

Medical Marijuana: The State of the Science

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Background

"Medical" cannabis, in some shape or form, is here to stay. Currently legal in 23 states and the District of Columbia,^[1] the paradoxical federal illegality of cannabis remains relevant, particularly in the eyes of many healthcare providers.^[2] The discrepancy between federal and state laws has created uncertainty about whether medical cannabis is legal and should be legal, and whether its use is in the best interest of physicians and their patients.

Physicians' ambivalence regarding medical cannabis was clearly illustrated in a 2013 survey of 520 members of the Colorado Academy of Family Physicians.^[3] The survey found that whereas only 19% of respondents believed that physicians should recommend medical cannabis, 80% agreed that it should be incorporated into medical school education, 82% agreed that it should be incorporated into residency training, and 92% agreed that it should be a topic of continuing medical education for practicing physicians. In addition, the majority of respondents agreed that there are significant mental and physical health risks associated with marijuana.

Undoubtedly, healthcare providers are left with more questions than answers about the use of medical cannabis. Some key questions include:

- Is it safe?
- Is there adequate evidence for its efficacy? If so, for what conditions is it effective?
- If it is sold in dispensaries rather than on street corners, should it be considered "medical"?
- If it is "medical," can it still be abused?
- Is marijuana medical, or do certain components of marijuana have medical benefit and are safe?

These key questions will be addressed in this review, with the goal of reducing provider confusion and offering guidance on how certain cannabinoids—if not whole-plant marijuana—can be integrated into evidence-based care.

THC vs Cannabidiol

Few users, and perhaps fewer healthcare providers, understand the composition of marijuana. The marijuana plant contains over 100 cannabinoids, which are the active chemical components of cannabis.^[4] Delta-9-tetrahydrocannabinol (THC) is considered the most psychoactive component of marijuana,^[5] and accordingly gets most of the press, both good and bad.

THC was first isolated and synthesized in 1964,^[6] and is responsible for the euphoria associated with marijuana use. Since 1985, synthetic THC has been available in the United States for medical use as dronabinol, a Schedule III substance, and nabilone, a Schedule II substance. Initially approved for

appetite stimulation in patients with AIDS and for chemotherapy-induced nausea and vomiting,^[7] dronabinol has been widely used off-label, often without adequate evidence.^[8]

Common side effects of dronabinol include drowsiness, unsteady gait, dizziness, inability to focus, confusion, mood changes, delusions, and hallucinations,^[9] all of which may be associated with poor tolerability. A recent randomized, placebo-controlled, crossover trial of dronabinol for the treatment of chronic pain found that dronabinol produced similar psychoactive effects as smoked marijuana,^[10] which may limit its use in persons with chronic pain. Similar side effects have been identified for nabilone,^[11] also bringing into question its clinical value. In a review, Russo^[12] suggested that these side effects preclude use of synthetic THC as the solution to incorporating medical cannabis into clinical practice.

Contrary to popular belief, THC is not necessarily the most relevant cannabinoid with medical applications.^[13] First isolated in 1934,^[14] cannabidiol (CBD) was partially synthesized from hashish in 1964,^[6] and fully synthesized several years later.^[15] Whereas the number of publications regarding cannabis has increased, little on CBD was published until the early 2000s, "with the confirmation of a plethora of pharmacological effects, many of them with therapeutic potential."^[16]

CBD was viewed as unimportant for many years. Research indicated that it mitigated the euphoria associated with THC,^[17] resulting in efforts to remove CBD from marijuana.^[18] The use of genetic engineering to remove CBD from marijuana is supported by findings of Burgdorf and colleagues^[19] in their examination of changes in the composition of marijuana seized by law enforcement in California between 1996 and 2008. They found that the concentration of THC increased from 2.17% to 9.93%, while the concentration of CBD decreased from 0.24% to 0.08%. These dramatic changes were less pronounced in marijuana seized close to the Mexican border compared with non-border areas, suggesting that genetic engineering of marijuana primarily occurred in the United States.

Although reducing the euphoria associated with marijuana by increasing the CBD content may not necessarily be of interest to the recreational marijuana industry, its medical application has been compelling.

Cannabis Use and Physical Health

Safety issues associated with the habitual use of smoked cannabis are discouraging. For many years, the myth of smoked cannabis being "healthier" or "no worse" than smoked tobacco was perpetuated by pro-marijuana groups. Nevertheless, clinical research has provided some answers about the comparative safety of marijuana and tobacco smoking, although certain factors may complicate their direct comparison.

Henry and colleagues^[20] noted in 2003 that both smoked cannabis and tobacco contain approximately 4000 chemicals and that these chemicals are essentially identical in both plants. However, given the ever-changing potency of cannabis and the fact that very few people smoke as much cannabis as tobacco, this direct comparison is difficult to make. Furthermore, the authors note that a high percentage of cannabis smokers are also tobacco smokers, thereby further confounding their relative safety risks.

In a recent systematic review by the American Academy of Neurology examining the cardiopulmonary impact of heavy marijuana smoking,^[21] the authors concluded that "smoking and possibly even use of vaporized preparations expose users to carbon monoxide and other respiratory toxins." Although the

authors of another recent review^[22] stated that the relationship between the long-term smoking of marijuana and lung cancer is unclear, they also concluded that marijuana smoking is associated with the inflammation of large airways, increased airway resistance, and lung hyperinflation, all of which are consistent with the development of chronic bronchitis.

