Marijuana Dependence: Not Just Smoke and Mirrors

Divya Ramesh, Joel E. Schlosburg, Jason M. Wiebelhaus, and Aron H. Lichtman

Abstract

Marijuana (*Cannabis sativa*) is the most commonly used illicit drug worldwide as well as in the Unites States. Prolonged use of marijuana or repeated administration of its primary psychoactive constituent, Δ^9-tetrahydrocannabinol (THC), can lead to physical dependence in humans and laboratory animals. The changes that occur with repeated cannabis use include alterations in behavioral, physiological, and biochemical responses. A variety of withdrawal responses occur in cannabis-dependent individuals: anger, aggression, irritability, anxiety and nervousness, decreased appetite or weight loss, restlessness, and sleep difficulties with strange dreams. But the long half-life and other pharmacokinetic properties of THC result in delayed expression of withdrawal symptoms, and because of the lack of contiguity between drug cessation and withdrawal responses the latter are not readily recognized as a clinically relevant syndrome. Over the past 30 years, a substantial body of clinical and laboratory animal research has emerged supporting the assertion that chronic exposure to cannabinoids produces physical dependence and may contribute to drug maintenance in cannabis-dependent individuals. However, no medications are approved to treat cannabis dependence and withdrawal. In this review, we describe preclinical and clinical research that supports the existence of a cannabinoid withdrawal syndrome. In addition, we review research evaluating potential pharmacotherapies (e.g., THC, a variety of antidepressant drugs, and lithium) to reduce cannabis withdrawal responses and examine how expanded knowledge about the regulatory mechanisms in the endocannabinoid system may lead to promising new therapeutic targets.

Key Words: Δ^9-tetrahydrocannabinol (THC); anandamide; cannabis dependence; CB_1 receptor; endogenous cannabinoid (endocannabinoid); fatty acid amide hydrolase (FAAH); marijuana; monoacylglycerol lipase (MAGL); withdrawal

Introduction

For more than 30 years marijuana has been the most-used illicit drug by teenagers and adults in the United States—42% of 18-year-olds and 82% of 50-year-olds report lifetime use (Johnston et al. 2010). Although the perception persists that marijuana use is innocuous and lacks dependence liability, the first record of cannabis withdrawal was published in the 1940s (Wallace and Cunningham 1944) and the medical community is now beginning to accept the idea that cannabis-related disorders represent a clinically significant public health problem (for review, Weinstein and Gorelick 2011). According to the Drug Abuse Warning Network, marijuana was involved in 374,435 hospital emergency department visits or 37.7% of all such visits involving an illicit drug in 2008, and marijuana users accounted for 18.5% of the 177,879 drug-related emergency department visits that year by patients seeking detoxification or substance abuse treatment services (SAMHSA 2011).

In this review, we discuss data from human surveys, retrospective and clinical studies, and preclinical research characterizing cannabis dependence. The preponderance of evidence suggests that cannabis dependence should be considered an important medical condition that requires clinical intervention. Cannabis-dependent individuals who cease using the drug experience a variety of withdrawal symptoms that are sufficiently severe to contribute to drug maintenance, thus highlighting its addictive properties. We review both clinical and preclinical studies examining a variety of pharmacotherapies to alleviate withdrawal signs.

Almost half a century has passed since the structure of the primary psychoactive constituent of *Cannabis sativa*, Δ^9-tetrahydrocannabinol (THC[1]), was first elucidated (Gaoni and Mechoulam 1964). Since then, more than 70 other phytocannabinoids have been discovered (Elsohly and Slade 2005) and hundreds, if not thousands, of cannabinoids have been synthesized.

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[1]Abbreviations that appear ≥3x throughout this article: 2-AG, 2-arachidonylglycerol lipase; CB, cannabinoid; FAAH, fatty acid amide hydrolase; MAGL, monoacylglycerol lipase; THC, Δ^9-tetrahydrocannabinol

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Studies have shown that THC and many other cannabinoids bind to and activate two types of cannabinoid (CB^1) receptors that have been cloned: CB_1 (Matsuda et al. 1990) and CB_2 (Gerard et al. 1991). CB_1 receptors, which are heterogeneously expressed throughout the central nervous system (CNS) and periphery (Felder and Glass 1998; Herkenham et al. 1990; Matsuda et al. 1993), are responsible for most of the pharmacological actions of THC, particularly in the CNS. CB_2 receptors are associated with immune cells (Klein et al. 2003) and were initially thought to be expressed solely in the periphery, but more recently they were found to be expressed in microglial cells (Cabral and Marciano-Cabral 2005) and in neurons (Van Sickle et al. 2005) in the brain.

A major breakthrough in cannabinoid pharmacology came with the discovery of the endogenous cannabinoids (endocannabinoids) *N*-arachidonylethanolamine (anandamide) (Devane et al. 1992) and 2-arachidonylglycerol (2-AG[1]) (Mechoulam et al. 1995; Sugiura et al. 1995). The endocannabinoid system comprises the CB receptors, the endocannabinoids, and the enzymes that regulate endocannabinoid biosynthesis and degradation (Ahn et al. 2008). Blockade of the enzymes fatty acid amide hydrolase (FAAH[1]) and monoacylglycerol lipase (MAGL[1]) raises brain levels of anandamide (Kathuria et al. 2003; Lichtman et al. 2004) and 2-AG (Long et al. 2009) respectively. These catabolic enzymes are targets for the development of selective inhibitors to treat cannabis-related disorders as well as pain, inflammation, and anxiety.

We review evidence from laboratory animal and human studies showing that repeated administration of cannabinoids can result in physical dependence. Emerging data indicate that cannabinoid-dependent laboratory animals and humans display physical withdrawal responses upon drug cessation. In addition, we provide an overview of preclinical and clinical research examining pharmacotherapies to treat cannabis dependence. In animal studies, THC administration and inhibition of endocannabinoid catabolic enzymes represent promising approaches to reduce cannabinoid withdrawal responses. We discuss several clinical studies showing that oral THC reduces cannabis withdrawal responses in cannabis-dependent patients.

