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Cannabis Withdrawal

11

Nicolas J. Schlienz and Ryan Vandrey

Introduction

Drug withdrawal refers to a constellation of symptoms that occur following abrupt cessation of chronic drug use. Though drug withdrawal can occur from stopping use of medication, it is most often encountered within the context of illicit, non-medicinal, drug use. The withdrawal symptoms that emerge following extended and frequent use of abused drugs are a key feature of what define substance use disorders [4, 85]. Further, there is accumulating neurobiological evidence that withdrawal drives the maintenance of problematic substance misuse through a mechanism of reward dysfunction and negative reinforcement [52]. Historically, there was debate and controversy regarding the existence of a valid and clinically meaningful cannabis withdrawal syndrome. However, extensive translational research has now firmly established that cannabis withdrawal occurs reliably in a subset of cannabis users, that it is pharmacologically specific to the use of cannabis, and that it is clinically meaningful within the context of treating cannabis use disorder (CUD). As a result, mitigating cannabis withdrawal has been targeted in several studies aiming to develop improved treatments for CUD (discussed in detail in other chapters of this book). There are also individual characteristics, such as sex, genetics, and co-occurring psychiatric disorders that have been associated with differences in the type or severity of cannabis withdrawal. This chapter will provide a detailed overview of the etiology and characterization of cannabis withdrawal with emphasis on its importance within the context of CUD.

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Phenomenology

Following an extended period of daily heavy use, termination of cannabis use is associated with the onset of a cannabis withdrawal syndrome that has been well-documented; has been observed in humans, rodents, and nonhuman primates; and has been reported in inpatient, outpatient, and clinical research settings [12, 14, 42].

Symptoms and Time Course

Symptoms Early controlled laboratory studies of cannabis withdrawal reported the onset of a series of withdrawal symptoms that emerged after a period of unrestricted cannabis self-administration. Following cessation from cannabis use in a controlled residential research unit, an inpatient sample of heavy users reported increased ratings of "anxiety," "irritability," and "stomach pain" [45]. Findings from multiple outpatient studies documented symptoms that also included anger, aggression, physical tension, nervousness, restlessness, depression, sleep difficulties, and loss of appetite [16, 55, 56]. The set of cannabis withdrawal symptoms that are most common, elicited reliably, and constitute DSM-5 cannabis withdrawal syndrome symptomatology [4] are outlined in Table 11.1 and include the following: irritability, anger/aggression, anxiety, sleep disturbance, appetite decline or weight loss, restlessness, and depressed mood. Less common symptoms include shakiness, chills, sweating, nausea/stomach pain, and tension [15, 43, 45, 55].

Time Course Findings from early investigations of cannabis withdrawal provided an initial understanding of symptom characteristics and demonstrated that symptoms generally emerge within 24–72 h following cessation from cannabis [15] and reach peak magnitude 2–5 days post-cessation [15, 44, 45, 55]. Studies conducted by Budney and colleagues [15] and Kouri and Pope [55] provided a broader understanding of the time course of cannabis withdrawal

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Table 11.1 DSM-5 cannabis withdrawal diagnostic criteria

Criterion A	Cessation of cannabis use that has been heavy and prolonged (i.e., usually daily or almost daily use over a period of at least a few months)
Criterion B	Three (or more) of the following signs and symptoms develop within approximately 1 week after Criterion A: 1. Irritability, anger, or aggression 2. Nervousness or anxiety 3. Sleep difficulty (e.g., insomnia, disturbing dreams) 4. Decreased appetite or weight loss 5. Restlessness 6. Depressed mood 7. At least one of the following physical symptoms causing significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills, or headache
Criterion C	The signs and symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
Criterion D	The signs or symptoms are not attributable to another condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance

based on self-reported symptoms during an extended period of abstinence. Most withdrawal symptoms resolve within 2–3 weeks and return to baseline levels [15, 55]. However, abstinence-induced insomnia may continue to persist, and reports of abstinence-related increases in vivid or strange dreams failed to return to baseline levels at the end of a 45-day abstinence period [15].

Validity, Reliability, and Clinical Significance

For years, the proposed existence of a cannabis withdrawal syndrome was met with great skepticism, and one early review of the literature concluded that the combination of methodological limitations of published findings and lack of controlled research rendered the recognition of a cannabis withdrawal syndrome as being premature [75]. However, an extensive body of research has now clearly demonstrated that the cannabis withdrawal syndrome is valid, reliable, and pharmacologically specific and produces distress and impairment in important areas of functioning [12, 14, 42].

