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Cannabis Withdrawal: A Review of Neurobiological Mechanisms and Sex Differences

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Abstract

Purpose of Review—This report provides an updated overview of pre-clinical and clinical research on the etiology and biological substrates of the cannabis withdrawal syndrome.

Recent Findings—Long-term cannabis use is associated with downregulation of type-1 cannabinoid receptors (CB_1). Reduced CB_1 receptor density is related to increased withdrawal during early abstinence, and the reduction in CB_1 receptor density reverses with extended abstinence. Females have been shown to have increased rate and severity of a subset of cannabis withdrawal symptoms compared with men.

Summary—Recent studies have extended knowledge of the biological processes and individual difference variables that influence cannabis withdrawal. However, caveats include small sample sizes in clinical studies, participant samples that are predominantly male, and limited examinations of endocannabinoids, enzymes that degrade endocannabinoids, negative allosteric modulators, and other neurobiological systems that may directly impact cannabis withdrawal symptom expression.

Keywords

Cannabis; Marijuana; Withdrawal; Cannabis Use Disorder; THC; Endocannabinoid System

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Compliance with Ethical Standards

Conflict of Interest

Dr. Nicolas J. Schlienz, Dr. Alan J. Budney, and Dr. Dustin C. Lee have no conflicts to report. Dr. Ryan Vandrey has served as a consultant or received honoraria from Zynerba Pharmaceuticals, Insys Therapeutics, Battelle Memorial Institute, and CW Hemp.

Human and Animal Rights and Informed Consent

All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

Introduction

Cannabis is the most widely used illicit substance in the U.S. and recent survey estimates indicate that the prevalence of cannabis use disorder is increasing [1, 2]. Abrupt termination of long-term, frequent use of cannabis is associated with the onset of a withdrawal syndrome [3–6]. Inclusion of cannabis withdrawal in the most recent revision to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [4] is the result of more than fifteen years of pre-clinical and clinical research examining the neurobiological mechanisms, physiology, and etiology of the cannabis withdrawal syndrome.

Though between-subject variability is evident, research has shown that most daily cannabis users experience cannabis withdrawal upon abrupt cessation. Symptoms of cannabis withdrawal lead to discomfort and are clinically meaningful. Specifically, symptoms of withdrawal can maintain cannabis use via negative reinforcement [6, 7], reduce the odds of initiating a quit attempt, and represent risk factors for relapse [3, 8]. As a result, a number of clinical studies have been conducted to evaluate behavioral and pharmacological interventions designed to mitigate the symptoms of cannabis withdrawal as a means of improving clinical outcomes for those trying to quit cannabis use [9–13]. Though studies of withdrawal have grown in number, a comprehensive understanding of the component mechanisms and neurophysiological substrates of withdrawal is underdeveloped.

Increased use of cannabis and the finding of heightened frequency of treatment admissions for cannabis use disorder underscores the need to wholly characterize the complex range of neurobiological variables that contribute to the development and expression of cannabis withdrawal. Recent work has called attention to the significance of sex differences in cannabis dependence and cannabis withdrawal [14]. Although cannabis use is more prevalent among males [1], females progress more rapidly from initial use to cannabis dependence [15, 16], exhibit worse treatment outcomes [17, 18], and experience greater withdrawal symptom severity [19]. Furthermore, evidence suggests that the endocannabinoid system, the primary neurobiological system implicated in cannabis withdrawal and cannabis reinforcement, is sexually dimorphic in nature [20] and may explain between-subjects variability in cannabis withdrawal [21].

The objective of the current review is to provide a summary of recent literature (past 5 years) on the neurobiological underpinnings and sex differences observed in cannabis withdrawal. Discussion of outcomes from studies conducted in rodents, non-human primates, and humans are included and our report concludes with a summary of the findings, acknowledges limitations and gaps in the literature, and provides recommendations for future research.

