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Medical Marijuana: What Physicians Need to Know

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As of March 2019, in the United States, "medical marijuana" has been approved in 33 states, the District of Columbia, Guam, and Puerto Rico.[1] Marijuana, however, remains a schedule I drug per the US Drug Enforcement Administration (DEA) based on its findings that marijuana (*a*) has a high potential for abuse, (*b*) has no currently accepted medical use in treatment in the United States, and (*c*) lacks accepted safety for use under medical supervision. Nevertheless, today the marketplace is flooded with over 2,500 "strains" of the marijuana plant (named variously as "Mango Kush," "Skywalker," "Purple Haze," "Obama Kush," and so-called cannabidiol [CBD] strains such as "Harlequin," "Ringo's Gift," "ACDC," and "Cannatonic") and marijuana-infused products (including edibles, concentrates, dabs, waxes, oils, and vaping fluids), each claiming unique, yet unproven, "medical" benefit. These products are not regulated by the US Food and Drug Administration (FDA) and do not meet the FDA standards for approval of other medications, although the product labels accompanying these products may appear similar to those seen with pharmaceutical medications.

This presents a challenge for physicians treating patients who use "medical marijuana" and tout the benefits of the products based on manufacturers' product labels. Furthermore, psychiatrists may encounter patients who are using medical marijuana for a psychiatric indication or may comanage patients who are receiving medical marijuana for a nonpsychiatric (medical) condition. This article is intended to provide physicians with an overview of "medical marijuana" and cannabinoids, the current state of the evidence (or lack thereof) for marijuana in psychiatric indications, and the potential risks, side effects, and drug interactions that may be encountered during psychiatric treatment of individuals who use "medical marijuana."

Overview of Marijuana and the Endocannabinoid System

Marijuana, or cannabis, typically refers to the dried, flowering tops of 3 main species of the cannabis plant, namely, *Cannabis indica, Cannabis sativa,* and *Cannabis ruderalis*. The flowering tops contain over 565 chemical constituents including > 120 phytocannabinoids, terpenoids, and flavonoids.[2] The most well-studied phytocannabinoids are Δ^9-tetrahydrocannabinol (THC) and CBD. THC is the main psychoactive constituent of marijuana. Unlike THC, CBD, another important constituent cannabinoid, is not known to have rewarding/reinforcing effects or perception altering effects. CBD is thought to have some effects with therapeutic potential, such as antiepileptic and anxiolytic effects.[3] While the effects of THC have been extensively studied and are well known, the reasons for individual differences in response and interactive effects of some of the other cannabinoids on the net effect of marijuana are not clear.

"Medical marijuana" strains are derived by cross-breeding *Cannabis indica* and *sativa* plant species to produce hybrids that vary in their contents of THC and CBD. Strains with THC content > 20% are considered "high THC," but strains need only have CBD > 4% to be considered "high CBD."

Phytocannabinoids are thought to exert their effects primarily via the endocannabinoid system and downstream effects on other neurotransmitter systems such as serotonin, GABA, and other G-protein–coupled receptors.[4] Endocannabinoids, primarily anandamide (AEA) and 2-arachidonoylglycerol (2-AG), are endogenous lipid neurotransmitters that inhibit the release of both GABA and glutamate. They hence maintain the balance of excitatory/inhibitory neurotransmitters in the brain.[5] They are synthesized and released on demand, activate cannabinoid receptor subtypes 1 and 2 (CB_1R and CB_2R), and are rapidly deactivated thereafter. In contrast, THC and other CB_1R agonists bind to cannabinoid receptors and activate them for a longer duration. THC is a weak partial agonist of both CB_1Rs and CB_2Rs. In contrast, the mechanism underlying CBD's effects is not fully understood as yet. Among the proposed mechanisms are negative allosteric modulation of THC and 2-AG,[6] inhibition of AEA reuptake, 5-HT_{1A} agonism, 5-HT_{2A} weak partial agonism, and a noncompetitive 5-HT_{3A} antagonism.[4]

Labeling

Unlike the standard FDA-approved labeling of commercially available medications in the United States, each state in the United States has its own requirements with regard to the product labeling of medical marijuana. While the majority of states require that the product label state the quantity of THC and CBD, some, such as Connecticut and Illinois, require that the level of tetrahydrocannabinolic acid (THCA) is also included, while others, such as Washington and Nevada, require that "total THC" content is listed. Most products labeled as "CBD-alone" typically also contain THC or THCA since they are derived from the whole plant. The potential benefits of CBD-alone products hence need to be evaluated in the context of potential risk of psychosis and other adverse psychiatric outcomes related to the presence of other cannabinoids in the product. Doses of THC as low as 2.5–5 mg have been shown to worsen psychosis despite adequate antipsychotic treatment.[7]

