

Cannabinoid Abuse and Addiction: Clinical and Preclinical Findings

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Cannabinoid abuse disorders represent a widespread public health issue, but there are no approved medications for their treatment. This review describes efforts to understand the mechanisms of cannabinoid abuse and its adverse effects, to identify molecular targets for pharmacotherapy, and to evaluate potential treatments in human volunteers and animal models of cannabinoid reward, withdrawal, and relapse.

CANNABIS AND CANNABINOIDS

Cannabis is typically used in the form of marijuana (made from dried leaves and flowers of *Cannabis sativa*) and hashish (made from resin glands of marijuana). In the last decade, synthetic cannabinoids, sprayed onto herbal substrates and marketed under names such as “Spice” or “K2,” have become increasingly prevalent. Like cannabis, these “spice drugs” are typically administered by combustion and inhalation.¹ Fifteen synthetic cannabinoids are currently classified as Schedule I substances, indicating high abuse potential but no approved medical use under the US Controlled Substance Act.² However, the active ingredients of spice drugs (e.g., JWH-018, JWH-073, JWH-200, and CP47,497) are not listed by the manufacturers and are constantly changing in response to legislature, making regulation and enforcement difficult.

Marijuana legalization efforts have been increasingly successful in the United States. At the time of publication, 23 states and the District of Columbia have legalized prescription use of marijuana for treatment of various medical conditions, and 5 states and the District of Columbia have also legalized marijuana for recreational use. Despite these changes in state laws, cannabis remains a Schedule I substance under federal law. In 2013, cannabis was the illicit drug with the largest number of persons reporting past year use.³ Although it remains to be seen, it seems likely that marijuana legalization will increase the already large number of people using and becoming dependent on cannabis.

Cannabis contains over 100 phytocannabinoids, but the pharmacological effects of many of them are not known. The main psychoactive component of cannabis is delta-9-tetrahydrocannabinol (THC; see **Figure 1**), which acts as a partial agonist at cannabinoid type-1 (CB₁) and CB₂ receptors.⁴ The actions of THC at

CB₁ receptors are considered to be critical for its psychoactive effects, but THC also acts at peroxisome proliferator-activated receptors and GPR55 receptors.⁴ Most cannabis preparations also contain cannabidiol (CBD), a cannabinoid that exerts pharmacological effects via multiple mechanisms (e.g., CB₁, CB₂, serotonin 5-HT_{1A}, peroxisome proliferator-activated receptor-gamma, opioid, and transient receptor potential vanilloid-1 receptors, modulation of endocannabinoid metabolism, and intracellular calcium metabolism) that are not yet fully understood.^{4,5} CBD has been shown to have antipsychotic, anticonvulsive, neuroprotective, and anxiolytic effects, and is believed to offset some of the undesirable psychotropic effects of THC.^{4,5} Cannabis also contains over 200 other chemicals, including terpenoids and essential oils, some of which might have pharmacological effects of their own or modulate the effects of other cannabis ingredients, including THC.

The potency of cannabis products (expressed as THC content) has increased steadily over the last four decades. The average THC concentration in confiscated marijuana in the United States increased from 1–2% in the 1970s to 10–11% in 2010.⁶ Reports from the Netherlands and other European countries show that THC content in cannabis can now reach close to 20%.⁷ Cannabis selectively bred for high THC content often has very low CBD content, and its use has been associated with higher occurrence of mental health problems among users (e.g., induction of psychosis in susceptible users, anxiety, panic attacks). Research in cannabis users demonstrate that cannabis with low CBD content produces stronger reinforcing effects and higher ratings of liking and wanting the drug, which could potentially make low-CBD cannabis more addictive.⁵ Unlike THC, which is a partial agonist at CB₁ receptors⁴, many synthetic cannabinoids are high-efficacy full agonists at CB₁ receptors.⁸ Furthermore,

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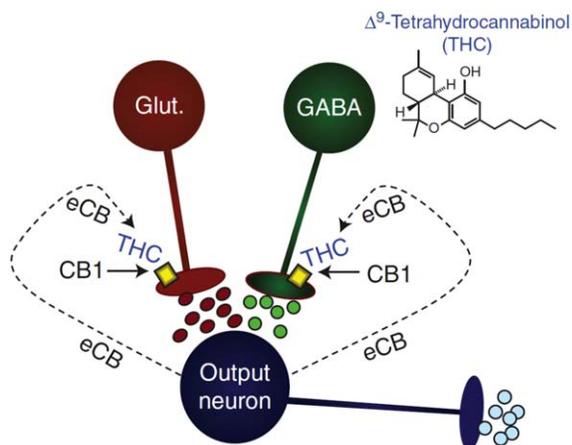


Figure 1 Generalized scheme of the sites of tetrahydrocannabinol (THC) action throughout the mammalian central nervous system (originally published in Hoffman and Lupica⁴³). Cannabinoid type-1 (CB₁) receptors are shown on both excitatory glutamatergic (Glut.) and inhibitory (GABA) axon terminals, and, in many cases, these synapses are formed with neurons providing output (output neuron) of central nuclei (e.g., hippocampal pyramidal neurons and medium spiny neurons in the nucleus accumbens and dorsal striatum). These presynaptic CB₁ receptors can be activated by endocannabinoids (eCBs) released upon depolarization of postsynaptic neurons or by administration of exogenous agonists, such as THC. Also shown is the chemical structure of THC (inset). Reproduced with permission of Cold Spring Harbor Laboratory Press.

synthetic cannabinoids are not typically mixed with CBD. Probably for these and other reasons, including high variability of the potency of spice drugs even within samples from the same package, spice drugs produce more frequent and more severe adverse effects than cannabis,⁷⁻⁹ and spice drug users have a 30 times higher risk of seeking emergency room assistance compared to cannabis users.⁷

For further information on the topics discussed in this section, please see **Supplementary Table S1** online, which also presents additional readings related to most of the other sections of this review.