In another recent review,^[23] the authors concluded that "smoking of cannabis is not medically recommended due to the potential respiratory tract, dangers of noxious compounds such as polycyclic aromatic hydrocarbons, tar and carbon monoxide." Suffice it to say, recent literature reviews addressing the pulmonary implications of smoking marijuana do not endorse the safety of its use.

Physical Health Risks

An abundance of literature has recently emerged identifying the physical and mental health risks associated with the use of THC. This is concerning, given that the THC content of marijuana has increased dramatically over the past two decades.^[20] Whereas Aggarwal and colleagues^[24] recently noted that natural cannabis contains a maximum THC concentration of 10%-15%, dispensary websites advertise strains with concentrations as high as 33%.^[25] There is also some evidence suggesting that the THC potency of "medical marijuana" is higher than that of marijuana illegally sold for recreational use.^[19]

In a recent review of the cardiovascular, cerebrovascular, and peripheral vascular effects of smoked marijuana, Thomas and colleagues^[26] identified an association between marijuana inhalation and higher rates of acute myocardial infarction and increased cardiovascular mortality. In addition, they described published case reports that identify a safety signal between cannabis use and stroke. Of considerable concern are data indicating diminution of the volumes of the hippocampus, amygdala, and cerebellum in adult and adolescent heavy users compared with healthy controls.^[27-29]

Although cannabis is not necessarily hepatotoxic, a study of 272 patients with chronic hepatitis C virus infection determined that daily marijuana smoking was a risk factor for progression of liver fibrosis.^[30] A relatively new diagnosis associated with heavy marijuana use is cannabinoid hyperemesis syndrome, which is characterized by cyclic nausea and vomiting and compulsive bathing; it is thought to be due to the rising levels of THC in marijuana.^[31] Conjunctivitis is the most common ocular adverse event associated marijuana use and may be related to an allergic response to *Cannabis sativa* pollen.^[32]

Long-term use of cannabis has an adverse impact on reproductive potential, as it disrupts the menstrual cycle, suppresses oogenesis, and impairs embryo implantation and development.^[33] Cannabis use may also have a detrimental effect on male reproductive health, as described in a recent review of published data by Barazani and colleagues.^[34]

Several problems are associated with marijuana use during pregnancy, because prenatal exposure influences brain development and can result in permanent cognitive impairment.^[35] Cognitive deficits resulting from prenatal exposure include inattention; impulsivity; and impairment in learning, memory, and certain aspects of executive functioning.^[36] In addition, prenatal exposure to cannabis has been associated with reduction of fetal growth.^[37]

Long-term cannabis use also has oral health implications. Uvulitis and nicotinic stomatitis are probably the two most common of several potential oral adverse effects.^[38]

Finally, from a population health perspective, we cannot ignore the association between cannabis use and mortality. A systematic review found that people who had used marijuana had higher rates of mortality from fatal motor vehicle accidents, AIDS, and lung cancer.^[39] In its totality, the available evidence should dispel the belief that marijuana is physically innocuous.

Cannabis Use and Mental Health

Relative to the literature on the physical health effects of cannabis use, the available literature on its mental health effects is quite abundant. Despite years of the widely embraced opinion to the contrary, we now know that cannabis is addictive. Symptoms specified in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) for cannabis withdrawal include irritability, nervousness, sleep difficulty, decreased appetite, restlessness, depressed mood, and physical symptoms and discomfort.^[40] The inclusion of all of these symptoms is supported by a broad base of evidence.^[41-44]

Depersonalization among cannabis users has been recognized for many years^[45]; this may be related to residual neurotoxicity associated with cannabis and the extended elimination half-life of cannabis metabolites.^[46]

The relationship between cannabis use and various psychopathologies and related psychiatric hospitalizations is gaining more attention with increased medical use.^[47] As early as 1944, Allentuck^[48] reported on the development of anxiety and dysphoria among study participants who received marijuana experimentally. Subsequently, hundreds of articles addressing negative emotional responses to marijuana have appeared in the literature.

A recent review^[49] concluded that the adverse psychological effects of marijuana are caused by THC and mitigated by CBD. Acute anxiety in response to THC is becoming more common as THC concentrations increase; lower concentrations tend to be anxiolytic, whereas higher concentrations tend to produce anxiety.^[50] However, although frequent marijuana smokers have a high prevalence of anxiety disorders and likewise, individuals with anxiety disorders have relatively high rates of marijuana use, we do not have sufficient evidence to determine whether marijuana use actually causes chronic anxiety disorders.^[51]

Data suggest that long-term use of marijuana increases the risk for depression,^[52] leads to more pronounced suicidal ideation,^[53] and heightens risk for suicide attempts.^[54] Of particular concern has been the susceptibility of the developing brain to depression and anxiety resulting from marijuana use. In a prospective cohort study,^[55] frequent marijuana use by teens predicted depression and anxiety later in life, and a more recent study^[56] determined that use of marijuana among adolescents was associated with adult-onset anxiety. However, the relationship between marijuana use and depression may be confounded by "common genetic influences."^[57]

The association between bipolar disorder and marijuana use is unclear; however, a recent systematic review^[58] found an association between cannabis use and earlier onset of initial mania and more frequent manic or depressive episodes. Despite this apparent association, the causal relationship between cannabis and onset of mania remains unclear.

