often require persistent family, school, or judicial leverage. In California there are few organized treatment resources for adolescents in trouble with marijuana. Most often, school counselors, pediatricians, and child psychiatrists serve as consultants and *de facto* psychotherapists for youth in trouble. In parental defiance situations, families with means often resort to a forced passage through an extended wilderness program. These programs are generally in remote rural areas where youth can be sequestered from their usual peers for one or more months and can be socialized into principles of recovery using methods that often resemble a blend of *Outward Bound* and boot camp. Some families will have the means to continue their child's treatment in equally isolated therapeutic boarding schools; others will return to the home environment where there are scant organized treatment or group support resources.

It is our thesis that the greatest risks of young-onset marijuana use are to education and learning, because school years are particularly vulnerable to many kinds of psychosocial disruptions. A minority of regular (10-19 days/mo.) and heavy ($\geq$20 days/mo.) users will transition to meeting criteria for dependence for some period of time.

This briefing summarizes the options and challenges for this cohort of the most severely affected.

Criteria for a Cannabis Use Disorder:

Marijuana use, even heavy use, is not the same as a clinical diagnosis of a Cannabis Use Disorder (CUD). For most youthful users marijuana dependence will be a self-limiting process [1]. And, unfortunately there is only a small literature, described below, studying the transition from regular recreational use to dependent use. Neither the amounts, nor the frequency, of cannabinoid consumption are presumptive evidence for a DSM-V Cannabis Use Disorder. DSM-V Clinical criteria emphasize consequences.

Although heavy users of marijuana are at a higher risk for developing a CUD, especially if they initiate use in early teen years, the majority do not go on to a lifelong course of dependence (addiction). Most teens who are regular and heavy users of marijuana will transition out to low or no regular use in their 20's and 30's. European data from EMCDDA (*European Monitoring Centre for Drugs and Drug Addiction*) has found that 20-50% of near-daily users will transition to meeting dependence criteria [2]. Data from the Christchurch cohort in New Zealand find that the majority of heavy users transition out by their late 20's and early 30's (please refer to Epidemiology briefing for more details).

DSM-V Criteria for a Substance Use Disorder
The *Diagnostic and Statistical Manual 5* defines a *substance use disorder* as the presence of at least 2 of 11 criteria, which are clustered in four groups:

Impaired Control:	**Risky Use:**
1. Taking more or for longer than intended, 2. Unsuccessful efforts to stop or cut down use, 3. Spending a great deal of time obtaining, using, or recovering from use, 4. Craving for substance.	1. Recurrent use in hazardous situations, 2. Continued use despite physical or psychological problems that are caused or exacerbated by substance use.
Social Impairment:	**Pharmacologic Dependence:**
1. Failure to fulfill major obligations due to use, 2. Continued use despite problems caused or exacerbated by use, 3. Important activities given up or reduced because of substance use.	1. Tolerance to effects of the substance, 2. Withdrawal symptoms when not using or using less.

DSM-V altered the framework for diagnosis. The DSM-IV distinction between abuse and dependence was dropped in favor of diagnosing Cannabis Use Disorder on a continuum of severity from no diagnosis (0-1 diagnostic criteria) to mild (2-3 criteria), moderate (4-5 criteria) and severe (6 or more criteria) [3]. This change unfortunately uses the same term (disorder) for lightweight as well as heavyweight problems. In addition, DSM-IV criteria were changed slightly, dropping "recurrent legal problems" and adding "craving." These changes lead to some difficulty comparing recent research with earlier work. Furthermore, many older studies have categorized subjects in terms of frequency of use (generally defining 20 days of use per month as heavy use), leading to additional difficulty comparing results. We believe that days of use in the prior month remains a valuable metric that is not captured in DSM-V.

Among the most common symptoms seen in the first 21 days of cannabis withdrawal are anger, irritability, anxiety, restlessness, decreased appetite, sleep difficulties, dream rebound, diverse physical complaints, and depressed mood [4, 5]. And it is well-established that daily users will

continue to excrete metabolites and test positive for cannabis for a month or more after cessation, although the clinical significance of this has not been established.

Screening Instruments:

Screening instruments are not necessarily diagnostic tools, but such brief instruments do help to determine which marijuana users might benefit from more thorough diagnostic assessments. In general, screening tools are better at scoring frequency of use than consequences of chronic use.

Piontek and colleagues have reviewed psychometric properties of several commonly used screening instruments [6-9]. The SDS (*Severity of Dependence Scale*) is a general scale for diverse drugs and there are conflicting opinions about its utility for adolescents [10, 11]. The CUDIT-R (*Cannabis Use Disorders Identification Test-Revised*) [12] has been tested in general populations and specific user samples. Although not a diagnostic instrument *per se*, the CUDIT-R 8-item screening tool distinguishes between different levels of cannabis use and rates problem severity, and this may facilitate matching of patients to treatment intensity. The CAST (*Cannabis Abuse Screening Test*) [7] has been tested in French adolescents. The CUPIT (*Cannabis Use Problems Identification Test*) [13] was developed in Australia with adolescents and adults.

At the present time, we have insufficient experience with these screening tools to recommend one over another.

Epidemiology of Cannabis Use Disorders & Treatment Needs:

National Data: The 2013 National Survey of Drug Use and Health by SAMHSA [14] reported that 1.76 million (7.1%) of 12-17 year olds used marijuana during the past month. In 2013, among all youths aged 12 to 17, an estimated 4.8% had used marijuana for the first time within the past year. An estimated 1.4 million first-time past year marijuana users initiated prior to the age of 18.

California Data: The table on the following page combines California Healthy Kids Survey (CHKS) data from 2011-13 with the Department of Education's estimates of projected enrollment for 2015-16. The most significant survey finding is that in 2015-16, before any legalization initiative, 6.1% of 11th graders are already heavy users, using marijuana 20 or more days each month, and another 2.9% are regular users, using 10-19 days each month. (Please refer to our epidemiology briefing for more details about adolescent youth patterns in California.) We believe that risks to educational progress are much greater than risks for persistent addiction or brain damage. Marijuana use is one of many factors that are clearly associated with decrements in school performance. At present it is not possible to tease out relative causality among other associated factors such as alcohol and drug use, family and peer-group effects, and culture.

California offers remarkably few public resources for treatment of *bona fide* severe cannabis use disorder (addiction/dependence). There are few treatment facilities that specialize in adolescent treatment of substance abuse. One example is *Thunder Road Adolescent Treatment Center* in Oakland [1], but most such programs are unstably funded by combinations of grants, insurance, and private pay. For-profit residential substance abuse facilities developed for adults, and often structured with spa-like amenities, sometimes offer residential tracks for adolescents. Such 28-day or longer programs typically do not satisfy cost-effectiveness criteria. Their costs can be

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[1] http://www.altabatessummit.org/thunderroad/

astonishingly high, and their longer term outcomes are touted but poorly documented. The truth about the natural history of the treatment of any addiction, including teenage cannabis dependence, is that relapse is a predictable, expectable part of the course. "I can have just one" is the most frequent pathway to a slip. What is needed to maintain abstinence and promote recovery, and what is mostly missing, is group support systems in the home community.

Estimated Marijuana Use in California High Schools 2015-16:

California High School Marijuana Use	Grade 9	Grade 10	Grade 11	Grade 12	Graduates	Total Gr. 9-12
Estimated Enrollment 2015-16	**496,021**	**489,532**	**470,944**	**489,939**	**416,058**	**1,946,436**
						1,325 Schools
Marijuana Use per Month	**CHKS**	**Estimate**	**CHKS**	**Estimate**		
Percent Zero Days	85.2%		78.0%			
Percent 1-2 Days	5.6%	7.0%	8.0%	8.0%		
Number 1-2 Days	27,777	34,267	37,676	39,195		138,915
Percent 3-9 Days	3.5%	4.2%	5.0%	5.0%		
Number 3-9 Days	17,361	20,560	23,547	24,497		85,965
Regular Percent 10-19 Days	1.9%	2.4%	2.9%	3.0%		
Number 10-19 Days	9,424	11,749	13,657	14,698		**49,529**
Heavy Percent 20 or more Days	3.8%	5.0%	6.1%	6.1%		
Number 20 or more Days	18,849	24,477	28,728	29,886		**101,939**
			H.S. Students using	**>1 days/month**		376,348
			H.S. Students using	**>3 days/month**		237,433
			H.S. Students using	**>10 days/month**		**151,468**
			H.S. Students using	**>20 days/month**		**101,939**

Families with means may initially rely on a month or more in a wilderness program, most of which are in remote rural settings (to interfere with running away). Such programs offer extended forced separations from family and peers and emphasize self-reliance activities such as camping to foster greater sense of responsibility and altruistic activities such as peer collaboration. They are something of a blend of *Outward Bound*, ropes courses, and boot camp—all in the service of socialization into a working concept of recovery and abstinence. This is, of course, only an initiation of treatment.