Reliability Core symptoms of cannabis withdrawal have been consistently documented in adults [13, 16, 43, 45, 55], adolescents [25, 26, 30, 32, 41, 68, 69, 77], and individuals with polysubstance use and comorbid psychopathology [9, 19, 49, 54, 82], and within incarcerated samples [70, 71, 76]. Further, cannabis withdrawal symptoms have been documented in treatment-seeking and non-treatment-seeking populations and across inpatient and outpatient settings. Thus, cannabis withdrawal is consistently observed across a variety of daily cannabis users and differs from data obtained from control samples of individuals who do not use cannabis [15, 55].

Pharmacological Specificity In addition to establishing the reliability of cannabis withdrawal, it must be demonstrated to be pharmacologically specific in order to be considered a valid withdrawal syndrome [12]. Preclinical and human laboratory studies provide clear evidence that cannabis withdrawal is mediated by the impact of chronic cannabis use on the CB1 receptor. Specifically, studies in nonhuman species show that withdrawal can be elicited via spontaneous cessation or administration of the CB1 inverse agonist SR141716A in animals chronically administered a CB1 agonist (e.g., THC, WIN55,212-2, CP55,940; for review see [60]). In contrast, withdrawal was not elicited by SR141716A in CB1 knockout mice chronically treated with THC [57]. In the human laboratory, multiple studies have demonstrated that cannabis withdrawal abates with either a return to cannabis use or the administration of oral THC [13, 17, 43, 81], but not with the administration of cannabis in which THC has been removed. A neuroimaging study showed that daily cannabis users had fewer CB1 receptors compared with matched controls and that the downregulation of CB1 receptors resolved within 30 days of supervised abstinence [50]. Though the change in regionally specific CB1 receptors was not significantly correlated with cannabis withdrawal in that study (possibly due to a relatively small and homogeneous sample), the degree of CB1 downregulation was positively correlated with years of cannabis use, and the time course of CB1 receptor rebound during abstinence is consistent with the time course of cannabis withdrawal. In summary, converging evidence indicates that cannabis withdrawal is pharmacologically specific to the administration of THC (via CB1 agonism) and likely results from neurobiological changes in the CB1 receptor that occur with long-term, frequent cannabis use.

Clinical Significance As discussed in the *Diagnostic and Statistical Manual for Mental Disorders (DSM)*, a valid drug withdrawal syndrome must produce clinically significant impairment or distress (Table 11.1). Evidence of this comes from several research studies. First, two outpatient studies demonstrated that withdrawal-related distress is

apparent to independent observers when daily cannabis users abruptly quit [13, 15]. In these studies, friends and family members of study participants reported observing increased aggression, anger, irritability, restlessness, and nervousness during periods when participants were not using cannabis compared with when they used cannabis. Spontaneous reports from observers to study staff in some cases indicated that cannabis abstinence resulted in changes in behavior or mood severe enough to negatively impact interpersonal relationships and raised concerns about the ability of the cannabis user to appropriately care for his/her children [15]. In other studies, the majority of non-treatment-seeking adult cannabis users indicated that cannabis withdrawal directly contributed to the decision to resume cannabis use during a quit attempt or was the motivating factor for use of other substances including alcohol, tobacco, and sedatives [18, 23, 59]. Recent work has also examined the relationship between cannabis withdrawal severity and functional impairment. In a controlled laboratory study of non-treatment-seeking heavy cannabis users that agreed to abstain from cannabis use for 2 weeks, prospective assessments of total cannabis withdrawal severity accounted for 51% of the variance in a hierarchical model examining predictors of functional impairment attributed to cannabis withdrawal [2]. Thus, the clinical significance of cannabis withdrawal is established by data consistently indicating that withdrawal is noticeable to observers, interferes with psychosocial functioning, directly contributes to failed quit attempts, and increases other substance use among those trying to quit.

