Cannabidiol as an Intervention for Addictive Behaviors: A Systematic Review of the Evidence

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ABSTRACT: Drug addiction is a chronically relapsing disorder characterized by the compulsive desire to use drugs and a loss of control over consumption. Cannabidiol (CBD), the second most abundant component of cannabis, is thought to modulate various neuronal circuits involved in drug addiction. The goal of this systematic review is to summarize the available preclinical and clinical data on the impact of CBD on addictive behaviors. MEDLINE and PubMed were searched for English and French language articles published before 2015. In all, 14 studies were found, 9 of which were conducted on animals and the remaining 5 on humans. A limited number of preclinical studies suggest that CBD may have therapeutic properties on opioid, cocaine, and psychostimulant addiction, and some preliminary data suggest that it may be beneficial in cannabis and tobacco addiction in humans. Further studies are clearly necessary to fully evaluate the potential of CBD as an intervention for addictive disorders.

KEYWORDS: review, cannabidiol, drug addiction, addictive behaviors, treatment

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Introduction

Drug addiction is a chronically relapsing disorder characterized by the compulsive desire to seek and use drugs with impaired control over substance use despite negative consequences.[1] In all, 162–324 million people between the ages of 15 and 64 have used an illicit substance worldwide in 2012, and approximately 183,000 deaths were thought to be drug related.[2] In the past decade the advent of new technologies has allowed for a better understanding of the neural mechanisms involved in addictive disorders. The glutamatergic and dopaminergic systems have been found to play an important role in the reinforcing effects of drugs and prolonged risk of relapse.[3–5] Moreover, the endocannabinoid system (ECBS) has been shown to influence the acquisition and maintenance of drug-seeking behaviors, through its role in reward and brain plasticity.[6,7] Cannabinoid receptors have been studied in addiction-related processes, with special attention paid to cannabinoid type 1 (CB1) receptors. Other ionotropic cannabinoid receptors are also linked to neurophysiological functions in the ECBS, such as transient receptor potential receptors, including transient receptor vanilloid potential 1 (TRVP1), which binds the endogenous cannabinoid anandamide (AEA)[5] (Supplementary Table 1 lists the abbreviations).

Among the compounds found to modulate the ECBS, Δ9-tetrahydrocannabinol (THC) has been widely studied since its discovery in the 1960s as the main component of cannabis extract. Its psychosis and anxiety-inducing addictive properties are well known.[8,9] In contrast, cannabidiol (CBD), the second most abundant component of cannabis – less studied than THC – has been shown to have anxiolytic, antipsychotic, antidepressant, and neuroprotective properties.[10–13] CBD acts on the ECBS as a weak inverse agonist on CB1 receptors, stimulates the TRVP1, and alters the hydrolysis of AEA by inhibiting fatty acid amine hydrolase.[14–16] CBD has been shown to be an agonist of 5-HT1a serotoninergic receptors and to regulate stress response and compulsive behaviors.[17] Moreover, CBD modulates allosterically μ and δ opioid receptors. The direct impact of CBD on glutamatergic neurotransmission is not known, but its protective effects on glutamate toxicity have been studied.[18,19] Altogether, CBD has been associated with many neural circuits involved in the acquisition of addiction and subsequent drug-seeking behaviors, making it an interesting pharmacological candidate to treat substance-use disorders.

In past years, several researchers have studied the effects of CBD on physical and mental health, and a growing number have focused on the effects of CBD on addiction. The main objective of this review is to systematically examine the existing preclinical and clinical evidence on the effects of CBD on addictive behaviors.

Materials and Methods

Search strategy. The literature search was conducted in two electronic databases, MEDLINE and PubMed. The search was restricted to English and French-language articles before 2015. Both the databases were independently searched by two reviewers (MP and RC), and the titles and abstracts were sorted followed by careful reading of the complete articles when relevant. A first reviewer (MP) explored the databases by combining pertinent key words (eg, CBD + Addiction; detailed search strategy and key words can be obtained from the corresponding author), while the second reviewer (RC) explored all the articles found on both databases with the keyword "cannabidiol". A third researcher (DJA) was consulted in the event of discrepancies occurring between the results of the two reviewers.