An additional concern is that the concentrations noted on the product labels are sometimes inaccurate. The FDA has issued warning letters regarding 45 such commercially available products since 2015, which either contain no cannabinoids despite claiming to do so or contain variable concentrations of THC, CBD, and THCA (https://www.fda.gov/newsevents/publichealthfocus/ucm484109.htm). In a study of 75 edible medical marijuana products from San Francisco and Los Angeles, California, and Seattle, Washington, 17% were accurately labeled, 23% were underlabeled, and 60% were overlabeled with respect to THC content, and 41% had undetectable levels of CBD.[8]

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Table 1. Psychiatric Conditions for Which Medical Marijuana Is Approved, by State

Condition	States Where Approved as Qualifying Condition
Anxiety	NJ
Autism	DE, MN, PA, CO, LA, MI, MO, UT
Agitation in Alzheimer's disease	AZ, AR, DC, DE, IL, ME, MI, MO NH, NY, ND, OH, OR, RI, UT
Cerebral palsy	CT
Generalized anxiety disorder (refractory)	WV
Posttraumatic stress disorder	AZ, AR, CO, CT, DE, FL, HI, IL, LA, ME, MD, MI, MN, MO, MT, NH, NJ, NV, NM, NY, ND, OH, OR, PA, UT, VT, WA, WV
Post-concussion syndrome	IL
Traumatic brain injury	IL, NH, OH, WA
Tourette's syndrome	AR, IL, MI, MO, MN, NJ, OH
Any other chronic or persistent medical symptom that substantially limits the ability of the person to conduct 1 or more major life activities OR cannot be effectively treated by ordinary medical measures	AK, CA, DC
Any condition for which treatment with medical marijuana would be beneficial, as determined by the patient's physician	DC, MA, MO

Table 2. Side Effects Associated With Marijuana Use

Acute use	Panic attack Acute psychosis Impaired decision-making ability Greater impulsivity and risk-taking Impaired coordination, psychomotor coordination (driving ability)
Chronic use	Tolerance, dependence, withdrawal, cannabis use disorder Impaired verbal memory, attention, psychomotor coordination (driving ability), drop in IQ, amotivation syndrome Psychosis, bipolar disorder(?): increased risk MDD: earlier age at onset, greater risk of suicidal ideation Anxiety disorders: earlier age at onset
Medical complications	Common: chronic bronchitis Uncommon: spontaneous pneumothorax, bullous emphysema, increased risk of lung cancer(?), worsening chronic obstructive pulmonary disease(?) Common: increased risk of cardiovascular events, ischemic stroke, myocardial infarction, transient ischemic attack Uncommon: cardiomyopathy and sudden cardiac death Uncommon: cyclical vomiting and compulsive bathing (cannabinoid hyperemesis syndrome)
Drug interactions	THC and CBD: metabolized by CYP3A4, 2C9, 2C19. Hence, serum levels are affected by inducers/inhibitors of these enzymes Smoked marijuana: CYP1A2 induction: increased theophylline clearance. (Potentially increases clearance [decreases efficacy] of antipsychotics metabolized by CYP1A2, ie, olanzapine and clozapine) CBD: via CYP3A4 inhibition: increases serum levels of clobazam CBD: via CYP2C9 inhibition: increases serum level of warfarin and diclofenac CBD: theoretically increases serum level of drugs metabolized by CYP2D6 and CYP3A4 (including antipsychotics, antidepressants) Increased expression of P-glycoprotein with THC: decreased brain levels of amisulpride, aripiprazole, olanzapine, risperidone, paliperidone, and other drugs that are substrates for P-glycoprotein

Abbreviations: CYP = cytochrome P450, MDD = major depressive disorder, THC = Δ^9-tetrahydrocannabinol.
Symbol: ? = evidence is unclear.

Current Evidence for the Use of "Medical Marijuana" in Psychiatric Indications

Medical marijuana has been approved for a number of psychiatric disorders in many states in the United States including posttraumatic stress disorder (PTSD), agitation in Alzheimer's disease, and Tourette's disorder (Table 1). A recent systematic review of the evidence found that, at the present time, the strength of evidence for the use of medical marijuana for these conditions was "very low."[9] The Veterans Administration Evidence-based Synthesis Program conducted a systematic review of marijuana in PTSD and concluded that further evidence is necessary to support claims of beneficial effects.[10] The 2013 American Psychiatric Association "Position Statement on Marijuana as Medicine" notes that "there is no current scientific evidence that marijuana is in any way beneficial for the treatment of any psychiatric disorder. In contrast, current evidence supports, at minimum, a strong association of cannabis use with the onset of psychiatric disorders. Adolescents are particularly vulnerable to harm, given the effects of cannabis on neurodevelopment."[11] There are no randomized controlled trials (RCTs) of adequate power that have examined the efficacy of marijuana for Tourette's disorder, PTSD, or Alzheimer's disease. The existing evidence is from studies of THC and nabilone that have been extrapolated to "medical marijuana." As discussed earlier, THC is one but not the only constituent of marijuana.

