Cannabis Use and the Endocannabinoid System: A Clinical Perspective

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Societal attitudes toward cannabis, both as a drug of abuse and as a potential therapeutic, have undergone a marked shift in the past 25 years, resulting in wide-scale changes in legalization, public policy, and marketing of cannabis and its constituents (cannabinoids, such as cannabidiol). Cannabis has abuse liability, producing positive subjective effects, and repeated use over time can result in a use disorder, which can include withdrawal symptoms (sleep disruption, irritability, anxiety, anorexia, craving), unsuccessful attempts to cut down or quit, and failure to fulfill obligations. The consequences of having a cannabis use disorder are rarely as destructive to individual lives as other drugs of abuse can be, which may lead to the perception that cannabis use disorder is a somewhat minor concern. However, a significant subset (10%−30%) of those using cannabis will develop cannabis use disorder (1), which is both distressing to the individual and not easy to overcome.

The past few decades have also borne witness to a tremendous advancement in our understanding of the endocannabinoid system, beginning with the groundbreaking discoveries of the cannabinoid receptors and endogenous cannabinoids (2). Although cannabis use has been documented for millennia, only relatively recently have we begun to understand the critical role of the endocannabinoid system in a wide array of psychophysiological functions.

Considering both the ubiquity of cannabis and cannabinoid use and the essential function of the endocannabinoid system, my objective in this review is to describe several key clinical issues regarding the interaction between cannabis use and endocannabinoid neurobiology.

PHYTOCANNABINOIDS

The cannabis plant has over 100 cannabinoids (unique components of the plant) (3), as well as hundreds of noncannabinoid terpenes (e.g., myrcene, limonene, pinene, *trans*-caryophyllene) and flavonoids, which contribute to the aroma, flavor, and color of cannabis (and some of which may have psychotropic effects that influence abuse liability, but controlled clinical research is needed). The more than 700 plant varieties (chemovars) of cannabis vary in their relative ratios of cannabinoid and noncannabinoid components (4), likely contributing to the range of psychoactive effects produced by distinct chemovars. Yet, despite the widespread marketing and use of cannabis products, exceedingly little is known about the specific effects of individual cannabinoids or other plant constituents because rigorous placebo-controlled investigation is limited by the numerous regulatory hurdles present when studying a Schedule I compound (5), defined by the U.S. Drug Enforcement Agency as having high abuse liability and no medical benefit.

By far, the cannabinoid that is best characterized is delta-9-tetrahydrocannabinol (THC), the primary psychoactive component of cannabis, which has been approved by the U.S. Food and Drug Administration (FDA) in oral, synthetic, or analogue form for over 40 years for the treatment of chemotherapy-induced nausea and vomiting (dronabinol, nabilone). The second cannabinoid that has undergone placebo-controlled testing is cannabidiol (CBD), which was FDA approved for the treatment of certain severe forms of epilepsy in 2018. Clearly there is widespread use of THC- and CBD-containing products outside of FDA-approved formulations, not to mention the marketing of minor cannabinoids, such as delta-8-THC, cannabinol, cannabigerol, cannabichromene, and delta-9-tetrahydrocannabivarin, for a range of potential therapeutic endpoints (often based on in vitro data). Overall, we have a very limited understanding of the impact of most cannabis constituents on abuse-related endpoints and on the endocannabinoid system.

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ENDOCANNABINOIDS

The endocannabinoid system, comprising the endocannabinoids anandamide and 2-arachidonoylglycerol, enzymes for their synthesis and degradation, and the cannabinoid receptor type 1 (CB1) and type 2 (CB2), is one of the most

ubiquitously expressed signaling systems in the brain, contributing to the regulation of stress response, anxiety, memory, pain, and motivated behavior across the lifespan (6–8). Endocannabinoid signaling also plays a critical role in the development, maturation, and sculpting of neural circuits that continues throughout adolescence (9).