Eligibility criteria. In order to be included, studies had to evaluate the outcomes of CBD on addictive behaviors, in any of the three phases of addiction (intoxication, withdrawal, and craving/relapse). Studies that focused on other outcomes only (anxiety, psychosis, pain, etc) were excluded. Studies evaluating the impact of CBD on addictive behaviors for all major types of substances of abuse (opioids, psychostimulants, cannabis, hallucinogens, sedatives, alcohol, tobacco, etc) have been included. Both studies on humans and animals were included. All types of study designs were included: clinical trials (randomized or not), observational, retrospective and prospective studies, and case reports.

Data extraction and analysis. When available, the following data were retrieved from the included studies: authors, publication year and journal, study design, characteristics of participants, sample size, objectives, type of intervention, results, and main limitations. According to a widely used conceptualization of addiction,[20] the effects of CBD on addictive behaviors were classified in three distinct phases: the intoxication phase, when the drug produces positive rewarding experiences; the withdrawal phase, when the user experiences acute physical and psychological withdrawal symptoms, and the relapse phase, when the user experiences cravings and is at risk of drug-seeking behaviors after abstinence.

Results

We identified 21 potentially eligible studies. After a careful review of articles, seven of those were excluded because their outcomes did not fit the purpose of this review or because they were duplicated (Supplementary Table 2 provides description of the excluded studies). Fourteen studies were included (Supplementary Fig. 1). Of those, nine were conducted on animals (seven experimental rat models, one experimental mice model, and two experimental models involving both rats and mice) and five on humans (one randomized placebo-controlled study, two crossover clinical studies, one randomized crossover clinical study, and one case report). Of the preclinical studies, five dealt with opioid, one with psychostimulant, one with opioid and psychostimulant, and two with cannabis addiction. Of the studies involving humans, three were related to cannabis, one to tobacco, and one to alcohol addiction (Supplementary Table 3 contains a detailed description of each study).

Included animal studies. *Effects of CBD on opioid-related addictive behaviors.* Studies were found on all three phases of opioid addiction. Using the intracranial self-stimulation (ICSS) paradigm (an operant conditioning method in which direct stimulation of brain areas by electrical or chemical means is rewarding), Katsidoni et al examined the effects of CBD on morphine's brain reward function.[21] They trained rats to ICSS, observed the impact of morphine (10 mg/kg) and CBD (5 mg/kg) on the ICSS threshold, and studied the involvement of 5-HT1A receptors in CBD's action by adding a selective 5-HT1a receptor antagonist. They found that CBD inhibited the decrease of the ICSS threshold by morphine and thus its reward-facilitating effect, without influencing motor function. Moreover, the 5-HT1A receptor antagonist reversed CBD's impact on the reward-facilitating effect of morphine.

Hine et al evaluated the effects of CBD on THC-induced attenuation of morphine abstinence syndrome.[22] After inducing morphine dependence in 33 rats and administrating tested agents (vehicle or CBD 10 mg/kg, followed by vehicle or THC 2 mg/kg), they induced withdrawal with naloxone and calculated an abstinence score based on specific signs (number of wet shakes or escapes, number of fecal boluses, presence of diarrhea, vocalization, abnormal posture, ear blanching, ptosis, chewing, or teeth chattering). The results showed that CBD alone did not influence the score, but reduced the number of fecal boluses, while increasing wet shakes. A synergic effect was revealed when CBD was combined to THC, which reduced the abstinence score to a greater extent than THC alone. Hine et al conducted another study, with the same objectives, doses, and methodology as the previous one.[23] Again, they found that CBD potentiated the THC-induced reduction in abstinence score and raised the number of turnings. Bhargava also investigated the effects of cannabinoids on morphine withdrawal syndrome.[24] Morphine dependence was induced in mice, various doses of cannabinoids were subsequently administered (including CBD 5, 10, 20 mg/kg), and withdrawal was precipitated with naloxone. The dose of naloxone required to provoke 50% of the mice to jump off of a platform was recorded during the withdrawal, as were defecation and rearing behaviors. CBD inhibited the naloxone withdrawal–induced jumping and reduced defecation and rearing behaviors. Chesher and Jackson assessed the response of THC, CBN, and CBD on quasi-morphine withdrawal syndrome (QMWS), elicited in 200 rats by administering a phosphodiesterase inhibitor followed by naloxone.[25] They calculated withdrawal scores based on observed behavioral signs; the results showed that CBD at all doses (5, 20, 80 mg/kg) had no effect on QMWS.

