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► To cite this version:

Saeideh Karimi-Haghighi, Yasaman Razavi, Daniela Iezzi, Andrew Scheyer, Olivier Manzoni, et al.. Cannabidiol and substance use disorder: Dream or reality. *Neuropharmacology*, 2022, 207, pp.108948. 10.1016/j.neuropharm.2022.108948 . hal-03653791

HAL Id: hal-03653791

<https://amu.hal.science/hal-03653791>

Submitted on 18 Jan 2024

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Published in final edited form as:

Neuropharmacology. 2022 April 01; 207: 108948. doi:10.1016/j.neuropharm.2022.108948.

Cannabidiol and substance use disorder: dream or reality

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Abstract

Background: Cannabidiol (CBD) is one of the major constituents of *Cannabis sativa* L. that lacks psychotomimetic and rewarding properties and inhibits the rewarding and reinforcing effects of addictive drugs such as cocaine, methamphetamine (METH), and morphine. Additionally, CBD's safety profile and therapeutic potential are currently evaluated in several medical conditions, including pain, depression, movement disorders, epilepsy, multiple sclerosis, Alzheimer's disease, ischemia, and substance use disorder. There is no effective treatment for substance use disorders such as addiction, and this review aims to describe preclinical and clinical investigations into the effects of CBD in various models of opioid, psychostimulant, cannabis, alcohol, and nicotine abuse. Furthermore, the possible mechanisms underlying the therapeutic potential of CBD on drug abuse disorders are reviewed.

Methods: The current review considers and summarizes the preclinical and clinical investigations into CBD's effects in various models of drug abuse include opioids, psychostimulants, cannabis, alcohol, and nicotine.

Results: Several preclinical and clinical studies have proposed that CBD may be a reliable agent to inhibit the reinforcing and rewarding impact of drugs.

Conclusions: While the currently available evidence converges to suggest that CBD could effectively reduce the rewarding and reinforcing effects of addictive drugs, more preclinical and clinical studies are needed before CBD can be added to the therapeutic arsenal for treating addiction.

Keywords

Cannabidiol; Addiction; Opioid; Psychostimulants; Cannabis; Nicotine; Alcohol

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Conflict of Interest

The authors declare that they have no conflict of interest.

1. Introduction

Drug addiction is a chronic, relapsing disorder characterized by compulsive drug-seeking, continued use despite harmful consequences, and long-lasting changes in the brain. This drug-seeking behavior is associated with craving and loss of control (Kranzler and Li, 2008). Over the last few decades, our understanding of the neuronal processes involved in drug abuse disorders has dramatically progressed. Notably; evidence has accumulated to suggest that the dopaminergic and glutamatergic systems are instrumental in the reinforcing and rewarding effects of drugs (Pierce and Kumaresan, 2006; Vatankhah et al., 2018). The mesolimbic reward circuit, mainly including the ventral tegmental area (VTA), nucleus accumbens (NAc), prefrontal cortex (PFC), central and basolateral amygdala, hippocampus (HIP), and hypothalamus plays a pivotal role in the processing of reward-associated addictive drugs (Cooper et al., 2017; Gardner, 2011; Volkow and Morales, 2015). The development of animal models of addiction and drug reward is a critical factor for progress in the identification of new therapeutic targets and understanding the biological basis of this disorder. There are various self-administration (SA) procedures to evaluate the reinforcing and motivational effects of the addictive substance. SA is helpful in clarifying the neurobiological and molecular mechanisms of drug-related behaviors and , therefore, essential in identifying strategies helpful in the intervention of human drug consumption, indicating predictive validity. In addition to SA, the conditioned place preference (CPP) paradigm is a model based on the component of reward-related to associative cognitive ability and learning to make predictions about future reward. The reinstatement of CPP with drug-seeking behavior can be used to study the molecular and neurobiological basis of drug craving, as there is significant correspondence between the events that induce drug-seeking in animals and those that provoke craving and cue reactivity in humans (García Pardo et al., 2017; Spanagel, 2017). Also, locomotor hyperactivity, exploratory hyperactivity, and stereotyped behavior have been investigated as acute behavioral responses to psychostimulants (Maurice and Romieu, 2004).

As a whole plant, *Cannabis L. sativa* (*cannabis*) comprises various non- psychotomimetic and non-addictive constituents that, taken in isolation, present medical opportunities and maybe more easily employed for use in medical applications (Hurd, 2017). Cannabidiol (CBD), the most abundant phytocannabinoid of cannabis after ⁹-tetrahydrocannabinol (THC), has generated significant hope in treating drug addiction (Calpe-López et al., 2019; Chye et al., 2019; Hurd, 2017). In the past two decades, a large body of basic and clinical research has revealed that CBD can be beneficial for treating neurological disorders such as epilepsy (Devinsky et al., 2014; Samanta, 2019), multiple sclerosis (Kozela et al., 2011), Parkinson's disease (Chagas et al., 2014; Zuardi et al., 2009), and Alzheimer's disease (Cheng et al., 2014; Martín-Moreno et al., 2011). Moreover, a substantial body of work has suggested that CBD improves cognition (Razavi et al., 2020) with anxiolytic (Gasparyan et al., 2020; Hahn, 2018), antidepressant (Linge et al., 2016; Zanelati et al., 2010), and antipsychotic-like effects (Elsaid et al., 2019; Scuderi et al., 2009), supporting its potential for the treatment of neuropsychiatric disorders including schizophrenia (Leweke et al., 2012; McGuire et al., 2018; Schoevers et al., 2020), mood disorders (Bartoli et al., 2021; Bonaccorso et al., 2019), anxiety disorders (Blessing et al., 2015; Skelley et al., 2020),

and drug addiction (Elsaid et al., 2019). Indeed, CBD modulates dopaminergic activity in the mesolimbic system (Murillo-Rodríguez et al., 2011) and decreases drug-induced dysregulation in the mesolimbic circuitry (Ren et al., 2009; Renard et al., 2016), and therefore may present an effective treatment against drug abuse.

Buprenorphine/Naloxone can be used as initial treatment for people are dependent on short-acting opioids or heroin, but these treatment strategies cannot successfully stop opiate craving entirely. Common side effects of buprenorphine include constipation, urinary retention, and mild respiratory depression (Cone et al., 1984). Further, reports already exist of buprenorphine-induced hepatitis, in particular when used intravenously. It has only recently been established that methadone, probably when prescribed in high doses, can cause cardiac problems (Krantz et al., 2007). Aside from opioids, treatment of psychostimulant addiction has been a major, and not fully met, challenge. For psychostimulants, there is no established maintenance medication that has met the criteria for regulatory approval (Shearer, 2008). Taking this all into consideration, new molecules should be discovered for treating drug abuse. Preliminary studies suggest that CBD may have therapeutic impacts helpful in treating drug use disorders (Crippa et al., 2013; Katsidoni, Anagnostou, & Panagis, 2013). Several studies suggest that CBD, a phytocannabinoid devoid of the psychoactive effects associated with THC, may have therapeutic effects for treating drug use disorders (Crippa et al., 2013; Katsidoni, Anagnostou, & Panagis, 2013). CBD is not associated with adverse cognitive effects, presents good safety and tolerability profiles in humans, and has a broad pharmacological spectrum of action (Zhornitsky & Potvin, 2012; niesink & van laar, 2013). As noted in this review: CBD has sedative, anti-craving, antidepressant, mood-stabilizing, and anxiolytic properties (Schier et al., 2012; Zhornitsky & Potvin, 2012; niesink & van laar, 2013; Robson, 2014). Moreover, CBD could effectively reduce the rewarding and reinforcing effects of some addictive drugs. Taken together, these data indicate that CBD may be clinically useful in attenuating the rewarding effects of substance abuse.

Thus, this review summarizes preclinical and clinical studies that have examined CBD as a novel pharmacological therapy in treating substance abuse disorders. In addition, possible molecular targets underlying CBD's mechanisms of action are discussed.