A growing body of literature supports the relationship between marijuana use and psychotic disorders, with acute and transient effects, acute and persistent effects, and delayed and persistent effects "that bear a striking resemblance to symptoms of schizophrenia" as seen in both observational and

experimental studies.^[59] Early and heavy cannabis exposure has been associated with psychosis later in life in numerous studies.^[60-63] However, a recent review^[64] indicated that exposure to cannabis can also result in acute psychotomimetic symptoms that may not persist beyond the period of intoxication.

Several risk factors have been implicated in augmenting the association between cannabis and psychosis; these include early age of exposure,^[65] history of childhood abuse,^[66] and family history of schizophrenia.^[67] Many genetic factors are believed to confer vulnerability to psychosis in individuals exposed to cannabis,^[68-70] representing a gene/environment interaction. In their recent review, Radhakrishnan and colleagues^[59] concluded that "the association between cannabis and psychosis fulfills many, but not all of the standard criteria for causality." The evidence for causality, however, is rapidly increasing.

Cannabis and Cognition

Published data support that heavy, long-term use of marijuana results in impairment in several areas of cognitive functioning. An evidence-based review of the literature^[71] found that heavy use of cannabis acutely impairs attention and concentration, inhibition and impulsivity, and working memory; findings for decision-making and risk-taking were mixed. However, in a study that used neuroimaging studies to evaluate the effect of marijuana on memory functioning, this relationship was difficult to interpret, given major differences in characteristics of the study populations involved.^[72]

The misperception that marijuana causes only transient cognitive impairments was rebuked by a recent prospective cohort study of over 1000 participants followed from birth until 38 years of age,^[73] which found that neuropsychological functioning was not fully restored among adolescent marijuana users after cessation. Although the extent to which long-term cannabis use results in permanent cognitive impairment remains controversial, the growing evidence of structural changes to the integrity of the brain due to chronic use among adults may be a significant concern for patients who use medical marijuana on a regular basis.^[74]

Is THC "Medical"?

As previously discussed, the tolerability of synthetic THC is limited, making its use in clinical practice dubious. Perhaps the greatest difficulty in assessing the efficacy of medical marijuana relates to an inability to define what elements make marijuana "medical."

For many years, taxonomists considered marijuana to be a single-species genus, until Small and Cronquist^[75] identified subspecies based on "intoxicant ability." Subsequently, we have learned considerably more, and we should speak of "medical marijuanas" rather than erroneously assuming that what is considered "medical" (or, for that matter, "recreational") cannabis represents one specific entity. Regardless, it is important to review some of the research that evaluates the efficacy of whole-plant marijuana for medical purposes.

Complicating the assessment of efficacy is the wide variety of disease states for which patients choose to use marijuana as an element of treatment. The nation's first medical cannabis law that was enacted (California's Compassionate Use Act of 1996) stipulated that marijuana could be recommended to a patient by a physician for "treatment of cancer, anorexia, AIDS, chronic pain, spasticity, glaucoma, arthritis, migraine, or any other illness for which marijuana provides relief."^[76] Although the law mentioned specific diseases, its clause referencing "any other illness for which marijuana provides relief" added a considerable degree of subjectivity to the Act.

States' medical cannabis laws all tend to be nonspecific, and all but three consider "pain" as an appropriate condition to authorize medical cannabis. In a recent survey,^[3] 94% of all medical cannabis registrants listed "severe pain" as their condition necessitating cannabis. Given the subjective nature of pain, providers would be challenged by the prospect of disproving a patient's report of pain. Accordingly, medical cannabis authorization has been extremely easy to obtain in states allowing it; data from Arizona indicate that between April and October of 2011, only seven of 14,925 applicants for medical marijuana registration were denied.^[77]

There is a paucity of high-quality data supporting the efficacy of medical cannabis—again, primarily owing to the lack of a definition of "medical" cannabis. Furthermore, the available literature is very inconsistent with regard to study endpoints and outcomes. For example, is "pain relief" sufficient as the sole dependent variable in assessing efficacy, or should functionality also be taken into consideration? Although some patients will report high levels of pain relief after using the high-THC/low-CBD concentration marijuana that is typically sold at dispensaries, few, if any, studies show evidence to the contrary that these agents will reduce function in the vast majority of patients owing to intoxication.

A lack of dosing uniformity is also of concern. The recent review released by the American College of Neurology^[21] considered six different disease states and symptoms and a variety of THC/CBD ratios and methods of administration (eg, oral, oromucosal, inhaled), with no assessment of patient function; the conclusions that could be drawn regarding efficacy were therefore limited.

For pain, the most common indication for medical cannabis, a review by Aggarwal^[78] noted that "little data are available on the risks associated with long-term medical use in published clinical trials," but for "notoriously difficult to treat conditions," cannabinergic pain medicines may have appropriate evidence of safety and efficacy. Although recommending smoked cannabis, Aggarwal did not address issues of dosing, functionality, and tolerability, but appropriately called for additional research.