Characteristics of the Cannabis Withdrawal Syndrome

The symptoms and time course of cannabis withdrawal are well documented and described in earlier literature reviews [5, 6, 22–24]. Here we provide a brief overview. The cannabis withdrawal syndrome typically onsets within 24–48 hours following abrupt cessation of frequent long-term use [25, 26]. Illustrated in Table 1, diagnostic symptoms of cannabis

withdrawal include irritability, anxiety, sleep disturbance, decreased appetite/weight loss, restlessness, depressed mood, and physical symptoms that elicit significant discomfort [5, 6, 22, 23]. Most symptoms reach peak magnitude 2–5 days post-cessation [26–29] and begin to remit and return to baseline levels within 2–3 weeks on average [25, 26, 29], though sleep disturbances may persist longer [26, 29].

The empirical literature examining cannabis withdrawal continues to expand and has been evaluated in several participant populations and across a range of settings. At the time of writing, cannabis withdrawal has been investigated in adolescent samples [30, 31], emerging adults [32], adult long-term, daily cannabis users [5, 22], and environments that include closed residential research units [27, 28, 33], outpatient settings [25, 26, 34], and within the context of clinical studies evaluating behavioral and pharmacological interventions for the treatment of cannabis use disorder [9, 10, 11, 13, 35].

Since the publication of initial formative reviews [5, 6, 22, 24], use of high temporal resolution assessment measures (i.e., ecological momentary assessment [EMA]) have recently been incorporated into the study of cannabis withdrawal [36, 37] and add to the literature by examining immediate antecedents to drug use in the natural environment in contrast to controlled research settings. In one study, Buckner et al. utilized EMA to explore factors close in proximity to cannabis use among participants initiating an unassisted quit attempt [36]. On cannabis use days, participants reported significantly higher withdrawal scores and greater negative affect compared to non-use days, and craving, nervousness/anxiety, and irritability were the most prevalent symptoms endorsed by participants. In a subsequent EMA study characterizing antecedents to cannabis use (ad libitum), Buckner and colleagues replicated their finding of greater withdrawal scores on cannabis use days compared to non-use days, and also found that participants cited withdrawal as a frequent motive for cannabis use [37]. Thus far, findings from data acquired using EMA methodology have provided valuable insight into the sequence and clinical significance of cannabis withdrawal.

The Mediating Roles of Δ^9-Tetrahydrocannabinol and the Endocannabinoid System

The cannabis plant contains hundreds of constituents, many of which are not fully understood [38]. The pioneering work of Gaoni and Machoulam identified Δ^9-tetrahydrocannabinol (THC) [39] as the primary psychoactive constituent of the cannabis plant. THC directly modulates the endogenous cannabinoid system (ECS), a diffuse mammalian biological system with extensive physiological impact. The ECS consists of type-1 (CB_1) and type-2 (CB_2) cannabinoid receptors, the endocannabinoid ligands anandamide (AEA) and 2-Arachidonoyl glycerol (2-AG), and the endocannabinoid catabolic enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) that degrade AEA and 2-AG, respectively [40–42].

Modulation of the ECS by THC and other cannabinoids found in the cannabis plant accounts for most acute effects of cannabis use. THC is a partial agonist at both CB_1 and CB_2 receptors and CB_1 receptors mediate the reinforcing effects of THC [43, 44]. CB_1 receptors

are found in high densities in the ventral tegmental area, nucleus accumbens, prefrontal cortex, hippocampus, the amygdala, and cerebellum, whereas CB_2 receptors are primarily localized to immune cells [44, 45]. CB_1 receptor agonists have inhibitory effects on the release of GABA and glutamate. Excitatory effects on dopamine (DA) are also evident, leading to increased extracellular DA levels in structures of the forebrain [46].

Notably, long-term cannabis use is associated with CB_1 receptor downregulation. In vivo studies in animals indicate that frequent administration of either THC or synthetic CB_1 receptor agonists (e.g. WIN 55,212-2) significantly reduces CB_1 receptor density [47, 48], indicative of physiological tolerance. Hirvonen and colleagues extended these findings to the human laboratory and observed significantly lower CB_1 receptor availability among daily cannabis smokers relative to healthy controls, and that the level of CB_1 receptor downregulation was significantly correlated with years of cannabis use [•49]. Then, following a 30-day period of supervised abstinence on a residential research unit, the daily cannabis users showed an increase in CB_1 receptor availability to levels comparable to the healthy controls. D'Souza et al. replicated and extended this work by examining cannabis withdrawal severity as a function of cannabinoid receptor availability [•50]. Results of that study showed that lower CB_1 receptor density (presumably due to greater CB_1 receptor downregulation) was associated with more severe cannabis withdrawal symptoms on the second day of abstinence, the time when peak withdrawal effects are typically observed [26–29].

