
Development and Consequences of Cannabis Dependence

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The past 10 to 15 years of clinical and basic research have produced strong evidence demonstrating that cannabis can and does produce dependence. Clinical and epidemiological studies indicate that cannabis dependence is a relatively common phenomenon associated with significant psychosocial impairment. Basic research has identified a neurobiological system specific to the actions of cannabinoids. Human and nonhuman studies have demonstrated a valid withdrawal syndrome that is relatively common among heavy marijuana users. Last, clinical trials evaluating treat-

ments for cannabis dependence suggest that this disorder, like other substance dependence disorders, is responsive to intervention, yet the majority of patients have much difficulty achieving and maintaining abstinence. Of concern, treatment seeking for marijuana dependence has increased almost twofold over the past 10 years. This report briefly reviews selected research literature relevant to our current understanding of cannabis dependence, its associated consequences, and treatment efficacy.

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The question of whether individuals become dependent on marijuana has fueled much controversy. For many years, the scientific community had been reluctant to acknowledge the dependence potential of cannabis because certain types of experimental findings were lacking. Until recently, attempts to demonstrate that nonhuman animals would self-administer cannabis (THC) in the laboratory were unsuccessful, which contrasted with that observed with most other drugs commonly abused by humans.^{1,2} Second, early studies of cannabis (THC) withdrawal failed to reveal a syndrome that included reliable and substantial physical symptoms such as those observed during classic opioid, sedative, or alcohol withdrawal.³ This lack of evidence for physiological dependence, combined with a poor understanding of the neurobiology of the effects of cannabis, cast further uncertainty regarding its dependence potential. Last, a paucity of clinical data on cannabis dependence occasioned several common beliefs that minimized its significance. Such beliefs included the following: the prevalence of cannabis dependence is very low, it exists only in the context of polydrug dependence, it is not associated with sub-

stantial functional impairment, and treatment is not necessary because users can quit easily on their own.⁴

In contrast, the past 10 to 15 years of clinical and basic research have produced strong evidence demonstrating that cannabis can and does produce dependence. Clinical and epidemiological studies indicate that cannabis dependence is a relatively common phenomenon associated with significant psychosocial impairment. Basic research has identified a neurobiological system specific to the actions of cannabinoids. Human and nonhuman studies have demonstrated a valid withdrawal syndrome that is relatively common among heavy marijuana users. Last, clinical trials evaluating treatments for cannabis dependence suggest that this disorder, like other substance dependence disorders, is responsive to intervention, yet the majority of patients have much difficulty achieving and maintaining abstinence. Below, we briefly review selected research literature relevant to our current understanding of cannabis dependence and its associated consequences.

RATES OF DEPENDENCE AND ASSOCIATED PROBLEMS

The fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* and the *ICD-10 Classification of Mental and Behavioural Disorders* consider cannabis dependence a reliable and valid psy-

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chiatric disorder, suggesting that individuals in the general population experience cannabis dependence in much the same way as they experience other substance dependence disorders.^{5,6} By definition, a diagnosis of substance dependence indicates that an individual is experiencing a cluster of cognitive, behavioral, or physiological symptoms associated with substance use yet continues to use the substance regularly. Epidemiological studies indicate that the lifetime prevalence of cannabis dependence approximates 4% of the U.S. population, the highest of any illicit drug.^{7,8} This high rate of cannabis dependence is clearly affected by the greater overall prevalence of marijuana use compared to the use of other illicit drugs of abuse. Rates of conditional dependence—that is, the risk of developing dependence among those who have used the drug—provide a better indicator of dependence potential. In this regard, cannabis has a substantial, albeit lower, rate of conditional dependence (9%) than substances such as alcohol (15%), cocaine (17%), heroin (23%), or tobacco (32%).⁸ More frequent use results in greater risk of dependence. For example, rates of cannabis dependence are estimated at 20% to 30% among those who have used at least five times, and even higher estimates (35%-40%) are reported among those who report near daily use.^{9,10}