Similarity to Other Withdrawal Syndromes

Across drugs of abuse, the expression and central characteristics of drug withdrawal syndromes include a constellation of symptoms that include behavioral, affective, and physical symptoms (for details see [84]) and, importantly, hold important treatment implications. Adapted from Vandrey et al. [79], Table 11.2 lists the symptoms of cannabis withdrawal that are also consistently observed in other drug withdrawal syndromes. Sleep disturbance, restlessness, change in appetite/weight, and mood disturbances are consistently observed symptoms of withdrawal across drugs of abuse. Overall, symptoms of the cannabis withdrawal syndrome share the most overlap with tobacco withdrawal, a finding that has been documented in both between- and within-subjects studies [18, 78, 79]. The key difference between cannabis withdrawal and nicotine withdrawal is that there are opposing effects on appetite and change in body weight (appetite and weight decrease during cannabis withdrawal and increase during tobacco withdrawal). Similarities and differences in the time course of cannabis and other withdrawal syndromes are summarized in Table 11.3. Symptoms of cannabis withdrawal

Table 11.2 Cannabis withdrawal symptoms present in other DSM-5 withdrawal syndromes

	Cannabis	Tobacco	Alcohol	Stimulants	Opioids
Abdominal pain[a]	X	–	–	–	–
Anger/aggression	X	X	–	–	–
Anxiety/nervousness	X	X	X	–	X
Appetite change	X	X	–	X	–
Autonomic hyperactivity	–	–	X	–	–
Depressed mood	X	X	–	X	X
Diarrhea	–	–	–	–	X
Difficulty concentrating	–	X	–	–	–
Fatigue	–	–	–	X	–
Fever/chills/sweating[a]	X	–	X	–	X
Hallucinations	–	–	X	–	–
Hand tremor	–	–	X	–	–
Headache	X	–	–	–	–
Irritability	X	X	–	–	X
Lacrimation/rhinorrhea	–	–	–	–	X
Muscle aches	–	–	–	–	X
Nausea/vomiting[a]	–	–	X	–	X
Psychomotor agitation/retardation	–	–	X	X	–
Restlessness	X	X	X	X	X
Seizures	–	–	X	–	–
Sleep difficulty	X	X	X	X	X
Strange dreams	X	–	–	X	–
Weight change	X	X	–	X	–

Note: "X" denotes the presence of a symptom
[a]Less common cannabis withdrawal symptoms

Table 11.3 Comparison of time course of cannabis withdrawal with other drug withdrawal syndromes

	Cannabis	Tobacco	Alcohol	Stimulants	Opioids
Onset	24–48 h	2–12 h	4–12 h	24 h	6–12 h
Peak	2–5 days	2–3 days	2–3 days	2–3 days	1–3 days
Duration	2–3 weeks	3–4 weeks	1–2 weeks	2–3 weeks	2 weeks

tend to emerge much more gradually (i.e., 24–48 h) compared with tobacco, alcohol, or opioid withdrawal. However, the time to peak withdrawal effects (2–5 days) and the overall duration of withdrawal (2–3 weeks) for cannabis are comparable to that which is observed for other substances [51].

Neurobiological Mechanisms

Identification of Δ^9-tetrahydrocannabinol (THC), the primary psychoactive constituent of the cannabis plant [67], and discovery of the elements that comprise the endocannabinoid system have provided a framework for understanding the neurobiological underpinnings of the cannabis withdrawal syndrome.

Cannabinoid Receptors

Discussed previously, preclinical data provide overwhelming support for the mediating role of the CB1 receptor in cannabinoid reinforcement, tolerance, and withdrawal [61]. In rodents, the role of the CB1 receptor in the expression of cannabinoid withdrawal has been predominantly examined using precipitated withdrawal paradigms [60]. Following repeated treatment with CB1 agonists (e.g., THC, CP 55,940, WIN 55,212-2), administration of the CB1 antagonist SR141716A precipitates cannabinoid withdrawal that is manifested by behavioral and somatic symptoms such as wet-dog shakes and forepaw tremors [60]. Related administration of CB1 agonists in preclinical studies is associated with a reduction in CB1 receptor availability (i.e., receptor downregulation) that reflects the development of cannabinoid tolerance [61].

Recently, demonstration of CB1 receptor downregulation was also demonstrated in a human laboratory study. Daily cannabis users completed positron emission tomography (PET) imaging before and after a 30-day residential cannabis detoxification [50]. Compared with healthy controls, the daily cannabis users exhibited reduced (approximately 20% less) CB1 receptor density in the neocortex and limbic cortex, but not in the basal ganglia, midbrain, thalamus, pons, or cerebellum during the first PET scan (before detoxification). Following the 30-day abstinence period, however, the CB1 receptor downregulation in the neocortex and limbic cortex had reversed and was no longer different from healthy controls. Notably, CB1 receptor downregulation in this study was more pronounced among individuals with a longer history of cannabis use.