As described in earlier reviews [5, 6, 22, 51], controlled pre-clinical and human laboratory studies clearly demonstrate that abrupt cessation of long-term exposure to THC reliably elicits cannabis withdrawal, which is dose-dependently suppressed by re-administration of THC. Further, administration of CB_1 antagonists reliably precipitate withdrawal in animals chronically treated with CB_1 agonists [51]. Combined with the neuroimaging data [•49, •50], these findings indicate that cannabis withdrawal stems from CB_1 receptor downregulation resulting from repeated exposure to CB_1 receptor agonists.

Beyond Exogenous Cannabinoids: Cannabis Withdrawal and Endocannabinoids

Given that CB_1 receptor agonists modulate cannabis withdrawal, the ECS is a viable focus for attenuating withdrawal and has become a therapeutic target in the treatment of cannabis use disorder. The two primary endocannabinoids, AEA and 2-AG, [42, 48, 52] are lipid molecules that bind to both CB_1 and CB_2 receptors. At CB_1, AEA and 2-AG are low- and high-efficacy agonists, respectively. AEA is degraded by the fatty acid amide hydrolase enzyme [FAAH; 53] and 2-AG by monoacylglycerol lipase [MAGL; 54]. Prevention of AEA degradation has been proposed as a possible therapeutic approach for the treatment of cannabis withdrawal by improving endocannabinoid tone and ECS regulation by increasing endogenous levels of AEA and 2-AG [55, 56].

Thus far, limited work has examined associations between FAAH/MAGL inhibitors and cannabis withdrawal. Using FAAH knockout mice, Schlosburg and colleagues measured the effects of FAAH and MAGL inhibitors on rimonabant-precipitated withdrawal in mice [57].

The authors failed to observe significant differences in withdrawal between FAAH (−/−) and FAAH (+/+) mice. The FAAH inhibitor URB597 significantly reduced paw tremors in FAAH (+/+) mice, whereas administration of MAGL inhibitor JZL184 had no influence on rimonabant-induced THC withdrawal. Subsequent to Schlosburg et al. [57], Falenski et al. examined the effects of repeated administration of THC or AEA on indices of withdrawal, tolerance, and dependence in mice with and without the FAAH genotype [58]. Compared with FAAH (−/−) mice treated with THC, FAAH (−/−) mice treated with AEA were observed to have markedly greater attenuation of rimonabant precipitated withdrawal. Compared with AEA, chronic administration of THC was associated with greater CB_1 receptor downregulation. Placed in the context of developing novel therapeutics for cannabis use disorder, these findings illustrate a reduced likelihood of tolerance/dependence associated with administration of AEA.

At the time of this writing, there are no published studies evaluating the effects of FAAH and MAGL inhibitors on cannabis withdrawal in humans. However, D'Souza and colleagues have recently completed a small clinical trial with the FAAH inhibitor PF-04457845 [59]. In that study, daily cannabis users who completed a 1-week residential abstinence period and received PF-04457845 reported less withdrawal relative to placebo. Randomization to PF-04457845 was also associated with greater reduction in cannabis use during a 4-week outpatient observation period compared with those who received placebo. Research in this topic area is of continued interest and worthy of exploration given the strong empirical ties between the ECS, the mesolimbic dopamine system, and both drug- and non-drug rewards [60, 61].

The Status of Findings for Sex Differences in Cannabis Withdrawal

Akin to other drugs of abuse, findings from multiple studies demonstrate that the reinforcing effects of cannabis and the subjective effects of THC may differ between males and females [14, 62, 63] and considerable pre-clinical data seemingly indicate that the ECS is sexually dimorphic [64–67]. In the U.S., past-year prevalence of cannabis use and cannabis use disorder has increased in both males and females [1, 2]. However, sex differences in the time between initial use of cannabis and development of cannabis use disorder have been identified. Compared with males, females progress from first cannabis use to cannabis use disorder at a much faster rate; this difference is referred to as the "telescoping" effect [68, 15, 16]. Female cannabis users have also been shown to have worse treatment outcomes compared with males [17, 18] and a sexually dimorphic ECS may contribute to these aforementioned sex differences. Sex differences in cannabis withdrawal relate to the telescoping effect (withdrawal is a component of cannabis use disorder) and may contribute to sex differences in treatment outcomes. Here, we summarize sex differences observed in pre-clinical and human laboratory studies of cannabis withdrawal, and refer the reader to earlier reviews [14, 21, 69].