Cannabis Use, Dependence, and Withdrawal in Humans

Although the current *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., called the DSM-IV; APA 1994) and *International Statistical Classification of Diseases and Related Health Problems* (10th ed., called the ICD-10; WHO 2007), the two most common guidebooks used by medical professionals to diagnose substance use disorders, include criteria and symptoms for diagnosing cannabis abuse and dependence, only the latter recognizes a withdrawal syndrome as a component of a cannabis dependence disorder. The DSM-IV reflects the attitude of many in medicine and the general public that cannabis is not a physically addictive substance in which a withdrawal syndrome can produce clinically relevant symptoms of a severity and duration to affect substance-use behavior. This belief is probably due to a multitude of factors, such as the relatively slow onset and unique constellation of the withdrawal syndrome.

Cannabis is the most commonly used illicit drug worldwide. In the United States approximately 56% of young adults (19–28 years old) have at least tried cannabis (Johnston et al. 2010). This high prevalence allows for many people to have personal or anecdotal experience with marijuana without necessarily having personal interactions with dependent users. Although only about 3–4% of individuals who have ever tried cannabis meet the criteria for a cannabis use disorder (compared with 15–25% for cocaine), the total number of Americans classified with such disorders is 4.3 million, more than twice that of cocaine and heroin combined (SAMHSA 2008).

The severity of cannabis withdrawal is not generally associated with symptoms that require hospitalization or are viewed as potentially life threatening. Furthermore, only a subset of regular marijuana users experience a clustering of symptoms upon cessation of use; estimates range from 1 in 6 to half of all such users (Budney et al. 1999; Wiesbeck et al. 1996). Common symptoms observed during cannabis withdrawal include anger, aggression, irritability, anxiety and nervousness, decreased appetite or weight loss, restlessness, and sleep difficulties with strange dreams (Budney and Hughes 2006). Although the immediate physical impact of these symptoms is mild when compared with certain other drugs of abuse, as discussed below the comprehensive impact of the cannabis withdrawal syndrome is becoming better understood.

Controlled Laboratory Studies

Before the cloning of cannabinoid receptors, discovery of the endogenous cannabinoid system, and development of selective cannabinoid agonists and antagonists, early studies of marijuana smokers indicated potential signs of tolerance and withdrawal (Williams et al. 1946). In the 1970s, Jones and colleagues set out to define the physiological and psychoactive effects of cannabis in controlled laboratory settings (Jones and Benowitz 1976; Jones et al. 1981). Human subjects were given varying oral doses of THC in a double-blind fashion, spaced evenly throughout the day to maintain consistent drug levels. THC produced profound tolerance after repeated administration, as assessed by the following: self-reported intoxication, time spent in REM sleep, psychomotor task performance, and numerous autonomic physiological effects. The investigators also identified a subset of behaviors that increased dramatically among subjects during the 4 days after cessation of the drug, including disturbances in sleeping and eating, sweats and chills, tremors and restlessness, and irritability. Most of these symptoms subsided after a resumption of THC intake or marijuana smoking (Jones et al. 1981; Jones and Benowitz 1976). Subsequent studies

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of marijuana smokers in the laboratory over periods of use and cessation replicated these findings but lacked the controls and precise measurements of the earlier laboratory studies (Georgotas and Zeidenberg 1979; Nowlan and Cohen 1977).

More recently, Haney and colleagues (1999) used data from both laboratory and survey findings to ascertain how heavy users of cannabis respond to use and abstinence in terms of cognitive function, subjective drug effects, and detailed cannabis-specific withdrawal symptoms. Parallel studies using identical methodologies evaluated the effects of oral THC and smoked marijuana. Both types of studies showed increases in ratings of anxiety and irritability and disturbances in food intake, but sleep patterns seemed more sensitive to abstinence from oral THC, and marijuana abstinence impaired performance on a task measuring attention. Other controlled studies reported that chronic marijuana users show deficits associated with complex decision making and cognitive planning (Hermann et al. 2009; Wesley et al. 2011; Whitlow et al. 2004). These studies marked a renewed effort to define the symptoms and impact of cannabis dependence.

Retrospective and Large Population Studies

Although laboratory studies provide for a controlled environment, increased compliance, and around-the-clock data collection, they generally incorporate relatively small sample sizes (on the order of a few dozen) and are conducted on a subset of relatively heavy cannabis users (for a critique of these and other studies discussed in this review, see Smith 2002). In contrast, large datasets are used in retrospective studies in which subjects are asked to recall their own attempts to abstain from marijuana use, providing insight into real-world conditions.

In one such study, thousands of people ranging from cannabis-naïve to daily smokers were interviewed about their cannabis withdrawal symptoms (Wiesbeck et al. 1996). Examining for symptoms similar to those found in laboratory studies, the authors noted that only a small percentage of infrequent and even daily users reported each withdrawal symptom. However, approximately 16% of the regular marijuana smokers recalled distinct clusters of withdrawal symptoms upon cessation, and these subjects were more than twice as likely to meet DSM-III criteria for cannabis and other drug dependencies.

Budney and colleagues (1999) conducted a retrospective study of a group seeking treatment for cannabis use and found that over half the subjects reported at least four moderate withdrawal symptoms during their last attempt to stop. A more recent multisite study established that retrospective reports of specific marijuana withdrawal symptoms were similar in a general population sample to symptoms in treatment-seeking individuals (Mennes et al. 2009).

Large-scale data collection, such as data mining of national surveys on drug use, has been a useful approach to investigate cannabis dependence. One study used the Australian National Survey of Mental Health and Wellbeing, in which the criteria of both the DSM-IV and ICD-10 were used to identify cannabis-dependent users. A very high percentage (>85%) of individuals classified as having cannabis dependence disorder by both sets of criteria were identified as using cannabis to abate withdrawal symptoms and failing either to control their use or to abstain (Swift et al. 2001).