THC binds with high affinity to the CB1 receptor, which mediates its abuse-related and reinforcing effects (10). CBD, which has low affinity for the cannabinoid receptors and lacks abuse liability (11, 12), has a complex pharmacology, acting on TRPV1, GPR55, 5-HT_{1A}, and adenosine receptors, among others (13).

Despite its essential role in CNS function, our understanding of the impact of repeated cannabis or cannabinoid use on the endocannabinoid system in humans is limited. Note that in discussing the impact of daily or repeated use of cannabis or cannabinoids on the endocannabinoid system, we are not distinguishing between "recreational" and "medical" use, as the distinction is a bit hazy. THC's therapeutic utility often occurs at concentrations associated with intoxication, which is aversive to some medical cannabis users (14) but increases the risk of cannabis use disorder for those who find it rewarding. In fact, data from a national survey (15) show that 1) over 80% of people who use cannabis for medical purposes also use it recreationally (16), and 2) those who reported using cannabis for both medical and recreational reasons had higher rates of cannabis use disorder (41%) than those who reported only using cannabis recreationally (25%). This is consistent with other epidemiologic data showing that cannabis users with chronic pain have higher rates of cannabis use disorder than those without chronic pain (17). Many factors contribute to the risk of developing a cannabis use disorder (e.g., route of administration, cannabinoid content, frequency of use throughout the day), but one factor is daily use, and >75% of those who report using cannabis products for medical use do so daily (18). Thus, cannabis misuse is a clear risk factor for those who use cannabis for therapeutic reasons.

We know that daily cannabis use is associated with a range of neuroadaptations in the endocannabinoid system (19), including down-regulation of the brain CB1 receptor, which reverses after ~2–14 days of abstinence (20–23), and reduced levels of fatty acid amide hydroxylase (FAAH; 14%−20%) (24, 25), the enzyme that metabolizes anandamide and is the primary regulator of its signaling in the brain (26).

Yet, the consequences of these adaptations in the endocannabinoid system are not well established. Preclinical data show that cannabinoid administration lowers circulating endocannabinoids (27), and we have preliminary data in near-daily cannabis smokers showing that heavier cannabis use is correlated with lower levels of circulating endocannabinoids (28). If, in fact, repeated cannabis use alters endocannabinoid levels, does this have an impact on therapeutic endpoints?

Consider chronic pain, one of the few indications for which there is sufficient placebo-controlled study to support the efficacy of THC or cannabis (29). Pain is a primary reason cited by patients for the medical use of cannabis (30–32). Cannabis or its constituents have been legalized for medical use throughout most of the United States, and the majority (62%) of medical indications approved across states are pain related (18, 33).

There is evidence that circulating levels of endocannabinoids inversely correlate with pain sensitivity. A single-nucleotide polymorphism in the gene for FAAH both raises circulating levels of anandamide and is associated with lower sensitivity to pain (34). If higher circulating anandamide levels correlate with reduced pain perception (27), are lower anandamide concentrations due to chronic cannabis use associated with *increased* pain sensitivity? In theory, once THC is metabolized, abstinent cannabis smokers could have low anandamide levels and no exogenous cannabinoids on board, and could thus have heightened pain sensitivity; in the absence of cannabis, the impact of cannabis-induced low anandamide levels on pain could emerge.

Although pain is the primary indication for medical cannabis use, we do not know what happens to pain sensitivity with repeated cannabis use or its abrupt cessation. There are currently no data on endocannabinoid levels during and following abrupt abstinence from cannabis to see if plasma endocannabinoid levels change over time, and if these changes correlate with measures of pain. Most human studies investigating circulating endocannabinoids have examined few individuals and single time points (27). Thus, research on how daily cannabis use and abstinence alter endocannabinoid levels, therapeutic outcomes, and abuse liability is critically needed to best guide patients and clinicians in the therapeutic use of cannabis and cannabinoids.