Finally, nabiximols, which has approximately a 1:1 THC/CBD ratio and oromucosal administration, was not considered, owing to the paucity of supportive data comparing efficacy and safety with other cannabis preparations. This is not to suggest that nabiximols is not beneficial in the treatment of several conditions, given findings of efficacy, safety, and tolerability in selected placebo-controlled trials.^[79-81] Proper dosing of nabiximols, however, has not been determined.^[82] Most relevant to this review, the lack of comparison with other cannabinoid-based products makes the role of nabiximols in solving the medical cannabinoid dilemma unclear.

In their review of herbal cannabis for rheumatologic conditions, Fitzcharles and colleagues^[23] noted the dilemma experienced by physicians: "Simply acceding to patient demands for a treatment on the basis of popular advocacy, without comprehensive knowledge of an agent, does not adhere to the ethical standards of medical practice...any recommended therapy requires proof of concept by sound scientific study that attests to both efficacy and safety." All but the most biased reviews articles on this topic conclude with generic statements, such as, "Medical cannabis appears to have some benefit in patients with certain conditions."^[83]

Multiple other systematic reviews of medical cannabis in which formulation, dosage, and route of administration were specified or were consistent across randomized controlled trials have failed to yield definitive conclusions regarding the safety and efficacy of medical cannabis for a variety of conditions.^[8,84-92] Considering this ambiguity, how are providers supposed to know which cannabinoids, formulations, dosages, and routes of administration are safe, tolerable, and effective, and in which conditions and which patients? Unfortunately, current arguments for the use of medical cannabis are

considerably more politically, and often emotionally, based, rather than scientifically based, resulting in the proliferation of "medical marijuana pseudoscience."^[93]

CBD: Some Semblance of Coherence?

CBD is finally becoming established in US medicine, not just in terms of developing an evidence basis but also in its increased legalization, availability, and clinical use. CBD is safer and more uniform in its composition than "medical marijuana," and it is associated with less variability in response to it, thereby giving it greater clinical value. In discussing variance in THC levels among strains, Smith^[94] wrote, "Cannabis is an elusive substance with properties that may preclude straightforward generalizations." A decade later, his words are still applicable, but not necessarily to CBD.

The Safety of CBD

The first study to support the safety of CBD in humans was conducted by Mechoulam and Carlini^[95] in 1978 and found no apparent toxic effects of CBD when administered to patients with epilepsy for a 3-month trial period. The safety profile of CBD was subsequently evaluated in a trial in which up to 300 mg of CBD was administered daily to patients with epilepsy and healthy volunteers for up to 4.5 months.^[96]

Safety data are also available from another relatively early trial that examined the efficacy of CBD for the treatment of Huntington disease, but found no evidence of symptom relief.^[97] Over the 6-week trial, there were no statistically significant differences between CBD and placebo in blood chemistry variables, blood pressure, pulse rate, and body weight. In a small 5-week study of CBD for treatment-resistant schizophrenia,^[98] the investigators identified no issues with safety; however, they did not provide substantial details on how they defined "safety." Similar findings were reported in a study of bipolar patients who received up to 1200 mg of oral CBD^[99]; however, the description of safety was similarly limited.

In a 3-week study in which participants were administered 10 mg of oral CBD daily,^[100] there were no changes in neurologic evaluation, which included electroencephalography; cardiac evaluation, as determined by electrocardiography; psychiatric evaluation; or clinical evaluation, which included blood chemistry and urinalysis. In a 4-week trial of patients with Parkinson disease receiving up to 400 mg of CBD daily, no cognitive or motor side effects were found in the study participants.^[101]

Finally, a study determined that acute CBD administration did not result in any significant toxic effects in humans, regardless of whether it was administered orally, by inhalation, or intravenously.^[102] A recent systematic review determined that clinical trials have suggested that sedation is observed only with higher doses of CBD.^[103]

Perhaps the greatest concern regarding the safety of CBD is its potential to cause immunosuppression. CBD may induce a biphasic response in the immune system, with higher doses potentially associated with inhibitory responses and lower doses potentially resulting in stimulatory process.^[104] Thus, clinicians should be cautious when recommending CBD for patients who are immunosuppressed until further research on dosing is conducted. Other than the potential issue of immunosuppression and sedation at very high doses, there does not appear to be any other safety issues associated with CBD.^[105]

Since the 1970s, we have known that CBD attenuates many of the undesirable effects of THC.^[106] Of note, for those who believe that THC can be of medicinal value, its risks and side effects need to be mitigated. In recreational users, use of marijuana with high THC and low CBD concentrations has been associated with reduction of hippocampal volume, suggesting that CBD may have a role in neuroprotection.^[29] A study of the role of cannabis in the development of psychosis found that CBD attenuated hippocampal volume loss, further implicating CBD in neuroprotection.^[107]

In terms of psychological functioning, Rottanburg and colleagues^[108] were the first to suggest that the use of marijuana with high levels of THC and low levels of CBD was associated with psychosis. Several subsequent studies have supported the role of CBD in mitigating THC-induced psychosis.^[109-112]

The potential of CBD to reduce anxiety associated with the use of marijuana with high THC concentrations has also been empirically supported. Zuardi and colleagues^[113] determined in 1982 that the anxiogenic effect of THC was reduced by roughly 50% when coadministered with CBD. Additional studies support the potential of CBD to mitigate THC-induced anxiety.^[106,114]

However, the overall body of empirical evidence has yielded inconsistencies in the effect of CBD on THC-induced anxiety, probably owing to variance in THC/CBD ratios of marijuana used in the studies.^[49] CBD has been reported to reduce the anxiety associated with cannabis withdrawal,^[115] but because this finding was from a single case report, additional research is needed.