2. A brief history of cannabidiol medicinal uses

The cannabis genus of flowering plants is mainly comprised of the *Sativa* species. *Cannabis sativa* was cultivated for medicinal and religious purposes in ancient Asia (Li, 1974; Zuardi, 2006). The first account of therapeutic application of cannabis occurred in 4000 BC to the treatment of pain, constipation, menstrual cramps, and malaria (Mikuriya, 1969; Touw, 1981). In the nineteenth century, the usage of cannabis as medicine initiated in western medicine for anti-inflammatory, analgesic, anticonvulsant, anesthetic, antitussive, antiemetic, and appetite purposes. Due to multiple factors, such as the discovery of vaccines and effective medications, cannabis' psychoactive properties, and its increasing recreational abuse, the medical use of cannabis reduced considerably during the twentieth century (Zuardi, 2006). In addition to these reasons, the lack of reliable and scientific documents to demonstrate the efficacy of cannabis led to the general abandonment of cannabis as a

pharmacotherapeutic agent in the medical community (Gabay, 2013). In the early 1960s, both THC and CBD structures were first determined and described by the Mechoulam lab (Gaoni and Mechoulam, 1964). Mechoulam's group evaluated the effect of cannabinoids in primates and suggested that the sedative effects of cannabinoids were related to THC, but not CBD (Mechoulam et al., 1970). Later on, Cunha et al. revealed that CBD treatment could ameliorate intense epilepsy (Cunha et al., 1980); unfortunately, this pioneering study was relatively ignored by the scientific and medical community. Charlotte Figi, who had suffered over 300 grand mal seizures per week, was treated with a high ratio CBD: THC strain of cannabis that led to a significant reduction in the episodes and alleviated their intensity (Maa and Figi, 2014). That article received international attention and helped promote CBD legislation as a medical treatment as its efficacy had been confirmed for medical and psychological problems. To date, Epidiolex (Lattanzi et al., 2021; Samanta, 2019) and Sativex® (Russo, 2016, 2018) have been approved for the treatment of seizures resultant of pediatric Lennox-Gastaut syndrome or Dravet syndrome as well as spasticity and neuropathic pain in patients with multiple sclerosis, respectively. Elsewhere, several studies have evaluated CBD usage to treat inflammation, neuropathic pain, anorexia, bacterial infections, and insomnia (Burstein, 2015; Maroon and Bost, 2018; Russo, 2018; Zlebnik and Cheer, 2016).

Since CBD carries mild side effects in animal preclinical and human studies (Iffland and Grotenhermen, 2017; Taylor et al., 2018), and exhibits no rewarding properties (Babalonis et al., 2017; Parker et al., 2004), it may be introduced as a great therapeutic candidate for drug abuse. Recently, it has been established that CBD is effective for the inhibition of reinforcing and rewarding properties of drugs (Calpe-López et al., 2019; Chye et al., 2019; Elsaid et al., 2019; Mandolini et al., 2018; Rodrigues et al., 2020) such as opioids (Hurd et al., 2015; Prud'homme et al., 2015), psychostimulants (Calpe-López et al., 2021; Rodrigues et al., 2020), alcohol (Nona et al., 2019; Turna et al., 2019), and cannabis (Freeman et al., 2019; Freeman et al., 2020) in both humans and animals. It should mention that most of the studies were designed to evaluate the application of CBD for the treatment of drug abuse. In contrast, some studies sought to identify receptors implicated in CBD's action in various animal models of drug abuse and addiction.

Regarding the safety of CBD, Taylor et al., 2018, in phase I, randomized, double-blind, placebo-controlled study, revealed that CBD was commonly well tolerated. Diarrhea, nausea, headache, and drowsiness were the most frequently reported adverse events across all trial arms in subjects taking CBD. All adverse effects were of mild to moderate severity; none was severe. There were no deaths or discontinuations in the trial (Taylor et al., 2018).

3. Mechanism of cannabidiol's action in the treatment of drug abuse

The best-characterized cannabis plant constituents are the phytocannabinoids, known primarily for their complex and sometimes psychogenic effects. The most abundant and well-described phytocannabinoids are THC and CBD (Lucas et al., 2018). THC is the primary psychoactive compound associated with cannabis which binds with high affinity (K_i values in the low nanomolar range) to cannabinoid receptors (CBRs) (Ligresti et al., 2016; Matsuda et al., 1990; Munro et al., 1993). These receptors, along with the

endocannabinoids (N-arachidonylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG)) and their synthesizing/degrading enzymes makeup the ECS. THC's agonist activity at these CBRs affects behavior, nociception, and appetite, as well as having anti-inflammatory, antitumoral, and antiemetic properties (Klimkiewicz, 2018). In addition to CBRs, other pharmacological targets participating in the effects of THC include: G protein-coupled receptor, transient receptor potentiation (TRP) channels, the serotonin 3A receptor (5HT_{3A}), peroxisome proliferator-activated receptor gamma (PPAR γ), glycine (Gly), and opioids receptors (Barann et al., 2002; De Petrocellis et al., 2011; De Petrocellis et al., 2012; De Petrocellis et al., 2008; Lauckner et al., 2008; Morales et al., 2017; Neeper et al., 2007; Qin et al., 2008; Ryberg et al., 2007; Sano et al., 2008; Vara et al., 2013; Vaysse et al., 1987; Xiong et al., 2011). Moreover, THC modulates the mesolimbic dopaminergic pathway, which plays an important and established role in drug-seeking and promotes behaviors associated with the reinforcing effects of drugs (Lupica et al., 2004; Panlilio et al., 2015; Zehra et al., 2018).

Although similar in structure to THC, CBD is considered the major non-psychoactive component of cannabis. However, recent evidence from high-dose clinical and preclinical trials indicates that some psychoactive effects may be associated with high plasma levels of CBD (Solowij et al., 2019; Spindle et al., 2020; Szaflarski et al., 2019; Taylor et al., 2018). From its first identification, in 1940 (Adams et al., 1940), CBD has been extensively studied and found to exert many potentially therapeutic pharmacological effects, displaying antipsychotic, antinociceptive, anticonvulsant, anxiolytic, anti-inflammatory, anti-oxidant, and neuroprotective properties (Bergamaschi et al., 2011; Calpe-López et al., 2019; Karimi-Haghighi et al., 2020; Razavi et al., 2020). Until now, CBD has been shown to exhibit minor adverse effects or toxicity and therefore demonstrates an acceptable safety profile in preclinical non-human and human studies (Iffland and Grotenhermen, 2017; Taylor et al., 2018), while exhibiting no rewarding effect (Babalonis et al., 2017; Parker et al., 2004). Based on these data, the use of CBD has recently been considered as a potential treatment for substance use disorders such as addiction. Even though the precise mechanisms by which it exerts its therapeutic action have not yet been clarified, it is known that within the CNS, CBD interacts with a wide range of receptors, enzymes, and other targets (Fig. 1).

Unlike THC, CBD is a negative allosteric modulator of cannabinoid type 1 (CB₁R) and 2 (CB₂R) receptors (Laprairie et al., 2015; Martínez-Pinilla et al., 2017) (Fig. 1). The role of CB₁R in substance abuse disorders is controversial and may depend upon the phase of drug abuse (Galaj et al., 2020; Parker et al., 2004). Amongst CB₁R inverse agonists or antagonists, application of AM251 or SR141716 has failed to reverse the ameliorative effects of CBD on cocaine-related reward (Galaj et al., 2020; Gerdeman et al., 2008), while the neutral antagonist AM4113 has been found to inhibit the suppressive impact of CBD on cue-induced reinstatement of cocaine-seeking (Luján et al., 2020).

Within the ECS, the molecular targets of CBD include TRP subfamily V1 channels (Fig. 1). TRP channels are involved in reward-seeking behaviors and addiction (Blednov and Harris, 2009; Marsch et al., 2007; Tian et al., 2010). Indeed, TRP channels have been identified in brain areas associated with emotional response and cognitive behaviors such as the HIP, thalamus, basal ganglia, hypothalamus, NAc, cerebral cortex, and locus coeruleus,

which play multiple and essential roles in regulating neuronal activity and synaptic plasticity (Sawamura, 2019). Several animal studies have demonstrated the involvement of TRPV1 not only in addiction to substance abuse, but also in subsequent behavioral changes such as depression or anxiety (Singh et al., 2019). It has also been shown that capsazepine and SB366791 (TRPV1 receptor antagonist) suppress METH-induced CPP and SA. Meanwhile, TRPV1- knockout mice fail to develop METH-induced CPP, suggesting a crucial role for these channels in the rewarding properties of drugs. Moreover, capsazepine treatment decreases dopamine levels in the NAc of mice previously exposed to METH (Tian et al., 2018).

Emerging evidence indicates that TRPV1 inhibition may be effective in treating opioid addiction. Infusion of CPZ into the NAc attenuates morphine-induced CPP (Heng et al., 2014), tolerance, and withdrawal phenotypes in mice. Following this, TRPV1(−/−) mice do not respond to morphine reward (Nguyen et al., 2014). Adamczyk et al. have further found that SB366791, a TRPV1 antagonist, reverses cocaine-induced reinstatement of previously extinguished cocaine-seeking behavior. Conversely, SB366791 did not reduce cocaine SA, suggesting that TRPV1 activity is not necessary for the reward response but is involved in the mechanisms underlying cocaine relapse (Adamczyk et al., 2012). Taken together, these data demonstrate involvement of TRPV1 channels in response to substance abuse, identifying this as an essential pharmacological target in addiction therapy.