Free self-help and group support services in the community such *Ala-Teen*[2] emphasize alcohol problems; and, adult self-help programs are typically uncomfortable settings for youth. AlaTeen is for children of alcoholics to deal with the impact of parental addiction. However, in some locales there are YPAA groups (*Young People in AA*). They have names like MCYPAA (Marin Co. YPAA), SACYPAA (Sacramento YPAA). The South Los Angeles group (SLACYPAA) often refers to "alcohol and other forms of alcohol" in order to include drugs.

Sustained treatment support remains difficult to find, in part, because so little is offered within the school system. Once again, there is a huge disparity between resources available for families with

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[2] http://www.al-anon.org/for-alateen

means and those without. Those with insurance may turn to pediatricians or child psychiatrists who typically only offer individual counseling, often with no expertise in addiction.

Juvenile Justice in California: The juvenile justice system remains a major provider of services for youth without means, but outcomes data are hard to find. The California Division of Juvenile Justice (DJJ), previously known as the California Youth Authority (CYA), is a division of the California Department of Corrections and Rehabilitation (CDCR) that provides education, training, and treatment services for California's most serious youth offenders. The DJJ maintains 11 correctional facilities, 4 conservation camps and 2 residential drug treatment programs. Following severe criticisms of youth prison conditions and a court order, the legislature mandated a major reorganization.

Having said that, most substance abuse services are actually offered as part of a community-based probation system—but we have not been able to find data on methods and outcomes. We do know that in California most juvenile marijuana arrests are plea-bargained and are more likely to lead to probation than incarceration. As noted in the *Mitigation of Legal Harms* briefing, it is not clear why some youth continue to be charged with misdemeanors while others are charged with infraction fines (possession of less than one ounce of marijuana became an infraction offense in 2011).

And, at this writing, we have insufficient knowledge to meaningfully comment on what constitutes "treatment" in this adjudicated system.
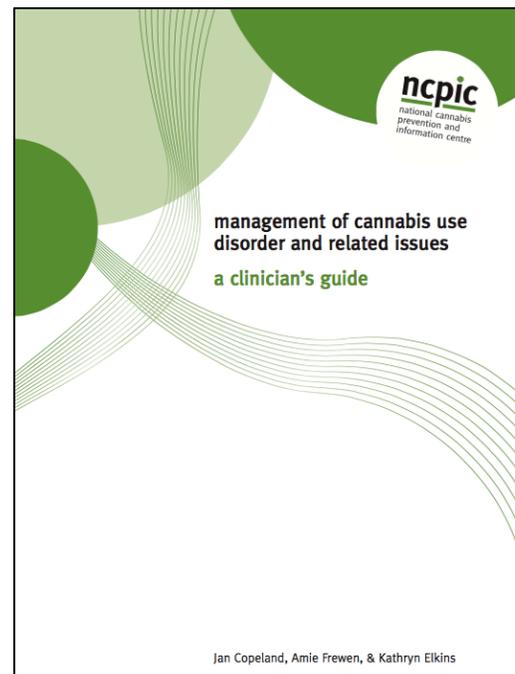
Insurance Coverage in California: In December 2014, the *California Society of Addiction Medicine* (CSAM) published a consumer guide and scorecard for substance abuse coverage in California under the Affordable Care Act bronze plans in *Covered California* [3]. This scorecard did not specifically analyze resources available for youth substance abuse treatment.

Significant CUD Treatment Studies:

There are several comprehensive reviews of treatment for Cannabis Use Disorders [15-19]. These summarize the still-limited research on a variety of methods. Of particular note are materials from Australia's *National Cannabis Prevention and Information Centre* (NCPIC)[4], a scientifically sound and balanced resource. Analogous in the U.S. are NIH's NIDA website[5] and the SAMHSA website[6].

In our opinion, the single best present-day guide to clinical treatment is the 115 page guide developed for NCPIC by Copeland, Frewen, and Elkins [15].

Several well-controlled studies are highlighted below to further inform the nature of the transitions from heavy use to dependence, a little-studied, but important topic, to better understand the frequency and risk factors for

[3] http://www.csam-asam.org/sites/default/files/pdf/csam_guide-scorecard-dec2014.pdf
[4] NCPIC: https://ncpic.org.au/
[5] NIDA: http://www.nih.gov/news/health/jun2014/nida-04.htm)
[6] SAMHSA: (http://www.samhsa.gov/atod/cannabis)

relapse from abstinence, and to emphasize the need for treatment methods that engage the family.

Transition from use to dependence: *National Household Survey 2001*: Chen et al. (2005) [20] analyzed adult and adolescent data from the 2000-2001 National Household Survey to better characterize the risks of cannabis dependence. They looked at 3,352 respondents who initiated cannabis use in the prior 2 years. Approximately 3.9% of recent-onset users developed dependence within 24 months. Risks were increased for onset before late-adolescence, for low income, and for poly-drug use prior to cannabis initiation.

Netherlands 2013: In van der Pol et al.'s large Dutch transition study of six hundred 18-30 year old *regular* users, 36.7% of them transitioned over three years to meeting diagnostic criteria for DSM-IV dependence on cannabis [21, 22]. The study evaluated vulnerability factors previously identified in general studies of illicit drug use and stress factors thought to be associated with dependence. Remarkably, cannabis exposure variables were not predictive of the transition from non-dependent to dependent cannabis use. They also unexpectedly found that none of the sociodemographic variables predicted cannabis dependence, except living alone. The baseline cannabis use variables that did predict cannabis dependence included a diagnosis of 12-month abuse, number of lifetime CUD symptoms, continual smoking and using in daytime, and coping motives for use. Lifetime and current mental disorders were frequent in both family members and participants but these disorders were not predictive. Smoking marijuana as a coping strategy emerged as a major predictive factor.

> This implies that in a young adult population, acute stressful events are stronger predictors of dependence than the presence of relatively stable vulnerability factors. A major financial problem was the strongest predictor among all negative life events. Also, living alone was a strong predictor....[22]

Transition back from abstinence to relapse: The *National Epidemiological Survey of Alcohol and Related Conditions* (NESARC) analyzed the odds of relapse of a *non-treatment population* of 2,350 adults (18 and over) [23]. The relapse to a CUD was only 6.6% over a 3.6 year window. Major depressive disorder was identified as a predictive factor for relapse. The investigators concluded that, "The odds of CUD relapse found in our study are much lower than those reported in studies of clinical samples possibly due to lower average severity of CUD, less psychiatric comorbidity and health issues, and less exposure to high-risk environments, among community rather than clinical samples [23] p.131".

Moore and Budney [24] studied 82 adults *in treatment* who had achieved at least two weeks of abstinence. Seventy-one percent relapsed at least once during the first 6 months of care.

Cannabis Youth Study (CYT), USA 2004: SAMHSA tested five short-term outpatient intervention models in four sites for adolescents with CUDs [25, 26]. Six hundred young (ages 15-16) cannabis users were predominately white males. The five forms of treatment offered in several combinations and intensities were (1) Motivational Enhancement Therapy (MET), (2) Cognitive Behavioral Treatment (CBT), offered in 5 or 12 session doses, (3) Adolescent Community Reinforcement Approach (ACRA), (4) Multidimensional Family Therapy (MDFT), and (5) Family Support Network (FSN).

All five interventions demonstrated statistically significant pre-post treatment improvements over 12 months as measured by days of abstinence and the percent of adolescents in recovery (no use or abuse/dependence problems and living in the community). Clinical outcomes were disappointingly similar across modalities and conditions. Indeed, the *Cannabis Youth Treatment Study* also showed

that, while the initial intervention was often effective, half of the adolescents experienced intermittent relapse one or more times after discharge. Two-thirds still reported substance use or related problems at 12-month follow-up. The study's authors concluded that cannabis diagnoses are best understood as chronic conditions requiring a need to focus more on long-term monitoring and care.

Multidimensional Family Therapy (MDFT), Europe 2013: In 2011, The *European Monitoring Center for Drugs and Drug Addiction* (EMCDDA 2013) reported that over 109,000 cannabis and cannabis-associated problem cases were reported by outpatient treatment services in the European Union [27]. Cannabis was second only to heroin. European investigators, having reviewed the CYT and other studies, decided on a large multi-site trial of MDFT as the most promising of the available interventions and tested it against individual psychotherapy (IP) a common intervention in Europe [28-30].