The demonstration of CB1 receptor downregulation in daily cannabis users was subsequently replicated [28]. Interestingly, CB1 receptor downregulation among daily cannabis users compared with healthy controls was observed across brain areas in this study and was found to be reversed after only 2 days of supervised cannabis abstinence. Further, the density of CB1 receptors was found to be inversely associated with cannabis withdrawal in that study.

Endocannabinoid Enzymatic Degradation and Inhibition

Whether variability in levels of endogenous cannabinoids influences cannabis withdrawal has been evaluated in preclinical and human laboratory research. Briefly, the primary endocannabinoids are anandamide (AEA) and 2-arachidonoylglycerol (2-AG), low- and high-efficacy agonists at the CB1 receptor site, respectively [33, 62]. AEA and 2-AG are produced on demand and degraded by the catabolic enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively. Thus far, the results of precipitated withdrawal paradigms in FAAH knockout mice have yielded equivocal findings. In one study, administration of FAAH and MAGL inhibitors reduced signs of precipitated withdrawal in mice treated with THC, but the impact of inhibiting the degradation of AEA and 2-AG was comparable between FAAH (−/−) and FAAH (+/+) mice [73]. In contrast, AEA attenuated rimonabant-precipitated withdrawal in FAAH (−/−) mice [36]. At the time of this writing, there are currently no published findings from studies investigating the impact of FAAH inhibition on cannabis withdrawal in humans. However, preliminary findings from one clinical trial (ClinicalTrials.gov Identifier: NCT01618656) demonstrated that administration of FAAH inhibitor PF-04457845 reduced withdrawal and cannabis use behavior compared to placebo [27]. Though research evaluating the therapeutic potential of pharmacological agents that target endogenous cannabinoid levels has not been fully examined, developments in this topic area are encouraging, and it remains to be determined whether preclinical findings are able to be translated to the human laboratory.

Individual Differences

Similar to other drug withdrawal syndromes [84], self-report ratings of cannabis withdrawal are subject to interindividual variability and may be influenced by factors such as socioeconomic and demographic variables, cannabis use characteristics, and interactions with co-occurring psychiatric conditions and polysubstance use.

Demographics

Relatively few studies of cannabis withdrawal have been conducted to evaluate differences in withdrawal expression by demographic characteristics. This may be due to the fact that most controlled studies of cannabis withdrawal have been conducted with relatively small and mostly homogeneous samples. In one study of non-treatment-seeking cannabis users, older adults were more likely to report increased anxiety and less likely to report increased sex drive during a previous period of sustained cannabis abstinence compared with younger adults [24]. Across two studies of cannabis treatment seekers, retrospective ratings of withdrawal during the last period of sustained abstinence among adults [16] and adolescents [77] showed that similar symptoms were endorsed in both samples, but the adults had a higher rate of withdrawal symptom incidence and severity compared with the younger cohort. However, age-related differences in the type or severity of cannabis withdrawal symptoms were not found in several other studies limited to adults [3, 59, 69]. Two studies evaluated the impact of race on cannabis withdrawal. In a study of non-treatment seekers, African American cannabis users were less likely to report anxiety, craving, sleep difficulty, and depression compared to Caucasians but were more likely to report increased libido [24]. However, in a second study of non-treatment seekers, African Americans were qualitatively more likely to report cannabis withdrawal, but this effect was not statistically significant [59]. Interestingly, one recent report indicated that there may be a genetic component to the development of cannabis use disorder, including the presence and severity of withdrawal [34].

A number of preclinical and human studies have evaluated sex differences in cannabis withdrawal. In one study of Sprague-Dawley rats treated with THC, significant reductions in locomotor activity were more common among females compared to males following abrupt THC withdrawal, and, in another, females spent significantly less time in the open arm of an elevated plus maze (preclinical model of anxiety) compared to males ([46]; c.f. [64]). In a survey of non-treatment-seeking adult cannabis users, females endorsed a significantly greater number of withdrawal symptoms during a prior quit attempt and were more likely to experience withdrawal overall. In a similar study, females were less likely to report craving and increased sex drive compared to males but were more likely to report upset stomach during previous quit attempts [24]. In a sample of treatment-seeking adults, females reported more severe total withdrawal and a greater number of individual withdrawal symptoms compared to males [48]. As described previously, preclinical data provide compelling evidence of a sexually dimorphic endocannabinoid system [5, 29, 37], and this may account for the significant differences between males and females in the presentation of cannabis withdrawal.