More recently, Ren et al evaluated the impact of CBD on heroin addiction vulnerability using a drug

self-administration (SA) rat model.[26] Rats were trained to acquire a stable heroin SA intake, with each active level press resulting in drug injection and the activation of a stimulus white light. The effects of CBD were examined during the maintenance and extinction phases of SA and during cue-induced reinstatement. The results of this study indicate that CBD (one dose of 5 mg/kg or 5 mg/kg once daily for 3 days) specifically inhibited conditioned cue-induced heroin-seeking behavior for up to 2 weeks following the last administration without affecting motor function. On the other hand, CBD failed to influence drug-seeking behavior initiated by heroine prime. Moreover, neither the maintenance nor the extinction phase of SA was modified by CBD.

Overall, CBD was found to have an impact on the intoxication and relapse phase of opioid addiction. Data on its effect during the withdrawal phase remain conflicting and vary based on co-administration of other cannabinoids such as THC.

Effects of CBD on psychostimulant-addictive behaviors. Few studies examined the effects of CBD on the intoxication and relapse phases of psychostimulant addiction. In the previously cited study, Katsidoni et al also assessed the effect of CBD on cocaine's brain reward function, with the same methodology and found that CBD (5 mg/kg) failed to inhibit a decrease in the ICSS threshold induced by cocaine (5 mg/kg).[21]

Parker et al assessed the impact of THC and CBD on cocaine- and amphetamine-induced conditioned place preference (CPP) in rats.[27] After inducing CPP with the aforementioned drugs, THC (0.5 mg/kg), CBD (5 mg/kg), or a vehicle was administered, and the rats were given an extinction trial. They found that both cannabinoids potentiated the extinction of cocaine- and amphetamine-induced place preference learning and that this effect was not reversed by the administration of a CB1 receptors antagonist. These effects were not mediated by learning or retrieval alteration and CBD did not have hedonic properties on its own. Moreover, they also studied the effects of cannabinoids on the establishment of stimulant CPP. In that case, CBD showed no impact.

Thus, CBD does not appear to have an impact on stimulants' rewarding effect, but one study suggests that it may influence addictive behaviors during the relapse phase.

Effects of CBD on cannabis-related addictive behaviors. Few studies have examined the effects of CBD administration on various outcomes during the intoxication and relapse phase of cannabis addiction. Vann et al assessed the effect of CBD on THC drug discrimination and CPP in rats and mice.[28] After inducing THC drug discrimination and CPP, they tested several combinations of CBD and THC at different doses. The results showed that CBD alone did not produce a THC discrimination stimulus. THC and CBD (0.3, 3, 30 mg/kg) injection did not alter the drug discrimination at any dose, compared to THC alone. While high doses of THC produced a conditioned place aversion, no CPP or conditioned place aversion was recorded with CBD alone. In combination, low doses of CBD (1, 10 mg/kg) reversed the conditioned place aversion induced by THC (10 mg/kg). Klein et al also assessed the impact of CBD on THC place-conditioning effects and found a trend toward place preference induced by the combination of CBD and THC (both 10 mg/kg).[29]

While CBD does not appear to be reinforcing on its own, its impact on cannabis-related addictive behaviors in animal models remains unclear.

Other substances. No animal study was found on hallucinogen-, sedative-, tobacco-, or alcohol-addictive behaviors.