The trans-national trial was called the *International Need for Cannabis Treatment* (INCANT) study. Study participants (n=450) were recruited at outpatient secondary level addiction, youth, and forensic care clinics in Brussels, Berlin, Paris, The Hague, and Geneva. Participants were adolescents (ages 13-18) with a recent cannabis use disorder. Both methods worked, but over 12 months, MDFT outperformed individual psychotherapy in reducing drug-using days and retaining subjects in treatment.

Clinical Challenges: Adult heavy users usually establish therapeutic contact themselves (often in response to a partner's pressure), but for adolescents, the parents are more likely to make the initial contact with a clinician. Most heavy marijuana users are not reluctant to discuss their use if their rationales for use are explored rather than attacked. The principles of motivational interviewing (MI) provide excellent guidelines for initiating dialogue about a patient's marijuana use [31, 32]. MI elicits behavior change by helping patients explore and resolve their latent ambivalence. It accepts that patients are at different levels of readiness for change and is non-judgmental and non-adversarial. The motivation to change arises from patients' articulation of warded-off ambivalent feelings, usually related to real-world consequences of use. Motivational Interviewing techniques require clinicians to engage in active dialogue [33, 34]. Even single session interventions have demonstrated significant declines in cannabis use at three month follow-up in both adults and adolescents [35].

Typical Patterns of Rationalization: Several common themes run through patients' denial that marijuana can cause problems. Generally speaking, most heavy users will state that they can quit any time they so desire, that marijuana is beneficial for them, that authorities and parents are hypocrites given their own use of alcohol and pills, and that they notice no difference in function when they quit for a few days.

- "Everyone I know uses weed."
- "It can't be harmful – it's natural and organic."
- "No one ever died from a marijuana overdose."
- "It makes me feel better. I feel more aware of things around me"
- "It helps me study boring subjects"
- "I have a medical marijuana card, and I have a right to treat my mood."

Individual assessment and treatment depends on developing a non-confrontational therapeutic relationship, beginning with eliciting the patient's experience with marijuana, often initially presented by the adolescent as entirely positive. Inevitably there have been some personal costs and getting to them will evoke the cognitive dissonance that is needed to drive change. The

principles of motivational interviewing respect patients' ambivalence and encourage them to wrestle with their own positive and negative facts.

Medication Studies for Treatment of CUD:

There is a small amount of research on medications, including oral THC [36], to reduce symptoms of cannabis withdrawal, and some medications may help in the short-term. However, there are no approved meds to reduce craving or to reduce the odds of relapse.

> Currently [April 2015], no medications are indicated for the treatment of marijuana use disorder, but research is active in this area. Because sleep problems feature prominently in marijuana withdrawal, some studies are examining the effectiveness of medications that aid in sleep. Medications that have shown promise in early studies or small clinical trials include the sleep aid zolpidem (Ambien®), an anti-anxiety/anti-stress medication called buspirone (BuSpar®), and an anti-epileptic drug called gabapentin (Horizant®, Neurotin®) that may improve sleep and, possibly, executive function. Other agents being studied include the nutritional supplement N-acetylcysteine and chemicals called FAAH inhibitors, which may reduce withdrawal by inhibiting the breakdown of the body's own cannabinoids. Future directions include the study of substances called *allosteric modulators* that interact with cannabinoid receptors to inhibit THC's rewarding effects.
>
> http://www.drugabuse.gov/publications/research-reports/marijuana/available-treatments-marijuana-use-disorders

Two of the medications that have been reported of value in treating cannabis dependence were administered in the context of structured psychosocial treatment. N-acetylcysteine (NAC), a research compound, that is available over the counter, more than doubled the odds of having negative urine cannabinoid tests as compared with placebo, with benefits detectable within a week of treatment initiation [37]. For cannabis dependent patients who have discontinued use, gabapentin substantially reduced withdrawal symptoms [38]. Sleep and mood disturbances were reduced, as was craving. Executive functions were improved within the first week, an important factor in patients' ability to make effective use of treatment. Such small studies have not been widely validated; and, neither medication is approved for use in treating cannabis use disorders.

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ENDNOTES:

1.   Farmer, R.F., et al., *Natural course of cannabis use disorders.* Psychol Med, 2015. **45**(1): p. 63-72.

   BACKGROUND: Despite its importance as a public health concern, relatively little is known about the natural course of cannabis use disorders (CUDs). The primary objective of this research was to provide descriptive data on the onset, recovery and recurrence functions of CUDs during the high-risk periods of adolescence, emerging adulthood and young adulthood based on data from a large prospective community sample. METHOD: Probands (n = 816) from the Oregon Adolescent Depression Project (OADP) participated in four diagnostic assessments (T1-T4) between the ages of 16 and 30 years, during which current and past CUDs were assessed. RESULTS: The weighted lifetime prevalence of CUDs was 19.1% with an average onset age of 18.6 years. Although gender was not significantly related to the age of initial CUD onset, men were more likely to be diagnosed with a lifetime CUD. Of those diagnosed with a CUD episode, 81.8% eventually achieved recovery during the study period. Women achieved recovery significantly more quickly than men. The recurrence rate (27.7%) was relatively modest, and most likely to occur within the first 36 months following the offset of the first CUD episode. CUD recurrence was uncommon after 72 months of remission and recovery. CONCLUSIONS: CUDs are relatively common, affecting about one out of five persons in the OADP sample prior to the age of 30 years. Eventual recovery from index CUD episodes is the norm, although about 30% of those with a CUD exhibit a generally persistent pattern of problematic use extending 7 years or longer.

2.   EMCDDA, *Cannabis. Annual Report 2009: The State of the Drugs Problem in Europe* 2009, European Monitoring Centre for Drugs and Drug Abuse: Lisbon. p. 38-47.

3.   Compton, W.M., et al., *Crosswalk between DSM-IV dependence and DSM-5 substance use disorders for opioids, cannabis, cocaine and alcohol.* Drug Alcohol Depend, 2013. **132**(1-2): p. 387-90.

   BACKGROUND: Ascertaining agreement between DSM-IV and DSM-5 is important to determine the applicability of treatments for DSM-IV conditions to persons diagnosed according to the proposed DSM-5. METHODS: Data from a nationally representative sample of US adults were used to compare concordance of past-year DSM-IV opioid, cannabis, cocaine and alcohol dependence with past-year DSM-5 disorders at thresholds of 3+, 4+, 5+ and 6+ positive DSM-5 criteria among past-year users of opioids (n=264), cannabis (n=1622), cocaine (n=271) and alcohol (n=23,013). Substance-specific 2 x 2 tables yielded overall concordance (kappa), sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV). RESULTS: For DSM-IV alcohol, cocaine and opioid dependence, optimal concordance occurred when 4+ DSM-5 criteria were endorsed, corresponding to the threshold for moderate DSM-5 alcohol, cocaine and opioid use disorders. Maximal concordance of DSM-IV cannabis dependence and DSM-5 cannabis use disorder occurred when 6+ criteria were endorsed, corresponding to the threshold for severe DSM-5 cannabis use disorder. At these optimal thresholds, sensitivity, specificity, PPV and NPV generally exceeded 85% (>75% for cannabis). CONCLUSIONS: Overall, excellent correspondence of DSM-IV dependence with DSM-5 substance use disorders was documented in this general population sample of alcohol, cannabis, cocaine and opioid users. Applicability of treatments tested for DSM-IV dependence is supported by these results for those with a DSM-5 alcohol, cocaine or opioid use disorder of at least moderate severity or severe cannabis use disorder. Further research is needed to provide evidence for applicability of treatments for persons with milder substance use disorders.

4.   Allsop, D.J., et al., *Quantifying the clinical significance of cannabis withdrawal.* PLoS One, 2012. **7**(9): p. e44864.

   BACKGROUND AND AIMS: Questions over the clinical significance of cannabis withdrawal have hindered its inclusion as a discrete cannabis induced psychiatric condition in the Diagnostic and Statistical Manual of Mental Disorders (DSM IV). This study aims to quantify functional impairment to normal daily activities from cannabis withdrawal, and looks at the factors predicting functional impairment. In addition the study tests the influence of functional impairment from cannabis withdrawal on cannabis use during and after an abstinence attempt. METHODS AND RESULTS: A volunteer sample of 49 non-treatment seeking cannabis users who met DSM-IV criteria for dependence provided daily withdrawal-related functional impairment scores during a one-week baseline phase and two weeks of monitored abstinence from cannabis with a one month follow up. Functional impairment from withdrawal symptoms was strongly associated with symptom severity (p=0.0001). Participants with more severe cannabis dependence before the abstinence attempt reported greater functional impairment from cannabis withdrawal (p=0.03). Relapse to cannabis use during the abstinence period was associated with greater functional impairment from a subset of withdrawal symptoms in high dependence users. Higher levels of functional impairment during the abstinence attempt predicted higher levels of cannabis use at one month follow up (p=0.001). CONCLUSIONS: Cannabis withdrawal is clinically significant because it is associated with functional impairment to normal daily activities, as well as relapse to cannabis use. Sample size in the relapse group was small and the use of a non-treatment seeking population requires findings to be

replicated in clinical samples. Tailoring treatments to target withdrawal symptoms contributing to functional impairment during a quit attempt may improve treatment outcomes.

