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Evidence for the Endocannabinoid System as a Therapeutic Target in the Treatment of Cannabis Use Disorder

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Abstract

Purpose of Review Cannabis use disorder (CUD) is highly prevalent. Psychotherapeutic treatment alone is not adequately effective, with few individuals achieving abstinence. Pharmacotherapeutic supplementation may improve efficacy, and the endocannabinoid system presents a target specifically dysregulated by heavy cannabis use. This review compiles current literature evaluating endocannabinoid modulation as a treatment strategy for CUD, with implications for future research.

Recent Findings Cannabinoid receptor agonists have been found to reduce cannabis withdrawal symptoms without a notable effect on relapse, and antagonists can produce severe psychiatric symptoms. Fatty acid amide hydrolase inhibitors and cannabidiol demonstrate the most promise in treating CUD thus far, but research with these compounds is still preliminary.

Summary Components of the endocannabinoid system may serve as unique treatment targets with differential efficacy for the treatment of cannabis use disorder as a whole. Further research is needed exploring novel methods for targeting endocannabinoid dysfunction in CUD.

Keywords Cannabis use disorder · Endocannabinoid system · Dronabinol · Nabiximols · Cannabidiol · FAAH

Introduction

Cannabis is the most commonly used illicit drug in the USA, and nearly one-fifth of individuals that have used cannabis in the past year meet DSM-5 criteria for cannabis use disorder (CUD) [1, 2•]. Though risk perceptions associated with cannabis use are currently in decline [3], treatment service utilization for individuals that primarily use cannabis is only third behind alcohol and opiates [4], and the likelihood of treatment utilization increases exponentially with CUD severity [5, 6]. Despite this demand, treatment options for CUD are extremely limited. Psychotherapeutic methods, such as motivational enhancement therapy and contingency management, are at best moderately efficacious [7]. Combined psychotherapy and pharmacotherapy may produce superior outcomes, but there is no pharmacotherapeutic intervention for CUD that has been approved by the US Food and Drug Administration (FDA) [7].

Evaluated pharmacotherapeutics have spanned a wide variety of drug classes targeting an array of neural systems [7]. The endocannabinoid system, however, presents a systemic target that may have superior efficacy in the treatment of CUD, though its full potential has not yet been elucidated. The aim of this review was to synthesize available data pertaining to the endocannabinoid system and its modulation as a therapeutic for CUD, with the goal of informing future pharmacotherapeutic research. Considerations to be made when transitioning these medications from the laboratory to the clinic are also discussed.

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The Endocannabinoid System

The primary psychoactive constituent of cannabis, Δ^9-tetrahydrocannabinol (THC), produces its hallmark effects via partial agonism of the cannabinoid type 1 receptor (CB1) in the CNS [8]. CB1 is part of an endogenous cannabinoid system (ECS) that extends from the CNS to the periphery [9]. This

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ECS is composed of two G protein-coupled receptors (CB1 and CB2) and their primary endogenous ligands, *N*-arachidonoylethanolamide (AEA) and 2-arachidonoylglycerol (2-AG). AEA and 2-AG act primarily via retrograde signaling in the CNS: they are produced on-demand by postsynaptic neurons before traveling backward across the synapse to bind to presynaptic CB1 and CB2 receptors [8]. By agonizing these receptors, much like THC, AEA and 2-AG inhibit further release of neurotransmitter from the presynaptic cell [8]. Myriad enzymes involved in the synthesis, degradation, and transport of AEA and 2-AG also comprise the ECS. For the purposes of this review, the most noteworthy of these enzymes are fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), which act as the primary degradative enzymes for AEA and 2-AG, respectively [10] (see Fig. 1 for a visual of endocannabinoid signaling and degradation).

The ECS is involved in a wide variety of internal processes that explain the breadth of effects associated with cannabis use and disorder. As with most drugs of abuse, cannabis consumption is associated with increased dopamine release within neural reward pathways, which occurs as a consequence of THC-CB1 receptor binding [11–13]. The ECS also appears to have a role in maintaining homeostasis, having been implicated in feeding [14–17], sleep [18–20], emotional regulation [21–25], and modulation of the stress response [26–28, 29•]. Accordingly, anorexia, sleep disturbance, and negative mood are all symptoms of cannabis withdrawal [30], and stress-coping is a commonly cited justification for both initiation and maintenance of cannabis use [31, 32]. At the molecular level, heavy cannabis use is associated with ECS dysregulation that includes CB1 downregulation [33–35] and reduced levels of FAAH in the brain [36, 37]. The effects of heavy cannabis use on AEA and 2-AG are presently unclear.