A similar large-scale study in the United States used data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). A comparison of frequent (≥3 times per week) use of cannabis alone versus in combination with other drugs showed a similar frequency of reported withdrawal symptoms associated with cannabis, with or without concurrent use of other substances (Hasin et al. 2008). The incidence of symptoms correlated highly with the amount of cannabis used, levels of distress, and subsequent general substance use to relieve symptoms. This association supports the notion that cannabis withdrawal symptoms contribute to the maintenance of cannabis use in dependent individuals.

Outpatient Cohort and Self-Report Studies

The largest volume of published research describes self-report and monitored outpatient studies, which allow for immediate reporting of symptoms and timeline information without constant supervision and monitoring. Measurement of urinary drug metabolites is a common method to verify initial drug use and abstinence from cannabis or other drugs.

Patients identified as heavy cannabis users typically show a moderate set of symptoms, both physical (e.g., weight loss) and psychological (e.g., marijuana craving), which appear within a day of halting cannabis use and usually abate in a week (Budney et al. 2001; Dawes et al. 2006; Kouri and Pope 2000; Preuss et al. 2010). This time course corresponds to rather precipitous drops in THC metabolites in the urine during the first few days of abstinence. Other common symptoms, such as irritability and aggression, can persist for weeks (Budney et al. 2003; Kouri et al. 1999).

Although many of these studies contain sample sizes not much larger than those of laboratory studies, they allow a more thorough examination of how cannabis withdrawal symptoms affect the daily life of users and can be readily performed by numerous treatment clinics to build a converging set of data from multiple sites.

Cannabis Withdrawal Syndrome in Perspective

The exact timeline and symptoms of the cannabis withdrawal syndrome vary across studies, but the growing consensus is that withdrawal symptoms contribute to continued drug use. Cannabis withdrawal is comparable in severity and scope to tobacco withdrawal and contributes to relapse to only a slightly lesser extent (Budney et al. 2008).

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Bonn-Miller and Moos (2009) evaluated marijuana use in male inpatients treated for substance use disorders in Department of Veterans Affairs residential substance abuse programs and reported that anxiety symptoms at treatment discharge were associated with a 12-month relapse to marijuana use. Although this finding is consistent with the idea that increases in anxiety after marijuana discontinuation may be predictive of relapse, the study did not report whether these patients were marijuana dependent.

Other studies also show that the occurrence of withdrawal symptoms may predict marijuana users who will relapse soon after a prolonged outpatient abstinence period (Chung et al. 2008; Cornelius et al. 2008) and increases the likelihood that these users will relapse into continued heavy use (Moore and Budney 2003). Withdrawal symptoms do not, however, appear to predict relapse after 2 or more years of abstinence (Arendt et al. 2007).

Studies are beginning to examine the interactions of cannabis use with other drug use and have shown that concurrent cessation of tobacco and cannabis use is associated with temporary increases in withdrawal severity compared with cessation of either alone (Vandrey et al. 2008), and the severity of cannabis withdrawal symptoms may lead to the increased use and craving of alcohol (Peters and Hughes 2010). Cannabis users often differentially use alcohol, tobacco, or cannabis to reduce the severity of specific symptoms (Copersino et al. 2006).

Taken together, the evidence shows that withdrawal from cannabis use produces a distinct syndrome that increases drug craving and use, thus necessitating research into therapeutic treatment.

Preclinical Studies of Cannabinoid Dependence

Preclinical studies in a variety of laboratory animals show that repeated administration of THC or other cannabinoid agonists results in dependence. Animal models for assessing dependence also measure reinforcing and rewarding properties—such as self-administration, conditioned place preference, and intracranial self-stimulation (for a complete review, Panagis et al. 2008)—as well as withdrawal signs, which can include both physiological symptoms and indicators of emotional state.

Characterization of Cannabinoid Withdrawal

The two general approaches used to induce a state of drug withdrawal in preclinical drug dependence studies are spontaneous withdrawal and precipitated withdrawal. Spontaneous withdrawal occurs after abrupt cessation of the drug, which is metabolized and cleared from the body. In precipitated withdrawal, an appropriate selective receptor antagonist is used to displace the agonist from the receptor, resulting in the rapid onset of withdrawal symptoms. The specific withdrawal symptoms, intensity, and duration depend on the pharmacological characteristics of the compound; drugs from the same class generally share similar withdrawal syndromes. The precipitated withdrawal model is used more often than the spontaneous model because of the long half-life of THC and because subtle withdrawal effects in the latter model are difficult to observe and quantify.

The results of preclinical studies using precipitated and spontaneous withdrawal procedures are shown in Table 1.

Spontaneous Cannabinoid Withdrawal in Laboratory Animals

Abrupt cessation of THC after prolonged administration results in delayed onset and long-duration withdrawal symptoms, so the quantification of abrupt withdrawal signs in laboratory animals is challenging (Huestis 2005) and often yields mixed results.

The study of somatic withdrawal signs from repeated administration of THC and other cannabinoids has been examined in different animal species. Although one study in rats reported a variety of abnormal behavior signs, such as tremors, wet-dog shakes, and hyperirritability (Kaymakcalan et al. 1977), other studies failed to find significant abrupt withdrawal signs either in rodents (Aceto et al. 1996; Leite and Carlini 1974) or in pigeons after chronic exposure to THC (McMillan et al. 1973). In contrast, rhesus monkeys chronically infused with intravenously administered THC (0.5 mg/kg of body weight 4x/day for 3 weeks) displayed substantial increases in gross movement, eye contact, and baring of teeth during the first week of abstinence (Fredericks and Benowitz 1980). These behavioral effects reflect "rebound" withdrawal symptoms, as they were initially suppressed by acute administration of THC. In another study, food-reinforced operant responding was decreased in monkeys after abrupt cessation of drug infusions (Beardsley et al. 1986). Spontaneous withdrawal responses also occurred after discontinuation of chronic administration of the full cannabinoid receptor agonists WIN 55212 in rats (Aceto et al. 2001) and CP 55940 in mice (Oliva et al. 2003).