Included human studies. *Effects of CBD on cannabis-related addictive behaviors.* Outcomes of CBD on all three phases of cannabis addiction were found. Crippa et al investigated the effects of CBD on cannabis addiction and its withdrawal syndrome.[30] They conducted an experimental trial on a 19-year-old female with cannabis dependence, who experienced withdrawal syndrome when she tried to cease cannabis use. CBD was administered for 11 days (300 mg on day 1, 600 mg on days 2–10, and 300 mg on day 11). Daily assessments using the Withdrawal Discomfort Score, Marijuana Withdrawal Symptom Checklist, Beck Anxiety Inventory, and Beck Depression Inventory showed a rapid decrease in withdrawal symptoms, leading to a score of zero in all tests by day 6. A 6-month follow-up showed a relapse in cannabis use, but at a lower frequency (one or twice a week vs. 7 days a week). In a naturalistic crossover clinical study, Morgan et al evaluated the impact of varying levels of CBD and THC on the acute effects of cannabis intoxication.[31] They studied 134 cannabis users on two different days, approximately 1 week apart: once sober and once intoxicated with their own chosen cannabis. Samples of the drug were analyzed and two groups were formed based on levels of CBD, low (<0.14%) versus high (>0.75%), each containing 22 participants. They found no difference in either group in their rating of feeling "stoned". Morgan et al conducted another study and evaluated the impact of CBD on the reinforcing effects of THC on addictive behavior.[32] They studied the implicit "wanting" and the explicit "liking" of cannabis on 94 cannabis users, by attentional bias to drug and food stimuli, pleasantness ratings, a marijuana-craving questionnaire, and a visual analog scale in a crossover design similar to that described above (drug-free day and intoxicated day with their own cannabis, two groups of 32 participants based on low or high CBD:THC ratios). Greater attentional bias to drug and food stimuli was found in the low CBD:THC ratio group on the short picture presentation interval of the dot-probe task on the intoxicated day (implicit "wanting"). However, a greater attentional bias to both stimuli was found in both groups on the longer picture presentation interval on the intoxicated day and on both short and long picture presentation intervals on the drug-free day. Moreover, a high CBD:THC ratio was associated with lower ratings of pleasantness for drug stimuli (explicit "liking"), while no group difference in craving or stoned ratings was noted.

Overall, preliminary data suggest a possible beneficial impact of CBD on the reinforcing effect of cannabis, while

a case report has shown positive outcomes for one patient treated with CBD during the withdrawal and relapse phase of cannabis dependence.

Effects of CBD on tobacco-related addictive behaviors. Only one study looked at the impact of CBD on tobacco addiction. Morgan et al studied the impact of CBD on nicotine addiction by conducting a randomized, double-blind, placebo-controlled study on 24 smokers who wished to stop smoking.[33] Two groups received either a CBD inhaler (400 μg/inhalation) or a placebo inhaler. They were told to use the inhaler whenever they felt the urge to smoke, to assess daily cigarette and inhaler use, and to monitor their craving once daily for 1 week. Cravings were measured at baseline and at the end of the week. A 2-week follow-up was organized to assess cigarette use. The results showed a significant reduction in the number of cigarettes smoked (≈40%) in the CBD inhaler group during the week of treatment, with a trend indicating a reduction after follow-up. Both groups also showed a reduction in cravings between day 1 and day 7, though not between day 1 and follow-up.

Effects of CBD on alcohol-addictive behaviors. Only the impact of CBD on the intoxication phase of alcohol addiction was extracted from the review of literature. Consroe et al assessed the effects of CBD on acute consumption of alcohol in 10 healthy volunteers in a randomized, double-blind, crossover study, by testing subjective responding after administration of alcohol (1 g/kg) and CBD (200 mg) alone or in combination.[34] They found that there was no difference in feelings of being "drunk", "drugged", or "bad" in alcohol-alone and alcohol plus CBD groups.

Other substances. No human study was found for opioid-, psychostimulant-, hallucinogen-, or sedative-addictive behaviors.