Physical Health Applications of CBD

The vast literature on CBD provides a reasonable evidence basis for the treatment of several physical and psychological conditions. As early as 1978, published data suggested that CBD administration was associated with freedom from seizures for 3 months^[95] and reduced seizure frequency in patients with epilepsy.^[96] Results of an unpublished placebo controlled trial from 1990 also suggested a reduction in seizure frequency.^[116]

In contrast, a recent Cochrane review concluded that there were insufficient high-quality studies to draw a reliable conclusion regarding efficacy, despite no reports of adverse events.^[117] Nevertheless, in a recent review, Cilio and colleagues^[118] noted that "pure CBD appears to be an ideal candidate among phytocannabinoids as a therapy for treatment-resistant epilepsy."

Patients with treatment-resistant pediatric epilepsies, such as Dravet syndrome and Lennox-Gastaut syndrome, may potentially benefit from CBD.^[119] Preliminary data from a phase 2/3 US clinical trial in 12 children with Dravet syndrome have been promising,^[120] prompting future plans to expand the study in the United Kingdom.^[121]

CBD has also been evaluated for the treatment of Parkinson disease. Recently, investigators found that CBD reduced the frequency of rapid eye movement sleep behavior disorder in patients with Parkinson disease, with no apparent side effects.^[122] Another recent study determined that although CBD did not significantly reduce motor symptoms and general symptoms of Parkinson disease, it significantly improved well-being and quality of life.^[123] In patients with dystonic movement disorders, CBD was found to reduce dystonia by 20%-50%.^[124]

A study of patients with intractable neurogenic symptoms from multiple sclerosis, spinal cord injury, brachial plexus injury, and limb amputation due to neurofibromatosis found that pain relief with CBD

was significantly improved compared with placebo, without unwanted side effects.^[125] However, a trial in patients with intractable cancer pain found only a nonsignificant reduction in pain associated with CBD compared with placebo.^[81] This may have been due to the low dose of CBD used: 20-30 mg oromucosally once daily. Although numerous studies of pain management have used combined THC/CBD, the relatively new understanding of the anti-inflammatory and antispasmodic benefits of CBD have limited the number of clinical trials of CBD monotherapy that have been published.

Hundreds of animal and human cell-line studies support the investigation of CBD for the treatment of various types of cancer. Given its safety profile and the preclinical data supporting its antiproliferative and proapoptotic effects and interference with several mechanisms in oncogenesis, phase 2 studies are now planned for CBD monotherapy in the treatment of solid tumors.^[126] In addition, the US Food and Drug Administration recently granted a manufacturer orphan drug designation for synthetic CBD as a treatment for glioblastoma multiforme and glioma, both of which are highly treatment-resistant malignancies.^[127]

Mental Health Applications of CBD

In an early study of human experimental anxiety, Zuardi and colleagues^[128] found that CBD had anxiolytic properties in participants exposed to a stressful situation. More recently, Crippa and colleagues^[129] reported anxiolysis in participants receiving CBD and used single-photon emission CT to determine that this effect was mediated by the action of CBD on the paralimbic and limbic areas of the brain. Similar findings have been observed when comparing THC and CBD in healthy volunteers: THC increased anxiety in response to intensely fearsome faces and CBD reduced subjective anxiety and autonomic arousal, as measured by skin conductance response.^[130]

Of greater clinical relevance, CBD was found to be superior to placebo in reducing anxiety in patients with generalized social anxiety disorder.^[131] This was confirmed by another placebo-controlled trial of treatment-naïve persons, which found an improvement in generalized social anxiety as measured by both subjective and physiologic parameters.^[132]

A recent double-blind, placebo-controlled trial found that CBD enhanced consolidation of fear extinction when administered after extinction.^[133] Collectively, these data suggest that CBD may be useful in the treatment of various anxiety disorders, including post-traumatic stress disorder.

Furthermore, CBD has been found to be superior to placebo in increasing sleep time among patients with insomnia.^[134] Despite its ability to reduce anxiety and induce sleep, CBD was found to have alerting properties in a study of nocturnal sleep and early-morning behavior.^[135] This paradoxical effect appears to be explained by the ability of CBD to provoke wakefulness at low doses and sedation at high doses.^[136]

There is also evidence that CBD has antipsychotic effects, as demonstrated by a study finding that CBD reduced ketamine-induced depersonalization in healthy volunteers.^[137] In a case report of a patient with schizophrenia who could not tolerate conventional antipsychotics, a significant reduction in psychotic symptoms was reported after administration of high-dose CBD for 4 weeks, with a return of symptoms after discontinuation.^[138]

In a 4-week study of patients with Parkinson disease who presented with at least a 3-month history of psychotic symptoms, oral CBD administration resulted in a significant reduction of these symptoms.^[101] A trial of patients with acute paranoid schizophrenia or schizophreniform psychosis found that CBD

resulted in a decrease in psychotic symptoms similar to that experienced by the patients receiving a traditional antipsychotic agent, but with a significantly improved side effect profile.^[139] These findings were confirmed in a more recent trial, with the authors attributing this effect to the potential of CBD to inhibit anandamide deactivation.^[140]

In a review, Zuardi^[141] asserted that "clinical studies suggest that CBD is an effective, safe and well-tolerated alternative treatment for schizophrenic patients." However, this conclusion may be premature. Although preliminary results have been promising, further larger-scale randomized controlled trials are needed in order to establish the efficacy of CBD for the treatment of psychosis.