Other psychiatric disorders for which "medical marijuana" is touted to be beneficial include autism, attention-deficit/hyperactivity disorder, sleep disorders, and psychosis, with inadequate evidence to support these claims.

There is great interest in CBD-alone products. The utility of CBD in psychiatric disorders including psychosis is, however, controversial.[12] While one RCT[13] showed improvement in Positive and Negative Syndrome Scale positive symptoms (CBD dose = 1,000 mg/d), another[14] (CBD dose = 800 mg/d) was negative. In the former study, the CBD group had lower levels of positive psychotic symptoms at the 6 week time point that were statistically significant, but the differences may be of small clinical significance. Two additional RCTs, judged to have a high risk of bias (71 total participants with schizophrenia or schizophreniform psychosis), found CBD (maximum dose 800 mg/d) to be comparable to amisulpride (800 mg/d) in chronic schizophrenia[14] and CBD (600 mg/d) not to be significantly different from placebo in first-episode schizophrenia.[15–17] Of note, the studies of CBD with adjunctive antipsychotics did not examine serum antipsychotic levels. This would be important to rule out a pharmacokinetic effect since CBD potentially inhibits cytochrome P450 (CYP)2D6.[18]

Risks Associated With Acute Marijuana Use

Acute marijuana intoxication can present with increased anxiety, panic attacks, acute psychosis, impaired decision-making, and greater risk-taking and impulsivity (Table 2).[19] THC acutely produces deficits in attention, verbal learning, working memory, and electrophysiologic indices of information processing.[7,20]

Risks Related to Chronic Use of Marijuana

The consequences of chronic marijuana use include development of tolerance, dependence, withdrawal, and cannabis use disorder; cognitive deficits such as impairment in attention, memory, IQ,

and driving ability; and amotivation syndrome.[21–24] The effects of marijuana use on adolescents are of particular concern, since adolescence is increasingly well recognized as a critical period of neurodevelopment.

Epidemiologic studies point to an association between marijuana use and increased risk of psychiatric disorders such as schizophrenia,[20,25] bipolar disorder,[23,26] major depressive disorder, and suicidal ideation.[27] Marijuana use has been associated with a worse course of illness, greater number of hospitalizations, and overall poorer outcomes in both schizophrenia and bipolar disorder[28–30] (also reviewed in Satre et al[31]).

Medical complications associated with chronic, heavy marijuana use include increased risk of pulmonary complications (chronic pulmonary obstructive disease, spontaneous pneumothorax, bullous emphysema, lung cancer)[32] and cardiovascular complications (myocardial infarction, cardiomyopathy, stroke, transient ischemic attack, and sudden cardiac death).[33,34] Chronic marijuana use is also associated with a syndrome of cyclic vomiting and compulsive bathing (cannabinoid hyperemesis syndrome), the diagnosis of which requires a high index of suspicion.[35]

Drug Interactions

THC and CBD are both substrates for cytochrome P450 enzymes. THC and CBD are also both metabolized by CYP2C9 and 3A4, while CBD is additionally metabolized by CYP2C19.[36] Serum levels of THC and CBD are hence altered by concomitant CYP3A4 inhibitors and inducers.

Clinically significant drug interactions include increased serum levels of clobazam (possibly via CYP3A inhibition), warfarin, and diclofenac (via CYP2C9 inhibition) with CBD[37] and with marijuana.[38] CBD is a potent inhibitor of CYP2D6, CYP2C19, and CYP3A4[39,40] in in vitro studies. Theoretically, CBD could increase serum levels of antipsychotics and antidepressants that are metabolized by these enzymes.[17,40] THC, on the other hand, has been shown to decrease brain concentrations of risperidone and its active metabolite, 9-hydroxyrisperidone, via induction of P-glycoprotein expression.[41]

Like cigarette smoking, smoking marijuana may induce CYP1A2. Consequently, frequent marijuana smokers have been shown to have a 42%–48% higher clearance of theophylline.[42] Also of clinical relevance is the finding that alcohol in combination with marijuana impairs driving ability at a lower blood alcohol level.

In summary, the use of medical marijuana presents a challenge to physicians, in the absence of good evidence of its efficacy. It is important for physicians to note that "medical marijuana" and THC are schedule I substances per the DEA in the United States. Therefore, even when US states permit their use under the guise of medical marijuana law, "prescribing" these compounds is not without liability. Additionally, as noted earlier, the contents in the product do not match the product label in many cases. It would be important for physicians to document a discussion of risks versus benefits, including acute and chronic side effects, drug interactions, and alternative treatment options.

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