CANNABINOID USE, ABUSE, AND DEPENDENCE IN HUMANS

Acute effects of cannabinoids

Inhalation of cannabis smoke is the generally preferred route of administration because it produces rapid effects and, unlike oral ingestion, can be easily titrated to a desired level of effect. Acute effects last for approximately two to three hours and are often described as a pleasant and relaxing experience. The unique mixture of depressant and stimulant effects is characterized by euphoria, easy laughter, talkativeness, sedation, distortion of time perception, increased perception of external stimuli, and memory lapses. Users typically experience increased appetite, dry mouth, tachycardia and blood pressure increase, and bronchodilation. A sense of well-being may alternate with dysphoria. The effects are individually variable and are influenced by the amount of cannabis (i.e., the dose of THC), first-time vs. repeated use, preexisting vulnerability to mental illness, and personality traits.¹⁰ Acute adverse effects of cannabis use include dysphoria, anxiety, panic

reactions, paranoia, and sometimes positive psychotic symptoms (e.g., auditory hallucinations, disorganized thought, and delusions of persecution).¹⁰⁻¹² Cannabis also impairs short-term memory and attention, judgment, motor coordination, performance of complex mental tasks, and reaction time,^{10,12} which can limit the ability to drive a car and operate machinery. Acute cannabis exposure doubles the risk of a motor vehicle accident, and THC blood levels of 2–5 ng/mL are associated with substantial driving impairment.¹³

At high doses, the frequency and seriousness of undesired acute effects of cannabis increases, especially in naive users.¹² Many short-term symptoms can manifest, such as depersonalization, derealization, disorientation, delusions, hallucinations, paranoid ideas, disordered thinking, irrational panic, psychomotor agitation, and emotional lability.^{10,11} Toxic or organic psychosis can be induced in people without history of severe mental illness. These problems generally resolve within a week of abstinence.

Many of the acute effects of synthetic cannabinoids (SCBs) are similar to those of cannabis and include euphoria, a feeling of well-being, relaxation, perceptual alterations, as well as mild memory and attention impairments.⁸ Users report that some SCBs have a shorter duration of effect and an earlier peak effect than cannabis, but pharmacokinetic profiles differ widely across SCBs, and the effects of various SCBs can last anywhere between one and six hours.⁷ Toxicity profiles of SCBs are similar to that of high doses of THC, but SCBs are more potent than THC, and SCB-laced spice drugs are highly variable in SCB concentration, which may lead to variable and unpredictable effects, as well as increased likelihood of serious side effects associated with accidental overdose.⁷ The use of SCBs can be followed by acute negative symptoms like paranoia, delusions, hallucinations, anxiety, panic attacks, suicidal ideation, extreme agitation, nausea, emesis, seizures, dizziness, ataxia, nystagmus, and drowsiness, as well as cardiovascular effects like hypertension, tachycardia, chest pain, or arrhythmias.^{7,8} Sixty percent of SCBs overdoses occur in people under 25 years of age, and inexperienced and/or young users are particularly sensitive to the toxic effects of SCBs.⁷ Spice drugs are more likely than cannabis to provoke psychosis in predisposed persons or schizophrenics, possibly because spice drugs do not contain CBD, which might have protective effects.⁷

Long-term effects of cannabinoids

Although it is difficult to establish causality by cannabinoid exposure in epidemiological studies, long-term cannabinoid use is associated with significant neurobiological, psychosocial, and general health problems.^{10,14} Regular cannabinoid use, particularly when started in adolescence, is associated with addiction, lasting cognitive impairment (e.g., lower IQ), poor educational outcome, diminished life satisfaction and achievement, and increased risk of psychotic disorders.^{14,15} The brain (including the endocannabinoid system) undergoes active developmental changes during adolescence and is more vulnerable to adverse effects of long-term exposure to THC.^{14,15} Functional and structural changes in the brains of marijuana smokers have been demonstrated.^{14,16} For example, adults who smoked marijuana regularly during adolescence have decreased functional connectivity in brain regions

Table 1 DSM-V diagnostic criteria for cannabis use disorder

A problematic pattern of cannabis use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Cannabis is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control cannabis use.
3. A great deal of time is spent in activities necessary to obtain cannabis, use cannabis, or recover from its effects.
4. Craving or a strong desire or urge to use cannabis.
5. Recurrent cannabis use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued cannabis use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of cannabis.
7. Important social, occupational, or recreational activities are given up or reduced because of cannabis use.
8. Recurrent cannabis use in situations in which it is physically hazardous.
9. Cannabis use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by cannabis.
10. Tolerance, as defined by either of the following:
 - a. A need for markedly increased amounts of cannabis to achieve intoxication or desired effect.
 - b. Markedly diminished effect with continued use of the same amount of cannabis.
11. Withdrawal, as manifested by either of the following:
 - a. The characteristic withdrawal syndrome for cannabis (refer to criteria A and B of the criteria set for cannabis withdrawal, **Table 2**).
 - b. Cannabis (or a closely related substance) is taken to relieve or avoid withdrawal symptoms.

Specify current severity:

Mild: Presence of 2–3 symptoms.

Moderate: Presence of 4–5 symptoms.

Severe: Presence of 6 or more symptoms.

DSM-V, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*.

important for learning, memory, executive functioning, and processing of habits and routines, which might be responsible for impairments such as lowered IQ.^{14,16} Recently, Volkow *et al.*¹⁷ showed that marijuana users have reduced brain reactivity to dopaminergic stimulation, and that this change might contribute to their negative emotionality (increased stress reactivity and irritability) and drug craving.