A review by Schubart and colleagues^[142] provides a more reasonable conclusion, stating that "evidence from several study domains suggests that CBD has some potential as an antipsychotic treatment." Similarly, the authors of a recent Cochrane review concluded that "there is some slight suggestion that cannabidiol may have some antipsychotic characteristics," again calling for additional research.^[143]

The potential role of CBD in the treatment of addictions is also relevant. In a recent trial, Morgan and colleagues^[144] found that smokers treated with CBD reduced the number of cigarettes that they smoked by 40%; in contrast, the number of cigarettes smoked by the placebo group was unchanged. Preclinical studies have supported the ability of CBD to reduce opioid-seeking behavior and attenuate the reward-facilitating effects of opioids; however, more research is needed to fully realize the role of CBD in addiction medicine. A phase 2 study on the short-term effects of CBD on reducing drug craving in heroin-dependent persons is now under way.^[145]

What to Make of the "Evidence" for CBD Efficacy

Although some clinical evidence supports the use of CBD, critics are accurate in their assessment that the vast majority of compelling empirical literature, at least at present, is derived from the copious body of animal and human cell line studies. As mentioned by several literature reviews, CBD is very promising as therapy in a variety of difficult-to-treat conditions. The available evidence on the efficacy of CBD needs to be considered in conjunction with its exceptional safety profile, which has been well established in clinical trials.

The standard treatments for many conditions have largely been minimally effective or associated with significant safety and tolerability issues that affect adherence. The issue of adherence was well documented in a historical cohort study that found suboptimal adherence to Parkinson disease medications in 67% of patients.^[146] Nonadherence may be even more problematic in the treatment of serious mental illness: A study comparing several antipsychotic medications demonstrated an overall 74% discontinuation rate.^[147] Furthermore, although we cannot yet claim that CBD is the cure for cancer, nonadherence to chemotherapy due to its devastating side effects may result in avoidable mortality.^[148]

Compared with standard treatments for many chronic diseases, the likelihood of problematic side effects or adverse events associated with CBD is small, and discontinuation in clinical studies is uncommon. In addition, given the anxiolysis associated with CBD, its use as an adjuvant therapy may mitigate many common side effects that are actually anxiety responses.

CBD as an Adjuvant Treatment

Unfortunately, data from clinical trials on the utilization of CBD as an adjuvant therapy are scarce. However, in numerous preclinical studies, CBD has been found to have synergistic and additive effects with different treatments.

For example, intranasal CBD administered with glatiramer acetate has been found to improve experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis, thereby potentially offering better treatment.^[149] In one of few studies conducted on cannabidiolic acid (a potent precursor of CBD), its addition to the dopamine antagonist metoclopramide resulted in a further reduction of nausea-induced conditioned gaping, suggesting a potential benefit as an adjuvant to antiemetics.^[150]

The potential of CBD as an adjuvant to antiepileptic drugs was supported in a preclinical study from 1977 in which CBD increased the anticonvulsant effects of phenytoin.^[151] Recently, a seminal study found that CBD in combination with morphine produced a synergistic effect to reduce chemically induced nociceptive pain, suggesting that CBD may have promise as an opioid-sparing agent.^[152]

Perhaps the most exciting potential for CBD as an adjuvant therapy has been in preclinical research on cancer and complications of chemotherapy. A study found that CBD in conjunction with temozolomide produced a strong antitumor response in both temozolomide-sensitive and temozolomide-resistant tumors.^[153] Recently, Ward and colleagues^[154] found that CBD is effective in inhibiting paclitaxel-induced neuropathic pain while producing additive effects to synergistic inhibition of breast cancer cell viability; an earlier study suggested that CBD prevents the development of paclitaxel-induced allodynia.^[155] These findings are important because they suggest that CBD can be effective in preventing chemotherapy-induced peripheral neuropathy, which affects as many as 64% of patients receiving chemotherapy.^[156]

Another recent study found a synergistic effect between CBD and bortezomib in arresting cell-cycle progression and inducing cell death in multiple myeloma cell lines.^[157] Of note, CBD was determined to increase drug uptake of multiple chemotherapeutic agents, potentiating cytotoxic activity in human glioma cells.^[158] Another human cell line experiment determined that CBD enhanced the proapoptotic effects of bicalutamide and docetaxel, two drugs frequently used to treat prostate cancer.^[159] CBD also appears to have a potential role in protecting against chemotherapy-induced cardiotoxicity, with preclinical research indicating that it ameliorates doxorubicin-induced cardiac injury.^[160]

Given these and similar findings in preclinical research, the initiation of clinical trials to evaluate the safety and efficacy of adjuvant CBD in the treatment of patients with cancer is anticipated.