The data from these studies suggest that the ability to observe and quantify spontaneous withdrawal effects in experimental animals depends on many factors including species, cannabinoid selection, duration of drug administration, time point at which withdrawal is assessed, and specific endpoints. Yet, although the spontaneous withdrawal approach presents with considerable challenges and may be prone to false negatives because of the slow elimination of THC and its metabolites (Huestis 2005), it is considered to be more valid than precipitated withdrawal for modeling human cannabis withdrawal.

Precipitated Cannabinoid Withdrawal in Laboratory Animals

The development of CB_1 receptor antagonists (e.g., rimonabant; Rinaldi-Carmona et al. 1994) has been highly useful in

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Table 1 Preclinical studies investigating cannabinoid withdrawal using precipitated and spontaneous withdrawal procedures

Species	Type of withdrawal	Agonist, dosing regimen, route of administration	Dependent variable	Reference
Mouse	Precipitated	THC, 6½ days: 10 mg/kg s.c. (b.i.d.)	Somatic signs	Cook et al. 1998
Mouse	Precipitated	THC, 5½ days: 10 20 mg/kg i.p. (b.i.d.)	Somatic signs, adenylyl cyclase overshoot in cerebellum	Hutcheson et al. 1998
Mouse	Precipitated	THC, 5½ days: 20 mg/kg i.p. (b.i.d.)	Somatic signs	Valverde et al. 2000
Mouse	Precipitated	THC, 6½ days: 10 mg/kg s.c. (b.i.d.)	Somatic signs	Lichtman et al. 2001a
Mouse	Precipitated	THC, 5½ days: 20 mg/kg i.p. (b.i.d.)	Somatic signs, body weight	Anggadiredja et al. 2003
Mouse	Spontaneous	CP, 6½ days: 0.5 mg/kg i.p. (b.i.d.)	Increased locomotor activity, endocrine gene transcription levels	Oliva et al. 2003
Mouse	Precipitated	THC, MAR, 5 days: 200 mg; 5 or 10 mg/kg i.v. (s.i.d.)	Somatic signs	Wilson et al. 2006
Mouse	Precipitated	THC, 5½ days: 20 mg/kg i.p. (b.i.d.)	Somatic signs	Tourino et al. 2007
Mouse	Precipitated	THC, 4½ days: 25 mg/kg s.c. (b.i.d.)	Somatic signs, activity	Huang et al. 2009
Mouse	Precipitated	THC, 5½ days: 50 mg/kg s.c. (b.i.d.); 10 mg/kg (s.i.d.)	Somatic signs	Schlosburg et al. 2009
Mouse	Precipitated	THC, AEA, 5½ days: 50 mg/kg s.c. (b.i.d.)	Somatic signs	Falenski et al. 2010
Mouse	Precipitated	THC, 10 days: 10 mg/kg s.c. (s.i.d.)	Anxiogenic effects (plus maze)	Huang et al. 2010
Mouse	Precipitated	JZL 184, THC, 10 days: 40 mg/kg i.p. (s.i.d.)	Somatic signs	Schlosburg et al. 2010
Rat	Precipitated	THC, 4 days: 0.5–4; 2.5–20; 12.5–100 mg/kg/hr i.p.	Somatic signs	Aceto et al. 1995
Rat	Precipitated	THC, 6½ days: 15 mg/kg i.p. (b.i.d.)	Activity	Tsou et al. 1995
Rat	Precipitated, spontaneous	THC, 4 days: 12.5–100; 2.5–20; 0.5–4 mg/kg/24 hr i.p. (cont.)	Somatic signs with precipitated only	Aceto et al. 1996
Rat	Precipitated	THC, 6½ days: 15 mg/kg i.p. (b.i.d.)	Somatic signs	Diana et al. 1998
Rat	Precipitated	CP, 6½ days: 0.4 mg/kg i.p. (b.i.d.)	Somatic signs, activity	Rubino et al. 1998
Rat	Precipitated	THC, 6 days: 10–30; 10–40; 10–50 mg/kg s.c. (b.i.d.)	Operant rate	Beardsley and Martin 2000
Rat	Precipitated, spontaneous	WIN, 4 days: 1–8; 2–16; 4–16 mg/kg/24 hr i.p. (cont.)	Somatic signs, body weight	Aceto et al. 2001
Rat	Precipitated	THC, 4 days: 12.5–100 mg/kg/24 hr i.p. (cont.)	Somatic signs	Breivogel et al. 2003
Rat	Precipitated	HU-210, 5½ days: 100 μg/kg i.p. (b.i.d.)	Somatic signs	Cui et al. 2001
Rat	Precipitated	THC, 8 days: 10 mg/kg i.p. (b.i.d.)	Somatic signs, activity	Gonzalez et al. 2004
Dog	Precipitated	THC, 10 days: 0.6–1 mg/kg i.v. (b.i.d.)	Somatic signs	Lichtman et al. 1998a
Monkey	Spontaneous	THC, 10 days: 0.05 mg/kg/hr i.v.	Operant rate suppression	Beardsley et al. 1986
Monkey	Precipitated, spontaneous	THC, continuous (drug discrimination study): 1 mg/kg (b.i.d.)	Somatic signs, operant rate suppression	Stewart and McMahon 2010

AEA, anandamide; b.i.d., twice a day; cont., continuous infusion; CP, CP 55940; HU-210, a synthetic cannabinoid; i.p., intraperitoneally; i.v., intravenously; MAR, marijuana; s.c., subcutaneously; s.i.d, once a day; THC, Δ^9-tetrahydrocannabinol; WIN, WIN 55212-2

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investigations of precipitated withdrawal in cannabinoid-dependent animals. Rimonabant binds with high affinity to the CB_1 receptor and antagonizes the pharmacological effects of many cannabinoid receptor agonist activities in both laboratory animals and humans (Compton et al. 1996; Huestis et al. 2001, 2007; Lichtman et al. 1998b; Rinaldi-Carmona et al. 1994; Winsauer et al. 1999).