5.   Budney, A.J. and J.R. Hughes, *The cannabis withdrawal syndrome.* Curr Opin Psychiatry, 2006. **19**(3): p. 233-8.

PURPOSE OF REVIEW: The demand for treatment for cannabis dependence has grown dramatically. The majority of the people who enter the treatment have difficulty in achieving and maintaining abstinence from cannabis. Understanding the impact of cannabis withdrawal syndrome on quit attempts is of obvious importance. Cannabis, however, has long been considered a 'soft' drug, and many continue to question whether one can truly become dependent on cannabis. Skepticism is typically focused on whether cannabis use can result in 'physiological' dependence or withdrawal, and whether withdrawal is of clinical importance. RECENT FINDINGS: The neurobiological basis for cannabis withdrawal has been established via discovery of an endogenous cannabinoid system, identification of cannabinoid receptors, and demonstrations of precipitated withdrawal with cannabinoid receptor antagonists. Laboratory studies have established the reliability, validity, and time course of a cannabis withdrawal syndrome and have begun to explore the effect of various medications on such withdrawal. Reports from clinical samples indicate that the syndrome is common among treatment seekers. SUMMARY: A clinically important withdrawal syndrome associated with cannabis dependence has been established. Additional research must determine how cannabis withdrawal affects cessation attempts and the best way to treat its symptoms.

6.   Legleye, S., D. Piontek, and L. Kraus, *Psychometric properties of the Cannabis Abuse Screening Test (CAST) in a French sample of adolescents.* Drug Alcohol Depend, 2011. **113**(2-3): p. 229-35.

PURPOSE: Psychometric and screening properties of the Cannabis Abuse Screening Test (CAST) were investigated using DSM-IV diagnoses of cannabis dependence (CD) and cannabis use disorders (CUD) as external criteria. Performance of the binary and the full version of the CAST were compared. METHODS: The sample consisted of 2566 French adolescents aged 17 who reported cannabis use 12 months prior to the survey. The Munich Composite International Diagnostic Interview (M-CIDI) was used as a gold standard for DSM-IV diagnoses. Internal consistency (Cronbach's alpha), construct validity (exploratory and confirmatory factor analyses, correlation of CAST scores with related variables), and criterion validity (Receiver Operating Characteristic analyses) were assessed. RESULTS: Both CAST versions were unidimensional and Cronbach's alpha was 0.748 for the binary and 0.775 for the full version. High and comparable AUC values indicate a good ability of both test versions to discriminate between individuals with and without a clinical diagnosis. Based on balanced sensitivity and specificity, the optimal cut-off scores for CD and CUD were 2 for the binary and 3 or 4 for the full version. While both versions largely overestimated CD prevalence, CUD prevalence was slightly underestimated. CONCLUSIONS: The binary and the full version of the CAST are equally useful for screening for cannabis-related disorders. Both clinical and research applications of the scale are possible. The CAST may be used for estimating CUD prevalence rather than CD prevalence. The ultimate choice of the cut-off depends on the purpose of the specific study using the CAST.

7.   Legleye, S., et al., *A validation of the Cannabis Abuse Screening Test (CAST) using a latent class analysis of the DSM-IV among adolescents.* Int J Methods Psychiatr Res, 2013. **22**(1): p. 16-26.

This paper explored the latent class structure of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (assessed with the Munich Composite International Diagnostic Interview). Secondly, the screening properties of the Cannabis Abuse Screening Test (CAST) in adolescents were assessed with classical test theory using the latent class structure as empirical gold standard. The sample comprised 3266 French cannabis users aged 17 to 19 from the general population. Three latent classes of cannabis users were identified reflecting a continuum of problem severity: non-symptomatic, moderate and severe. Gender-specific analyses showed the best model fit, although results were almost identical in the total sample. The latent classes were good predictors of daily cannabis use, number of joints per day and age of first experimentation. The CAST showed good screening properties for the moderate/severe class (area under receiver operating characteristic curve > 0.85) and very good for the severe class (0.90). It was more sensitive for boys, more specific for girls. Although structural equivalence across gender was rejected, results suggest small gender differences in the latent structure of the DSM-IV. The performance of the CAST in screening for the latent class structure was good and superior to those obtained with the classical DSM-IV diagnoses.

8.   Piontek, D., L. Kraus, and D. Klempova, *Short scales to assess cannabis-related problems: a review of psychometric properties.* Subst Abuse Treat Prev Policy, 2008. **3**: p. 25.

AIMS: The purpose of this paper is to summarize the psychometric properties of four short screening scales to assess problematic forms of cannabis use: Severity of Dependence Scale (SDS), Cannabis Use Disorders Identification Test (CUDIT), Cannabis Abuse Screening Test (CAST) and Problematic Use of Marijuana (PUM). METHODS: A systematic computer-based literature search was conducted within the databases of PubMed,

PsychINFO and Addiction Abstracts. A total of 12 publications reporting measures of reliability or validity were identified: 8 concerning SDS, 2 concerning CUDIT and one concerning CAST and PUM. Studies spanned adult and adolescent samples from general and specific user populations in a number of countries worldwide. RESULTS: All screening scales tended to have moderate to high internal consistency (Cronbach's alpha ranging from .72 to .92). Test-retest reliability and item total correlation have been reported for SDS with acceptable results. Results of validation studies varied depending on study population and standards used for validity assessment, but generally sensitivity, specificity and predictive power are satisfactory. Standard diagnostic cut-off points that can be generalized to different populations do not exist for any scale. CONCLUSION: Short screening scales to assess dependence and other problems related to the use of cannabis seem to be a time and cost saving opportunity to estimate overall prevalences of cannabis-related negative consequences and to identify at-risk persons prior to using more extensive diagnostic instruments. Nevertheless, further research is needed to assess the performance of the tests in different populations and in comparison to broader criteria of cannabis-related problems other than dependence.

9.   Piontek, D., et al., *The validity of DSM-IV cannabis abuse and dependence criteria in adolescents and the value of additional cannabis use indicators.* Addiction, 2011. **106**(6): p. 1137-45.

AIMS: This study assessed the validity of DSM-IV cannabis abuse and dependence criteria in an adolescent general population sample and evaluated the usefulness of additional cannabis use indicators. DESIGN AND SETTING: Data came from the 2008 Survey on Health and Consumption during the Day of Defense Preparation (ESCAPAD), a cross-sectional self-administered survey conducted in France. PARTICIPANTS: The analytical sample comprised 3641 adolescents aged 17-19 years who reported cannabis use in the past 12 months. MEASUREMENTS: To assess DSM-IV criteria of cannabis abuse and dependence, the Munich Composite International Diagnostic Interview (M-CIDI) was used. As additional cannabis use indicators, daily use, use when alone and use before midday were assessed. Confirmatory factor analyses and two-parameter logistic item response theory (IRT) models were run. Differential item functioning was assessed using the IRT log-likelihood ratio approach. RESULTS: A one-factor model comprising both abuse and dependence criteria showed the best fit to the data. Abuse item legal problems showed the greatest severity, whereas dependence items larger/longer and tolerance were found least severe. Discriminatory power was lowest for impaired control and legal problems. Additional cannabis use indicators increased the precision of the overall DSM-IV criterion set. Gender-based differential item functioning was observed for items tolerance, withdrawal and use before midday. CONCLUSION: The current DSM conceptualization with two distinct and graded diagnostic classes has limited validity among adolescents. In forthcoming revisions of the classification system, several existing criteria should be revised or dropped, new indicators of substance use disorders should be included and gender should be considered.

10.   Martin, G., et al., *The Severity of Dependence Scale (SDS) in an adolescent population of cannabis users: reliability, validity and diagnostic cut-off.* Drug Alcohol Depend, 2006. **83**(1): p. 90-3.