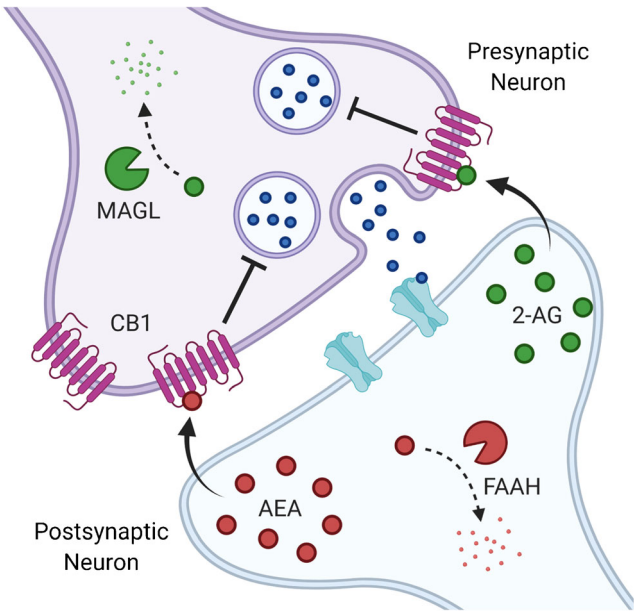

Fig. 1 Illustration of endocannabinoid retrograde signaling in the CNS and hydrolysis by the degradative enzymes FAAH and MAGL. Figure created using Biorender.com

Taken together, it would seem that normalizing endocannabinoid signaling that has been disrupted by heavy cannabis use could serve as an effective and specific therapeutic target for CUD. Indeed, this treatment strategy follows a precedent first established in the treatment of opioid and nicotine use disorders, that of agonist replacement therapy. The ECS also presents additional druggable targets for CUD in the form of biosynthetic and degradative enzymes, for which activity can be either facilitated or inhibited to indirectly modulate endogenous cannabinoid levels. Enzymatic manipulation may produce similar outcomes to an agonist replacement therapy, but with lower abuse liability and reduced intoxication.

While there are many unique pharmacotherapeutic targets available within the context of the ECS, a more conventional approach, the exogenous antagonist, is presently nonviable. One such antagonist, the CB1 inverse agonist rimonabant, showed preliminary efficacy in attenuating cannabis use preclinically and in humans [38–40], but research efforts halted following demonstration of adverse psychiatric side effects, namely, increased prevalence of anxiety, depression, and suicidality [41]. Neutral antagonists, which merely block activity at a given receptor rather than produce effects opposite to those of an agonist, may present as equally effective treatment options [40] with a more favorable side effect profile [42–44]. However, research in humans is limited and a direct effect on CUD has yet to be assessed. Further, it is possible that this class of drugs would still have some degree of negative psychiatric effects, as chronic neutral antagonism would still preclude endogenous cannabinoid signaling necessary for mood regulation. This is an important consideration, as presence of such side effects might further disincentivize treatment adherence in this already difficult to treat population, even if they are less severe than those produced by inverse agonists.

Dronabinol

Dronabinol, an orally bioavailable formulation of THC, is FDA-approved for the prophylaxis of chemotherapy-induced nausea and vomiting and for use in the stimulation of appetite and prevention of weight loss in patients with acquired immunodeficiency syndrome (AIDS) [45]. As a direct CB1 agonist, there is a substantial theoretical basis to support its utility as a treatment of CUD, and multiple studies have explored its potential as an intervention for cannabis withdrawal specifically.