Somatic Withdrawal Signs

Soon after the discovery of rimonabant, two independent groups used this antagonist in rats to demonstrate somatic precipitated withdrawal signs—wet-dog shakes, forepaw fluttering, chewing, increased horizontal and vertical activity, retropulsion, and ptosis (Aceto et al. 1995; Tsou et al. 1995). Rimonabant also precipitated a profound withdrawal syndrome in mice that were chronically exposed to either THC or marijuana smoke (Wilson et al. 2006). Withdrawal signs such as paw tremors and wet-dog shakes are observed consistently across all strains (Cook et al. 1998; Huang et al. 2009). Other signs such as mastication, sniffing, and piloerection are of low frequency but are scored in a cannabinoid composite withdrawal index (Hutcheson et al. 1998; Ledent et al. 1999; Lichtman et al. 2001b; Tzavara et al. 2000). In THC-dependent dogs, rimonabant precipitated a withdrawal syndrome that included distinct gastrointestinal signs (e.g., diarrhea, vomiting, excessive salivation), decreases in social behavior, and increases in restless behavior and trembling (Lichtman et al. 1998a).

In naïve animals, rimonabant can also produce pharmacological effects that resemble withdrawal symptoms, although these effects are far less in magnitude than those elicited by rimonabant in cannabinoid-dependent subjects (for review, Lichtman and Martin 2005), including increases in ear scratching, head shakes, and increased grooming behavior (Cook et al. 1998; Darmani and Pandya 2000).

These studies show that it is critical to include appropriate vehicle-treated control groups in studies using a CB_1 antagonist to precipitate cannabinoid withdrawal to control for intrinsic effects of the drug at testing. Nonetheless, the observation that rimonabant elicits a far greater magnitude of withdrawal-like behavior (e.g., head shakes and paw tremors) in subjects that experience repeated administration of THC or repeated exposure to marijuana smoke than in control animals (Cook et al. 1998; Wilson et al. 2006) supports the use of the precipitated withdrawal model.

Aversive and Subjective Signs

There are few reports examining aversive or emotional responses in rodents undergoing cannabinoid withdrawal. Rimonabant challenge to THC-dependent mice led to less time in the open-arm component of the elevated plus maze test (Huang et al. 2010), suggesting an anxiogenic-like effect in subjects undergoing cannabinoid withdrawal, but failed to elicit aversive or dysphoric effects in the conditioned place avoidance test (Hutcheson et al. 1998).

Other studies have focused on subjective signs of cannabinoid withdrawal. Monkeys chronically treated with THC demonstrated robust discrimination of the CB_1 antagonist rimonabant (McMahon 2006; McMahon and France 2003; Stewart and McMahon 2010), and THC discontinuation produced a similar discriminative stimulus to rimonabant in THC-treated animals. The data suggest that the interoceptive cues of THC cessation–induced abstinence are mediated by the CB_1 receptor.

Precipitated Withdrawal with Other Cannabinoid Agonists

Rimonabant has precipitated withdrawal signs after chronic administration of other cannabinoid agonists such as anandamide, methanandamide, WIN 55212, CP 55940, and HU-210 (Aceto et al. 1998, 2001; Rodriguez de Fonseca et al. 1997; Rubino et al. 1998).

The withdrawal syndrome precipitated after chronic anandamide administration is not as robust as that precipitated with other cannabinoids (Costa et al. 2000; Falenski et al. 2010). Mice with persistently elevated anandamide levels after inhibition of FAAH with the inhibitor URB597 and mice lacking the FAAH enzyme do not show any withdrawal symptoms after rimonabant administration (Falenski et al. 2010; Schlosburg et al. 2009).

In contrast, rimonabant elicited a mild intensity of somatic withdrawal signs in mice treated chronically with the irreversible MAGL inhibitor JZL 184 that produced a tenfold increase in levels of 2-AG (Schlosburg et al. 2010). Thus, increases of the two primary endocannabinoids in the brain result in different consequences of physical dependence. This difference may be related to brain 2-AG levels that are already two orders of magnitude greater than the brain levels of anandamide and to the fact that 2-AG is a full CB_1 agonist and anandamide a partial CB_1 agonist (Howlett and Mukhopadhyay 2000).

Neurobiological Adaptations during Cannabinoid Dependence

Preclinical studies are now beginning to identify the molecular changes that result from repeated exposure to and cessation of cannabinoid use. Such studies provide indicators of the adaptations that drive withdrawal symptomatology and thus improve strategic targeting of therapeutics.

Chronic administration of cannabinoid agonists results in downregulation of the CB_1 receptor in several brain regions as measured by radioligand binding (Breivogel et al. 1999). Similarly, chronic treatment with THC produces a time- and region-dependent desensitization of CB_1 activity in the G protein (Breivogel et al. 1999; Romero et al. 1997). Other evidence of dysregulation in the endocannabinoid system includes region-specific alterations in endocannabinoid content after precipitated withdrawal in rats and mice (Gonzalez et al. 2004).

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Alterations in numerous other neurotransmitter systems are also associated with withdrawal from THC in rodents. After chronic administration of THC, brain levels of serotonin decrease concurrent with increases in its primary metabolite (Taylor and Fennessy 1978, 1982). The finding that various serotonin uptake inhibitors elicited writhing, backward kicks, jumps, and wet-dog shakes in THC-dependent rats suggests serotonergic involvement in cannabinoid withdrawal-like behavior (Verberne et al. 1980). In addition, histamine levels in the brain decrease during initial exposure to THC and during somatic withdrawal induced by the serotonin reuptake inhibitor clomipramine (Verberne et al. 1985). Several studies have shown evidence of upregulation and release of the stress-related peptide corticotropin-releasing factor upon precipitated withdrawal, a common phenomenon during withdrawal from many drugs of abuse (Gonzalez et al. 2004; Rodriguez de Fonseca et al. 1997).