Cannabis Use History and Characteristics

The impact of prior cannabis use characteristics on withdrawal symptom expression during abstinence has been examined in a subset of cannabis withdrawal studies. Among non-treatment-seeking adults, greater lifetime cannabis use was found to increase the likelihood of experiencing withdrawal, and, additionally, the endorsement of at least weekly use was associated with significantly greater cannabis withdrawal severity compared with less frequent use [59]. Similarly, among frequent cannabis users, the total amount of cannabis consumed in the month preceding the quit attempt was positively associated with the total number of withdrawal symptoms reported, though the strength of this association was small [38]. In contrast to this, other studies of treatment-seeking adolescents and non-treatment-seeking adults failed to observe a significant relationship between quantity of cannabis use and withdrawal severity [3, 68].

Comorbid Psychopathology

Findings from laboratory studies and recent population survey estimates indicate that individuals with substance use disorders also report co-occurring psychiatric conditions, including anxiety, mood, and trauma- and stress-related disorders, at rates greater than in the general population [40, 47]. In addition, research on substance use disorders suggests that individuals with co-occurring substance use and psychiatric disorders tend to be more likely to experience withdrawal, and, among those who do experience withdrawal, it is usually of greater intensity and severity in the presence of a co-occurring mental health disorder (e.g., [1, 83]). However, the impact of both co-occurring substance use and psychiatric disorders on cannabis withdrawal is not well understood and is limited to a small number of empirical studies. Cannabis withdrawal is clearly evident in adult patients receiving residential detoxification from multiple drugs of abuse, including cannabis [49]. Compared to adult

outpatients without opioid dependence, adults with opioid dependence are more likely to report cannabis withdrawal-related sleep disturbances [82]. Similarly, adult inpatients with and without heroin dependence reported a comparable number of cannabis withdrawal symptoms, but analysis of individual items indicated that patients with heroin dependence experienced less irritability/anger/aggression, restlessness, and somatic complaints [19]. A study of patients in a residential detoxification unit in Australia showed that withdrawal severity was greater among those who had received treatment for mental health problems in the 6 months prior to admission, but secondary substance use was not associated with different withdrawal [31]. A robust cannabis withdrawal effect was observed in adult cannabis users with schizophrenia, with a majority of those reporting that they had taken some action, including resumed cannabis use, to mitigate withdrawal symptoms during past periods of abstinence [9]. In a sample of treatment-seeking adolescents, Greene et al. found no evidence of a relation between prospective assessments of cannabis withdrawal and psychiatric symptoms on percentage of days abstinent at follow-up [41]. At present, Schuster and colleagues addressed a significant gap in the literature by examining the impact of psychiatric comorbidity on cannabis withdrawal scores over time in a sample of non-treatment-seeking young adults [74]. Compared to individuals without a psychiatric diagnosis, individuals with a psychiatric diagnosis tended to experience greater cannabis withdrawal, but this finding was only evident during the first week of abstinence; groups reported comparable scores at subsequent time points.

Clinical Implications

A comprehensive understanding of the symptoms and severity of cannabis withdrawal has a series of important implications that are pertinent to the maintenance of daily cannabis use and the overall likelihood of achieving sustained abstinence.

Withdrawal as a Negative Reinforcer

It is well-established that drug use is motivated by basic reinforcement processes [35, 53]. From a negative reinforcement framework, cannabis withdrawal is known to elicit significant discomfort, and individuals frequently identify cannabis withdrawal as one of the major reasons listed as contributing to relapse following periods of cannabis abstinence [18, 23, 26, 59]. More recently, data acquired using ecological momentary assessment techniques have illustrated that cannabis self-administration is closely related in time to the report of cannabis withdrawal symptoms [10, 11].

Predictive Validity

While several studies have implicated cannabis withdrawal as a reason for returning to use after periods of abstinence, the reliability and significance of the association between cannabis withdrawal and treatment outcomes are not fully understood. Part of the difficulty here is that not all individuals entering in clinical trials are able to achieve abstinence, and those that do often quit at different times and for variable duration, which makes prospective evaluation of withdrawal during treatment difficult to systematically achieve. The most common approach has been to retrospectively evaluate the presence and severity of withdrawal among those who quit. The limitation of that approach is that the data is subject to recall and attribution biases. However, prospective data collection results in the inclusion of "withdrawal" assessments conducted in individuals when they are still using cannabis. This has been addressed in some studies by measuring withdrawal in a residential treatment setting.