CBD has also been evaluated as an adjuvant treatment for psychiatric conditions. Gomes and colleagues^[161] demonstrated that CBD attenuated catalepsy induced by haloperidol, suggesting its potential as an adjuvant in the treatment of psychotic disorders. Recently, a study demonstrated that dual-step administration of the partial NMDA agonist D-cycloserine and CBD resulted in the disruption of reconsolidation of traumatic memories,^[162] suggesting implications for the treatment of post-traumatic stress disorder. When considered in conjunction with the growing body of clinical studies supporting the efficacy of CBD monotherapy, these preclinical investigations of adjuvant CBD further support the tremendous therapeutic potential of CBD for a wide variety of conditions.

The Dosing Dilemma With CBD

How to dose CBD is a common question among practitioners. Indeed, preclinical and clinical research indicates an extremely wide range of doses that have been used. Although we are far from knowing what doses are ideal, taking into account pharmacogenomic variance among individuals is critical.

Studies often refer to "high-dose" and "low-dose" CBD, although a review of the literature indicates considerable variability in how these are defined. For example, Zhornitsky and Potvin^[103] defined "high-dose" oral CBD as 150-600 mg/day.

In addition to set daily doses, weight-based dosing has also been used. Some investigators have extrapolated findings on weight-based doses from animal studies to humans, which is problematic, as demonstrated by the significant variance in bioavailability among rats and mice.^[163]

Bioavailability also varies greatly depending on route of administration of CBD. Studies have demonstrated bioavailability of the administered dose of 34%-46% for intranasal administration^[164] and 40% for vaporization.^[165] In contrast, the bioavailability of oral CBD is thought to be as low as 6%, owing to significant first-pass metabolism.^[166]

Whereas the bioavailability of oromucosal nabiximols has been found to be over 90%, with rapid onset of action,^[167] the published literature indicates that the bioavailability of oromucosal CBD has not yet been assessed. However, the available data on oromucosal administration of nabiximols have been extrapolated to CBD, with many providers recommending oromucosal administration. Given the absence of evidence supporting oromucosal administration of CBD, there is a clear need for future research to confirm that this is the optimal route of administration.

Cannabinoid medicine is still in its infancy; thus, dosing is not necessarily scientifically based, and confusion is common among healthcare providers. However, unlike marijuana and THC, the risks associated with CBD are extremely low, with not a single case report of CBD overdose in the literature.

Regardless, the dose of CBD should be titrated to effect, emphasizing the adage "start low, go slow." Before the dangers of so-called medical marijuana were understood, experts recommended titrating it to effect.^[168] However, as we have learned more about the dangers of the progressively stronger and more toxic marijuana that is marketed as "medical," this recommendation is inappropriate.

Until we begin to see emergency department visits associated with CBD increase (which, in fact, has been empirically associated with "legalized" marijuana^[169]), titrating doses to effect is probably the most sound strategy. At present, "CBD products are not produced under the guidance of good manufacturing practices (GMP) and are not subject to regulations governing labeling, purity, and reliability. In other words, currently, there is no guarantee of consistency between products, or even differing lots produced by the same manufacturer."^[170]

Some experts recommend that we wait until the US Food and Drug Administration approves CBD and other cannabinoid-based medicines, so that the approved products are subject to standardization and we have better understanding of bioavailability to inform dosing.^[171] Numerous others, however, suggest that the safety data of CBD are so compelling (particularly compared with whole-plant cannabis products) that there is probably little harm in considering it for treatment-resistant conditions.

The Complex Regulatory Issues Surrounding CBD

The legal status of CBD is complex on both a federal and state level. CBD can be extracted from two sources: from *Cannabis sativa* (along with many other phytocannabinoids) or from industrial hemp, which can contain no more than 0.3% THC.^[172] CBD is legal in the 23 states and the District of Columbia where cannabis products are permitted for medical use. In these states, medical authorization is required to purchase CBD, as is the case for all cannabis products. However, finding a CBD product is often extremely challenging in these states, because dispensaries have recognized that their profitability is dependent on their ability to provide consumers with high-THC concentration, euphoria-producing products. Tragically, as CBD mitigates the euphoria associated with THC, dispensaries in states where they are minimally regulated have little interest in selling high-CBD concentration strains, and typically charge more for strains high in THC.

Although its federal legal status is still questionable, the Agriculture Act of 2014 authorizes states to permit hemp cultivation for research purposes, again provided that the THC content is no greater than 0.3% by weight.^[173] Growing industrial hemp has been illegal without a US Drug Enforcement Administration (DEA) permit under the Controlled Substance Act, but it can legally be imported; imports of hemp seeds increased from 92 metric tons in 2005 to 2272 metric tons in 2013.^[174]

Currently, there are 11 states where medical marijuana is not legal, but low-THC (~0.3%–3%)/high-CBD (~5%–15%) concentration cannabinoid products have been legalized for clinical research and treatment. Some of these states restrict the sources of CBD-rich products and specify the diseases for which they can be accessed for treatment, whereas others do not.^[175]

Despite state regulation, CBD has become readily available over the internet, with one website (<http://cannabisoilforsale.net/>) claiming that hemp-based CBD products "are fully legal in all 50 states when sold as nutritional supplements." This claim is based on a unanimous decision by the Ninth Circuit Court of Appeals, which determined that the DEA "cannot regulate naturally-occurring THC not contained within or derived from marijuana, i.e., non-psychoactive hemp is not included in Schedule I. The DEA has no authority to regulate drugs that are not scheduled, and it has not followed procedures required to schedule a substance. The DEA's definition of 'THC' contravenes the unambiguously expressed intent of Congress in the Controlled Substances Act (CSA) and cannot be upheld."^[176]

Irrespective of the ambiguity of the law, hemp-based CBD products are available and being used and probably will become progressively more accepted by patients, healthcare providers, and federal and state governments.