The Severity of Dependence Scale (SDS) is a five-item scale that has been reported to be a reliable and valid screening instrument for dependence and a measure of dependence severity in adults across several substance classes. To date no data have been reported on its performance in a population of adolescent cannabis users. The current study assessed the psychometric properties of the SDS in a community sample of 14-18-year-old adolescent cannabis users (n=100). Internal consistency (alpha=0.83) and test-retest coefficients (ICC=0.88) were high and a principal components analysis of the scale found all items to load on a single factor. Total SDS score correlated significantly with frequency of cannabis use and number of DSM-IV dependence criteria met, indicating good concurrent validity. Receiver Operating Characteristic curve analysis was used to determine the most appropriate SDS cut-off score for use as an indicator of cannabis dependence, with optimal discrimination at an SDS score of 4. These findings indicate that the SDS is a reliable and valid measure of severity of cannabis dependence among adolescents, has high diagnostic utility, and that an SDS score of 4 may be indicative of cannabis dependence.

11.   van der Pol, P., et al., *Reliability and validity of the Severity of Dependence Scale for detecting cannabis dependence in frequent cannabis users.* Int J Methods Psychiatr Res, 2013. **22**(2): p. 138-43.

The Severity of Dependence Scale (SDS) measures with five items the degree of psychological dependence on several illicit drugs, including cannabis. Its psychometric properties have not yet been examined in young adult frequent cannabis users, an eminently high-risk group for cannabis dependence. Internal consistency and criterion validity of the SDS were investigated within an enriched community based sample of 577 Dutch frequent (>/= three days per week in the past 12 months) cannabis users between 18-30 years. Criterion validity was tested against the Composite International Diagnostic Interview (CIDI) 3.0 DSM-IV diagnosis cannabis dependence, and psychometric properties were assessed separately for males and females and for ethnic subgroups. Principal component analysis showed that all items of the scale loaded on a single factor and reliability of the SDS total score was good (Cronbach's alpha = 0.70). However, criterion validity against the CIDI

diagnosis cannabis dependence was low: area under curve (AUC) was 0.68 (95% confidence interval: 0.64-0.73) and at the optimal differentiating cut-off (SDS >/= 4), sensitivity was 61.3% and specificity 63.5%. Results were similar for subgroups on gender and ethnicity. While internal consistency of the SDS is good, its use as a screener to differentiate between dependence and non-dependence within populations of young adult frequent cannabis users is not recommended.

12.   Adamson, S.J., et al., *An improved brief measure of cannabis misuse: the Cannabis Use Disorders Identification Test-Revised (CUDIT-R).* Drug Alcohol Depend, 2010. **110**(1-2): p. 137-43.

        BACKGROUND: Cannabis is widely used and significant problems are associated with heavier consumption. When a cannabis misuse screening tool, the CUDIT, was originally published it was noted that although it performed well there was concern about individual items. METHODS: 144 patients enrolled in a clinical trial for concurrent depression and substance misuse were administered an expanded CUDIT, containing the original 10 items and 11 candidate replacement items. All patients were assessed for a current cannabis use disorder with the SCID. RESULTS: A revised CUDIT-R was developed containing 8 items, two each from the domains of consumption, cannabis problems (abuse), dependence, and psychological features. Although the psychometric adequacy of the original CUDIT was confirmed, the CUDIT-R was shorter and had equivalent or superior psychometric properties. High sensitivity (91%) and specificity (90%) were achieved. CONCLUSIONS: The 8-item CUDIT-R has improved performance over the original scale and appears well suited to the task of screening for problematic cannabis use. It may also have potential as a brief routine outcome measure.

13.   Bashford, J., R. Flett, and J. Copeland, *The Cannabis Use Problems Identification Test (CUPIT): development, reliability, concurrent and predictive validity among adolescents and adults.* Addiction, 2010. **105**(4): p. 615-25.

        AIMS: To describe the empirical construction and initial validation of the Cannabis Use Problems Identification Test (CUPIT), a brief self-report screening instrument for detection of currently and potentially problematic cannabis use. DESIGN: In a three-phase prospective design an item pool of candidate questions was generated from a literature review and extensive expert consultation. The CUPIT internal structure, cross-sectional and longitudinal psychometric properties were then systematically tested among heterogeneous past-year users. PARTICIPANTS: Volunteer participants were 212 high-risk adolescents (n = 138) and adults (n = 74) aged 13-61 years from multiple community settings. MEASUREMENTS: The comprehensive assessment battery included several established measures of cannabis-related pathology for CUPIT validation, with DSM-IV/ICD-10 diagnoses of cannabis use disorders as criterion standard. FINDINGS: Sixteen items loading highly on two subscales derived from principal components analysis exhibited good to excellent test-retest (0.89-0.99) and internal consistency reliability (0.92, 0.83), and highly significant ability to discriminate diagnostic subgroups along the severity continuum (non-problematic, risky, problematic use). Twelve months later, baseline CUPIT scores demonstrated highly significant longitudinal predictive utility for respondents' follow-up diagnostic group membership. Receiver operating characteristic (ROC) analysis identified a CUPIT score of 12 to be the optimal cut-point for maximizing sensitivity for both currently diagnosable cannabis use disorder and those at risk of meeting diagnostic criteria in the following 12 months. CONCLUSIONS: The CUPIT is a brief cannabis screener that is reliable, valid and acceptable for use across diverse community settings and consumers of all ages. The CUPIT has clear potential to assist with achievement of public health goals to reduce cannabis-related harms in the community.

14.   SAMHSA. *Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings*. NSDUH Series H-48, HHS Publ No (SMA) 14-4863 2014 SAMHSA;   This report presents detailed results from the 2013 National Survey on Drug Use and Health (NSDUH), an annual survey sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA). The survey is the primary source of information on the use of illicit drugs, alcohol, and tobacco in the civilian, noninstitutionalized population of the United States aged 12 years old or older. Approximately 67,500 persons are interviewed in NSDUH each year. Unless otherwise noted, all comparisons in this report that are described using terms such as "increased," "decreased," or "more than" are statistically significant at the .05 level.

15.   Copeland, J., A. Frewen, and K. Elkins. *Management of cannabis use disorder and related issues (NCPIC Australia)*. 2009   National   Cannabis   Prevention   and   Information   Centre;   Available   from: https://ncpic.org.au/media/1594/management-of-cannabis-use-disorder-and-related-issues-a-clinicians-guide.pdf

16.   Copeland, J. and W. Swift, *Cannabis use disorder: epidemiology and management.* Int Rev Psychiatry, 2009. **21**(2): p. 96-103.

        This paper provides an overview of the epidemiology of cannabis use, cannabis use disorders and its treatment. Cannabis is the most commonly used illicit drug internationally. While use is decreasing in the developed world, it appears to be stable or increasing in developing countries and some indigenous communities. Early initiation

and regular adolescent use have been identified as particular risk factors for later problematic cannabis (and other drug) use, impaired mental health, delinquency, lower educational achievement, risky sexual behaviour and criminal offending in a range of studies. It is estimated that approximately one in ten people who had ever used cannabis will become dependent with risk increasing markedly with frequency of use. There has been an increase in the proportion of treatment provided for cannabis use. There are as yet no evidence-based pharmacotherapies available for the management of cannabis withdrawal and craving. Relatively brief cognitive behavioural therapy and contingency management have the strongest evidence of success, and structured, family-based interventions, provide potent treatment options for adolescents. With criminally involved young people and those with severe, persistent mental illness, longer and more intensive therapies provided by interdisciplinary teams may be required.

17. McRae, A.L., A.J. Budney, and K.T. Brady, *Treatment of marijuana dependence: a review of the literature.* J Subst Abuse Treat, 2003. **24**(4): p. 369-76.

     Until recently, relatively little research has focused on the treatment of marijuana abuse or dependence; however, marijuana use disorders are now receiving increased attention. This paper reviews the initial clinical trials evaluating the efficacy of outpatient treatments for adult marijuana dependence. Findings from five controlled trials of psychotherapeutic interventions suggest that this disorder appears responsive to the same types of treatment as other substance dependencies. Moreover, these initial studies suggest that many patients do not show a positive treatment response, indicating that marijuana dependence is not easily treated. Strengths and weaknesses of the data are presented. Preliminary data from less controlled studies relevant to the treatment of marijuana dependence are discussed to suggest future research areas. Although very few studies on treatment for marijuana abuse and dependence have been completed, the initial reports identify promising treatment approaches and demonstrate a need for more research on the development of effective interventions.

18. NIDA *Principles of Drug Addiction Treatment: A Research-Based Guide.* 2009.

19. Budney, A.J., et al., *Marijuana dependence and its treatment.* Addict Sci Clin Pract, 2007. **4**(1): p. 4-16.

     The prevalence of marijuana abuse and dependence disorders has been increasing among adults and adolescents in the United States. This paper reviews the problems associated with marijuana use, including unique characteristics of marijuana dependence, and the results of laboratory research and treatment trials to date. It also discusses limitations of current knowledge and potential areas for advancing research and clinical intervention.