Cannabis addiction develops with heavy chronic use, and involves symptoms such as difficulty controlling or limiting use even in the face of adverse effects on users' daily lives. The lifetime risk of dependence (defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* 1994 (*DSM-IV*) criteria) among all cannabis users is estimated at about 9% and increases to one in six among those who initiate use in adolescence.^{14,15,18} Addiction is a complex disease determined by many factors, including genetics. Research on genetic variants associated with cannabis addiction is limited compared to nicotine and alco-

hol. So far, single nucleotide polymorphisms in *CNRI* and fatty acid amide hydrolase genes have been linked to cannabis addiction phenotypes.¹⁹ In a recent study, functional connectivity magnetic resonance imaging demonstrated that cannabis users with genetic variation in *CNRI* (rs1406977 G carriers) had greater functional connectivity in the left ventrolateral prefrontal cortex and reduced working memory behavioral accuracy compared with other groups.²⁰

Reliable information on doses of cannabis and patterns of use in regular users are often difficult to obtain. "Heavy" or "regular" use has been defined in epidemiological studies as daily or near daily use.¹⁵ This type of use over years carries high risks of adverse health effects. Recently, Hughes *et al.*²¹ reported on characteristics of marijuana use in a group of participants that used marijuana more than five times a week. They found that, within this population, daily users tend to use multiple times per day, use multiple modes of administration, show more signs of intoxication, and have high rates of tobacco use. Co-use of tobacco and cannabis is common, probably because of factors such as the relatively easy availability of both drugs and the common route of administration. Ninety percent of cannabis users report being cigarette smokers at some point during their lifetime,¹⁹ and co-use, which is often long term, increases negative health consequences (e.g., chronic bronchitis). Simultaneous cessation of tobacco and cannabis use leads to a more challenging withdrawal syndrome that can have implications for addiction treatment.¹⁹ Persistent tobacco use is associated with a poorer response to treatment for cannabis use disorders, and vice versa.^{19,22}

Cannabis use disorder

From a clinical perspective, the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V* 2013) presents an improved approach to substance use disorders by combining abuse and dependence criteria into one disorder, and by adding "craving or a strong desire or urge to use the substance" as a criterion for substance use disorder.²³ *DSM-V* now recognizes a Cannabis-Related Disorders category that includes cannabis use disorder, cannabis intoxication, cannabis withdrawal, other cannabis-induced disorders, and unspecified cannabis-related disorder. The *DSM-V* diagnostic criteria for Cannabis Use Disorder are listed in **Table 1**. Relatively little is known about the development and natural course of cannabis use disorders in the general population. Similar to other drug addictions, cannabis addiction is a chronic disorder characterized by repeated attempts to quit followed by relapse. Repeated exposure to cannabinoids results in tolerance to the subjective and performance-impairing effects of cannabis and also induces physical dependence that is characterized by a withdrawal syndrome upon cessation of drug use.²⁴

Over time, cannabis withdrawal has gained recognition as a clinically significant phenomenon.^{25,26} Because of overwhelming preclinical, clinical, and epidemiological evidence, cannabis withdrawal has been added to *DSM-V* and is included as one of the criteria for cannabis use disorder.²³ Symptoms of cannabis withdrawal are described in **Table 2**. Cannabis withdrawal is associated with functional impairment of normal daily activities and contributes to relapse.^{24,26,27} Relapse rates observed for

Table 2 DSM-V diagnostic criteria for cannabis withdrawal

- 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).
- 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.
- C. 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.
- D. The signs or symptoms in criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.

DSM-V, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*.

cannabis use disorders are comparable to those for other abused drugs, and only 15–37% of patients undergoing psychotherapeutic and pharmacological interventions achieve continued abstinence.²² Besides withdrawal-induced craving, other precipitators of relapse to drug use are stress and cue-elicited craving. Exposure to marijuana-related cues increases craving in dependent individuals and is linked to increased brain responses in the limbic amygdala, hippocampus, and ventral striatum.²⁸

Other consequences of heavy chronic cannabis use can be depersonalization and amotivational syndrome, although it is unclear whether the latter involves a change in motivation as opposed to a change in attention or simply a state of intoxication.^{10,11} There are high rates of comorbidity between cannabis use and other psychiatric disorders, including psychosis (schizophrenia), depression, anxiety disorders, bipolar disorder, certain personality disorders, and other substance use disorders.^{10–12} Heavy cannabis use can also cause neurocognitive deficits that persist for several days or weeks after cessation of cannabis intake, and memory and attention impairments may persist and worsen with increasing years of use and with the initiation of use during adolescence.¹⁴ Consequences of cannabis use also manifest in the respiratory, digestive, cardiovascular, and reproductive systems.^{10,12}

Synthetic cannabinoids

Because spice drugs are a relatively recent phenomenon, the long-term psychopathological and physical effects of SCBs are not well known. Tolerance to SCBs develops quickly, and chronic SCB

users could meet criteria for cannabis use disorders.^{1,7} Cases of withdrawal syndrome have been reported with the following symptoms: craving, restlessness, nightmares, tachycardia, hypertension, nausea, sweating, headaches, muscle twitches, severe anxiety, chest pains, cramping, and chills.^{8,9}

Treatment of cannabis use disorders: clinical and human laboratory studies

Over the past 20 years, there has been a steady increase in the number of regular cannabis users in the United States; in the year 2013, over 8 million people were using 20 or more times per month, and more people (about 845,000) were treated for cannabis use than for any other illicit substance.³ There are currently no approved medications for treating cannabis use disorders. The most successful psychotherapeutic models include cognitive-behavioral therapy, motivational enhancement therapy, contingency management, and family-based therapies.^{29,30} However, nonresponse and relapse rates among patients remain high (70%), and there has been a call for the development of effective pharmacotherapies to complement the psychosocial therapies.²⁹ Studies of potential medications in humans have focused mainly on promoting the initiation of abstinence, reducing withdrawal symptoms, and preventing relapse.

Among potential medications that have been tested, the most promising results have been obtained with replacement therapy using CB₁ agonist medications. Dronabinol (Marinol) is a synthetic form of THC approved for treatment of nausea associated with chemotherapy and for use as an appetite stimulant for AIDS or patients with cancer. Dronabinol was tested in several within-subject, placebo-controlled, human-laboratory studies. Reduction of withdrawal symptoms was observed, but no effect on cannabis self-administration or relapse was found.³⁰ These effects were confirmed by a large clinical trial with dronabinol in combination with behavioral therapies.³¹ Recently, a human laboratory study with nabilone, a synthetic, highly bioavailable THC analogue with clinical indications similar to those of dronabinol, showed promise for reduction of withdrawal symptoms and relapse.³² An alternative to use of direct CB₁ agonists is pharmacological inhibition of the enzymes (fatty acid amide hydrolase and monoacylglycerol lipase) that degrade the endogenous CB₁ agonists anandamide and 2-arachidonoylglycerol, respectively. These inhibitors enhance and prolong the effects of endocannabinoids when and where they are released in the brain, and might therefore be useful as a replacement therapy or for relieving withdrawal. Currently, the fatty acid amide hydrolase inhibitor PF-04457845 is in clinical testing for efficacy in treatment of marijuana withdrawal. PF-04457845 was well tolerated in previous clinical trials,³³ and no cannabis-like adverse effects have been reported.