In one study, cannabis users who had initiated a quit attempt in the past month indicated in a phone interview that withdrawal symptoms significantly contributed to relapse [18]. Greater than 50% of participants reported that aggression, anger, anxiety, craving, depressed mood, difficulty concentrating, irritability, restlessness, and sleep difficulty had contributed to failed quit attempts. In data obtained from two clinical trials conducted with treatment-seeking adolescents, cannabis withdrawal was predictive of a rapid relapse to cannabis dependence and more severe problems associated with cannabis use, but not cannabis use frequency posttreatment [20, 25]. In a placebo-controlled trial evaluating buspirone for cannabis dependence, McRae-Clark et al. found that participants who failed to report significant attenuation of cannabis withdrawal symptoms were less likely than others to achieve sustained abstinence confirmed by a negative urine sample during treatment [66]. A study of emerging adults receiving outpatient treatment demonstrated a trend that cannabis withdrawal predicted days to first lapse [30]. Gorelick et al. also found that non-treatment-seeking adults who met DSM-5 criteria for cannabis withdrawal had a shorter abstinence period during their most serious past quit attempt compared with individuals that did not report withdrawal [38].

In contrast to these findings, Arendt and colleagues found that cannabis withdrawal scores among individuals receiving inpatient or outpatient treatment were not predictive of subsequent relapse to cannabis use [6]. Similarly, a study of adolescents in outpatient treatment for cannabis use problems failed to find a significant relation between withdrawal and percentage of abstinent days at a 1-year follow-up [41]. However, the authors of that study noted that there was a moderating effect of whether or not the adolescents acknowledged having a problem with cannabis use at the outset of

treatment. Additionally, two recent clinical trials of pharmacotherapies for cannabis use disorder have shown significant reductions in cannabis withdrawal. The controlled trial of dronabinol failed to demonstrate an effect of the medication on cannabis use outcomes despite withdrawal attenuation [58], but the trial of gabapentin showed both a suppression of withdrawal and increased abstinence that was suggestive that withdrawal attenuation contributed toward the reduction in use [65]. These findings need to be replicated in larger follow-up trials.

To identify specific features of cannabis withdrawal that significantly predict relapse, Allsop et al. created and tested three separate models containing somatic variables, affective variables, and a third model that combined somatic and affective withdrawal variables [2]. Interestingly, only the somatic variables model significantly predicted relapse and inspection of individual variables included in the model indicated that physical tension was the only significant predictor variable. Overall, it appears that cannabis withdrawal is somewhat predictive of treatment outcomes, but there is variability in response across studies. Further, it remains to be determined whether withdrawal suppression is a viable mediator of cannabis use outcomes and, thus, an appropriate clinical target in developing novel treatments for CUD.

Conclusion

Cannabis withdrawal is a valid clinical syndrome that emerges following abrupt cessation of frequent cannabis use. Symptoms of cannabis withdrawal are predominantly behavioral and affective in nature and include irritability/anger/aggression, nervousness/anxiety, sleep difficulty (e.g., insomnia, strange or vivid dreams), decreased appetite or weight loss, restlessness, and depressed mood. Physical symptoms include abdominal/stomach pain, shakiness/tremors, sweating, fever, chills, or headache, but these are experienced less frequently [15, 43, 45, 55]. A consistent time course has been established; upon cessation, symptoms emerge within 24–48 h, reach peak intensity on days 2–5, and resolve within 2–3 weeks, though sleep difficulties may persist [15, 55]. Importantly, cannabis withdrawal produces significant discomfort and functional impairment [2], and work has also demonstrated that cannabis withdrawal is a significant factor that maintains regular use and reduces the likelihood of initiating a quit attempt [12, 14]. Compared with other drug withdrawal syndromes, the signs and symptoms of cannabis withdrawal are most comparable to the symptoms experienced during tobacco withdrawal. In contrast to the onset of withdrawal from tobacco, alcohol, and opioids, symptoms of cannabis withdrawal emerge and reach peak severity more gradually.