An additional empirical question is how varying cannabinoid concentrations in cannabis affect therapeutic or abuse-related outcomes. Among medical cannabis consumers, >95% report that they prefer THC-CBD combination products to either in isolation, with ~71% preferring CBD-predominant chemovars. Those who are more experienced with cannabis seek products with higher THC content (18), and with experience, novice users also seek higher THC content (35).

These findings raise two questions. First, does this preference reflect differences in efficacy and abuse liability as a function of THC and CBD content? That is, do patients start to prefer higher THC chemovars over time because they produce positive subjective effects, because they are more efficacious therapeutically, or does this preference reflect tolerance to the effects of THC, where patients feel less therapeutic or positive subjective effects after repeated use and therefore seek higher THC content? The answer to these questions has considerable public health significance given the widespread use of cannabis for pain.

We know that tolerance to cannabis effects develops differentially across endpoints. For example, in HIV-positive research volunteers who received oral THC (10 mg q.i.d.) for 16 days, tolerance developed to THC's therapeutic effect

on caloric intake in less than 7 days, while there was no evidence of tolerance to abuse-related outcomes over the 16 days of THC administration (36). If cannabis's therapeutic effects diminish with repeated use, patients might use more cannabis, which could help explain the higher incidence of cannabis use disorder in medical cannabis patients relative to those who report using it only recreationally.

The second question concerns the influence of CBD on THC's therapeutic or abuse-related effects. There is a perception that CBD reduces THC- or cannabis-related intoxication, but this is not well supported in either clinical (12, 37) or preclinical studies (38, 39). In fact, CBD appears to inhibit FAAH. There are clinical data showing that repeated CBD administration increases circulating levels of anandamide and two other FAAH substrates, palmitoylethanolamide and oleoylethanolamide (40). Given the vast numbers of individuals reporting daily cannabis use, understanding how varying cannabinoid constituents affect endocannabinoids and abuse-related and therapeutic endpoints is essential.

THE ENDOCANNABINOID SYSTEM AND CANNABIS MISUSE

Individuals vary considerably in their response to cannabis, with some finding it enormously pleasurable and relaxing and others having the opposite response, becoming anxious and paranoid, and thus being less likely to develop problematic patterns of cannabis use. Cannabis strength and the vast number of chemovars available, varying in their concentration of cannabinoid and noncannabinoid constituents, certainly have an impact on the subjective response to cannabis (41).

Yet, there may also be a genetic component to the individual response to cannabis. There is a common loss-of-function mutation in the gene for FAAH, for example, that reduces enzyme expression and activity, resulting in elevated anandamide levels, increased fronto-amygdala connectivity, and reduced anxiety-like behaviors (42). Among Caucasian individuals who tried cannabis, those carrying this genetic polymorphism were less likely to develop cannabis dependence than wild-type carriers (43), perhaps suggesting that individuals who have relatively more endogenous cannabinoids (due to less enzymatic degradation) are less prone to misuse cannabis. Admittedly, there are a great number of inconsistences across candidate gene studies, so more work is needed, but variability in FAAH expression has clear functional consequences and likely contributes to vulnerability to developing cannabis use disorder.

HARNESSING THE ENDOCANNABINOID SYSTEM TO TREAT CANNABIS USE DISORDER

In 2018, 12% of those receiving substance use disorder treatment in the United States reported cannabis as their primary drug of abuse (44). Yet the vast majority of patients seeking treatment for cannabis use disorder have difficulty significantly reducing cannabis use or achieving abstinence. Psychotherapeutic approaches have utility (45), but safe and effective medications are needed to improve treatment outcome. Direct targeting of the endocannabinoid system is a promising approach.

As with most substance use disorders, agonist therapy—that is, activating the same receptor as the drug of abuse with a full or partial agonist—can be an efficacious treatment approach (e.g., buprenorphine or methadone for opioid use disorder or nicotine replacement or varenicline for tobacco use disorder). In the dozen or so medications tested in the human laboratory or in clinical trials, oral THC or its analogue, nabilone, reduced symptoms of cannabis withdrawal while producing minimal abuse-related effects, likely because of the slow onset and long duration of action when cannabinoids are orally or oromucosally administered. However, dronabinol has not been shown to robustly reduce cannabis use in clinical trials (46, 47).