CBD acts as a TRPV1 agonist. Indeed, the pharmacological action of CBD is similar to some natural and synthetic TRPV1 agonists, as it first binds vanilloid receptor type 1 and then induces its desensitization (Bisogno et al., 2001). Interestingly, the administration of a TRPV1 antagonist blocks some of CBD's effects (Long et al., 2006). In agreement with this, anti-nociceptive and analgesic effects following capsaicin administration were inhibited by the TRPV1 antagonists, CPZ, SB366791, and I-RTX (Onizuka et al., 2011; Su et al., 1999; Wu et al., 2005). In the SA paradigm, CPZ, along with WAY100135 (5HT1A antagonist) and AM630 (CB2R antagonist), prevented the inhibitory effect of CBD on cocaine SA and cocaine-induced enhancement in brain-stimulation, while administration of CID16020046 (GPR55 antagonist) and naloxone (opioid receptor antagonist) did not affect cocaine SA (Galaj et al., 2020). As above, the suppressive effect of CPZ could be explained by its antagonist effects at TRPV1 receptors. The precise mechanism of action underlying the beneficial effects of CBD mediated by TRPV1 remains somewhat unclear. The simplest explanation, as suggested by Galaj, is the desensitization of TRPV1 receptors following CBD's binding. CBD, similarly to both natural and synthetic TRPV1 agonists, induces TRPV1 receptor desensitization (Bisogno et al., 2001). Another possibility is that CBD increases levels of anandamide via inhibition of fatty acid amide hydrolase (FAAH) or fatty acid-binding proteins actions (Bisogno et al., 2001), which subsequently suppresses cocaine-taking and seeking behavior (Adamczyk et al., 2012) by activation of both CB1Rs and TRPV1 channels (Fenwick et al., 2017). As extensively reported by Scherma and co-authors (Scherma et al., 2019), increasing AEA levels via FAAH-blockade (e.g., URB597 or AM404) leads to a reduction in nicotine-induced CPP and SA. In addition, this pharmacological intervention can attenuate some adverse effects related to withdrawal from substances of abuse (Cippitelli et al., 2011; Ramesh et al., 2013; Vela et al., 1995; Zhou et al., 2017).

CBD has also been shown to facilitate the neurotransmission mediated by the serotonin 1A receptor (5-HT_{1A}). Serotonergic transmission is strongly implicated in substance abuse disorders, including addiction to substances such as cocaine, METH, amphetamine (AMPH), and morphine, which interfere with the functionality of monoamine transporters for serotonin, dopamine, and noradrenaline, leading to addiction-related behavior in humans and animals (Koe, 1976; Müller et al., 2007; Ross and Renyi, 1967, 1969). Serotonergic neurons, which originate from the dorsal raphe nucleus (Ishimura et al., 1988), are involved in the modulation of reward-related behaviors (Luo et al., 2015; McDevitt et al., 2014). Indeed, these neurons project to brain areas associated with significant behavioral effects of substance of abuse, such as the VTA and NAc (Müller et al., 2007). Many of these serotonergic neurons express 5-HT_{1A} auto-receptors localized at the somatodendritic compartment, functioning to regulate neuronal excitability (Müller et al., 2007). Katsidoni et al. demonstrated that CBD suppresses the rewarding properties of morphine, an effect which was reversed by intra-dorsal raphe pretreatment with the selective 5HT_{1A} receptor antagonist, WAY-100635 (Katsidoni et al., 2013), thus suggesting 5HT_{1A} receptors as a CBD molecular target. Although the precise mechanism of action has not been elucidated, the authors posit that activating 5-HT_{1A} receptors by CBD might decrease extracellular serotonin concentrations, leading to reduced mesolimbic activity. Moreover, as mentioned above, WAY100135 prevented the inhibitory effect of CBD on cocaine SA and cocaine-induced enhancement in a brain-stimulation paradigm (Galaj et al., 2020), effects which may also be mediated in part by the modulation of serotonergic transmission.

It has been ascertained that CBD exhibits activity at some additional receptors, including the type 2 dopamine receptor (D₂R; partial agonist) (Seeman, 2016), mu- and delta-opioid receptors (negative allosteric modulator) (Kathmann et al., 2006), γ -Aminobutyric acid (GABA) type A receptor (positive allosteric modulator) (Bakas et al., 2017), Glycine α ₃ receptors (GlyR; positive allosteric modulator) (Xiong et al., 2011), type 1 dopamine receptor (D₁R) (Nouri et al., 2021), and α ₇-nicotinic receptors in CA1 (Mahgoub et al., 2013). Accordingly, CBD decreases μ -opioid (Oprm1) gene expression in the NAc (Viudez-Martínez et al., 2018), underlining its potential role in treating opioid use disorder. Because CBD acts as a positive allosteric modulator of GlyR α ₃ (Xiong et al., 2011), it may be considered as a novel alternative therapeutic agent for the treatment of neuropathic pain since this receptor is involved in the management of chronic pain (Acuña et al., 2016). Importantly, GlyRs have also been found in critical brain regions associated with addiction processes, including the NAc and VTA (Jonsson et al., 2009; Jonsson et al., 2012), where they seem to play an important role in reward transmission (Ye et al., 2004). Therefore, the potential of positive allosteric modulators of these receptors in treating reward disorders such as drug addiction should be thoroughly evaluated.

Although molecular studies conducted by Seeman (Seeman, 2016) have shown that CBD binds D₂R, the significance of such interaction in the modulation of reward mechanisms has not been demonstrated (Volkow et al., 2017). Though less relevant among CBD's molecular targets, it is known that dopamine receptors have a crucial role in some regions of the mesolimbic system involved in reward processes, including the HIP and NAc. Haghighparast and his colleagues investigated the possible link between D₂R in the dorsal HIP and the effects of intracranioventricular administration (ICV) of CBD on METH-induced

CPP. They demonstrated that ICV administration of CBD during the acquisition and expression phase could reduce METH-induced CPP. Significantly, this effect was reversed by intra-CA1 injection of Sulpiride. Furthermore, the latter did not affect METH-induced CPP in the absence of CBD. Therefore these results demonstrate that CBD modifies the reward properties of METH via D2R in the HIP (Hassanlou et al., 2021). The authors also demonstrated that intra-NAc administration of both D1 and D2R antagonists impaired CBD's inhibitory impact on the expression phase of METH (Sharifi et al., 2021). Based on this, we strongly suggest that these results underline the importance of the dopamine receptors as CBD's targets in the modulation of METH's rewarding properties.

Additionally, several studies have reported that CBD may modulate dopamine signaling in reward circuitry. For example, bilateral PFC infusion of CBD elicits a reduction in dopamine turnover (Rossignoli et al., 2017). Further, CBD alleviates the cumulative effects of cocaine, including increases in extracellular dopamine in the NAc (Galaj et al., 2020), expression of dopamine transporter genes (Calpe-López et al., 2021; Gasparyan et al., 2020), and the dopamine synthesizing enzyme tyrosine hydroxylase (TH) in the VTA (Gasparyan et al., 2020; Viudez-Martínez et al., 2018). Microinjection of CBD in the shell of the NAc hinders neuronal dopaminergic activity in the VTA (Renard et al., 2016). Together, these data suggest significant participation of the dopaminergic system in the effects of CBD in behaviors associated with reward.

CBD may also exert activity at the PPAR- γ (Jadoon et al., 2016), primarily known for participation in the regulation of inflammatory responses and the expression of genes related to lipid and glucose homeostasis (Rajasekaran et al., 2015). Recently, PPAR- γ receptors have received increased attention for the potential treatment of drug addiction owing to their presence in addiction-related brain regions such as the VTA (Melis et al., 2010; Moreno et al., 2004). Several preclinical studies have demonstrated that PPAR- γ agonists, pioglitazone and rosiglitazone, reduce voluntary ethanol consumption in two bottle-choice paradigms in rodents (Stopponi et al., 2011), modulate opioid-related behaviors (De Guglielmo et al., 2015), and attenuate sensitization to METH and cocaine (Maeda et al., 2007; Miller et al., 2018). In agreement with these findings, clinical studies have shown that PPAR- γ agonists can reduce cravings for nicotine, cocaine, and heroin (Jones et al., 2017; Schmitz et al., 2017) without affecting opioid dependence (Schroeder et al., 2018). Thus, CBD as a PPAR- γ agonist (Jadoon et al., 2016) could be considered a novel pharmacological therapy to treat negative symptoms associated with addiction.

Finally, CBD's function has been found to depend upon the mTOR/p70S6K signaling pathway; direct injection of CBD to the shell of the NAc selectively increases the phosphorylation states of this signaling pathways, whereas direct blockade of these molecular effects in the shell of NAc via administration of Torin 2 (a selective mTOR inhibitor) and PF4708671 (a novel and selective inhibitor of p70S6K) is sufficient to reverse the effects of CBD on AMPH-induced sensitization and prepulse inhibition (PPI) deficits (Renard et al., 2016). Pretreatment with various doses of CBD following METH injection dose-dependently attenuated METH-induced alterations in p-GSK-3 β , p-GSK-3 β /GSK-3 β , pAKT, and p-AKT/AKT ratios across PFC, HPC, and VTA, and NAc (Yang et al., 2020). ICV infusion of CBD (10 μ g/5 μ L) significantly dampens the mRNA expression level of

IL-1 β , IL-6, and IL-10 in the PFC, as well as reducing levels of TNF- α , IL-1 β , and IL-6 in the HIP (Karimi-Haghighi et al., 2020) (Fig. 1). Thus, the ameliorative properties of CBD on behavioral vioural and neurochemical perturbations elicited by drugs of abuse involve multiple pathways, receptor systems, and enzymatic modulatory effects.