20. Chen, C.Y., M.S. O'Brien, and J.C. Anthony, *Who becomes cannabis dependent soon after onset of use? Epidemiological evidence from the United States: 2000-2001.* Drug Alcohol Depend, 2005. **79**(1): p. 11-22.

     In this paper we estimate the risk of becoming cannabis dependent within 24 months after first use of cannabis and examine subgroup variation in this risk. The study estimates are based on the National Household Survey on Drug Abuse conducted during 2000-2001, with a representative sample of U.S. residents ages 12 and older (n=114,241). A total of 3352 respondents were found to have used cannabis for the first time within a span of up to 24 months prior to assessment. An estimated 3.9% of these recent-onset users developed a cannabis dependence syndrome during the interval since first use (median interval duration approximately 12 months). Excess risk of cannabis dependence was found for those with cannabis onset before late-adolescence, those with family income less than US dollars 20,000, and those who had used three or more drugs before the first use of cannabis (i.e., tobacco, alcohol, and other drugs). While these findings generally support previous study results, this study's focus on recent-onset users more closely approximates prospective and longitudinal research on the incidence (risk) of becoming cannabis dependent soon after onset of cannabis use, removing the influence of users with long-sustained or persistent cannabis dependence developed years ago.

21. van der Pol, P., et al., *The Dutch Cannabis Dependence (CanDep) study on the course of frequent cannabis use and dependence: objectives, methods and sample characteristics.* Int J Methods Psychiatr Res, 2011. **20**(3): p. 169-81.

     This paper presents an overview of the prospective cohort design of the Dutch Cannabis Dependence (CanDep) study, which investigates (i) the three-year natural course of frequent cannabis use (>/= three days per week in the past 12 months) and cannabis dependence; and (ii) the factors involved in the transition from frequent non-dependent cannabis use to cannabis dependence, and remission from dependence. Besides its scientific relevance, this knowledge may contribute to improve selective and indicated prevention, early detection, treatment and cannabis policies. The secondary objectives are the identification of factors related to treatment seeking and the validation of self report measures of cannabis use. Between September 2008 and April 2009, baseline data were collected from 600 frequent cannabis users with an average age of 22.1 years, predominantly male (79.3%) and an average cannabis use history of 7.1 years; 42.0% fulfilled a (12-month DSM-IV) diagnosis of cannabis dependence. The response rate was 83.7% after the first follow up at 18 months. The second and last follow-up is planned at 36 months. Computer assisted personal interviews (CAPI) were conducted which

covered: cannabis use (including detailed assessments of exposure, motives for use and potency preference); use of other substances; DSM-IV internalizing and externalizing mental disorders; treatment seeking; personality; life events; social support and social functioning.

22.   van der Pol, P., et al., *Predicting the transition from frequent cannabis use to cannabis dependence: a three-year prospective study.* Drug Alcohol Depend, 2013. **133**(2): p. 352-9.

BACKGROUND: Frequent cannabis users are at high risk of dependence, still most (near) daily users are not dependent. It is unknown why some frequent users develop dependence, whereas others do not. This study aims to identify predictors of first-incidence DSM-IV cannabis dependence in frequent cannabis users. METHODS: A prospective cohort of frequent cannabis users (aged 18-30, n=600) with baseline and two follow-up assessments (18 and 36 months) was used. Only participants without lifetime diagnosis of DSM-IV cannabis dependence at baseline (n=269) were selected. Incidence of DSM-IV cannabis dependence was established using the Composite International Diagnostic Interview version 3.0. Variables assessed as potential predictors of the development of cannabis dependence included sociodemographic factors, cannabis use variables (e.g., motives, consumption habits, cannabis exposure), vulnerability factors (e.g., childhood adversity, family history of mental disorders or substance use problems, personality, mental disorders), and stress factors (e.g., life events, social support). RESULTS: Three-year cumulative incidence of cannabis dependence was 37.2% (95% CI=30.7-43.8%). Independent predictors of the first incidence of cannabis dependence included: living alone, coping motives for cannabis use, number and type of recent negative life events (major financial problems), and number and type of cannabis use disorder symptoms (impaired control over use). Cannabis exposure variables and stable vulnerability factors did not independently predict first incidence of cannabis dependence. CONCLUSIONS: In a high risk population of young adult frequent cannabis users, current problems are more important predictors of first incidence cannabis dependence than the level and type of cannabis exposure and stable vulnerability factors.

23.   Florez-Salamanca, L., et al., *Probability and predictors of cannabis use disorders relapse: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).* Drug Alcohol Depend, 2013. **132**(1-2): p. 127-33.

BACKGROUND: This study aims to estimate the odds and predictors of Cannabis Use Disorders (CUD) relapse among individuals in remission. METHODS: Analyses were done on the subsample of individuals with lifetime history of a CUD (abuse or dependence) who were in full remission at baseline (Wave 1) of the National Epidemiological Survey of Alcohol and Related Conditions (NESARC) (n=2350). Univariate logistic regression models and hierarchical logistic regression model were implemented to estimate odds of relapse and identify predictors of relapse at 3 years follow up (Wave 2). RESULTS: The relapse rate of CUD was 6.63% over an average of 3.6 year follow-up period. In the multivariable model, the odds of relapse were inversely related to time in remission, whereas having a history of conduct disorder or a major depressive disorder after Wave 1 increased the risk of relapse. CONCLUSIONS: Our findings suggest that maintenance of remission is the most common outcome for individuals in remission from a CUD. Treatment approaches may improve rates of sustained remission of individuals with CUD and conduct disorder or major depressive disorder.

24.   Moore, B.A. and A.J. Budney, *Relapse in outpatient treatment for marijuana dependence.* J Subst Abuse Treat, 2003. **25**(2): p. 85-9.

The current study provides an initial examination of lapse and relapse to marijuana use among 82 individuals who achieved at least 2 weeks of abstinence during outpatient treatment for marijuana dependence. Seventy-one percent used marijuana at least once (i.e., lapsed) within 6 months of initial abstinence, averaging 73 days (SD = 50) till lapsing. Similarly, 71% of those who lapsed, relapsed to heavier use defined as at least 4 days of marijuana use in any 7-day period. Early lapses were more strongly associated with consequent relapse. Previous studies have noted that marijuana-dependent outpatients experience difficulty initiating abstinence from marijuana much as do those dependent on other substances. The present data suggest that these similarities extend to difficulty maintaining abstinence.

25.   Dennis, M., et al., *The Cannabis Youth Treatment (CYT) Study: main findings from two randomized trials.* J Subst Abuse Treat, 2004. **27**(3): p. 197-213.

This article presents the main outcome findings from two inter-related randomized trials conducted at four sites to evaluate the effectiveness and cost-effectiveness of five short-term outpatient interventions for adolescents with cannabis use disorders. Trial 1 compared five sessions of Motivational Enhancement Therapy plus Cognitive Behavioral Therapy (MET/CBT) with a 12-session regimen of MET and CBT (MET/CBT12) and another that included family education and therapy components (Family Support Network [FSN]). Trial II compared the five-session MET/CBT with the Adolescent Community Reinforcement Approach (ACRA) and Multidimensional Family Therapy (MDFT). The 600 cannabis users were predominately white males, aged 15-

16. All five CYT interventions demonstrated significant pre-post treatment during the 12 months after random assignment to a treatment intervention in the two main outcomes: days of abstinence and the percent of adolescents in recovery (no use or abuse/dependence problems and living in the community). Overall, the clinical outcomes were very similar across sites and conditions; however, after controlling for initial severity, the most cost-effective interventions were MET/CBT5 and MET/CBT12 in Trial 1 and ACRA and MET/CBT5 in Trial 2. It is possible that the similar results occurred because outcomes were driven more by general factors beyond the treatment approaches tested in this study; or because of shared, general helping factors across therapies that help these teens attend to and decrease their connection to cannabis and alcohol.

26.   Compton, W.M. and B. Pringle, *Services research on adolescent drug treatment. Commentary on "The Cannabis Youth Treatment (CYT) Study: main findings from two randomized trials".* J Subst Abuse Treat, 2004. **27**(3): p. 195-6.

One conclusion we can draw from this effort is that btreatment worksQ—that is, treatment can reduce cannabis use and support recovery. All five interventions have fairly consistent results on clinical outcomes, whether measured in terms of days of abstinence or recovery at the 3-, 6-, 9- and 12-month followup points. Even a more sophisticated analysis, based on random regression models of alternative continuous measures of outcome, demonstrates similar results. In these more complex analyses, some variation appears among the treatments, but the results still imply general effectiveness of all the interventions without consistent differences across the sites.