Dronabinol has been demonstrated to attenuate cannabis withdrawal symptoms in both inpatient and outpatient laboratory settings [46, 47]. Dronabinol given at a dose of 10 mg five times daily in a laboratory environment decreased cannabis

craving and withdrawal symptoms while producing no intoxication [46]. An outpatient evaluation in non-treatment seeking, daily cannabis users also showed a reduction in withdrawal symptoms with dronabinol at doses of 10 or 30 mg three times daily compared with placebo treatment [47]. A greater reduction in withdrawal symptoms was noted with the 90 mg/day dose compared with the 30 mg/day dose. However, some signs of cannabis-like intoxication were associated with the higher dose, as were some drug effects such as euphoria and drug-liking. A within-subject crossover study of short-term dronabinol (0, 30, 60, and 120 mg/day for five consecutive days) also found a dose-dependent suppression of cannabis withdrawal, without decrements in cognitive performance [48]. No impact of dronabinol on the subjective effects of smoked cannabis was observed.

Laboratory studies investigating whether dronabinol alters cannabis self-administration have had mixed results. Hart and colleagues [49] found no effect of dronabinol 40–80 mg/day on cannabis self-administration. In a subsequent trial, dronabinol (60 mg/day) did not decrease cannabis self-administration alone, though a reduction was noted when dronabinol was administered in combination with the adrenergic agonist lofexidine [50]. In contrast, a recent trial comparing 12 days of high-dose dronabinol (180–240 mg/day), 120 mg/day dronabinol, and placebo found reduced cannabis self-administration in both dronabinol conditions [51]. These results suggest higher dronabinol doses may be needed to impact cannabis use behavior, perhaps due to its limited bioavailability.

Based on the above promising data in cannabis withdrawal, as well as the established utility of agonist substitution therapy in other use disorders, dronabinol was evaluated in a large randomized, placebo-controlled trial in which cannabis-dependent adults received either dronabinol (40 mg/day) or placebo over a 12-week period with concomitant psychosocial treatment [52]. Both treatment groups reported a reduction in cannabis use during the trial. Dronabinol was shown to improve retention in the trial and to reduce withdrawal symptoms; however, there was no effect of dronabinol on cannabis use. Negative findings were also reported in a large, placebo-controlled trial of concurrent dronabinol (60 mg/day) and lofexidine (1.8 mg/day), with no treatment differences observed in cannabis abstinence, withdrawal symptoms, or treatment retention [53]. Together, these trials suggest limited potential of dronabinol for cannabis abstinence promotion.

Nabilone

Nabilone (Cesamet™) is a synthetic cannabinoid that is FDA-approved to treat nausea associated with cancer chemotherapy [54]. Like dronabinol, nabilone is an oral medication that acts as an agonist at CB1 and CB2 [55] and produces similar interoceptive effects to THC in individuals that regularly use cannabis [56, 57]. As such, nabilone represents a potential agonist replacement therapy for CUD. Notably, nabilone appears to have a lower abuse liability relative to smoked cannabis [58, 59], though this may be dose-dependent [60] and is likely in large part attributable to the difference in route of administration.

Given other similarities to dronabinol, it is unsurprising that nabilone produces similar effects in the context of cannabis dependence, i.e., reduces withdrawal symptoms [61] without promoting abstinence in an outpatient setting [62]. It is important to note that the dose used in the treatment trial (2 mg) was substantially lower than that used in the laboratory by Haney and colleagues [61]. However, higher doses in previous laboratory studies were associated with substantial increases in "Good Drug Effects", "Drug Liking", and "Take Again" [56, 57, 60]. Thus, it is difficult to reconcile increasing the dose of nabilone given in an outpatient setting with these apparent increases in abuse liability. This is further substantiated by the lack of efficacy of dronabinol in promoting abstinence from cannabis, given the similarities between these medications.

A more suitable role for nabilone in the treatment of CUD may be as an adjunctive pharmacotherapy. A laboratory study found that daily nabilone and nightly zolpidem improved sleep and reduced anxiety and irritability during a withdrawal period [63]. This combination did not produce significant increases in "Drug Liking" or "Take Again" relative to placebo. Unfortunately, the combination was not directly compared with nabilone alone, and the addition of zolpidem did not significantly attenuate sleep-related withdrawal symptoms moreso than nabilone alone did in a prior study [61], although the doses of nabilone used herein were slightly lower. It is therefore difficult to ascertain where these findings fall in a broader therapeutic context. Similarly, combined nabilone and varenicline attenuated withdrawal symptoms in individuals that use both cannabis and tobacco without appreciable effects on a laboratory model of relapse [64]. While in these cases ineffective, the lack of considerable drug interactions and continuing attenuation of withdrawal symptoms may be indicative of a more nuanced role for nabilone in the treatment of CUD moving forward.