Dispensaries and Medical Marijuana

Medical cannabis products are typically sold in dispensaries, which have become ubiquitous in some areas, such as Denver, Colorado.^[178] Despite their legality, dispensaries may sell few products that are particularly "medical," because the majority of what is sold is the same quality of marijuana sold on the streets and carries the same health risks.^[178]

Questions also have been raised regarding the legitimacy of dispensaries' clientele. A recent study found that most dispensary customers had initiated marijuana use in adolescence, with one half presenting with indications of risky alcohol use and 20% presenting with recent histories of prescription medication or illicit drug abuse.^[179]

Emerging data suggest that dispensaries have deleterious societal effects, such as diversion to adolescents who are treated for substance abuse,^[180] increased adult treatment admissions for

marijuana dependence and alcohol abuse,^[181] and increased unintentional pediatric marijuana exposure.^[182] The current dispensary system results in unlicensed "pharmacists" dispensing marijuana, who are unlikely to inform customers of the dramatic physical and mental health risks associated with marijuana use and lack expertise on potential drug/drug interactions.^[183]

Finally, the THC potency in states with legally protected dispensaries is significantly higher than that in states without dispensaries.^[184] Pacula and Lundberg^[185] convincingly argue that it is not the medical marijuana laws per se, but rather the dispensary systems, that drive down the price of marijuana and lead to increased use in both established and new users.

Research on the THC/CBD ratio of marijuana sold in dispensaries is sorely needed, although at present, there is no evidence that the overwhelming majority of the cannabis sold in dispensaries is in any way, shape, or form "medical." This supports the argument that the dispensary system, as it exists presently, needs to be dismantled. Legislation such as that being proposed by a group of physicians in Florida stipulating that "medical marijuana" should contain a maximum of 5% THC and a minimum of 10% CBD would go a long way toward legitimizing cannabis as "medicine" and dispensary systems.

Recreational and Medical Use: The Need to "Separate Church and State"

Recreational use of marijuana is now legal in four states and will probably increase. Few would argue that the United States has won the "war on drugs" and that incarcerating marijuana users is a sound policy. Although medical cannabinoids have great potential to ameliorate considerable suffering, the data indicate that most of what is considered "medical marijuana" is used for recreational purposes. People using marijuana recreationally may be self-medicating, often for depression.^[186] However, is the same not true for individuals who abuse alcohol? Or prescription opioids?

In some states, such as Washington, it is extremely difficult to find low-THC/high-CBD concentration cannabis products in dispensaries. Of note, and somewhat tragically, many recreational marijuana retailers are advertising low-THC/high-CBD concentration strains, for which they are charging exorbitant prices. The irony is that the dispensaries are profiting by charging higher prices for high-THC/low-CBD concentration strains.

Although the US Department of Justice (DOJ) has postured toward shutting down the dispensary business in the past,^[187] no significant changes have happened since dispensaries first opened. Although the media has sensationalized DEA raids shutting down dispensaries that were allegedly operating illegally, these are very profitable businesses that continue to proliferate, often claiming that they help ameliorate suffering when they may in fact be perpetuating it.^[188]

In 2013, the DOJ issued guidelines clearly defining what types of activities could potentially result in DOJ action.^[189] Furthermore, the passage of the Consolidated and Further Continuing Appropriations Act in 2014 now prohibits the use of federal resources to interfere with individual states' implementation of their own medical marijuana laws.^[190] DEA raids would be expected to decrease as a result of this.

Regardless, a reduction of aggressive DEA behavior does not necessarily suggest that the dispensaries are providing a service to the communities in which they operate, or even to the physically and mentally ill patient populations whom they purportedly serve. At this point, at least in the state of Washington, we are witnessing a transition from legitimate patients seeking "medicine" from

"medical marijuana" dispensaries to seeking low-THC/high-CBD concentration products from recreational marijuana providers.

Summary

Medical cannabinoids are here to stay, but intellectual honesty is imperative if we are moving toward exploiting their potential benefits. Owing to rising THC concentrations of products, "medical" marijuana is rarely good medicine. This review has identified the dangers associated with whole-plant marijuana, whether used for recreational or for supposedly medical purposes.

CBD, on the other hand, has a rich and expanding body of empirical support for safety, and more recently, for clinical efficacy in the treatment of numerous refractory conditions. However, it is premature to consider CBD a panacea for all that ails our patients. With legislative changes, access to CBD for both experimental and clinical use will become progressively less complicated, which should result in the publication of high-quality research of its efficacy and safety.

In addition, ease of access should help us better comprehend such issues as ideal routes of administration and dosing. With the facilitation of access to CBD that we are witnessing, in conjunction with problems associated with medical marijuana dispensary systems, is there any reason to not dismantle the dispensary systems as they currently exist? Recreational marijuana is a completely separate issue, and we owe it to our patients—as well as to society as a whole—to make sure that these entities are not joined. Only such a "separation of church and state" will result in unlocking of some of the mysteries surrounding medical cannabinoids, thereby allowing us to increase our treatment armamentaria.

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