An alternative to administering exogenous CB1 agonists is to increase concentrations of endogenous cannabinoids by blocking their enzymatic degradation. D'Souza and colleagues (48) demonstrated that a FAAH inhibitor reduced cannabis withdrawal symptoms and cannabis use in recently abstinent cannabis-dependent men. This finding led to an ongoing multisite randomized clinical trial testing this FAAH inhibitor as a potential treatment for cannabis use disorder (ClinicalTrials.gov identifier: NCT03386487).

Another innovative approach targeting the endocannabinoid system is to directly block THC's abuse-related effects. The use of naltrexone for the treatment of opioid use disorder is an example of this type of antagonist approach, but unlike naltrexone, a competitive CB1 antagonist is not an option for treatment of cannabis use disorder. Rimonabant, an orthosteric CB1 antagonist, reduced the abuse-related effects of cannabis (49) but also produced serious psychiatric side effects (depression, suicidality, anxiety) when given repeatedly (50), suggesting that endocannabinoids play an important role in mood regulation and that blocking the CB1 receptor with a competitive antagonist produces serious risk.

An alternative antagonist approach is to reduce only a subset of CB1-mediated effects. CB1 agonists initiate G-protein- and β arrestin-1-mediated intracellular signaling cascades that include inhibition of the adenylate cyclase pathway, resulting in decreased cAMP, and activation of the mitogen-activated protein kinase (MAPK) pathway, resulting in ERK1/2 activation (51). Several years ago, Piazza and his team at the Institut National de la Santé et de la Recherche Médicale discovered that the neurosteroid pregnenolone binds to a specific site on the CB1 receptor (distinct from where THC binds), and selectively inhibits THC-induced activation of MAPK without modifying CB1 agonist binding or G-protein mediated cellular responses (cAMP). Unlike orthosteric antagonists like rimonabant, which block CB1 agonist binding and thereby decrease all intracellular

signaling cascades, pregnenolone does not modify agonist binding to the CB1 receptor, does not alter G-protein-mediated responses (cAMP inhibition), and selectively inhibits the increase in MAPK activity (52).

Importantly, this selective inhibition appears to decrease the abuse-related and reinforcing effects of cannabis or CB1 agonists without producing the vast range of negative effects associated with rimonabant, such as anxiety-like behavior and decreased food intake. Because pregnenolone is an unsuitable medication (very short half-life, rapid metabolism to active steroids, low oral bioavailability [52]), Aelis Farma has modified pregnenolone's chemical structure and developed a new medication, AEF0117, that functions as a signaling specific inhibitor of the CB1 receptor. AEF0117 maintains the pharmacodynamic characteristics of pregnenolone but is not metabolized to active steroids, is well absorbed, and has a long half-life.

Our group has conducted early-phase studies with AEF0117, showing good safety and tolerability in both healthy volunteers and daily cannabis smokers, with no evidence of precipitated withdrawal or physical or psychological discomfort. Preliminary data suggest that AEF0117 reduced both the abuse-related subjective effects of smoked cannabis and rates of self-administration. These results, confirming preclinical data showing that AEF0117 does not produce any of the adverse effects associated with rimonabant, support an upcoming multisite randomized clinical trial to test AEF0117 in patients seeking treatment for cannabis use disorder.

CONCLUSIONS

Little is known about the impact of daily cannabis use on the endocannabinoid system, despite its critical importance to CNS function. There have been few well-controlled studies assessing how daily use of ecologically relevant cannabis chemovars affect measures of abuse potential, therapeutic outcome, and the endocannabinoid system. For therapeutic cannabis use, mitigating abuse liability while maintaining therapeutic efficacy is the goal, and neither clinicians nor patients have the evidence needed to make decisions about benefits versus risks such as cannabis use disorder (5). Meaningful progress on this timely and far-reaching issue is needed.

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