Cannabidiol

Cannabidiol (CBD) has a broad and complex pharmacological profile, interacting with many classes of receptors, enzymes, and other targets. Although similar in structure to THC, CBD binds poorly to CB1 and CB2 [65]. However, CBD still has pharmacological activity within the ECS: it acts as a negative allosteric modulator of the CB1 receptor, as well as inhibits the reuptake and hydrolysis of AEA [66, 67].

Outcomes from some human laboratory studies suggest that CBD can block acute adverse pharmacodynamic effects of THC such as anxiety [68] and memory impairment [69], leading to speculation that CBD may mitigate the effects of THC; this "dampening" effect is consistent with activity as a CB1 negative allosteric modulator. Further, anxiolytic effects may be attributable to inhibition of AEA hydrolysis, as this is also a known quality of FAAH inhibitors [29•]. However, a study comparing acute doses of oral CBD (200, 400, and 800 mg) and placebo in the context of smoked cannabis among regular cannabis users reported no impact of CBD on cannabis self-administration, subjective effects, or physiologic responses [70]. Further, Solowij and colleagues [71] evaluated the impact of vaporized low (4 mg) and high (400 mg) CBD given in conjunction with THC. Low doses of CBD enhanced the intoxicating effects of THC, particularly in infrequent cannabis users, while high doses of CBD were associated with a reduction of intoxicating effects.

Two trials to date have evaluated longer-term oral CBD administration in cannabis users. An open-label trial evaluated 200 mg daily CBD administration for 10 weeks among 20 frequent cannabis users [72]. Compared with baseline, participants reported fewer depressive and psychotic symptoms after CBD treatment and demonstrated improvement in cognitive measures. Increased euphoria when smoking cannabis was also reported. Recently, Freeman and colleagues [73••] published results from a 4-week adaptive trial in which three doses (200, 400, and 800 mg) of oral CBD were compared with placebo during a cannabis cessation attempt. Following an initial treatment phase ($n = 48$), the 200 mg dose was deemed inefficacious and the trial continued with the 400 mg, 800 mg, and placebo arms ($n = 34$). At end of treatment, both doses of CBD were associated with lower THC-COOH/creatinine ratios and modest reductions in self-report days per week of cannabis use relative to placebo; however, treatment effects were not found at follow-up timepoints. Of note, there was some indication of an inverted-U dose-response curve, with the 200 mg dose deemed inefficacious and marginal indication that the 400 mg dose was superior to the 800 mg dose. No serious adverse events were noted, although lower sleep quality was reported among individuals in the 400 mg group. Limitations of the study include brief treatment period and insufficient sample sizes to robustly estimate effect sizes, making it difficult to fully ascertain the impact of CBD in promoting abstinence from cannabis.

Nabiximols

Nabiximols is an oromucosal spray composed of THC (2.7 mg/spray), CBD (2.5 mg/spray), and various terpenoids. It is approved in the United Kingdom, Canada, and other countries primarily for the treatment of spasticity related to multiple sclerosis; it is not currently FDA-approved in the USA, although registry trials are ongoing.

In regard to CUD, an initial study evaluated a six-day course of nabiximols (maximum daily dose 86.4 mg THC and 80 mg CBD) compared with placebo among 51 treatment-seeking cannabis-dependent individuals during an inpatient admission [74]. Nabiximols reduced cannabis withdrawal symptoms and improved retention in treatment, but no medication effect was observed on time to cannabis relapse or reductions in cannabis use following medication cessation. Trigo and colleagues [75] evaluated fixed versus self-titrated doses of nabiximols and placebo for cannabis withdrawal and craving during one-week abstinence periods in an outpatient trial. High fixed doses of nabiximols (108 mg THC/100 mg CBD daily) reduced cannabis withdrawal compared to placebo, but did not reduce cannabis craving; limited efficacy was noted with the lower self-titrated doses.