4. Cannabidiol used in addiction medicine

In preclinical studies, the effect of CBD on the reinforcing and rewarding impacts of various types of substance abuse in animal models including SA and CPP paradigms in different phases (acquisition, reinforcement, expression), extinction, drug-seeking, and reinstatement, locomotion, and addiction have been investigated (Table 1). Clinical trial studies are summarized in Table 2.

4.1. Opioids

Although opioids top the list of problematic drugs causing the most burden of disease and drug-related deaths worldwide, only a tiny percentage of opioid addicts receive care; this care is commonly based on targeting opioid receptors and does not effectively inhibit opiate craving in all patients (Sharma et al., 2016; Wang et al., 2019).

The impacts of CBD on heroin SA and seeking behavior have been evaluated using an experimental rat model. CBD failed to change steady-state heroin SA, extinction behavior, or drug-seeking caused by a heroin primer administration in rats. Conversely, CBD was found to prevent the reinstatement of cue-induced heroin seeking (Ren et al., 2009). Another study, conducted in an experimental animal model, evaluated the effects of CBD on the reward-facilitating and brain reward function effect of morphine by using the intracranial self-stimulation (ICss) paradigm in rats. CBD (5 mg/kg) inhibited the reward-facilitating impact of morphine. Moreover, CBD (5 mg/kg) did not affect the efficacy of brain stimulation. In contrast, higher doses (10–20 mg/kg) increased ICss thresholds, indicating that brain reward function is decreased by acute administration of CBD. ICss thresholds were lowered by morphine but increased by CBD, suggesting that CBD is unlikely to exhibit abuse potential (Katsidoni et al., 2013) (Table 1).

Moreover, CBD's influence on the rewarding characteristic of morphine in the CPP paradigm has also been evaluated. CBD (10 mg/kg) pretreatment effectively prevented opioid reward in mice (Markos et al., 2018) (Table 1).

Following these discoveries, CBD's effects in animal models of opioids addiction were more thoroughly considered. In morphine-dependent rats, CBD's impact on THC-induced attenuation of morphine abstinence syndrome was investigated. Before naloxone administration for the precipitation of acute withdrawal symptoms, rats were pre-treated with either vehicle or CBD (10 mg/kg), accompanied by either THC (2 mg/kg) or vehicle injection. CBD alone did not influence abstinence scores, but in cooperation with THC, lessened the abstinence scores more than THC alone (Hine et al., 1975) (Table 1).

Additional evidence has demonstrated the attenuating effect of CBD on morphine withdrawal. CBD (5, 10, or 20 mg/kg) was investigated in morphine-dependent mice and on

naloxone-precipitated withdrawal symptoms. Therein, CBD attenuated jumping, defecation and rearing behavior in the mice (Bhargava, 1976). In another study, the effects of CBD (5, 20, or 80 mg/kg) were tested on mice given morphine before naloxone for precipitated quasi-morphine withdrawal syndrome. However, none of the CBD doses successfully in ameliorating the behavioral signs of withdrawal (Chesher and Jackson, 1985) (Table 1).

CBD employed for its effects on opioid craving has also been tested in human translational studies. In one study, three groups of patients received fentanyl (0.5 or 1 µg/kg) on two different occasions, with each group receiving either 400 or 800 mg of CBD or a placebo. CBD was well tolerated at all dosages, and co-administration with fentanyl did not induce respiratory depression symptoms or any cardiovascular complications (Manini et al., 2015) (Table 2).

Cue-induced craving and anxiety in heroin-abstinent individuals were decreased by acute CBD administration (400 or 800 mg), further demonstrating efficacy for CBD in ameliorating clinical signs and symptoms critical to the continued cycle of addiction. Additionally, there was a prolonged impact on these measures one week after short-term repeated CBD treatment. CBD also reduced physiological measures of stress reactivity, such as increased heart rate and cortisol levels, induced by salient drug cues without impacting cognition (Hurd et al., 2019) (Table 2).

4.2. Psychostimulants

Compulsive drug-seeking and substance abuse, despite negative physical consequences (seizures, ischemic strokes, and acute liver injury) and precipitated mental health disorders (anxiety, cognitive impairments, and psychotic symptom), have been determined as characteristics of psychostimulant abuse (Brownlow and Pappachan, 2002). Epidemiological investigations have declared that the number of cocaine abusers is increasing (Mena et al., 2013), and cocaine abuse has been identified as a significant public health problem impacting roughly 20 million individuals globally (Richards et al., 2016). While many studies have sought to identify efficient remedies for psychostimulant abuse, there is no FDA-approved medicine for psychostimulant abuse disorders, including cocaine, METH, and AMPH (Czoty et al., 2016; Mariani and Levin, 2012).

In the SA model, CBD (10-40 mg/kg) dose-dependently blocked acquisition and reduced total intake of cocaine in both rats and mice (Galaj et al., 2020; Luján et al., 2020), in addition to lowering voluntary consumption and progressive-ratio breaking point in mice (Luján et al., 2018). Further, CBD shifted the cocaine dose-response curve downward and lowered the breaking point under a progressive-ratio schedule of reinforcement in rats (Galaj et al., 2020) (Table 1). In terms of METH, CBD (80 mg/kg; IP) reduced the motivation towards METH SA in rats (Hay et al., 2018).

In terms of drug-seeking, CBD (in a gel volume of ≈640 µl/kg corresponding to ≈15 mg/kg CBD) attenuated context-induced and stress-induced drug-seeking without inducing tolerance/desensitization to CBD, nor sedative effects or interference with normal motivated behavior after cocaine (0.25 mg/infusion in the volume of 0.1 ml over 4 s on a fixed ratio 1) SA in rats (Gonzalez-Cuevas et al., 2018). Mahmud and their colleagues reported that CBD

treatment (5 or 10 mg/kg, IP) could not to block cue-induced cocaine-seeking following a 14 days withdrawal period from cocaine SA (0.5 mg/kg/infusion) under a progressive ratio schedule of reinforcement in rats (Mahmud et al., 2017).

Elsewhere, CBD (20 mg/kg) failed to impact extinction training but reduced 'extinction burst' behavior, defined as the paradoxical enhancement of operant responding in mice (Luján et al., 2021) (Table 1).

Several preclinical researches studies were assigned to evaluate the effect of CBD on the reinstatement of cocaine-seeking in the SA paradigm. It was reported that CBD (10 mg/kg) potentiated stress-induced reinstatement of cocaine-seeking behavior (Luján et al., 2021) while cocaine-induced reconsolidation and priming-induced reinstatement remained unchanged following CBD treatment in mice (Luján et al., 2018). In contrast, Luján et al., 2020 indicated that CBD treatment suppressed cue-induced reinstatement of cocaine-seeking in mice (Luján et al., 2021) (Table. 1).

In CPP paradigm studies, repeated CBD injection (10 and 20 mg/kg) reduced cocaine (10 or 15 mg/kg)-induced CPP (Chesworth and Karl, 2020; Luján et al., 2018) without any effect on behavioral sensitization in mice (Luján et al., 2018). Moreover, the mice treated with CBD (10 mg/kg) exhibited decreased cocaine preference and consolidation of cocaine memory (Chesworth and Karl, 2020). In terms of AMPH, bilateral infusion of CBD (100 ng/0.5 μ L) in the NAc shell reduced its sensitization, psychotomimetic behaviors (hyperlocomotion and sensorimotor gating deficits), and dopaminergic neuronal activity within the VTA of rats (Renard et al., 2016) (Table. 1).

Regarding METH, CBD (40 and 80 mg/kg; IP) suppressed METH-induced CPP in a dose-dependent manner (Yang et al., 2020). Meanwhile, ICV infusion of CBD inhibited both acquisition (10 and 50 μ g/5 μ L) and expression (50 μ g/5 μ L) phases (Anooshe et al., 2021); while, it enhanced sensitization (10 μ g/5 μ L) of METH-induced CPP in rats (Khanegheini et al., 2021). Elsewhere, intra-CA1 microinjection of D1R antagonist impaired CBD's suppressive impact on the acquisition and expression phases of METH-induced CPP in rats (Nouri et al., 2021). In our recent study, intra-NAc administration of either D1R or D2R antagonist impaired CBD's suppressive effect on the expression phase, while just a D2R antagonist alone inhibited the CBD's impact on the acquisition phase of the METH-induced CPP (Sharifi et al., 2021).

Regarding the extinction phase, CBD (5 mg/kg) facilitated the extinction of both cocaine (mice and rats) (Calpe-López et al., 2021; Parker et al., 2004) and AMPH-elicited CPP in rats (Parker et al., 2004). Conversely, Chesworth and Karl reported that CBD could not to modulate the extinction of cocaine-induced CPP in mice (Chesworth and Karl, 2020).