Those who develop cannabis dependence willingly seek treatment for problems related to their use. For example, Stephens and colleagues¹¹ reported that more than 350 adults sought treatment during a 3-month period in response to newspaper advertisements offering assessment and treatment for persons concerned about their marijuana use. The majority of those patients were not currently abusing other substances, and most reported multiple signs of dependence. Such treatment-seeking patterns and profiles have been replicated in other U.S. and Australian studies.^{12,13} National trends gleaned from the Treatment Episode Data Set¹⁴ indicate that the number of adults and adolescents who seek and enroll in treatment for marijuana-related problems is not small and has been increasing during the past decade. Indeed, the demand for treatment for marijuana-related problems at state-approved substance abuse programs doubled between 1992 and 1996 across the United States, such that the percentage of illicit drug abuse treatment admissions for marijuana (23%) approximated that for cocaine (27%) and heroin (23%). Similar increases in rates of treatment seeking for cannabis problems during the 1990s have been reported in Australia.¹⁵ Interestingly, treatment admissions for individuals younger than age 20 comprise about 45% of all admissions.¹⁴ Also, approximately 50% of individuals seeking treatment for cannabis-related prob-

lems have some involvement with the criminal justice system.

The severity and specificity of the problems among adults seeking treatment for marijuana-related problems have been well documented. The great majority of these patients have been using marijuana for more than 10 years, use marijuana on a daily basis, use multiple times per day, and clearly meet *DSM* dependence criteria.¹¹⁻¹³ They exhibit substantial psychosocial impairment and psychiatric distress, report multiple adverse consequences, report repeated unsuccessful attempts to stop using, and perceive themselves as unable to quit. The most common consequences mentioned are procrastination, bad/guilty feelings, low productivity, low self-confidence, interpersonal/family problems, memory problems, and financial difficulties. A study directly comparing marijuana- with cocaine-dependent outpatients demonstrated that the two groups exhibited similar types of problems, but the marijuana abusers generally showed a less severe dependence syndrome.¹² Both groups met multiple *DSM-III-R* dependence criteria, although the cocaine group reported a significantly greater number of criteria (7.7 vs. 6.3). The groups did not differ on the Medical, Legal, Family/ Social, or Psychiatric severity scales of the Addiction Severity Index, but the cocaine group scored higher on the Employment severity scale. The cocaine group also scored higher on the ASI Drug and Alcohol severity scales, reflecting greater polydrug abuse in the cocaine treatment population. Both groups showed clinically significant elevations on standardized psychiatric symptom scales, but few between-groups differences were observed. Sociodemographics such as marital status, income, and employment status also did not differ.

Although marijuana-dependent outpatients do not typically experience the acute crises or dramatic consequences that many times drive alcohol-, cocaine-, or heroin-dependent individuals into treatment, they clearly show psychosocial impairment that warrants clinical attention. In summary, evidence for a cannabis dependence disorder is strong and indicative of a disorder of substantial severity.

CANNABIS WITHDRAWAL

Evidence of a withdrawal syndrome has generally been deemed a classic marker of the dependence potential of a substance. In the 1970s, nonhuman studies of cessation following chronic THC administration provided evidence of a withdrawal response, but the effects were not consistent and were deemed mild compared with other substances such as opiates and sedatives.³ Early

studies with humans in residential laboratories also found evidence of withdrawal.³ Common symptoms included decreased appetite, irritability, restlessness, sleep difficulties, and uncooperativeness. These effects were characterized as mild, transient, and without serious medical complications and thus were considered clinically insignificant when compared to the dramatic medical and physiological symptoms associated with severe opiate, sedative, or alcohol withdrawal. Hence, investigation of cannabis withdrawal waned during the 1980s.