Discussion

Analysis of studies. The present review aims to examine the available evidence showing the effects of CBD on different addictive behaviors, in both animals and humans. While neural mechanisms implicated in this process are yet to be completely understood (eg, its action on the ECBS or the modulation of pharmacokinetic properties of drugs), CBD seems to influence specific phases of addiction for only certain substances of abuse (Supplementary Table 4). CBD appears to have an impact on the intoxication phase of opioid addiction in animals, by reducing the reward-facilitating effect of morphine on the ICSS threshold.[21] Data on CBD's impact on the withdrawal phase of opioid dependence tend to show no[22,23,25,26] or little[24] benefits when administered alone, but may act in synergy with THC on opioid withdrawal.[22] Finally, and possibly most importantly, CBD influences the relapse phase of opioid addiction by decreasing cue-induced, drug-seeking behaviors.[26] Other promising data are related to psychostimulant addiction, as preliminary data suggest that CBD may be worth further investigation to prevent relapse[27] even though it does not seem to alter the rewarding properties of this class of substance.[21] Studies on the impact of CBD on cannabis addiction in animals are conflicting, as they evaluated CBD's effects on THC only (not cannabis). No evidence was found for the intoxication and relapse phases of cannabis addiction,[28,29] with no results for the withdrawal phase.

Human studies have interestingly focused on substances for which few, if any, data are available in animal models of addiction. CBD's impact on the intoxication phase of cannabis addiction in humans seems complex. While it affects the implicit wanting and explicit liking, it does not influence the subjective feeling of being stoned or the craving sensation associated with the drug.[32] Moreover, only one case report evaluated the effects of CBD on the last phases of addiction, which showed benefits for the withdrawal phase and perhaps even for the relapse phase.[30] Considering these results, evidence suggesting that CBD has a beneficial impact on the intoxication, withdrawal, and relapse phases of cannabis addiction in humans is thus preliminary at best, although intriguing given the lack of pharmacological options for these conditions. In the case of tobacco addiction, CBD may have a therapeutic effect by reducing the number of cigarettes consumed by users who are still actively smoking[33] No data were found on the possible effects of CBD on withdrawal symptoms and risk of relapse among individuals who quit smoking. Further studies will be necessary to clarify CBD's role in cannabis and tobacco addiction, using longer follow-up period and larger sample size including participants who initiate abstinence. Finally, CBD does not exhibit a potential impact on the alcohol addiction intoxication phase in humans,[34] and again, no data were found on the other phases of this addiction.

As previously mentioned, CBD exercises its effects via several neural mechanisms relevant to addictive disorders. Its action on the ECBS as a weak inverse agonist on CB1 receptors has been suggested to play a role in substance-use disorder, but other mechanisms are also involved. Ren et al studied the postmortem brain of rats and found that CBD normalized the heroin-induced changes in CB1 receptor mRNA expression and AMPA GluR1 in the nucleus accumbens, even after 2 weeks of treatment. This suggests a long-term impact on neural mechanisms relevant to opioid relapse.[26] Moreover, the fact that CBD inhibits the reuptake and hydrolysis of AEA could explain some of its potential effects on cannabis withdrawal syndrome and other addictive processes. In contrast, Parker et al found that a CB1 receptor antagonist failed to reverse the effects of CBD on the psychostimulant relapse phase, suggesting that other neuronal circuits than the ECBS may be involved.[27] For example, CBD's effect on 5-HT1a serotoninergic receptors may be highly relevant in drug reward and stress vulnerability, a well-known trigger of craving and subsequent relapse in addicted individuals. More studies are needed to clarify the exact mechanisms through which CBD influences addictive behaviors, in addition to the

endocannabinoid, glutamatergic, and serotoninergic systems. These mechanisms may well be different for each substance of abuse and each addictive phase.

Another potential mechanism by which CBD could exert its effects on substances of abuse is by modulating their pharmacokinetic properties. Reid and Bornheim investigated the effects of cannabinoids on blood and/or brain pharmacokinetics of several drugs of abuse in mice.[35] The results showed that CBD increased brain levels of THC in a dose- and time-dependent fashion (no effect in co-administration), as with brain and blood levels of cocaine and norcocaine and brain levels of PCP, with little or no effect on brain levels of morphine, methadone, or 3,4-methylenedioxy-methamphetamine. The time-dependent relation suggests that a metabolite of CBD may be responsible for this phenomenon. Klein et al also studied the impact of CBD on THC blood and brain levels in rats.[29] They found that CBD raised THC levels and lowered THC metabolite (THC-COOH and 11-OH-THC) levels. They hypothesized that this finding was related to hepatic microsomal drug metabolism, via the deactivation of specific cytochrome P450s.[36] Although CBD may increase the rate of entry of certain drugs into the brain, complex interactions call for a more thorough investigation of the true impact on addiction-related outcomes. For example, Consroe et al found that pretreatment with CBD produced a diminution in blood alcohol level[34] with no major impact on objective and subjective response to alcohol in humans.