In the context of reinstatement, cocaine-induced reconsolidation and priming-induced reinstatement remained unchanged following CBD (10 mg/kg) treatment (Chesworth and Karl, 2020; Luján et al., 2018). However, in other studies, CBD at different doses blocked priming- and stress-induced reinstatement of cocaine in mice (Calpe-López et al., 2021) and the reconsolidation of propensity for environment-paired cocaine in rats (De Carvalho and Takahashi, 2017). Regarding METH abuse, CBD administration during the extinction period

(80 mg/kg; IP) (Hay et al., 2018) or at the time of the reinstatement (10 µg/5 µL; ICV) inhibited reinstatement of METH-induced CPP (Karimi-Haghighi and Haghparast, 2018) (Table 1). Moreover, the d,l-AMPH-conditioned rats that were treated with CBD (5 or 10 mg/kg, IP) did not exhibit reinstatement, the AMPH-induced enhancement in D1R and D2R in the PFC and ventral striatum, the AMPH-induced reduction in dopamine transporter in both PFC and ventral striatum, nor the decrease in TH in the ventral striatum (Metz et al., 2021) (Table 1).

Chesworth and Karl reported that CBD (10 mg/kg) treatment reduced the intensity of cocaine-induced locomotion in mice (Chesworth and Karl, 2020) and blunted the expression of locomotor sensitization induced by cocaine and caffeine co-administration in rats (Prieto et al., 2020) (Table 1). It should note that CBD (15–60 mg/kg) did not change locomotion but prevented D-AMPH-induced hyperlocomotion elicited without catalepsy induction in mice (Moreira and Guimarães, 2005).

AMPH (10 mg/kg) disrupted the PPI test, while CBD (15–60 mg/kg) administration alone had no such effect. CBD pretreatment attenuated the AMPH-disruptive effects on PPI test after systemic (30 and 60 mg/kg) or intra-NAc (60 nmol; 0.2 µL) administration in mice (Pedrazzi et al., 2015) (Table 1).

In addiction models of psychostimulant abuse, ICV administration of CBD (160nmol) over the abstinence period ameliorated the METH-induced deficiency in long-term memory, as well as METH-induced hyperlocomotion and disruption in spatial memory following chronic METH exposure in rats (Razavi et al., 2020) (Table 1). CBD (40 mg/kg; i.p.) treatment normalized signs of disturbance of spontaneous cocaine withdrawal (15 mg/kg/day at day one and rising to 60 mg/kg/day at day 11 for three times a day), including motor and somatic signs. It elicited an anxiolytic effect in mice (Gasparyan et al., 2020).

In clinical trials, thirty-one crack-cocaine-dependent men were treated with CBD (300 mg/day) or placebo for ten days. Despite promising evidence presented above from preclinical studies of rodent models, there was no evidence for CBD decreasing craving levels as compared to placebo groups. Thus, CBD was unable to interfere with symptoms of crack-cocaine withdrawal and craving (Meneses-Gaya et al., 2020). Moreover, the risk for cocaine relapse was similar in CBD- and placebo-receiving participants (Mongeau-Pérusse et al., 2021) (Table 2).

4.3. Marijuana

Marijuana refers to dried leaves, flowers, stems, and seeds from the hemp plant, *Cannabis sativa*. The plant contains the mind-altering chemical, ⁹-THC, and other related compounds. Individuals suffering from cannabis use disorder, CBD (400 and 800 mg) was efficacious to reduce rates of cannabis abuse (Freeman et al., 2020). It should be emphasized that all data regarding CBD treatment in marijuana abuse has been collected from controlled clinical trial studies.

In a separate case study, a 19-year-old woman with a history of smoking 4–8 cannabis cigarettes per day since age 13 and exhibiting cannabis withdrawal syndrome was treated

with CBD for ten days in the following regimen: 300 mg on Day 1 and 11; 600 mg on Days 2–10. Daily symptom assessments demonstrated the absence of significant withdrawal, anxiety, and dissociative symptoms during the treatment (Crippa et al., 2013) (Table 2).

Elsewhere, twenty frequent cannabis users daily received CBD (200mg) in a 10-week, open-label trial while continuing their regular cannabis use. All subjects were evaluated at baseline and post-treatment by psychological and physiological tests. CBD was well-tolerated without exhibiting notable deleterious effects; some participants even retrospectively declared a decrease in euphoria when smoking cannabis. No cognitive defects nor detrimental effects on the psychological condition were observed. Furthermore, participants underwent considerably fewer depressive and psychotic-like symptoms at posttreatment compared to baseline. They showed amelioration in the cannabis-abuse-induced deficits in attentional switching, memory, and verbal learning. These particular findings correlated with increased plasma concentration of CBD (Solowij et al., 2018). Elsewhere, Solowij et al. 2018, pretreatment of CBD (200, 400, and 800 mg, p.o.) failed to alter reinforcing, physiological, or positive impacts of smoked cannabis (Haney et al., 2016) (Table 2).

In an additional study, long-term heavy cannabis users showed a reduction in HIP volume (Yücel et al., 2016; Yücel et al., 2008), and gray matter density. An inverse correlation of the ratio THC/CBD with the volume of the right HIP was noted. CBD correlated positively with gray matter concentration, but not with gray matter volume in the bilateral HIP (Demirakca et al., 2011). Daily oral treatment by CBD (200 mg) in regular cannabis abusers increased left subicular complex volume, including left parasubiculum, presubiculum, and subiculum, with medium-large effect sizes. An enhancement in the right CA1 volume over the trial was found mainly in heavy users. The plasma concentration of CBD also correlated with right subicular complex and total right HIP growth in heavy users (Beale et al., 2018) (Table 2).

Nabiximols (Sativex; containing THC 2.7 mg/dose and CBD 2.5 mg/dose) has been found to significantly reduce scores on the cannabis withdrawal scale, as well as cravings, irritability, and depression in cannabis dependent individuals (Allsop et al., 2014). Three-month treatment with Sativex (up to 113.4 of THC/105 mg of CBD) concurrent with weekly motivational enhancement therapy and cognitive behavioral therapy reduced cannabis use with no significant increases in withdrawal in cannabis-dependent participants. Craving scores increased during the first two weeks but progressively returned to baseline levels from the third week of treatment (Trigo et al., 2016) (Table 2).

4.4. Alcohol

CBD has also exhibited therapeutic potential for treating alcohol use disorder. CBD's effects on ethanol reinforcement, motivation, and relapse in mice were shown in a recent study. Ethanol use, SA, CPP, and ethanol-induced relapse were all reduced upon CBD administration (Viudez-Martínez et al., 2018). In another study, rats were trained to self-administer alcohol at 24h intervals for seven days and then treated with CBD. CBD diminished the stress-induced drug-seeking behavior and alcohol's sedative effects and inhibited the motivation for alcohol SA. These effects of CBD persisted for up to five months, while the plasma levels of CBD were evident for only three days. Elsewhere, CBD

lessened measures of impulsivity and anxiety in alcohol-dependent mice (Gonzalez-Cuevas et al., 2018) (Table 1).

The positive effects of CBD detected in the animal models of alcohol addictions justified further studies evaluating the therapeutic effects of CBD in patients seeking treatment for alcohol use disorder (Nona et al., 2019; Turna et al., 2019) (Table 1).

In one clinical study, CBD's impact on alcohol intoxication was investigated in ten healthy volunteers, who were administered either placebo, 1 g/kg of alcohol, 200 mg of CBD, or both alcohol and CBD in a double-blind, cross-over design. Compared to placebo, the participants received alcohol and CBD and those consumed alcohol alone suffered significant impairments of motor and psychomotor performance and conveyed significant overestimations of time. The study results suggest either negligible or minimally enhancing effects of alcohol consumption in combination with CBD. Strangely enough, while practically no impacts of CBD on objective or subjective observations of intoxication were detected, the combination of alcohol and CBD yielded significantly lower levels of blood alcohol compared to alcohol given alone (Consroe et al., 1979) (Table 2). In sum, the favorable effects of CBD on alcohol-related harms and addiction phenotypes in preclinical propose that CBD can be an effective alternative to treat alcohol use disorder; however, more studies are needed.

4.5. Nicotine

The use of an inhaler of CBD (administering 400 µg) for one week significantly reduced the number of cigarettes smoked by ~40% of subjects during treatment. However, this reduction was not concurrent with a change in cigarette craving across the week (Morgan et al., 2013).

Elsewhere, CBD (single 800-mg oral dose) reversed attentional bias to cigarette cues and diminished explicit pleasantness during abstinence such that cigarette stimuli were rated as less pleasant after CBD treatment (Hindocha et al., 2018b) while verbal or spatial working memory and impulsivity were improved by CBD during tobacco abstinence (Hindocha et al., 2018a) (Table 2).