Drugs acting as antagonists or antagonist/inverse agonists at CB₁ receptors (like rimonabant) represent an alternative approach to the treatment of cannabis addiction by directly blocking the subjective and reinforcing effects of THC. Initial findings were promising as rimonabant attenuated the subjective and physiological effects of smoked marijuana.³⁴ Unfortunately, rimonabant has been withdrawn from clinical use due to

psychiatric side effects (anxiety, depression, and suicidality).³⁵ As noted below, it is possible that CB₁ antagonists that lack inverse-agonist effects might be safer than rimonabant but still block the effects of THC.

Functional, bidirectional interactions between the endogenous cannabinoid and opioid systems have been demonstrated in numerous studies. Treatment with mu-opioid antagonists, such as naltrexone, represents a possible approach to reducing the reinforcing effects of THC.³⁶ However, acute naltrexone administration can increase the positive subjective effects of cannabis in marijuana smokers.³⁷

A number of antidepressants, anxiolytics, and antipsychotics have been assessed for treatment of cannabis addiction in humans, with little success. These include escitalopram, atomoxetine, fluoxetine, venlafaxine, buspirone, bupropion, nefazodone, mirtazapine, and quetiapine.²⁹ Promising effects were observed with the α_2 -adrenergic receptor agonist lofexidine, especially in combination with dronabinol³⁸; the combination of dronabinol and another α_2 -adrenergic receptor agonist, clonidine, is currently being studied in cannabis-dependent schizophrenics (ClinicalTrials.gov). The antiepileptic gabapentin has also shown promise in attenuating withdrawal severity and reducing cannabis use.³⁹ N-acetylcysteine, an over-the-counter supplement that might work by normalizing glutamate activity, also decreased cannabis use.⁴⁰ CBD alone or in combination with THC (Sativex) is currently under investigation in several clinical trials for management of cannabis use disorders (ClinicalTrials.gov). A recent meta-analysis of controlled trials of pharmacotherapies for cannabis dependence led the authors to conclude that the available evidence is limited at this point, but that CB₁ agonist therapy shows the most promise, followed by gabapentin and N-acetylcysteine.⁴¹

Neurobiology of cannabinoid addiction

Much of the information available concerning the neurobiology of addiction and the effects of cannabinoids have been obtained with animal research, as described in the following sections of this article. The mesolimbic dopaminergic system has a well-established role in the reinforcing effects of drugs of abuse, including cannabinoids, with the nucleus accumbens and ventral tegmental area (VTA) regions playing major roles. In humans, low dopaminergic tone during withdrawal and reduced behavioral and striatal reactivity to the dopaminergic stimulation in marijuana abusers have been linked to negative emotionality and addiction severity and craving.¹⁷ Cannabinoid CB₁ receptors are located presynaptically in the brain reward circuitry and their activation inhibits neurotransmitter release (see **Figure 1**). Depending on the presynaptic signal (glutamatergic or GABAergic), activation of CB₁ receptors by exogenous or endogenous cannabinoids can suppress or facilitate postsynaptic response and modulate dopamine release. In this process, the endocannabinoids (anandamide or 2-arachidonoylglycerol) act as retrograde messengers, as they are released on demand from postsynaptic neurons. Thus, the endocannabinoid system can modulate dopaminergic reward circuits, which suggests that endocannabinoids

also play a major role in the mechanisms underlying drug addiction.

Prolonged exposure to cannabinoids causes complex adaptations in the brain's neuronal circuits and their components. Changes have been uncovered in synaptic transmission and plasticity, CB₁ receptor density and function, signaling cascades (e.g., MAPK/ERK1/2), and gene expression after chronic cannabinoid treatment. Detailed discussion of the many findings concerning the neurobiology of cannabis addiction, dependence, and withdrawal are beyond the scope of this review, so we recommend the following reviews for further reading: Fratta and Fattore,⁴² Hoffman and Lupica,⁴³ and Covey *et al.*⁴⁴

Animal models of cannabinoid reward, relapse, and withdrawal

Compared to drug classes such as opioids, stimulants, and depressants, cannabis is widely recognized as having less potential to produce dependence and addiction. However, cannabis and SCBs do produce these effects, and techniques developed for studying drugs, such as cocaine and heroin, have proven useful in modeling these effects in animals. At least initially, addictive drugs are used because they have rewarding effects, producing euphoria and reinforcing the drug-taking behavior. Through the processes of conditioning and learning, specific cues in the environment gain control of behavior, activating and guiding the complex sequences of actions required to obtain, prepare, and self-administer the drug. Over time, this behavior can become increasingly habitual and resistant to change. Even after a long period of abstinence, reexposure to the drug or drug-related cues can induce relapse.

Drug self-administration

Drug self-administration is the preeminent animal model of drug use because it bears a close resemblance to human drug-taking and involves similar forms of conditioning and learning, with at least partial congruence of the underlying neural circuitry. When allowed to self-administer a drug by performing a simple response, such as pressing a lever, laboratory animals will self-administer most of the same drugs as humans. However, in early studies in which animals were allowed to self-administer THC, they did not develop the stable patterns of intake seen in regular cannabis users. Eventually, reliable procedures for obtaining robust intravenous THC self-administration in squirrel monkeys were developed in our laboratory⁴⁵ using relatively low doses, within the same range self-administered by human cannabis smokers. Several laboratories have also successfully obtained intravenous self-administration of the SCB CB₁ agonist WIN55,212-2 in rats^{46,47} and mice.⁴⁸

The initial demonstration of THC self-administration in squirrel monkeys was performed in monkeys that had prior experience self-administering cocaine,⁴⁵ but subsequent work showed that THC is readily self-administered by monkeys with no prior drug experience.⁴⁹ The dose-effect function for THC self-administration has the inverted-U shape typical of other drugs of abuse (**Figure 2**), with low doses maintaining little or no responding (presumably because of weak reinforcing effects), moderate doses maintaining high rates of responding