At the intracellular level, the cyclic adenosine monophosphate (cAMP) second messenger signaling system appears to be involved in modulating cannabinoid withdrawal. Rimonabant administered to THC-dependent mice resulted in significant increases in basal and forskolin-stimulated adenylyl cyclase activity in the cerebellum but not in other regions (Hutcheson et al. 1998). Similar results were obtained with calcium-calmodulin-stimulated cyclase activity from the cerebella of THC-dependent rats undergoing precipitated withdrawal (Rubino et al. 2000). Rimonabant-precipitated cannabinoid withdrawal also results in upregulation of protein kinase A (PKA) activity, which is downstream of cAMP, in the cerebella of THC-dependent rats (Tzavara et al. 2000). Infusions of the cAMP blocker Rp-8Br-cAMPs into the cerebellum of rats undergoing precipitated withdrawal attenuated PKA activity and the expression of withdrawal signs. Conversely, infusion of Sp-8Br-cAMPs, a cAMP analogue, into the cerebellum elicited cannabinoid withdrawal somatic signs in drug-naïve mice. These findings provide strong evidence for the functional role of the cAMP cascade, particularly in the cerebellum, in modulating withdrawal from cannabinoids.

Pharmacotherapy for Cannabinoid Withdrawal

Attenuation of Cannabinoid Withdrawal Signs in Laboratory Animals

The development of preclinical cannabinoid withdrawal models has made it possible to evaluate potential therapeutic agents for the treatment of cannabis dependence. Compounds investigated for reducing cannabinoid withdrawal responses include cannabinoid substitutes, such as THC and inhibitors of endocannabinoid catabolic enzymes, and non-cannabinoid drugs, such as lithium and clonidine (Table 2).

Early studies reported that reintroduction of THC (1) alleviated decreases in operant responding in nonhuman primates undergoing spontaneous withdrawal (Beardsley et al. 1986), (2) decreased clomipramine-precipitated THC withdrawal symptoms in rats (Verberne et al. 1981), and, more recently, (3) reversed rimonabant-precipitated withdrawal signs in THC-dependent mice (Lichtman et al. 2001a). In addition, the α_2-adrenergic agonist clonidine dose-dependently attenuated the intensity of precipitated somatic withdrawal signs (Lichtman et al. 2001a) and reduced rimonabant-induced head shaking and rimonabant discriminative stimulus in THC-dependent monkeys (Stewart and McMahon 2010).

In contrast, THC dose-dependently attenuated the intensity of rimonabant-precipitated paw tremors in mice rendered dependent on marijuana smoke, but marijuana itself failed to reverse the precipitated withdrawal effect (Wilson et al. 2006). The lack of effect of marijuana itself was attributed to the lower THC brain levels after exposure to marijuana smoke (203 ng of THC per g of brain tissue) compared with intravenous injection of THC (1862 ng of THC per g of brain tissue).

Morphine also reduced the intensity of rimonabant-precipitated withdrawal signs in THC-dependent mice (Lichtman et al. 2001b), and lithium, a mood stabilizer, prevented the expression of withdrawal signs precipitated by the CB_1 antagonist AM 251 in rats treated repeatedly with the potent synthetic cannabinoid HU-210 (Cui et al. 2001).

With the discovery of endocannabinoids, there has been interest in targeting the degradative enzymes of these naturally occurring ligands (Clapper et al. 2009; Piomelli 2004). Schlosburg and colleagues (2009) showed that the FAAH inhibitor URB597 attenuated the intensity of paw tremors and head shakes in THC-dependent mice challenged with rimonabant and that the selective MAGL inhibitor JZL 184 also alleviated the intensity of withdrawal signs.

If targeting endocannabinoid catabolic enzymes is indeed a viable approach to treat cannabis withdrawal, it is important to know whether these inhibitors would themselves have abuse or dependence liability. FAAH inhibitors have been extensively investigated in a variety of such paradigms. Importantly, it has been demonstrated that URB597 does not produce rewarding effects in the rat conditioned place preference paradigm, does not substitute for THC in the drug discrimination paradigm, and is not self-administered by nonhuman primates (Gobbi et al. 2005; Justinova et al. 2008). In addition, rimonabant does not precipitate any apparent withdrawal symptoms in mice treated subchronically with URB597 (Schlosburg et al. 2009) or the FAAH inhibitor PF-3845 (Schlosburg et al. 2010).

There is also supporting biochemical evidence that chronic treatment with FAAH inhibitors does not lead to long-term neural adaptations. Once-daily dosing with URB597 for 5 weeks exerted its pharmacological effects without altering CB_1 messenger RNA levels (Bortolato et al. 2007). Likewise, repeated dosing of PF 3845 did not lead to desensitization or downregulation of CB_1 receptors and did not alter CB_1 receptor–mediated synaptic plasticity of hippocampal neurons. In contrast, repeated treatment with a high dose of the MAGL inhibitor JZL184 led to mild cannabinoid

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Table 2 Preclinical and clinical studies evaluating pharmacological agents in reducing cannabinoid withdrawal responses