5. Conclusion

The therapeutic effects of CBD have been evaluated in both animal models and preliminary clinical trials conducted in individuals with different types of neuropsychiatric disorders, including drug abuse disorders. Several studies have proposed that CBD may be a reliable agent to inhibit the reinforcing and rewarding impact of drugs. However, further preclinical and clinical studies are necessary to confirm the potential for CBD as an intervention for the treatment of drug abuse disorders. It should be mentioned that its efficacy depends upon a wide range of factors such as the sequence of injection, administration route, and dosage/dose ratio. The studies reviewed in this article sought to consistently ascertain the tolerability profile of CBD when administered to the animal and human subjects. However, precise attention must be given to potential drug-drug interactions between CBD as a potent inhibitor of CYP 2C and CYP 3A enzymes and other agents metabolized by these two enzymes (Ujváry and Hanuš, 2016). Moreover, several main toxicological parameters are yet

to be investigated in earnest. For example, CBD affects on hormones (Bergamaschi et al., 2011; Iffland and Grotenhermen, 2017).

Finally, future attempts should be encouraged to clarify the relationship between the ECS, glutamatergic, serotonergic, and the immune system (all systems impacted by CBD treatment) since these systems are all involved in the regulation of the rewarding properties of drugs. Overall, CBD treatment can be a novel tool with some potential applications in treating substance use disorders and their comorbidity; however, more trials are needed to establish real clinical utility. Future studies could take these restrictions into account and focus on evaluating CBD's effects in the various stages of psychotic disorders, considering the high prevalence of comorbidity with substance abuse disorder.

Funding Source

This review was supported by grant (No. 99007925) from the Iran National Science Foundation, Tehran, Iran. The authors also would like to thank the Neuroscience Research Center, Shahid Beheshti University of Medical Sciences, for cooperating with this study. Work in the Manzoni lab was supported by the Institut National de la Santé et de la Recherche Médicale (INSERM); the INSERM-NIH exchange program (A.F.S.) and the NIH (R01DA043982 & R01DA046196-02 O.J.M.).

Abbreviations

2-AG	2-Arachidonoylglycerol
AMPH	Amphetamine
AEA	N-arachidonylethanolamine
BSR	Brain-Stimulation Reward
CBD	Cannabidiol
CB1R	Cannabinoid type 1 receptor
CB2R	Cannabinoid type 2 receptor
CBRs	Cannabinoid receptors
CPP	Condition Place Preference
CPZ	Capsazepine
CNS	Central nervous system
D₁R	type 1 dopamine receptor
D₂R	type 2 dopamine receptor
ECS	Endocannabinoid system
FAAH	Fatty acid amide hydrolase
GlyRs	Glycine receptors

GABA	γ -Aminobutyric acid
HIP	Hippocampus
ICss	Intracranial self-stimulation
ICV	Intracerebroventricular
METH	Methamphetamine
NAc	Nucleus accumbens
PFC	Prefrontal Cortex
PPAR-γ	Peroxisome proliferator-activated receptor
PPI	Prepulse inhibition
pERK1–2	phosphorylated Extracellular signal-regulated kinase phosphorylation
SA	Self-administration
TH	Tyrosine hydroxylase
THC	Δ^9 -tetrahydrocannabinol
TRP	Transient receptor potential cation channel
VTa	Ventral tegmental area
5-HT1A	Serotonergic receptor 1A
5-HT3A	Serotonergic receptor 3A

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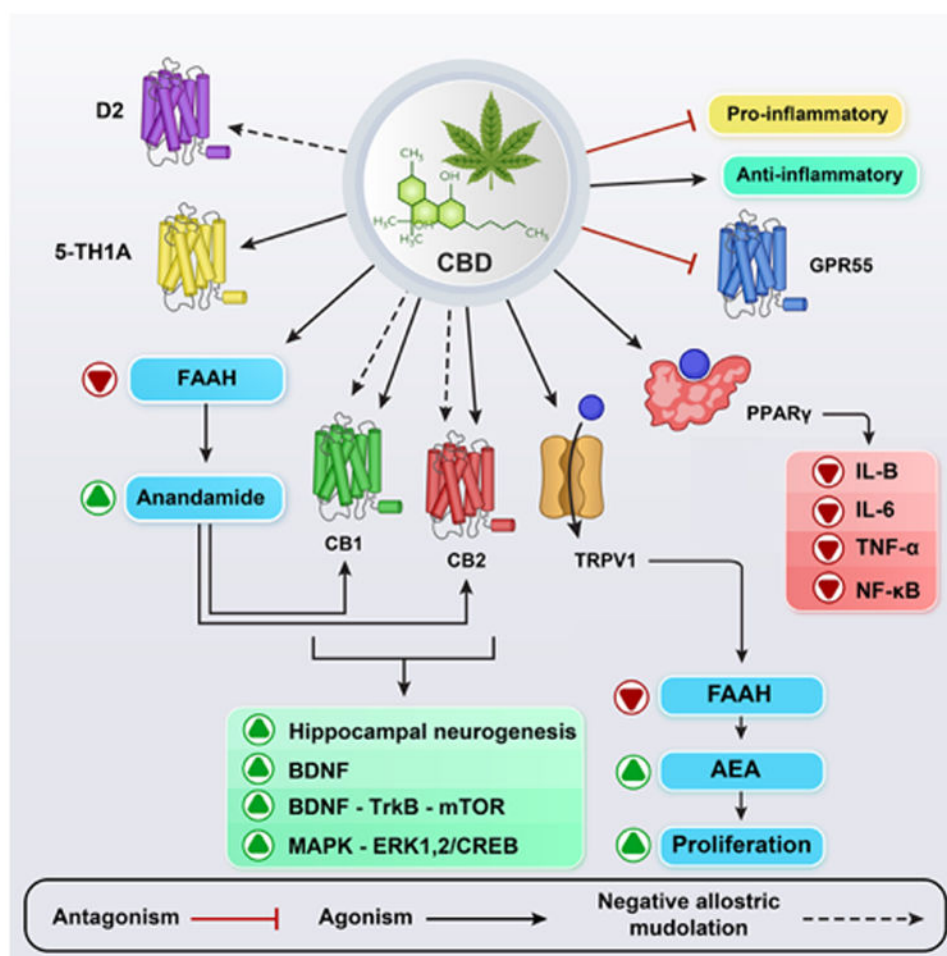


Fig. 1.
Schematic representation of the mechanisms underlying the CBD's actions on the effects were elicited by drug abuse.

Table 1.

Summary of animal studies regarding CBD's effect on drug abuse

Authors	Title	Sample	Substance abuse	Evaluation method	CBD Dose (mg/kg)	Primary outcomes
Hine et al. (1975)	Differential effect of cannabidiol and cannabidiol on THC-induced responses during abstinence in morphine-dependent rats	Rats	Morphine	Abstinence		CBD increases the attenuation of precipitated abstinence signs. CBD potentiates rotational behavior during morphine abstinence.
Bhargava et al. (1976)	Effect of some cannabinoids on naloxone-precipitated abstinence in morphine-dependent mice	Male Swiss-Webster mice	Morphine	Dependency	5, 10, and 20; IP	CBD inhibits the naloxone-precipitated morphine abstinence and two signs of morphine abstinence, defecation and rearing behavior.
Chesher et al. (1985)	The quasi-morphine withdrawal syndrome: effect of cannabidiol, cannabidiol and tetrahydrocannabinol	Male Sprague-Dawley rats	Morphine		5, 20, and 80; IP	CBD is without effect at the dosage levels used.
Ren et al. (2009)	Cannabidiol, a nonpsychotropic component of cannabis, inhibits cue-induced heroin seeking and normalizes discrete mesolimbic neuronal disturbances	Male Long-Evans rats	Heroin	SA	5 and 20; IP	CBD fails to alter stable intake of heroin SA, extinction, or priming-induced heroin seeking while attenuates heroin-seeking behavior reinstated by exposure to a conditioned cue.
Kasidoni et al. (2012)	Cannabidiol inhibits the reward-facilitating effect of morphine: involvement of 5-HT1A receptors in the dorsal raphe nucleus	Male Sprague-Dawley rats	Morphine and cocaine	Intracranial self-stimulation	5, 10 and 20; IP	CBD inhibits the reward-facilitating effect of morphine, but not cocaine. This effect is reversed by pre-treatment with an intra-dorsal raphe injection of WAY-100635.
Markos et al. (2018)	Effects of Cannabidiol on Morphine Conditioned Place Preference in Mice	Male C57BL/6 mice	Morphine	CPP	2.5, 5, 10, and 20; IP	CBD produces an attenuation of morphine CPP and so at a dose void of an aversive effect.
Hudson et al. (2019)	Cannabidiol counteracts the psychotropic side-effects of δ -9-tetrahydrocannabinol in the ventral hippocampus through bidirectional control of ERK1–2 phosphorylation	Male Sprague-Dawley rats	Morphine	CPP	100 ng	Intra- ventral HIP infusion of THC potentiates salience attribution in morphine CPP; CBD coadministration reverses these changes by downregulating pERK1–2 signaling.
Parker et al. (2004)	Effect of low doses of 9-tetrahydrocannabinol and cannabidiol on the extinction of cocaine-induced and amphetamine-induced conditioned place preference learning in rats	Male Sprague-Dawley rats	Cocaine and AMPH	CPP	5; IP	CBD potentiates the extinction of both cocaine and AMPH-induced CPP and this effect is not reversed by SR141716.
De Carvalho et al. (2016)	Cannabidiol disrupts the reconsolidation of contextual drug-associated memories in Wistar rats	Male Wistar rats	Cocaine and morphine	CPP	5 and 10; s.c.	CBD impairs the reconsolidation of preference for the environment paired with both morphine and cocaine. Moreover, CBD reduces morphine-CPP and subsequent conditioned place aversion precipitated by naltrexone.
Mahmud et al. (2016)	Effects of an acute cannabidiol treatment on cocaine self-administration and cue-induced cocaine seeking in male rats	Male Long Evans rats	Cocaine	SA	5 and 10; IP	CBD is unable to attenuate cocaine SA and cue-induced cocaine seeking after a withdrawal period of 14 days.
Alegre-Zurano et al. (2018)	Cannabidiol effects on cocaine-seeking behavior and incubation of craving in mice.	Male CDI mice	Cocaine	SA	20; IP	CBD reduces ongoing cocaine intake, but fails to alter the subsequent demand task performance, incubation of cocaine craving and abstinence period.