The discovery of a cannabinoid receptor¹⁶ and the synthesis of a cannabinoid antagonist¹⁷ renewed scientific interest in cannabis withdrawal. These advances provided a better neurobiological understanding of the drug's mechanism of action and a means for conducting antagonist challenge studies on cannabinoid withdrawal. As reviewed elsewhere in this report, such studies have demonstrated a marked, precipitated withdrawal syndrome in rats and dogs.^{18,19} Recent studies on withdrawal in humans have also appeared in the literature. Two placebo-controlled inpatient studies, using moderate doses of oral THC and smoked marijuana, demonstrated withdrawal effects that included anxiety, decreased contentment and food intake, depressed mood, irritability, restlessness, sleep difficulty, and stomach pain.^{20,21} Controlled outpatient studies have since provided data on the reliability, validity, time course, and clinical significance of cannabis withdrawal. One study examining 3-day abstinence periods in heavy daily marijuana smokers validated specific effects of marijuana abstinence and showed they were reliable and of clinically significant magnitude.²² Specifically, decreased appetite, sleep difficulty, strange dreams, aggression, anger, irritability, restlessness, craving for marijuana, and weight loss were documented during marijuana abstinence periods. A second outpatient study documented withdrawal during a 28-day period of abstinence in a similar population of daily marijuana smokers.²³ Symptoms similar to those reported in earlier studies remained elevated for at least 7 to 14 days, as did Hamilton Depression and Anxiety scale scores. Last, preliminary findings from a study examining a 45-day marijuana abstinence period indicate that cannabis abstinence symptoms in heavy marijuana users are of clinically significant magnitude and follow a time course similar to that of other types of substance withdrawal.²⁴

Clinical population studies of cannabis withdrawal have been consistent with results observed in the laboratory, providing further support for a syndrome of clinical significance. The majority of adolescents in residential treatment and adults in outpatient treat-

ment for cannabis dependence report histories of marijuana withdrawal with symptom profiles similar to those observed in the laboratory studies.^{11,13,25,26} For example, we administered a 4-point (*none, mild, moderate, and severe*), 22-item Marijuana Withdrawal Symptom Checklist to cannabis-dependent outpatients enrolled in a treatment research clinic and found that 85% reported at least four abstinence symptoms.²⁵ The most frequently reported symptoms were cravings (95%), irritability (86%), nervousness (79%), depressed mood (74%), restlessness (74%), sleep difficulty (71%), and anger (71%). For many, these symptoms were substantial, as 47% rated four or more symptoms in the severe category. Thus, most cannabis-dependent patients seeking treatment perceive and expect that they will experience withdrawal symptoms when they stop smoking.

Many of the symptoms of the cannabis withdrawal syndrome overlap with those of other withdrawal syndromes and perhaps most resemble those observed with nicotine withdrawal.²⁷ Studies examining neurochemical responses in animals following exposure to and withdrawal from cannabinoids have observed reductions in mesolimbic dopamine transmission and elevations in extracellular-releasing factor concentrations in the limbic system that closely resemble the responses seen with other major drugs of abuse.^{28,29} The behavioral consequences of these neurobiological changes are consistent with the type of negative affective symptoms reported by patients withdrawing from cannabis and other substances and may be primary contributing factors to the development and maintenance of drug dependence. In summary, recent research on cannabis withdrawal furthers the argument that cannabis dependence is more similar to other well-recognized types of substance dependence than was previously believed.

TREATMENT STUDIES

The first randomized controlled trial evaluating treatment for adult cannabis dependence did not appear in the literature until 1994.³⁰ Three additional randomized trials have now been published.³¹⁻³³ Results across studies indicate that the same types of psychosocial treatments found effective for other substance dependence disorders are effective for cannabis dependence. Coping-skills training, relapse prevention, and motivational enhancement therapies have demonstrated efficacy compared to delayed treatment controls.^{32,33} Contingency management interventions that provide positive reinforcement contingent on abstinence from cannabis, documented by urinalysis testing, can en-

hance treatment outcomes when integrated with other effective therapies.³¹ Similar types of interventions have demonstrated efficacy in clinical trials for alcohol, cocaine, and opiate dependence.³⁴⁻³⁶