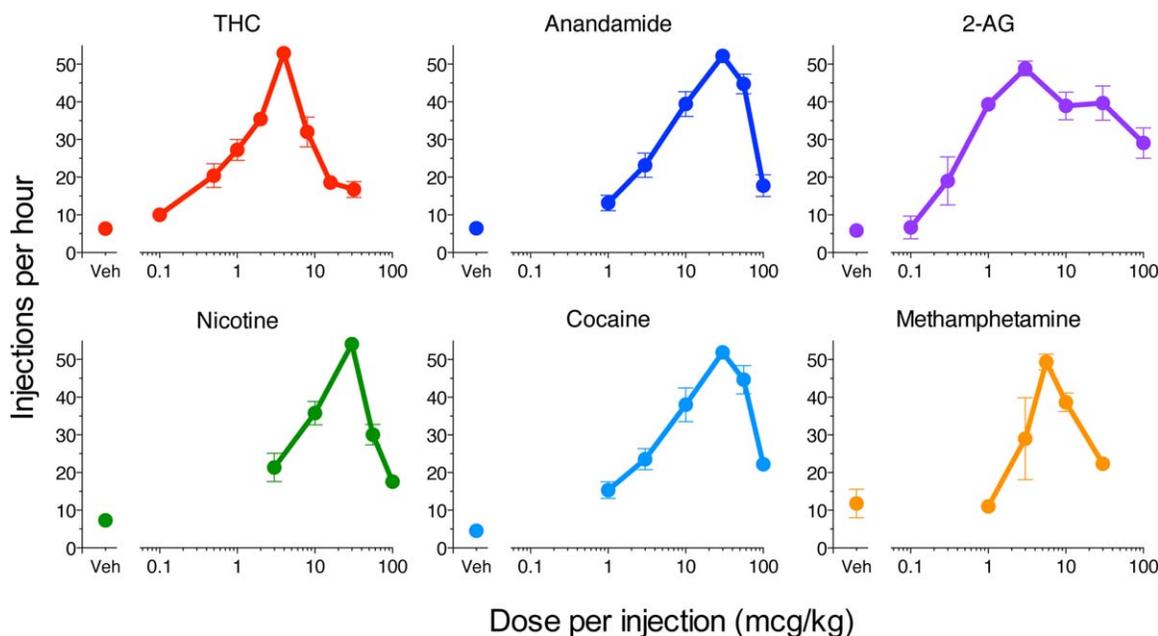


Figure 2 Dose-response curves for self-administration of various intravenous drugs in squirrel monkeys. Ten lever-press responses (FR10) were required for each injection, and there was a 60-second time-out period after each injection, during which responses had no programmed consequences. The numbers of injections per 1-hour session are shown as a function of the dose of tetrahydrocannabinol (THC), the endogenous cannabinoids anandamide, and 2-arachidonoylglycerol (2-AG), nicotine, cocaine, or methamphetamine when offered as intravenous solutions. Each point represents mean \pm SEM from three to four monkeys. Data previously unpublished as shown, obtained using procedures that parallel those described in studies by Justinova *et al.*^{36,49,51,52,72,73,75}

(presumably because of strong reinforcing effects), and high doses maintaining moderate-to-low responding (presumably because of strong reinforcing effects accompanied by satiating effects or behaviorally disruptive side effects, such as sedation).

THC self-administration is blocked by pretreatment with the cannabinoid CB₁ antagonist rimonabant, suggesting that activation of CB₁ receptors is central to cannabinoid reward; the fact that rimonabant has this effect at doses that do not alter food or cocaine self-administration indicates that it selectively affects cannabinoid reward as opposed to producing a nonselective disruption of operant behavior.^{45,50} Interpretation of this finding is somewhat complicated by the fact that rimonabant can also decrease the reinforcing effects produced by other drug classes (most notably nicotine) and the conditioned reinforcing effects of cues associated with these drugs; nonetheless, these findings make sense in light of the hypothesis that CB₁ antagonists reduce the rewarding effects of drugs, drug-associated cues, and even non-drug reinforcers, such as food, because the endogenous cannabinoid system modulates the common reward system circuitry that underlies the effects of all these reinforcers. This interpretation is consistent with the finding that anandamide⁵¹ and 2-arachidonoylglycerol,⁵² the main endogenously occurring ligands for the CB₁ receptor, are self-administered by squirrel monkeys when they are offered as an intravenous solution (**Figure 2**).

The conditioned reinforcing effects of THC-associated cues have been studied in squirrel monkeys by using a second-order schedule.⁵⁰ In this procedure, every tenth lever-press response produces a brief illumination of a colored stimulus light; the first

stimulus produced after 30 minutes is accompanied by intravenous infusion of THC. Under these conditions, the brief stimulus becomes a conditioned reinforcer, producing substantially higher and more persistent response rates than would occur if only the drug were presented. This chain of behavior guided by drug-associated cues provides a simplified model of the process by which environmental cues maintain complex sequences of drug-seeking behavior in the human drug-abuse environment. Discontinuation of the brief stimuli produces an immediate 60–75% decrease of the THC-seeking response.