Authors	Title	Sample	Substance abuse	Evaluation method	CBD Dose (mg/kg)	Primary outcomes
Luján et al. (2018)	Repeated Cannabidiol treatment reduces cocaine intake and modulates neural proliferation and CB1R expression in the mouse hippocampus	Male CD1 mice	Cocaine	CPP SA	5, 10, 20, and 30; IP	CBD attenuates cocaine-induced CPP, voluntary consumption and progressive ratio breaking point in the SA paradigm, but not drug-induced reinstatement.
Gonzalez-Cuevas et al. (2018)	Unique treatment potential of cannabidiol for the prevention of relapse to drug use: preclinical proof of principle	Male Wistar rats	Cocaine and alcohol	SA	2.5 g/ 100 g; TD	CBD reduces context and stress-induced cocaine seeking. CBD decreases the experimental anxiety and development of high impulsivity with an alcohol dependence history.
Luján et al. (2020)	The pharmacological reduction of hippocampal neurogenesis attenuates the protective effects of cannabidiol on cocaine voluntary intake	Male CD-1 mice	Cocaine	SA	10 and 20; IP	CBD reduces cocaine SA behavior acquisition and total cocaine intake.
Galaj et al. (2020)	Cannabidiol attenuates the rewarding effects of cocaine in rats by CB2, 5-TH1A and TRPV1 receptor mechanisms	Male Long-Evans rats	Cocaine	SA	3–20; IP	CBD inhibits cocaine SA, cocaine-enhanced brain-stimulation reward, and enhanced extracellular dopamine in the NAc. Also, CBD's effect is blocked by AM630, WAY100135 and Capsazepine.
Chesworthand Karl (2020)	Cannabidiol (CBD) reduces cocaine-environment memory in mice	Adult male C57BL/6J mice	Cocaine	CPP	10; IP	CBD reduces preference for the cocaine-paired context, cocaine consolidation, and modifies cocaine-induced locomotion. CBD fails to change reconsolidation, the rate of extinction, and cocaine-primed reinstatement.
Gasparyan et al. (2020)	Cannabidiol modulates behavioral and gene expression alterations induced by spontaneous cocaine withdrawal	Male CD-1 mice	Cocaine	Spontaneous withdrawal	10, 20, and 40; IP	CBD normalizes motor and somatic signs disturbances in cocaine withdrawal. Moreover, the CBD administration blocks enhanced dopamine transporter and TH gene expression, regulates the decrease of CB1 and promotes the upregulation of CB2R gene expression.
Prieto et al. (2020)	Cannabidiol prevents the expression of the locomotor sensitization and the metabolic changes in the nucleus accumbens and prefrontal cortex elicited by the combined administration of cocaine and caffeine in rats	Male Wistar rats	Cocaine and caffeine	Locomotor sensitization	20; IP	Locomotion is increased in CBD treated animals; however, the expression of the combination of cocaine and caffeine sensitization is blunted.
Luján et al. (2021)	CB1 receptor antagonist AM4113 reverts the effects of cannabidiol on cue and stress-induced reinstatement of cocaine-seeking behavior in mice	Male CD-1 mice	Cocaine	SA	20; IP	CBD reduces 'extinction burst' responding, blocks the cue-induced reinstatement, this recent effect is inhibited by AM4113. CBD facilitates stress-induced reinstatement in CB1R-dependent mechanism.
Calpe-López et al. (2021)	Cannabidiol prevents priming- and stress-induced reinstatement of the conditioned place preference induced by cocaine in mice	Male CD-1 mice	Cocaine	Extinction and reinstatement	30 and 60	CBD inhibits priming- and stress-induced reinstatement of cocaine CPP and reverses cocaine increased dopamine transported gene expression in the VTA.
Moreira et al. (2005)	Cannabidiol inhibits the hyperlocomotion induced by psychotomimetic drugs in mice	Male Swiss mice	D- AMPH	Hyperlocomotion	15–60; IP	CBD inhibits hyperlocomotion without inducing catalepsy. Moreover, CBD is devoid of effect on locomotion.

Authors	Title	Sample	Substance abuse	Evaluation method	CBD Dose (mg/kg)	Primary outcomes
Pedrazzi et al. (2015)	Cannabidiol effects in the prepulse inhibition disruption induced by amphetamine	Male Swiss mice	AMPH	AMPH-induced PPI impairment	60 nmol in the NAc; 15, 30, and 60; IP	CBD attenuates the AMPH -induced PPI disruption. Also, CBD infusion into the NAc seems to be sufficient for the attenuation of PPI disruption.
Renard et al. (2016)	Cannabidiol counteracts amphetamine-induced neuronal and behavioral sensitization of the mesolimbic dopamine pathway through a novel mTOR/p70S6 kinase signaling pathway	Male Sprague Dawley rats	AMPH	Psychomotor sensitization	100 ng	Intra-shell of NAc infusion of CBD attenuates AMPH-induced sensitization.
Metz et al. (2021)	Cannabidiol prevents amphetamine relapse and modulates D1- and D2-receptor levels in mesocorticolimbic brain areas of rats	rats	AMPH	CPP	5 or 10; IP	CBD modulates at basal levels the dopaminergic targets in the assessed brain areas, prevents AMPH relapse, and decreases anxiety-like behavior in AMPH-CPP animals
Karimi-Haghighi et al. (2018)	Cannabidiol inhibits priming-induced reinstatement of methamphetamine in REM sleep deprived rats	Adult male albino Wistar rats	METH	CPP	10 µg	ICV administration of CBD hinders the METH-induced reinstatement even in REM sleep deprived rats.
Karimi-Haghighi et al. (2019)	Cannabidiol modulates the expression of neuroinflammatory factors in stress- and drug-induced reinstatement of methamphetamine in extinguished rats	Adult male albino Wistar rats	METH	CPP	10 µg	CBD decreases the expression of IL-1β, IL-6, and IL-10 in the PFC, and also, TNF-α, IL-1β, and IL-6 in the HIP. Furthermore, CBD treatment before REM sleep deprivation augments the TNF-α, IL-1β, IL-6, and IL-10 levels in the HIP.
Hay et al. (2019)	Cannabidiol treatment reduces the motivation to self-administer methamphetamine and methamphetamine-primed relapse in rats	Male Sprague Dawley rats	METH	SA	20, 40, and 80; IP	CBD decreases the motivation to METH SA and reduces METH-primed relapse after extinction.
Jaehne et al. (2019)	The effect of cannabidiol on psychosis-like behavior induced by methamphetamine and MK-801 in mice: a negative report	C57BL/6 mice	METH	Locomotor activity	10	Pretreatment with CBD had no effect on the hyperlocomotion induced by METH or MK-801.
Yang et al. (2020)	Cannabidiol attenuates methamphetamine-induced conditioned place preference via the Sigma1R/AKT/GSK-3β/CREB signaling pathway in rats	Male Sprague-Dawley rats	METH	CPP	10, 20, 40, and 80; IP	CBD inhibits METH- CPP and causes differential inhibitory responses in the Sigma1R, p-AKT, p-GSK3β, and p-CREB across various brain regions.
Razavi et al. (2020)	Neuroprotective effect of chronic administration of cannabidiol during the abstinence period on methamphetamine-induced impairment of recognition memory in the rats	Adult male albino Wistar rats	METH	Chronic exposure	32 and 160 nmol	ICV infusion of CBD improves spatial memory and reverses short- and long-term memory that are impaired by chronic exposure of METH.
Anooshe et al. (2021)	Cannabidiol efficiently suppressed the acquisition and expression of methamphetamine-induced conditioned place preference in the rat	Adult male albino Wistar rats	METH	CPP	2, 10, and 50 µg	ICV infusion of CBD suppresses both acquisition and expression phases of METH-CPP without any side effect on the locomotion.
Razavi et al. (2021)	Cannabidiol modulates the expression of neurotrophin signaling pathway in chronic exposure methamphetamine rats during abstinence period	Adult male albino Wistar rats	METH	Chronic exposure	10 and 50µg	ICV administration of CBD increases the mRNA expression levels of BDNF/TrkB; RAF1, and NGF/TrkA in the HIP during abstinence.