Species	Type of withdrawal	Agonist, dosing regimen	Withdrawal response	Treatment drug	Effect on withdrawal	Reference
Mouse	Precipitated	THC, 6½ days: 10 mg/kg s.c. (b.i.d.)	Somatic signs	Clonidine	Attenuation	Lichtman et al. 2001a
Mouse	Precipitated	THC, 5½ days: 20 mg/kg i.p. (b.i.d.)	Somatic signs, body weight	Prostaglandin E_2	Attenuation	Anggadiredja et al. 2003
Mouse	Precipitated	THC, MAR, 5 days: 200 mg; 5, 10 mg/kg/i.v. (s.i.d.)	Somatic signs	Marijuana	No effect	Wilson et al. 2006
Mouse	Precipitated	THC, 5½ days: 20 mg/kg i.p. (b.i.d.)	Somatic signs	MDMA	Attenuation	Tourino et al. 2007
Mouse	Precipitated	THC, 5½ days: 10/50 mg/kg s.c. (s.i.d./b.i.d.)	Somatic signs	URB597, JZL 184	Attenuation	Schlosburg et al. 2009
Rat	Precipitated	HU-210, 5½ days: 100 μg/kg i.p. (b.i.d.)	Somatic signs	Lithium	Attenuation	Cui et al. 2001
Monkey	Precipitated, spontaneous	THC, cont., 1 mg/kg (b.i.d.)	Head shaking, withdrawal drug discrimination	THC and CP WIN and clonidine; diazepam and cocaine	Full attenuation Partial attenuation of drug discrimination No attenuation	Stewart and McMahon 2010
Human	Spontaneous	MAR, 6 ± 1 days/wk, 6–7 joints/day, inhalation	Subjective ratings	Bupropion	Exacerbation	Haney et al. 2001
Human	Spontaneous	MAR, ad libitum/5 joints/day, inhalation	Subjective ratings	Nefazodone	Partial attenuation	Haney et al. 2003
Human	Spontaneous	MAR, 1 joint/session, inhalation	Craving, subjective ratings	THC, divalproex	Attenuation; decreased craving, but exacerbated other symptoms	Haney et al. 2004
Human	Spontaneous	MAR, ad libitum, inhalation	Subjective ratings	Divalproex	No effect	Levin et al. 2004
Human	Spontaneous	MAR, ad libitum	MAR use	Quetiapine (open-label, pilot study)	Reduction in use	Potvin et al. 2004
Human	Spontaneous	MAR, 1–15 joints daily, inhalation	Somatic, MCQ	Lithium (pilot study)	Inconclusive	Bowen et al. 2005
Human	Spontaneous	MAR, ad libitum, inhalation	Subjective ratings	Buspirone (pilot study)	Attenuation	McRae et al. 2006
Human	Spontaneous	MAR, 28½ days/month, 2.6 times/day average, inhalation	Various addiction mood inventories	THC	Attenuation	Budney et al. 2007

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Human	Spontaneous	MAR, ad libitum	Subjective ratings	THC	Reversed anorexia weight loss, decreased some withdrawal symptoms, but increased sleep onset latency, did not decrease marijuana relapse	Haney et al. 2008
				Lofexidine	Worsened abstinence-related anorexia, did not attenuate withdrawal, but improved sleep; decreased relapse	
Human	Spontaneous	MAR, ad libitum	Subjective ratings	Atomoxetine	No effect (adverse gastrointestinal effects)	Tirado et al. 2008
Human	Spontaneous	MAR, ad libitum	Subjective ratings	Buspirone	No significant effects	McRae-Clark et al. 2009
Human	Spontaneous	MAR, ad libitum	Subjective ratings	Lithium (open-label study)	Inconclusive results	Winstock et al. 2009

b.i.d., twice a day; cont., continuous infusion CP, CP 55940; HU-210, a synthetic cannabinoid; i.p., intraperitoneally; i.v., intravenously; MAR, marijuana; MDMA, 3,4-methylenedioxymethamphetamine; MCQ, Marijuana Craving Questionnaire; s.c., subcutaneously; s.i.d., once a day; THC, Δ^9-tetrahydrocannabinol; WIN, WIN 55212-2

withdrawal signs after rimonabant administration, as well as regionally dependent changes in CB_1 receptor downregulation and desensitization in the brain and impaired endocannabinoid-mediated synaptic plasticity (Schlosburg et al. 2010).

The differential actions of prolonged MAGL and FAAH inhibition are not fully understood and may be partly attributed to (1) higher concentrations of 2-AG compared with anandamide after sustained blockade of the respective degradative enzyme of each endocannabinoid and/or (2) differences in the efficacy of these endocannabinoids at the CB_1 receptor. It remains to be established whether repeated administration of lower doses of JZL184 leads to cannabinoid dependence or changes in CB_1 receptor function. Nonetheless, these studies provide proof of principle that bolstering endogenous anandamide or 2-AG through the inhibition of their respective catabolic enzymes may be viable approaches to reduce cannabis withdrawal symptoms.

Attenuation of Cannabis Withdrawal Symptoms in Humans

In recent years efforts to identify treatments for cannabis dependence disorders have increased considerably. Most of the current research is limited to small-scale laboratory models and small open-label trials. Medications investigated in the clinical laboratory setting include cannabinoid substitutes (e.g., THC) and a select group of noncannabinoid agents (e.g., divalproex, buspirone, bupropion, lithium, nefazodone, and lofexidine; see Table 2). Many of these compounds were selected because of their effectiveness in treating specific symptom clusters or their overall clinical evidence in treating opiate or tobacco-use disorders. For a recent review of pharmacological treatment of cannabis dependence, see Weinstein and Gorelick (2011).

Cannabinoid Substitution

Dronabinol, or oral synthetic THC, has been reliably reported to reduce withdrawal symptoms in cannabis-dependent individuals. In the first inpatient study, dronabinol (10 mg, 5x/day for 6 days) significantly decreased drug cravings, anxiety, chills, misery, and troubled sleep and reversed decreases in food intake (Haney et al. 2004). The findings of this study were extended to an outpatient setting that showed that dronabinol (10 or 30 mg, 3x/day for 15 days) attenuated cannabis withdrawal symptoms such as aggression, craving, troubled sleep, and irritability (Budney et al. 2007). In a subsequent study, dronabinol administered at 20 mg, three times a day for 8 days, decreased symptoms of cannabis withdrawal such as restlessness, anorexia, and chills (Haney et al. 2008). The most recent study reported that dronabinol (200 mg, 2x/day for 8–10 weeks) improved treatment retention and alleviated withdrawal symptoms in marijuana-dependent subjects (Levin et al. 2011).