Efforts to determine the neurobiological underpinnings of cannabis reinforcement facilitated the identification of the endocannabinoid system. Basic science research has established that the endocannabinoid system serves as the primary biological mechanism of cannabis withdrawal. Data indicate that cannabis withdrawal is mediated by downregulation of the CB1 receptor and can be mitigated by administration of CB1 agonists. Demonstration of the neurobiological underpinnings and pharmacological specificity of cannabis withdrawal represented a critical step in establishing its validity and broad medical acceptance. Recent preclinical data also provide compelling evidence of a sexually dimorphic endocannabinoid system [46] that may explain the finding that, compared to males, females report more rapid development of cannabis use disorder and an increased number and severity of withdrawal symptoms [24, 48]. How fluctuating levels and degradation of the endogenous cannabinoids AEA and 2-AG impact cannabis withdrawal remains unknown and represents a focused area of research still in its infancy.

Akin to other validated drug withdrawal syndromes, variability in cannabis withdrawal between subjects is evident. Aside from the sex differences described above, there are studies that suggest longer durations of cannabis use, age, race, co-use of other substances, the presence of comorbid psychopathology, and heredity may influence subjective appraisals of cannabis withdrawal. However, retrospective and prospective studies of cannabis withdrawal have yielded equivocal results for most of these relations and represent areas that warrant additional research.

Establishing the validity and clinical significance of the cannabis withdrawal syndrome has several implications. Recognition of the cannabis withdrawal syndrome in the DSM-5 highlights the significance of the cannabis withdrawal syndrome, and validation of the signs and symptoms that characterize cannabis withdrawal is highly valuable for both clinicians and researchers and can help ensure diagnostic accuracy and inform the development of novel behavioral and pharmacological interventions. The validation and clinical significance of the cannabis withdrawal syndrome also have important public health considerations. Treatment admissions for cannabis have increased [72], and additionally, findings from recent population surveys have illustrated a sharp decrease in the general public's perception of the risk of harm from smoking cannabis ([8, 21]; see also [8]). Though the mechanisms that may contribute to the observed decline in the perceived risks associated with cannabis use are not fully understood, official recognition of a cannabis withdrawal syndrome may partly convey the consequences of long-term frequent use of cannabis.

Most studies that have evaluated the clinical importance of cannabis withdrawal indicate that the presence or severity of withdrawal is associated with cannabis use outcomes among those trying to quit. This has led to a number of efforts to develop pharmacotherapies as

adjuncts to the treatment of cannabis use disorder [7, 22, 39, 63, 80]. However, drawing accurate conclusions from research designed to evaluate the impact of cannabis withdrawal (i.e., symptoms, intensity, and severity) on treatment outcomes faces several challenges. Cannabis withdrawal is predominantly based on retrospective self-report questionnaires and susceptible to recall and attribution bias. Perhaps the best indication of the clinical importance of reducing cannabis withdrawal as a means to improve cannabis treatment outcomes was the trial by Mason and colleagues [65] in which gabapentin reduced withdrawal and increased abstinence. However, that was a relatively small clinical trial that requires replication, especially in light of the outcomes of reduced withdrawal in the absence of reduced cannabis use in the dronabinol trial conducted by Levin et al. [58]. To date, there has been no definitive study to demonstrate that attenuation of cannabis withdrawal mediates the likelihood of achieving sustained cannabis abstinence or prevention of relapse during a quit attempt.

Additional research is needed to fully determine the impact of cannabis withdrawal on the development and maintenance of CUD. In particular, there is a strong need to better understand individual differences in withdrawal expression and impact on clinical outcomes. Enhanced basic science research on the unique contributions of specific components of the endocannabinoid system may also better highlight the precise neurobiological mechanisms of specific cannabis withdrawal symptoms and may help to delineate the physiological mechanisms that account for the documented individual differences in the magnitude and duration of withdrawal observed in some studies. Studies evaluating the unique impact of specific withdrawal symptoms (e.g., anxiety, sleep disturbance) on clinical outcomes (e.g., abstinence initiation, relapse) would be beneficial in determining more targeted therapeutic approaches to treating cannabis use disorder. Finally, it is unclear whether individuals using cannabis for medicinal purposes are at the same risk of experiencing cannabis withdrawal upon cessation as those using cannabis for nonmedical purposes. Systematic evaluation of the rate, severity, and consequences of cannabis withdrawal in this population is urgently needed given the rapid growth in the number of individuals using cannabis for purported therapeutic purposes.

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