Authors	Title	Sample	Substance abuse	Evaluation method	CBD Dose (mg/kg)	Primary outcomes
Khaneqheini et al. (2021)	Cannabidiol enhanced the development of sensitization to the expression of methamphetamine-induced conditioned place preference in male rats	Adult male albino Wistar rats	METH	CPP	10, 50, 100, and 200 µg	ICV administration of CBD during the sensitization phase, shifted the establishment of METH-CPP toward a lower dose.
Nouri et al. (2021)	Involvement of hippocampal D1-like dopamine receptors in the inhibitory effect of cannabidiol on acquisition and expression of methamphetamine-induced conditioned place preference	Adult male albino Wistar rats	METH	CPP	10 and 50 µg	Intra-CA1 infusion of SCH23390 impairs CBD's suppressive impact on both acquisition and expression phases of METH-CPP.
Hassanlou et al. (2021)	Cannabidiol modulates the METH-induced conditioned place preference through D2-like dopamine receptors in the hippocampal CA1 region	Adult male albino Wistar rats	METH	CPP	10 and 50 µg	Intra-CA1 administration of sulpiride reversed the decreasing effects of CBD on METH-CPP in both acquisition and expression phases.
Sharifi et al., 2021	Cannabidiol impairs the rewarding effects of methamphetamine: Involvement of dopaminergic receptors in the nucleus accumbens	Adult male albino Wistar rats	METH	CPP	10 and 50 µg	Intra-NAc administration of either SCH23390 or Sulpiride impaired CBD's inhibitory impact on the expression phase, while just Sulpiride inhibited the CBD's impact on the acquisition phase of the METH-CPP.
Vuudez-Martínez et al. (2017)	Cannabidiol reduces ethanol consumption, motivation and relapse in mice	Male C57BL/6 J mice	Alcohol	Oral SA Two-bottle choice	60 and 120, IP.	CBD attenuates ethanol consumption and preference in the two-bottle choice, ethanol intake, the number of effective responses in the oral ethanol SA, and ethanol-induced relapse. It decreases gene expression of TH in the VTA, Oprm1, CB1R and GPR55 in the NAc and increases CB2R in the NAc.

Table 2.

Summary of clinical studies regarding CBD's effect on drug abuse

Authors	Title	Sample	Substance abuse	Evaluation method	CBD Dose (mg/kg; p-o)	Primary outcomes
Manini et al. (2015)	Safety and pharmacokinetics of oral cannabidiol when administered concomitantly with intravenous fentanyl in humans	Healthy volunteers	Fentanyl	Double-blind, placebo-controlled cross-over	400 and 800	After low-dose CBD, tmax occurred at 3 and 1.5 hours in sessions 1 and 2, respectively. After high-dose CBD, tmax occurred at 3 and 4 hours in sessions 1 and 2, respectively.
Hurd et al. (2019)	Cannabidiol for the reduction of cue-induced craving and anxiety in drug-abstinent individuals with heroin use disorder: a double-blind randomized placebo-controlled trial	Men and women with heroin use disorder	Heroin	Double-blind randomized placebo-controlled trial	400 and 800	Acute CBD administration reduces cue-induced craving and anxiety in heroin-abstinent individuals. There no serious adverse effects.
Meneses-Gaya et al. (2020)	Cannabidiol for the treatment of crack-cocaine craving: an exploratory double-blind study	Men with a diagnosis of crack-cocaine dependence	Crack-cocaine	Craving	300	CBD had no effect on craving levels and indicators of anxiety, depression, and sleep alterations.
Mongeau-Pérusse et al. (2021)	Cannabidiol as a treatment for craving and relapse in individuals with cocaine use disorder: a randomized placebo-controlled trial	Adult women with moderate to severe use disorder	Cocaine	Craving and relapse	800	Cocaine craving or relapse is unaffected by CBD among people being treated for cocaine abuse disorder.
Demirakca et al. (2011)	Diminished gray matter in the hippocampus of cannabis users: Possible protective effects of cannabidiol	Male chronic recreational cannabis users	Cannabis			An inverse correlation of the ratio THC/CBD with the volume of the right HIP is observed. CBD positively correlates with gray matter concentration in the bilateral HIP.
Crippa et al. (2013)	Cannabidiol for the treatment of cannabis withdrawal syndrome: a case report	19-year-old woman with cannabis withdrawal syndrome	Cannabis	Case report	300 - 600	CBD may have therapeutic effect in cannabis withdrawal syndrome, at least in patients with no psychiatric comorbidities.
Allsop et al. (2014)	Nabiximols as an agonist replacement therapy during cannabis withdrawal a randomized clinical trial	DSM-IV-TR cannabis dependence	Cannabis	A randomized clinical trial	Maximum daily dose 80	Nabiximols reduces the severity and duration of cannabis withdrawal and improves retention rates during inpatient treatment as well as cravings.
Trigo et al. (2016)	Sativex associated with behavioral-relapse prevention strategy as treatment for cannabis dependence: a case series	Cannabis dependence	Cannabis	Pilot phase of a double-blind placebo-controlled trial	Sativex (up to 105 mg of CBD)	Sativex is well tolerated by all participants. The amount of cannabis use decreases with no increases in withdrawal.
Haney et al. (2016)	Oral cannabidiol does not alter the subjective, reinforcing or cardiovascular effects of smoked cannabis	Cannabis smokers	Cannabis	Multi-site, randomized, double-blind	200, 400, and 800	Cannabis SA and cannabis ratings did not vary as a function of CBD.
Solowij et al. (2018)	Therapeutic effects of prolonged cannabidiol treatment on psychological symptoms and cognitive function in regular cannabis users: a pragmatic open-label clinical trial	Cannabis users	Cannabis	Pragmatic open-label clinical trial	200	CBD-treated participants report reduction in euphoria when smoking cannabis, fewer depressive and psychotic-like symptoms and improvements in attentional switching, verbal learning, and memory.

Authors	Title	Sample	Substance abuse	Evaluation method	CBD Dose (mg/kg; p.o)	Primary outcomes
Beale et al. (2018)	Prolonged cannabidiol treatment effects on hippocampal subfield volumes in current cannabis users	Cannabis users	Cannabis	Open-label pragmatic trial	200.	Associations between greater right subicular complex and total HIP volume and higher plasma CBD concentration are evident, particularly in heavy users.
Morgan et al. (2018)	Individual and combined effects of acute delta-9-tetrahydrocannabinol and cannabidiol on psychotomimetic symptoms and memory function	Cannabis users	Cannabis	A randomised, double-blind crossover	16; INH	CBD alone reduces PSI scores in light users only. Cannabis users may show a blunted anti-psychotic response to CBD.
Freeman et al. (2020)	Cannabidiol for the treatment of cannabis use disorder: a phase 2a, double-blind, placebo-controlled, randomised, adaptive Bayesian trial	DSM-5 cannabis users	Cannabis	Double-blind, placebo-controlled, randomised	200, 400, and 800	CBD exceeds the primary endpoint criterion for reducing cannabis use during treatment.
Consoer et al. (1979)	Interaction of cannabidiol and alcohol in humans	Healthy post graduate student volunteers	Alcohol	Double-blind, crossover, randomized design	200	Alcohol plus CBD produces decrements of motor and cognitive responses and subjective alteration. CBD decreases blood alcohol levels. .
Morgan et al. (2013)	Cannabidiol reduces cigarette consumption in tobacco smokers: Preliminary findings	Cigarette smokers	Tobacco	Double-blind placebo controlled	400 µg	CBD significantly reduces the number of cigarettes smoked by ~40% during treatment.
Hindocha et al. (2018)	Cannabidiol reverses attentional bias to cigarette cues in a human experimental model of tobacco withdrawal	Cigarette smokers	Tobacco	Randomized, double-blind crossover	800	CBD reverses automatic attentional bias is directed away from cigarette cues. CBD reduces explicit pleasantness of cigarette images. Craving and withdrawal are unaffected by CBD.
Hindocha et al. (2018)	The effects of cannabidiol on impulsivity and memory during abstinence in cigarette dependent smokers	Cigarette smokers	Tobacco	Double-blind placebo-controlled crossover	800	CBD does not improve verbal or spatial working memory, or impulsivity during tobacco abstinence.