Reinstatement

Manipulations, such as discontinuing delivery of THC and/or THC-associated cues, can be used as part of the reinstatement model of relapse. This imposed abstinence causes drug seeking to drop to very low levels, at which point monkeys can be given an automatic, experimenter-delivered infusion of THC or another drug at the beginning of the session to see if it increases (i.e., primes) the drug-seeking response. Alternatively, cues can be presented that previously signaled the availability of THC or were previously associated with THC delivery. These drug-priming and cue-induced reinstatement procedures, respectively, model the relapse-triggering effects of drug reexposure and cue reexposure known to affect human drug users. Using these procedures, Justinova *et al.*⁵⁰ found that experimenter-administered infusions of THC, anandamide, or methanandamide (a long-acting form of anandamide) could reinstate THC seeking. Interestingly, morphine was also able to induce reinstatement of THC-seeking, but

cocaine was not, consistent with rodent research indicating that the cannabinoid and opioid systems of the brain interact in a mutually enhancing fashion.⁵³ Also consistent with this hypothesis, the μ -opioid receptor antagonist naltrexone can decrease ongoing THC self-administration in monkeys.³⁶

Rodent procedures

Nonhuman primates are phylogenetically close to humans and provide an invaluable model of many human neurobiological systems. However, there is a wealth of knowledge and neuroscience techniques that have accrued from the study of rodents, and it is fitting that drug abuse research should involve rodents when they can provide a valid model of human behavior and physiology. It is unclear why THC does not maintain robust self-administration behavior in rodents, even when offered to rats that have been trained to self-administer the synthetic CB₁ agonist WIN55,212-2.⁴⁷ However, the fact that rodents do self-administer WIN55,212-2 allows them to be useful for modeling aspects of cannabis use that are difficult or impossible to study experimentally in humans or nonhuman primates, such as initial acquisition of cannabis use and the effects of irreversible treatments, such as genetic or intracranial manipulations. For example, Deiana *et al.*⁵⁴ found differences between three strains of rats in acquisition of WIN55,212-2 self-administration. Studies with intracranial microdialysis in rats, which is essentially a nonreversible treatment, have shown that levels of dopamine in the shell of the nucleus accumbens increase during WIN55,212-2 self-administration but not the core⁵⁵; this is not simply an artifact of motor activity because dopamine levels did not increase when WIN55,212-2 delivery was discontinued, despite high levels of lever pressing. In prodynorphin knockout mice, the dose-response curve for WIN55,212-2 self-administration was shifted to the left compared with wild-type controls, and in wild type mice, the kappa-opioid antagonist nor-binaltorphimine enhanced acquisition of WIN55,212-2 self-administration.⁴⁸

Place conditioning

Alternative, less direct measures that have been used to assess reward-related effects of cannabinoids in rodents include place conditioning, drug discrimination, and microdialysis. In place conditioning, the effects of a drug are associated with one of two distinctive compartments of an apparatus, and the drug's vehicle (placebo) is associated with the other compartment. In a subsequent test, the rodent is allowed access to both compartments; a preference for the drug-associated compartment indicates that the features of that compartment have become conditioned reinforcers, which implies that the effects of the drug are reinforcing. One advantage of such place-conditioning procedures is that they are sensitive not only to reinforcing effects but also to aversive effects of a drug, which can lead to avoidance of the drug-associated compartment. There is some evidence that low doses of THC produce place preference in rats, and higher doses produce place avoidance.⁵⁶ However, in most studies, THC and WIN55,212-2 have produced either conditioned place aversion or no preference for either compartment.

Aversive effects, such as anxiety and panic, also occur in human cannabis¹⁰ and spice drug⁸ users and therefore warrant further study in animal models. Some recent studies have suggested that aversive effects of THC might depend on CB₁-induced noradrenergic signaling in the nucleus accumbens,⁵⁷ and that aversive effects can be attenuated or reversed by prior cannabinoid exposure in adolescent rats.⁵⁸ Exposing rodents to THC before the place-conditioning procedure can facilitate development of a preference for the THC-associated compartment, possibly because the first exposure is more likely to be aversive.⁵⁹ The tendency of rodents to show mainly aversive effects in place-conditioning studies with CB₁ agonists are consistent with their lack of robust THC self-administration, although it is not clear whether these aversive effects mask rewarding effects or whether the rewarding effects in rodents are simply weak because of differences between their reward systems and those of humans and nonhuman primates.

Drug discrimination

In drug-discrimination procedures, subjects are trained to detect whether they have received a certain psychoactive drug. For example, in a typical procedure, rats are trained in an apparatus with two levers; pressing one lever produces food pellets on days when the rat has been injected with THC before the training session, and pressing the other lever produces food pellets on days when the rat has been injected with placebo. When the rat has learned to accurately detect THC, tests can be performed by injecting a novel test substance, a different dose of THC, or a combination of THC and another drug. The rat's choice of levers during the test indicates whether the test substance produces interoceptive effects similar to THC, some of which are presumably analogous to subjective effects, such as drug "high" in humans. Many test drugs have been evaluated with this procedure, and it has proven to be highly selective. That is, test drugs that do not act at CB₁ receptors do not produce THC-like interoceptive effects, even if the test drug has strong abuse potential; THC-like effects are only produced by full or partial CB₁ agonists, including anandamide and synthetic agonists found in spice drug preparations. Therefore, even though drug discrimination does not directly measure reinforcement, it is logical to expect that novel drugs that produce interoceptive effects similar to those of THC could also have abuse potential and other adverse effects similar to those of THC. Testing with drug combinations indicates that nicotine can potentiate the effects of THC, possibly through nicotine-induced release of endogenous anandamide,⁶⁰ and that morphine can also potentiate the effects of THC⁶¹; such effects could provide a mechanism for the reported enhancements in rewarding effects¹⁹ produced by co-users of cannabis and other drugs.

Intracranial and ex vivo procedures

Intracranial microinjection and microdialysis procedures can provide information about brain areas and neurochemistry involved in cannabinoid reward. In a study of opioid-cannabinoid interactions in rats, microinjection of beta-endorphin into the VTA (but not the accumbens shell) potentiated the effect of THC in a

drug discrimination procedure.⁶¹ In another study, Zangen *et al.*⁶² allowed rats to self-administer microinjections of THC directly into specific brain areas. They found that THC had reinforcing effects in the nucleus accumbens and VTA, regions known to be involved in reward, but that it did not have reinforcing effects in the substantia nigra. Further testing with a place-conditioning procedure in which THC was microinjected into subregions of these areas indicated that THC had reinforcing effects in the posterior VTA and posterior shell of the accumbens, but not in the anterior VTA, medial accumbens, or posterior accumbens. These findings suggest that systemically administered THC does have rewarding effects in rodents, but that these effects are masked or counteracted by effects in brain areas that are not congruent with (or have a weaker influence in) human and nonhuman primate brains.