27.   Hoch, E., et al., *CANDIS treatment program for cannabis use disorders: findings from a randomized multi-site translational trial.* Drug Alcohol Depend, 2014. **134**: p. 185-93.

BACKGROUND: In a recent paper, we reported the efficacy of a modular cognitive-behavioral intervention for treating adolescents and adults with cannabis use disorders (CUD). In this study, we examine the outcome of this intervention after translating it into clinical practice. METHODS: A multi-site, randomized controlled trial of 279 treatment seekers with ICD-10 cannabis use disorders aged 16- 63 years was conducted in 11 outpatient addiction treatment centers in Germany. Patients were randomly assigned to an Active Treatment (AT, n=149) or Delayed Treatment Control (DTC, n=130). Treatment consisted of 10 sessions of fully manualized individual psychotherapy that combined Cognitive-Behavioral Therapy, Motivational EnhancementTherapy and problem-solving training. Assessments were conducted at baseline, during each therapy session, at post-treatment and at three and six month follow-ups. RESULTS: At post assessment 53.3% of AT patients reported abstinence (46.3% negative urine screenings) compared to 22% of DTC patients (17.7% negative drug screenings) (p<0.001, Intention-to-treat analysis). AT patients improved in the frequency of cannabis use, number of cannabis dependence criteria, severity of dependence, as well as number and severity of cannabis-related problems. Effect sizes were moderate to high. While abstinence rates in the AT group decreased over the 3-month (negative urine screenings: 32.4%) and 6-month (negative urine screenings: 35.7%) follow-up periods, the effects in secondary outcomes were maintained. CONCLUSIONS: The intervention can successfully be translated to and applied in clinical practice. It has the potential to improve access to evidence-based care for chronic CUD patients.

28.   Rigter, H., et al., *Multidimensional family therapy lowers the rate of cannabis dependence in adolescents: a randomised controlled trial in Western European outpatient settings.* Drug Alcohol Depend, 2013. **130**(1-3): p. 85-93.

BACKGROUND: Noticing a lack of evidence-based programmes for treating adolescents heavily using cannabis in Europe, government representatives from Belgium, France, Germany, The Netherlands, and Switzerland decided to have U.S.-developed multidimensional family therapy (MDFT) tested in their countries in a trans-national trial, called the International Need for Cannabis Treatment (INCANT) study. METHODS: INCANT was a 2 (treatment condition)x5 (time) repeated measures intent-to-treat randomised effectiveness trial comparing MDFT to Individual Psychotherapy (IP). Data were gathered at baseline and 3, 6, 9 and 12 months thereafter. Study participants were recruited at outpatient secondary level addiction, youth, and forensic care clinics in Brussels, Berlin, Paris, The Hague, and Geneva. Participants were adolescents from 13 through 18 years of age with a recent cannabis use disorder. 85% were boys; 40% were of foreign descent. One-third had been arrested for a criminal offence in the past 3 months. Three primary outcomes were assessed: (1) treatment retention, (2) prevalence of cannabis use disorder and (3) 90-day frequency of cannabis consumption. RESULTS: Positive outcomes were found in both the MDFT and IP conditions. MDFT outperformed IP on the measures of treatment retention (p<0.001) and prevalence of cannabis dependence (p=0.015). MDFT reduced the number of cannabis consumption days more than IP in a subgroup of adolescents reporting more frequent cannabis use (p=0.002). CONCLUSIONS: Cannabis use disorder was responsive to treatment. MDFT exceeded IP in decreasing the prevalence of cannabis dependence. MDFT is applicable in Western European outpatient settings, and may show moderately greater benefits than IP in youth with more severe substance use.

29.   Rigter, H., et al., *INCANT: a transnational randomized trial of multidimensional family therapy versus treatment as usual for adolescents with cannabis use disorder.* BMC Psychiatry, 2010. **10**: p. 28.

BACKGROUND: In 2003, the governments of Belgium, France, Germany, the Netherlands and Switzerland agreed that there was a need in Europe for a treatment programme for adolescents with cannabis use disorders and other behavioural problems. Based on an exhaustive literature review of evidence-based treatments and an international experts meeting, Multidimensional Family Therapy (MDFT) was selected for a pilot study first, which was successful, and then for a joint, transnational randomized controlled trial named INCANT (INternational CAnnabis Need for Treatment). METHODS/DESIGN: INCANT is a randomized controlled trial (RCT) with an open-label, parallel group design. This study compares MDFT with treatment as usual (TAU) at and across sites in Brussels, Berlin, Paris, The Hague and Geneva. Assessments are at baseline and at 3, 6, 9 and 12 months after randomization. A minimum of 450 cases in total is required; sites will recruit 60 cases each in Belgium and Switzerland, and a maximum of 120 each in France, Germany and the Netherlands.Eligible for INCANT are adolescents from 13 through 18 years of age with a cannabis use disorder (dependence or abuse), with at least one parent willing to take part in the treatment. Randomization is concealed to, and therefore beyond control by, the researcher/site requesting it. Randomization is stratified as to gender, age and level of cannabis consumption.Assessments focus on substance use; mental function; behavioural problems; and functioning regarding family, school, peers and leisure time.For outcome analyses, the study will use state of the art latent growth curve modelling techniques, including all randomized participants according to the intention-to-treat principle.INCANT has been approved by the appropriate ethical boards in Belgium, France, Germany, the Netherlands, Switzerland, and the University of Miami Miller School of Medicine. INCANT is funded by the (federal) Ministries of Health of Belgium, Germany, the Netherlands, Switzerland, and by MILDT: the Mission Interministerielle de Lutte Contra la Drogue et de Toximanie, France. DISCUSSION: Until recently, cannabis use disorders in adolescents were not viewed in Europe as requiring treatment, and the co-occurrence of such disorders with other mental and behavioural problems was underestimated. This has changed now.Initially, there was doubt that a RCT would be feasible in treatment sectors and countries with no experience in this type of study. INCANT has proven that such doubts are unjustified. Governments and treatment sites from the five participating countries agreed on a sound study protocol, and the INCANT trial is now underway as planned. TRIAL REGISTRATION: ISRCTN51014277.

30.   Rowe, C., et al., *Implementation fidelity of Multidimensional Family Therapy in an international trial.* J Subst Abuse Treat, 2013. **44**(4): p. 391-9.

Implementation fidelity, a critical aspect of clinical trials research that establishes adequate delivery of the treatment as prescribed in treatment manuals and protocols, is also essential to the successful implementation of effective programs into new practice settings. Although infrequently studied in the drug abuse field, stronger implementation fidelity has been linked to better outcomes in practice but appears to be more difficult to achieve with greater distance from model developers. In the INternational CAnnabis Need for Treatment (INCANT) multi-national randomized clinical trial, investigators tested the effectiveness of Multidimensional Family Therapy (MDFT) in comparison to individual psychotherapy (IP) in Brussels, Berlin, Paris, The Hague, and Geneva with 450 adolescents with a cannabis use disorder and their parents. This study reports on the implementation fidelity of MDFT across these five Western European sites in terms of treatment adherence, dose and program differentiation, and discusses possible implications for international implementation efforts.

31.   Arkowitz, H., W.R. Miller, and S. Rollnick, *Motivational interviewing in the treatment of psychological problems*. Second edition. ed. Applications of motivational interviewing. 2015, New York: The Guilford Press. pages cm.

32.   Miller, W.R. and S. Rollnick, *Motivational interviewing : helping people change*. 3rd ed. Applications of motivational interviewing. 2013, New York, NY: Guilford Press. xii, 482 p.

33.   Gray, E., J. McCambridge, and J. Strang, *The effectiveness of motivational interviewing delivered by youth workers in reducing drinking, cigarette and cannabis smoking among young people: quasi-experimental pilot study.* Alcohol Alcohol, 2005. **40**(6): p. 535-9.

AIM: To test whether a single session of Motivational Interviewing (MI) focussing on drinking alcohol, and cigarette and cannabis smoking, would successfully lead to reductions in use or problems. METHODS: Naturalistic quasi-experimental study, in 162 young people (mean age 17 years) who were daily cigarette smokers, weekly drinkers or weekly cannabis smokers, comparing 59 receiving MI with 103 non-intervention assessment-only controls. MI was delivered in a single session by youth workers or by the first author. Assessment was made of changes in self-reported cigarette, alcohol, cannabis use and related indicators of risk and problems between recruitment and after 3 months by self-completion questionnaire. RESULTS: 87% of subjects (141 of 162) were followed up. The most substantial evidence of benefit was achieved in relation to alcohol consumption, with those receiving MI drinking on average two days per month less than controls after 3 months. Weaker evidences of impact on cigarette smoking, and no evidence of impact on cannabis use, were

obtained. CONCLUSIONS: Evidence of effectiveness for the delivery of MI by youth workers in routine conditions has been identified. However, the extent of benefit is much more modest than previously identified in efficacy studies.