Across two experimental paradigms that used adolescent male and female Sprague Dawley rats, Harte-Hargrove et al. found evidence of significant sex-dependent withdrawal effects in THC-treated rats [20]. In the first experiment, significant reductions in locomotor activity were only observed among THC-treated female rats, relative to female controls, on the first

day of abstinence; no effects of abstinence on locomotor activity were observed among males. In the second experiment, THC-treated female rats exhibited significantly greater anxiety relative to female controls on the first day of abstinence, measured as time spent in the open arm of an elevated plus maze. THC-treated male rats demonstrated the opposite effect and spent more time in the open arm during abstinence. In contrast with Harte-Hargrove et al. [20], Marusich et al. failed to observe sex differences in withdrawal among adult male and female rats maintained on THC (30 mg/kg twice daily) using a rimonabant (CB_1 inverse agonist)-induced withdrawal procedure [70].

Human research examining sex differences in cannabis withdrawal is limited. Females are underrepresented in both human laboratory studies of cannabis withdrawal and clinical trials of cannabis use disorder treatment. Most data on sex differences have come from post-hoc analyses, and the majority of studies in this area lack sufficient statistical power to detect meaningful effects. Copersino et al. retrospectively assessed cannabis withdrawal in a convenience sample of cannabis users and found that females endorsed significantly fewer instances of craving, increased sex drive, and greater instances of upset stomach compared to males [71]. More recently, Herrmann et al. reported findings from a randomized clinical trial for the treatment of cannabis use disorder, and while males and females did not differ with regard to quantity of current cannabis use, females had significantly greater total withdrawal scores, endorsed a significantly higher incidence of withdrawal symptoms, and were more likely to experience irritability, violent outbursts, and nausea [19]. There was no difference between females and males on the average severity of individual withdrawal symptoms, however, among those who reported experiencing nervousness/anxiety, restlessness, or increased aggression during their last quit attempt, severity ratings of those symptoms were greater for females compared with males. Notably, none of the human studies controlled for menstrual phase in female volunteers, which may have impacted cannabis withdrawal expression. In combination with the pre-clinical findings, sex differences in cannabis withdrawal are evident, yet the mechanisms that explain withdrawal dimorphism are not explicit.

Conclusions

Over the past decade, significant advances in pre-clinical and human laboratory research have produced a broader understanding of the neurobiological mechanisms implicated in the onset, signs, and symptoms of the cannabis withdrawal syndrome. CB_1 receptor agonists alleviate and CB_1 receptor antagonists precipitate the cannabis withdrawal syndrome [9]. Recent work has documented cannabis-induced alterations in CB_1 receptor availability (i.e., downregulation) among samples of heavy daily cannabis users that negatively correlated with withdrawal symptom severity suggesting that cannabis withdrawal is mediated, at least in part, by neural adaptations to CB_1 receptors due to chronic cannabis use [•49, •50]. Further, recovery of CB_1 receptors to levels of matched healthy controls has been observed following one month of abstinence, and is in alignment with the time frame when cannabis withdrawal typically resolves in clinical samples [5].

In addition to modulation of CB_1 receptors, there is evidence that long-term cannabis use can impact endocannabinoid levels, and that endocannabinoid tone is altered during

cannabis withdrawal. Anandamide (AEA) and 2-Arachidonoyl glycerol (2-AG) are low- and high-efficacy agonists at the CB_1 receptor, respectively, and enzymatic degradation of AEA by fatty acid amide hydrolase (FAAH) and 2-AG by monoacylglycerol lipase (MAGL) have been proposed as mediating mechanisms of cannabis withdrawal. However, controlled studies that carefully examine the direct relation between endogenous cannabinoids and cannabis withdrawal are sparse.