Two randomized clinical trials have evaluated nabiximols as a potential treatment for CUD. One 12-week trial compared a flexible dose of nabiximols (up to 113.4 mg THC/105 mg cannabidiol daily) with placebo in conjunction with motivational enhancement and cognitive behavioral therapy in 50 individuals [76]. Nabiximols reduced cannabis craving compared with placebo; however, no significant differences in cannabis withdrawal or cannabis use were observed. Recently, a larger trial ($n = 128$) reported a reduction in self-reported cannabis using days among individuals receiving nabiximols relative to placebo both during treatment and at a three-month follow-up assessment [77•, 78]. No between-group differences were found in cannabis withdrawal, craving, or periods of abstinence, nor in health or psychosocial outcomes. In both trials, nabiximols was well-tolerated, but treatment retention was low. Nabiximols may have some promise for the treatment of CUD if findings related to cannabis use can be replicated.

FAAH Inhibitors

FAAH inhibitors increase levels of AEA through selective inhibition of its primary catabolic enzyme [79]. This increased AEA produces anxiolytic and antidepressant effects [79, 80]. FAAH inhibitors, like exogenous CB1 agonists, have been shown to alleviate symptoms of cannabis withdrawal in mice [81] but are distinguished from these drugs by their lack of readily apparent abuse liability [82–84]. Only one trial has been completed thus far in cannabis-dependent men, but these preliminary outcomes are promising [85••]. Men that received the FAAH inhibitor PF-04457845 not only exhibited attenuated withdrawal symptoms but also self-reported reduced cannabis use, which was confirmed by urine toxicology [85••]. Though limited by inclusion of only men and a fairly brief treatment period to truly assess risk of relapse, these findings warrant

further exploration. Also of note is the lack of serious adverse events that resulted from chronic treatment with PF-04457845 [85••]. Despite the severe neurological side effects associated with the FAAH inhibitor BIA 10–2474 [86], this present study corroborates previous work indicating such side effects are more likely attributable to BIA 10–2474 itself rather than the class of FAAH inhibitors as a whole [87]. Nevertheless, strict vigilance must be maintained until further data are acquired to ensure safety of study participants moving forward.

Conclusions

Despite the high prevalence of CUD [1], current treatment options are at best only moderately effective and there is no FDA-approved pharmacotherapy for its treatment [7]. The ECS presents an attractive pharmacotherapeutic target, given its specific dysregulation by heavy cannabis use and the clinical success of agonist replacement therapy for opioid and nicotine use disorders. The most effective method for targeting the ECS, however, remains unclear. While CB1 antagonism may effectively reduce cannabis use, severe psychiatric side effects preclude its use in a treatment setting, especially given the high rate of psychiatric comorbidity already prevalent among individuals with CUD [88]. In contrast, synthetic CB1 agonists, such as dronabinol and nabilone, attenuate withdrawal symptoms during an abstinence period but have no apparent impact on cannabis use in an outpatient setting and bear the additional burden of potential abuse liability. Cannabidiol- and FAAH inhibitor-based treatments appear efficacious for both reducing cannabis use and curtailing associated withdrawal symptoms, but research is limited.

Future research should aim to expand on these preliminary positive outcomes. A large, multisite clinical trial is currently in progress evaluating the FAAH inhibitor PF-04457845 for the treatment of CUD (NCT03386487). Surprisingly, there are currently no randomized clinical trials in progress assessing cannabidiol for CUD, despite its apparent efficacy in the more modest treatment trials detailed herein. The absence of a large-scale randomized clinical trial supporting the utility of CBD in the treatment of CUD is at odds with its widespread availability and often-advertised clinical benefit in the context of addiction. It is imperative that future research addresses this discrepancy.

Pharmacological interventions for CUD have not yet been able to reliably demonstrate efficacy in both withdrawal symptom alleviation and relapse prevention. However, many of the treatments assessed thus far have been constrained to direct agonist or antagonist approaches to CB1. These only scratch the surface of the available drug targets in a complex endocannabinoid system and appear to be limited in their therapeutic potential. Unique approaches to targeting the ECS, such as cannabidiol, FAAH inhibitors, or other treatments that have not yet advanced to clinical trials (e.g., MAGL inhibitors), may prove advantageous over previous strategies given their distinct pharmacological properties.

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Compliance with Ethical Standards

Conflict of Interest Dr. McRae-Clark reports she has received medication support for a NIH-funded grant from Pfizer Pharmaceuticals.

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

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