34. McCambridge, J., et al., *Encouraging GP alcohol intervention: pilot study of change-orientated reflective listening (CORL).* Alcohol Alcohol, 2004. **39**(2): p. 146-9.

AIMS: To test the feasibility of delivery and potential value of a brief motivational enhancement intervention targeting GPs in relation to alcohol as a public health issue, and to compare data obtained with similar attempts to influence GP intervention with drug users. METHOD: 21 GPs who were not involved in the treatment of drug dependence received a telephone-administered 'change-orientated reflective listening' (CORL) intervention, based on Motivational Interviewing, with an informational adjunct. Assessments were made at baseline and at 2-3 months of activity and willingness to deliver specified alcohol-related interventions, plus overall therapeutic commitment and motivation. Qualitative data was obtained. RESULTS: There was no change over time in the sample as a whole, with very modest evidence of benefit among individual practitioners. Comparisons with cannabis and drug misuse intervention targets suggest that it may be more difficult to alter views on intervening with drinkers. CONCLUSIONS: Further attempts are needed to influence practitioner motivation, based on improved understanding of GP views on the delivery of alcohol interventions.

35. McCambridge, J. and J. Strang, *The efficacy of single-session motivational interviewing in reducing drug consumption and perceptions of drug-related risk and harm among young people: results from a multi-site cluster randomized trial.* Addiction, 2004. **99**(1): p. 39-52.

AIM: To test whether a single session of motivational interviewing (discussing alcohol, tobacco and illicit drug use) would lead successfully to reduction in use of these drugs or in perceptions of drug-related risk and harm among young people. DESIGN: Cluster randomized trial, allocating 200 young people in the natural groups in which they were recruited to either motivational interviewing (n=105) or non-intervention education-as-usual control condition (n=95). SETTING: Ten further education colleges across inner London. PARTICIPANTS: Two hundred young people (age range 16-20 years) currently using illegal drugs, with whom contact was established through peers trained for the project. INTERVENTION: The intervention was adapted from the literature on motivational interviewing in the form of a 1-hour single-session face-to-face interview structured by a series of topics. MEASUREMENTS: Changes in self-reported cigarette, alcohol, cannabis and other drug use and in a range of drug-specific perceptions and other indicators of risk and harm. Measurement at recruitment and follow-up interview 3 months later. FINDINGS: A good follow-up rate (89.5%; 179 of 200) was achieved. In comparison to the control group, those randomized to motivational interviewing reduced their of use of cigarettes, alcohol and cannabis, mainly through moderation of ongoing drug use rather than cessation. Effect sizes were 0.37 (0.15-0.6), 0.34 (0.09-0.59) and 0.75 (0.45-1.0) for reductions in the use of cigarettes, alcohol and cannabis, respectively. For both alcohol and cannabis, the effect was greater among heavier users of these drugs and among heavier cigarette smokers. The reduced cannabis use effect was also greater among youth usually considered vulnerable or high-risk according to other criteria. Change was also evident in various indicators of risk and harm, but not as widely as the changes in drug consumption. CONCLUSIONS: This study provides the first substantial evidence of non-treatment benefit to be derived among young people involved in illegal drug use in receipt of motivational interviewing. The targeting of multiple drug use in a generic fashion among young people has also been supported.

36. Vandrey, R., et al., *The dose effects of short-term dronabinol (oral THC) maintenance in daily cannabis users.* Drug Alcohol Depend, 2013. **128**(1-2): p. 64-70.

BACKGROUND: Prior studies have separately examined the effects of dronabinol (oral THC) on cannabis withdrawal, cognitive performance, and the acute effects of smoked cannabis. A single study examining these clinically relevant domains would benefit the continued evaluation of dronabinol as a potential medication for the treatment of cannabis use disorders. METHODS: Thirteen daily cannabis smokers completed a within-subject crossover study and received 0, 30, 60 and 120mg dronabinol per day for 5 consecutive days. Vital signs and subjective ratings of cannabis withdrawal, craving and sleep were obtained daily; outcomes under active dose conditions were compared to those obtained under placebo dosing. On the 5th day of medication maintenance, participants completed a comprehensive cognitive performance battery and then smoked five puffs of cannabis for subjective effects evaluation. Each dronabinol maintenance period occurred in a counterbalanced order and was separated by 9 days of ad libitum cannabis use. RESULTS: Dronabinol dose-dependently attenuated cannabis withdrawal and resulted in few adverse side effects or decrements in cognitive performance. Surprisingly, dronabinol did not alter the subjective effects of smoked cannabis, but cannabis-induced increases in heart rate were attenuated by the 60 and 120mg doses. CONCLUSIONS: Dronabinol's ability to dose-dependently suppress cannabis withdrawal may be therapeutically beneficial to individuals trying to stop cannabis use. The absence of gross cognitive impairment or side effects in this study supports safety of

doses up to 120mg/day. Continued evaluation of dronabinol in targeted clinical studies of cannabis treatment, using an expanded range of doses, is warranted.

37. Gray, K.M., et al., *A double-blind randomized controlled trial of N-acetylcysteine in cannabis-dependent adolescents.* Am J Psychiatry, 2012. **169**(8): p. 805-12.

OBJECTIVE: Preclinical findings suggest that the over-the-counter supplement N-acetylcysteine (NAC), via glutamate modulation in the nucleus accumbens, holds promise as a pharmacotherapy for substance dependence. The authors investigated NAC as a novel cannabis cessation treatment in adolescents, a vulnerable group for whom existing treatments have shown limited efficacy. METHOD: In an 8-week double-blind randomized placebo-controlled trial, treatment-seeking cannabis-dependent adolescents (ages 15-21 years; N=116) received NAC (1200 mg) or placebo twice daily as well as a contingency management intervention and brief (<10 minutes) weekly cessation counseling. The primary efficacy measure was the odds of negative weekly urine cannabinoid test results during treatment among participants receiving NAC compared with those receiving placebo, in an intent-to-treat analysis. The primary tolerability measure was frequency of adverse events, compared by treatment group. RESULTS: Participants receiving NAC had more than twice the odds, compared with those receiving placebo, of having negative urine cannabinoid test results during treatment (odds ratio=2.4, 95% CI=1.1-5.2). Exploratory secondary abstinence outcomes favored NAC but were not statistically significant. NAC was well tolerated, with minimal adverse events. CONCLUSIONS: This is the first randomized controlled trial of pharmacotherapy for cannabis dependence in any age group to yield a positive primary cessation outcome in an intent-to-treat analysis. Findings support NAC as a pharmacotherapy to complement psychosocial treatment for cannabis dependence in adolescents.

38. Mason, B.J., et al., *A proof-of-concept randomized controlled study of gabapentin: effects on cannabis use, withdrawal and executive function deficits in cannabis-dependent adults.* Neuropsychopharmacology, 2012. **37**(7): p. 1689-98.

There are no FDA-approved pharmacotherapies for cannabis dependence. Cannabis is the most widely used illicit drug in the world, and patients seeking treatment for primary cannabis dependence represent 25% of all substance use admissions. We conducted a phase IIa proof-of-concept pilot study to examine the safety and efficacy of a calcium channel/GABA modulating drug, gabapentin, for the treatment of cannabis dependence. A 12-week, randomized, double-blind, placebo-controlled clinical trial was conducted in 50 unpaid treatment-seeking male and female outpatients, aged 18-65 years, diagnosed with current cannabis dependence. Subjects received either gabapentin (1200 mg/day) or matched placebo. Manual-guided, abstinence-oriented individual counseling was provided weekly to all participants. Cannabis use was measured by weekly urine toxicology and by self-report using the Timeline Followback Interview. Cannabis withdrawal symptoms were assessed using the Marijuana Withdrawal Checklist. Executive function was measured using subtests from the Delis-Kaplan Executive Function System. Relative to placebo, gabapentin significantly reduced cannabis use as measured both by urine toxicology (p=0.001) and by the Timeline Followback Interview (p=0.004), and significantly decreased withdrawal symptoms as measured by the Marijuana Withdrawal Checklist (p<0.001). Gabapentin was also associated with significantly greater improvement in overall performance on tests of executive function (p=0.029). This POC pilot study provides preliminary support for the safety and efficacy of gabapentin for treatment of cannabis dependence that merits further study, and provides an alternative conceptual framework for treatment of addiction aimed at restoring homeostasis in brain stress systems that are dysregulated in drug dependence and withdrawal.