Microdialysis allows sampling of neurochemical levels in specific brain areas. Reward-related microdialysis research has focused mainly on the VTA and nucleus accumbens in rats. Extracellular dopamine levels in the shell of the nucleus accumbens are increased by systemic treatment with THC, WIN55,212-2, or anandamide, or by direct injection of THC into the VTA or nucleus accumbens, and such effects are blocked by pretreatment with a CB₁ antagonist, an opioid antagonist, or a serotonin-specific reuptake inhibitor.

Ex vivo preparations, such as in brain slices containing VTA neurons, also provide insight into the neurophysiological underpinnings of cannabis reward and neuroadaptations to cannabinoid exposure. For example, THC increases the firing of *ex vivo* VTA dopamine neurons, but these cells show tolerance to the effects of THC if the rat was repeatedly exposed to THC *in vivo* (i.e., before dissection).⁴⁴ Nucleus accumbens glutamate neurons show changes in synaptic plasticity after *in vivo* THC exposure, and this might underlie lasting effects of THC exposure, such as altering the rewarding effects of other drugs.⁴³

Withdrawal

Chronic cannabis users typically experience unpleasant withdrawal symptoms when use is discontinued. These symptoms are much less severe than those associated with withdrawal from chronic opioid or depressant use, but aversive enough to encourage continued cannabis use and interfere with cessation attempts in some individuals. Animal models of cannabis withdrawal typically involve automatic exposure to THC, as opposed to self-administration. As in humans, the effects induced by simply discontinuing exposure in animals are not severe and can be hard to detect, probably because of the slow elimination of lipophilic compounds, such as THC, from the brain. However, investigation of the mechanisms of withdrawal can be facilitated by using precipitated withdrawal procedures. In these procedures, withdrawal symptoms are precipitated by administering a CB₁ antagonist to rats that have received THC exposure for periods as short as four days⁶³; these symptoms include scratching, face rubbing, licking, wet-dog shakes, arched back, and ptosis. Like humans undergoing abstinence-induced cannabis withdrawal, rats undergoing precipitated THC withdrawal show sex differences in severity of symptoms.⁶⁴ Precipitated withdrawal effects can also

be observed as a disruption of learned behavior, such as food-reinforced lever pressing.⁶⁵ In rhesus monkeys, drug discrimination has been used to model mild cannabis withdrawal by training subjects to distinguish between a low dose of THC with vs. without a dose of the CB₁-antagonist rimonabant.⁶⁶ When vehicle was substituted for the usual THC administration in these monkeys but no rimonabant was given, they responded on the rimonabant-appropriate lever; when the CB₁ agonists WIN55,212-2 or CP55,940 were given instead of THC and no rimonabant was given, the monkeys responded as if they had received THC. However, in these tests, rimonabant given after WIN55,212-2 failed to reverse the effects of WIN55,212-2, suggesting that non-CB₁ effects of WIN55,212-2 (and possibly other SCB agonists) are relevant to their subjective effects.

Because the withdrawal signs induced by cannabinoid antagonists in THC-dependent rats are not observed in THC-naive control rats, they seem to be due to development of tolerance and other neuroadaptations in response to repeated THC exposure. Tolerance and dependence develop after daily exposure to THC or synthetic cannabinoids for periods as short as 3–14 days. Findings in rodents suggest that tolerance is due to downregulation of CB₁ receptors, and that aversive withdrawal symptoms involve increases in corticotropin-releasing hormone and decreases in dopamine signaling (see Supplementary Table S1).

Gateway effects

Animal models provide a means of objectively studying the effects of THC exposure under controlled conditions. Repeated exposure to THC can have effects on behavior that last well beyond the last exposure, altering the effects of other drugs administered weeks or months after THC exposure is discontinued. Compared to vehicle-exposed controls, rats with a history of THC exposure have higher levels of intake when allowed to self-administer heroin.⁶⁷ A history of THC exposure decreased the reinforcing effects of cocaine,⁶⁸ but increased the reinforcing effects of nicotine.⁶⁹ The latter finding could be important because nicotine is normally a much weaker reinforcer than cocaine or heroin, but difficult to quit once regular use is established. Although animal models have not been used to evaluate the possibility that prior or simultaneous exposure to drugs, such as nicotine and alcohol, alter the reinforcing effects of cannabis, this is an area that deserves attention because it might provide insight into the mechanisms underlying the common gateway-like progression⁷⁰ from alcohol and tobacco use to cannabis use and then to drugs, such as cocaine and heroin.

Preclinical findings concerning potential medications for cannabis use disorders

There are currently no medications approved for the treatment of cannabis dependence, despite the fact that there is high demand for treatment and a clear need for more effective treatment options. Animal models of cannabinoid reward and relapse provide a means of identifying potential molecular targets for the development of pharmacotherapies that could be worth testing in humans. Four such targets have been pursued in the squirrel monkey model of cannabis abuse but that have not yet been

tested in clinical trials are: cannabinoid antagonism, opioid antagonism, adenosine antagonism, and modulation of $\alpha 7$ nicotinic receptors.

Cannabinoid antagonism

As mentioned above, treatment with CB₁ antagonists, such as rimonabant, can block the rewarding effects of THC in animals and humans; monkeys treated with rimonabant self-administer very few THC infusions and show resistance to the relapse-inducing effects of reexposure to THC and THC-associated environmental cues.^{45,50} However, it should be noted that monkeys quickly resume THC self-administration when rimonabant is discontinued; this has been a general finding with all pharmacological treatments that block the rewarding effects of drugs. In addition, rimonabant has the potential to precipitate withdrawal symptoms in THC-dependent individuals, which could potentially lead to noncompliance if it were prescribed as a treatment for cannabis use disorder. Furthermore, when rimonabant was prescribed as a treatment for obesity, it was associated with depression-like side effects and was subsequently withdrawn from the market.³⁵ However, it is possible that the adverse effects of rimonabant are due to its inverse-agonist properties, in which case a neutral CB₁ antagonist devoid of these properties might be both safe and effective, but this remains to be seen. If so, it might be expected that CB₁-antagonist treatment for cannabis dependence would parallel opioid-antagonist treatment for opioid dependence, in that it would be helpful as an adjunct to psychotherapy in individuals motivated to quit (i.e., willing to comply with antagonist treatment).