The aforementioned study comparing characteristics of marijuana- and cocaine-dependent outpatients¹² found that the marijuana patients were more ambivalent and less confident about stopping their marijuana use than the cocaine group was about stopping use of cocaine. These observations suggest that marijuana users might have at least as much difficulty as cocaine patients in initiating abstinence in treatment settings. Indeed, the magnitude of treatment response observed across the marijuana trials appears similar to that achieved with treatments for other substance dependence disorders. Only the minority (20%-40%) of cannabis-dependent patients achieve abstinence during treatment, although more do show clinically significant reductions in marijuana use and associated problems.³⁰⁻³³ In comparison, a recent study of an effective treatment for cocaine dependence (community reinforcement therapy plus contingency management) reported similar abstinence rates.³⁵ Approximately 40% of the cocaine patients who received this intervention, as well as 20% of those receiving community reinforcement therapy without contingent reinforcement, were abstinent at the end of treatment. Similarly, in a large multisite study on treatments for alcohol dependence (Project Match), approximately 20% to 25% of outpatients who received behavioral coping-skills therapy or motivational enhancement therapy were abstinent at the end of treatment.³⁷ Rates of relapse among cannabis-dependent patients also appear similar to other substances. A substantial proportion (approximately 30%) of individuals who achieve 2 or more weeks of abstinence relapse to pretreatment levels of use during the 6 months following treatment.³⁸

Of course, cross-study comparisons of treatment outcome pose many methodological problems; nonetheless, the cursory comparison provided here suggests that the treatment response of cannabis-dependent outpatients is similar to that observed with other substances of abuse. Clearly, like other substance dependencies, cannabis dependence is not easily treated, and there appears to be ample room for enhancement of outcomes.

SUMMARY AND FUTURE DIRECTIONS

Recent advances indicate that dependence develops to cannabis in much the same way as with other drugs. As with other abused substances, many individuals

use cannabis without significant consequence, but others misuse, abuse, or become dependent and experience adverse outcomes. Substantial impairment in psychosocial functioning occurs with cannabis dependence, although in general such effects appear less severe than those associated with alcohol, heroin, or cocaine dependence. Nonetheless, substantial numbers of individuals seek treatment for cannabis dependence, and the effectiveness of such treatments appears similar in magnitude to that observed with treatments for other drug dependencies.

Future clinical research efforts might focus on the development of more potent psychosocial interventions, testing of pharmacotherapies, and combined approaches. For example, marijuana abusers may benefit from treatment approaches that seek to reduce drug use by systematically applying natural or contrived consequences (i.e., contingency management) to enhance and sustain efforts to quit using.³¹ Such approaches may be particularly beneficial in this population because their motivation to change appears to be lower and more variable than other types of drug abusers, perhaps because the acute consequences of cannabis dependence are not as severe. Combining effective psychosocial treatments offers another method that may enhance treatment effectiveness. Behavior therapy, motivational enhancement therapy, and contingency management can be easily integrated and tested in controlled trials; indeed, initial evaluations of such efforts have shown promise.^{31,39}

Although youth younger than age 20 account for almost half the treatment admissions for marijuana dependence, no randomized controlled trials specifically for adolescent marijuana dependence have been published. A recent multisite study has been completed, and preliminary findings are consistent with those reported with adults.⁴⁰ Behaviorally based treatments appear effective, but the magnitude of treatment response leaves much room for improvement. Additional controlled trials are needed in this area. Moreover, criminal justice system involvement prompts a substantial proportion of treatment admissions for cannabis dependence, particularly in young adults and adolescents, yet clinical approaches that systematically integrate the judicial system into the treatment process have yet to be tested.

Pharmacotherapies for cannabis dependence have not been evaluated. Now that the validity and severity of cannabis dependence disorder have been established, a neurobiological cannabinoid system has been identified, and the treatment response achieved with effective psychosocial therapies has identified many nonresponders, the exploration of potential medica-

tions for cannabis dependence is warranted. The identification of the cannabinoid receptor (CB1), which has a central role in mediating the psychoactive effects of marijuana, creates new opportunities for the development of agonist or antagonist therapies. The use of medications to alleviate withdrawal symptoms will likely prove useful in treatment efforts. Moreover, as with nicotine and alcohol dependence, the identification of compounds that affect mood or craving may also show efficacy for treating cannabis dependence.

Last, many marijuana abusers may avoid seeking treatment because of ambivalence about the seriousness of their problem. Efforts directed at this non-treatment-seeking population could create opportunities to provide services that reduce problematic marijuana use. One such intervention, the Marijuana Check-Up, is currently under investigation and has shown promise.⁴¹

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