Haney and colleagues (2008) also showed that a combination of dronabinol and lofexidine, an α_2-adrenergic receptor

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agonist, produced the most robust improvements in sleep and decreased marijuana withdrawal symptoms and cravings relative to each medication by itself. Yet, despite the preclinical efficacy of another α_2-adrenergic receptor agonist, clonidine, lofexidine by itself had a sedating effect, worsened abstinence-related anorexia, and did not robustly attenuate withdrawal, although it improved sleep and decreased the likelihood of marijuana relapse.

Differences in the effects of α_2-adrenergic receptor agonists between preclinical and clinical studies may point to a possible limitation of cannabinoid withdrawal models. However, clonidine has not been evaluated for efficacy in reducing withdrawal in cannabis-dependent patients, and lofexidine has yet to be examined in preclinical models of cannabinoid withdrawal. In addition, the use of pharmacotherapy for cannabis withdrawal needs to be weighed against side effects, as clonidine and, to a lesser extent, lofexidine produce orthostatic hypotension.

In all of the studies described above, dronabinol itself did not produce any adverse effects, was well tolerated, and lower doses were not significantly distinguishable from placebo treatment.

Noncannabinoid Agents

Various other medications have been evaluated in inpatient studies for the treatment of cannabis withdrawal, largely with mixed results.

The antidepressant nefazodone (450 mg/day) decreased anxiety and muscle pain but did not alleviate irritability, misery, or troubled sleep during marijuana withdrawal (Haney et al. 2003). However, hepatotoxicity with this drug resulted in its removal from the market.

Bupropion (a drug used commonly in the cessation of tobacco use and for the attenuation of associated withdrawal symptoms) administered at 300 mg/day worsened ratings of irritability, restlessness, depression, and troubled sleep compared with placebo maintenance during marijuana withdrawal (Haney et al. 2001). The failure of bupropion to treat marijuana withdrawal underscores the need to treat cannabinoid withdrawal as a unique syndrome and not simply as another form of smoking cessation.

The clinical utility of atomoxetine (a norepinephrine reuptake inhibitor indicated for attention deficit hyperactivity disorder) to treat cannabis withdrawal was investigated in a small open-label study which showed that doses of 20 to 80 mg a day for 11 weeks tended to reduce marijuana use in cannabis-dependent individuals ($p = 0.06$) (Tirado et al. 2008). However, the potential benefit of this medication was negated by adverse gastrointestinal effects (nausea, vomiting, dyspepsia, and loose stools) in the majority of patients.

An open-label study reported that the anxiolytic agent buspirone did not significantly decrease cannabis withdrawal symptoms (McRae-Clark et al. 2009).

Divalproex, a mood stabilizer, when given once a day (1500 mg/day for 29 days), decreased marijuana craving during abstinence but increased ratings of anxiety, irritability, and tiredness (Haney et al. 2004). In a clinical double-blind trial with divalproex (500–2000 mg/day for 6 weeks), there was no effect on any withdrawal measures in the treatment groups in comparison with the placebo group. There was, however, increased incidence of divalproex-related adverse reactions and poor patient compliance during the trial (Levin et al. 2004).

Lithium has been tested for effectiveness in the treatment of cannabis withdrawal. Following results from preclinical studies (Cui et al. 2001), a small ($n = 9$), community-based, open-label study of the effects of lithium (600–900 mg/day for 6 days) on non-treatment-seeking individuals meeting DSM-IV criteria for cannabis dependence found a reduction in withdrawal signs in 50% of the patients (Bowen et al. 2005). Another study also reported that lithium (500 mg, 2x/day for 7 days) reduced the incidence of cannabis withdrawal symptoms, including depression and anxiety, with relatively few adverse effects (Winstock et al. 2009).

A case study with varying doses of the atypical antipsychotic quetiapine (100–1200 mg for 6 months) given to cannabis users with schizophrenia or bipolar disorder reported reduced cannabis use in these patients over the course of treatment (Potvin et al. 2004). However, the results of the study were complicated by concurrent treatments with antidepressants, gabapentin, or methadone in some patients.

Conclusions

Research has firmly established the existence of a clinically significant and distinct cannabis withdrawal syndrome, characterized by anger, aggression, irritability, anxiety or nervousness, decreased appetite or weight loss, restlessness, and sleep difficulties with strange dreams. Dependent individuals may continue to use marijuana to avoid these and other withdrawal symptoms.

Laboratory animal models of cannabinoid withdrawal have been useful not only for characterizing and investigating the neurobiology of cannabinoid dependence but also for assessing potential pharmacological agents for therapeutic use. However, not all positive results in preclinical testing translate to clinical success, probably because of the wide variety of symptoms, both physical and psychological, observed in humans.

The clinical studies described in the preceding section indicate that cannabinoid substitutes, such as THC, show the greatest promise to treat cannabis withdrawal. However, although THC reliably reduces withdrawal responses in cannabinoid-dependent humans and laboratory animals, this drug is also primarily responsible for marijuana's pharmacological effects and thus raises concern about the long-term outcome of this type of substitution therapy. Indeed, repeated THC administration has been well established to produce dependence. In contrast, inhibition of the endocannabinoid catabolic enzyme FAAH reduces the severity of cannabinoid withdrawal in animal models of THC dependence and,

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unlike THC, FAAH inhibitors do not appear to have reinforcing properties or dependence liability.

Given the relatively mild nature of the withdrawal syndrome and the political and public perception of cannabis dependence as a public health concern, there would have to be negligible abuse potential and side effects associated with any pharmacotherapeutic option. Further clinical studies are necessary to ascertain whether endocannabinoid catabolic enzyme inhibitors are effective for reducing withdrawal in cannabis-dependent individuals with minimal adverse impacts.

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