An unfortunate characteristic common to many research disciplines is the underrepresentation of female participants. Though several initiatives have been proposed to increase female representation in research [72], this concern has not been resolved. The observation of female underrepresentation is particularly evident in the study of cannabis withdrawal where females have been excluded from studies in order to eliminate the estrous cycle as a potential confound of withdrawal symptom expression. However, this characteristic may hinder advances to the understanding of cannabis withdrawal.

Female underrepresentation in studies of cannabis withdrawal is problematic given the finding that female cannabis users transition from initial use to developing cannabis use disorder more rapidly than males, and variability in cannabis withdrawal may contribute to this pattern. In addition, pre-clinical data suggests that there are sex differences in the ECS and that cannabis withdrawal can differ in both symptom type and severity for females. Specifically, retrospective self-reports of cannabis withdrawal suggest that, compared to males, female cannabis users are more likely to experience irritability, violent outbursts, and nausea during cannabis withdrawal, have a greater number of withdrawal symptoms, and experience an increased severity of a subset of withdrawal symptoms. Collectively, these findings point to withdrawal as a potentially more important therapeutic target for females seeking treatment for cannabis use disorder and may explain why, on average, females tend to have worse treatment outcomes. Additional research is needed to determine whether differences in the rate at which females develop cannabis use disorder and/or experience withdrawal may relate to differential downregulation of CB_1 or alterations in endocannabinoid tone. Though pre-clinical work has illustrated the moderating role of ovarian hormones evidenced by marked attenuation of cannabinoid-seeking behavior in ovariectomized female rats [73], the potential impact of the female menstrual cycle on cannabis withdrawal has not been adequately addressed. Research is also needed to prospectively evaluate the impact of cannabis withdrawal severity on treatment retention and abstinence rates among males and females attempting to abstain from daily cannabis use.

Though the endocannabinoid system appears to be the primary mechanism for the cannabis withdrawal syndrome, other neurobiological systems may also contribute. For example, the nicotinic cholinergic and endocannabinoid systems have substantial overlap with respect to receptor distribution in the brain, and studies show that pharmacological modification of one system, impacts the reinforcing effects of drugs (e.g. THC, nicotine) targeting the other [74]. One experiment showed that nicotine withdrawal increased AEA in the amygdala, hypothalamus, and prefrontal cortex, and decreased AEA in the hippocampus of rats chronically exposed to nicotine, but to our knowledge, no studies have directly evaluated whether the nicotinic cholinergic receptor system impacts cannabis withdrawal effects. Ongoing efforts to broaden the understanding of the impact of the nicotinic cholinergic

system on cannabis withdrawal are needed, especially given that cannabis and tobacco co-use is common [75] and that tobacco use is associated with greater psychosocial problems, lower abstinence rates and increased risk for cannabis relapse among those in treatment for cannabis use disorder [76–79].

To conclude, the ECS appears to be the principal neurobiological mechanism underpinning the cannabis withdrawal syndrome. THC is the principal psychoactive component of the cannabis plant and is a partial agonist at CB_1 and CB_2 receptor sites. Chronic use of cannabis is associated with CB_1 receptor downregulation. Abrupt cessation of heavy prolonged cannabis use gives rise to symptoms that include irritability, nervousness, sleep disturbance, decreased appetite, restlessness, depressed mood and additional physical symptoms (abdominal pain, shakiness/tremors, sweating, fever, chills, or headache). These effects are reversed by administration of THC, indicative of pharmacological specificity. The expression of cannabis withdrawal is a likely result of dysregulation of the ECS indicated by receptor downregulation and alterations in endogenous cannabinoid ligands. Emerging evidence also suggests that sex differences appear to contribute to variability observed in the cannabis withdrawal syndrome across animal and human studies. Increased understanding of potential non-cannabinoid mechanisms of cannabis withdrawal remains to be elucidated. Additional research is also needed that incorporates the use of neuroimaging assessment measures (EEG, fMRI) during the onset and peak effects of cannabis withdrawal, which may inform the development of pharmacological and behavioral interventions in the treatment of cannabis use disorder.

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Table 1

DSM-5 Cannabis Withdrawal 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.