While CBD seems to have direct effects on addictive behaviors, its therapeutic potential could also be enhanced by several properties that contribute indirectly to addictive disorders. For example, its antianxiety properties are well known at doses of 300–600 mg[12,37] and CBD seems to have antidepressant[11] and anticonvulsant[38,39] effects. Its impact on pain has been investigated, especially in combination with THC in Sativex treatment for chronic pain[40,41] and is relevant since chronic pain can induce or perpetuate drug abuse.

CBD has been shown to be a safe compound in both animals and humans, which is of critical importance from a therapeutic point of view. Many studies evaluated the side effect profile of CBD in various contexts and reported no significant or serious adverse events, other than mild sedation and nausea.[39,41–43] Daily doses as high as 1500 mg were well tolerated in humans.[44] CBD is not hedonic on its own, neither in animals nor humans.[21,27,28,34] Moreover, CBD has some protective properties that may be useful in attenuating deleterious effects related to other drug consumption. CBD protects mice from hepatotoxicity induced by cocaine by inactivating P450s,[36,45] reduces glutamate- and ethanol-induced neurotoxicity in rats with its antioxidant potential,[19,46] and potentially diminishes the neurotoxicity of THC by reducing brain volume loss.[47] Altogether, CBD may also be indirectly beneficial in drug addiction due to its beneficial effects in the treatment of common substance-use disorder comorbidities and complications.

Limitations. The present systematic review has its own limitations, including the lack of a mechanism to exclude publication bias and the fact that no search for unpublished studies was achieved. A limited number of studies on the direct impact of CBD on addictive behaviors are available in the literature, and the majority use animal models of addiction. Five human studies were found, but the sample sizes of the majority of these were small, and only two of them were randomized, double-blind studies. Moreover, all substances were not represented in both animal and human studies. The small number of studies in each category and their heterogeneity makes the comparison difficult, if not impossible.

Conclusions

CBD is an exogenous cannabinoid that acts on several neurotransmission systems involved in addiction. Animal studies have shown the possible effects of CBD on opioid and psychostimulant addiction, while human studies presented some preliminary evidence of a beneficial impact of CBD on cannabis and tobacco dependence. CBD has several therapeutic properties on its own that could indirectly be useful in the treatment of addiction disorders, such as its protective effect on stress vulnerability and neurotoxicity. Overall, emerging data remain very limited and are far from being conclusive; well-designed, randomized, controlled trials are necessary at this point to determine whether these properties translate into significant improvements on clinical outcomes in human populations. The importance of this area of research is emphasized by an increasing number of studies that are currently being conducted in the United States (source: www.clinicaltrials.gov) regarding the effects of CBD on cannabis and opioid addiction and there is one ongoing Canadian study on cocaine addiction (source: www.cihr-irsc.gc.ca). The dreadful burden of substance-use disorder worldwide, combined with the clear need for new medication in the addiction field, justifies the requirement of further studies to evaluate the potential of CBD as a new intervention for addictive behaviors.

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Author Contributions

Conducted the literature search independently: MP, RC. Provided consultation in the event of discrepancies occurring between the results of the two reviewers: DJ-A. Provided summaries of previous research studies and wrote the first draft of the manuscript: MP. All authors contributed to and have approved the final manuscript.

Supplementary File

Supplementary Table 1. Table of abbreviations.

Supplementary Table 2. Characteristics of excluded studies.

Supplementary Table 3. Detailed characteristics of included studies.

Supplementary Table 4. Summary of included studies, by substance and addiction phase.

Supplementary Figure 1. Flow chart of the selection process of published studies.

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