Opioid antagonism

Based on findings that the opioid and cannabinoid systems can modulate each other, the opioid antagonist naltrexone was evaluated in the squirrel monkey THC self-administration model. In an initial study,³⁶ naltrexone did not affect cocaine self-administration, but it consistently decreased THC self-administration on each of the five consecutive days of testing. However, in a later study with a different schedule of reinforcement, the effect of naltrexone on THC self-administration dissipated after two days of treatment.⁵⁰ In the first study, every 10th lever response produced a THC infusion, and approximately 50 THC infusions could be obtained over the course of each one-hour session. In the second study, every 10th response produced brief presentation of a visual stimulus, but the stimulus was only accompanied by THC infusion once, at the end of the session. Therefore, these two studies differed in both the potential rate of drug delivery and the role of drug associated cues. Thus, the findings suggest that naltrexone can block the reinforcing effects of THC, but may not be effective at blocking the conditioned reinforcing effects of THC-associated cues, which are believed to play a major role in maintaining drug seeking in humans.

Adenosine antagonism

Adenosine A_{2A} receptors form interactive heteromeric complexes with cannabinoid CB₁ receptors in the striatum, and systemic treatment with the A_{2A} antagonist MSX-3 can counteract the

motor depressant effects of intrastriatal infusion of the CB₁ agonist WIN55,212-2 in rats.⁷¹ In squirrel monkeys, a 1 mg/kg dose of MSX-3 shifted the dose-response curve for THC or anandamide self-administration downward, consistent with a decrease in reward, but a 3 mg/kg dose of MSX-3 shifted the curve to the left, consistent with enhanced reward.⁷² It was hypothesized that the opposite effects of the 1 and 3 mg/kg doses of MSX-3 on cannabinoid self-administration were due to MSX-3 acting preferentially at presynaptic A_{2A} receptors at low doses, but at both presynaptic and postsynaptic receptors at higher doses. This hypothesis was strongly supported in a subsequent study using antagonists selective for presynaptic and postsynaptic A_{2A} receptors.⁷³ The presynaptic antagonist SCH-442416 shifted the dose-response curve for THC self-administration to the right, indicating a blockade of THC's rewarding effects, but the postsynaptic antagonist KW-6002 shifted the curve to the left, indicating an enhancement of THC's rewarding effects. These findings indicate that presynaptic A_{2A} antagonists, like SCH-442416, should be further investigated as potential treatments for cannabis use disorders.

Cholinergic manipulations

The ability of adenosine A_{2A} antagonists to modulate cannabinoid reward are consistent with the hypothesis that activation of CB₁ receptors increases corticostriatal neurotransmission by decreasing cortical GABAergic signaling, which, in turn, could produce glutamate release and glutamate-dependent dopamine release in the striatum.⁷³ This possibility was further supported by the finding that reward-related effects of cannabinoids (but not cocaine) in rats are decreased by drugs that decrease corticostriatal glutamatergic neurotransmission; these drugs include not only adenosine A_{2A} antagonists but also $\alpha 7$ nicotinic acetylcholine receptor antagonists, such as methyllycaconitine. Specifically, the $\alpha 7$ antagonist methyllycaconitine blocked the interoceptive effects of THC in a drug-discrimination procedure, decreased WIN55,212-2 self-administration, and decreased THC-induced dopamine release in the shell of the nucleus accumbens in rats.⁷⁴ Unfortunately, antagonists acting directly at $\alpha 7$ nicotinic receptors tend to produce central and peripheral side effects that limit their usefulness as medications. However, the activity of $\alpha 7$ receptors can be decreased, possibly with fewer side effects, by administering an inhibitor of kynurenine 3-monooxygenase (KMO), which enhances endogenous levels of kynurenic acid, a negative allosteric modulator of $\alpha 7$ receptors.

The effects of negative allosteric modulation of $\alpha 7$ receptors were extensively studied in squirrel monkeys and rats by administering the KMO inhibitor, Ro 61-8048.⁷⁵ KMO inhibition decreased WIN55,212-2 self-administration in rats and THC self-administration in monkeys. Food and cocaine self-administration were not affected, indicating that KMO inhibition did not produce a nonselective impairment of lever-pressing behavior. Treatment with the KMO inhibitor blocked the relapse-like effects induced by reexposure to THC, WIN55,212-2, or THC-associated cues after a period of abstinence. Microdialysis experiments in rats indicated that systemic KMO inhibition attenuated the ability of THC to induce dopamine release

in the nucleus accumbens shell and VTA. These findings suggest that KMO inhibition could be a viable strategy for treating cannabis use disorders.⁷⁵

SUMMARY

Cannabis and SCBs are increasingly available and increasingly abused. The addictive potential and the seriousness of adverse effects associated with these drugs is less than those associated with some controlled but legal drugs, including prescription opioids, alcohol, and nicotine. However, cannabis abuse disorders (and concomitant psychiatric effects) do occur in substantial numbers of cannabinoid users, and there is a clear need for new and improved treatment options. Although prevention and behavioral/psychosocial treatments for these disorders should clearly be emphasized, there should also be efforts to develop effective pharmacotherapies. Research into potential medications for cannabis abuse disorders is still in a very early stage, but some possible molecular targets have been identified. Studies in humans suggest that replacement therapy with CB₁-receptor agonists can reduce withdrawal symptoms, and that the antiepileptic gabapentin and the over-the-counter amino acid prodrug N-acetylcysteine might be useful for reducing cannabis use. In animal models, interactions between the endogenous systems that underlie the effects of cannabinoids, opioids, and nicotine suggest that addictive effects of these drugs might be enhanced when they are combined, but also that medications that decrease the activity of any one of these systems might decrease cannabis use. Selective adenosine antagonists also show promise in animal models of cannabinoid use. There is evidence that genetics can affect susceptibility to cannabinoid reward and addiction, and that adolescents are particularly susceptible to cannabinoid-induced addictive effects and lasting cognitive deficits. Finally, as a wider range of synthetic cannabinoids come to be abused, there will continue to be a need for research to learn more about these drugs and to assess their potential for harm.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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