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Review Article

Clinical uses of cannabis and cannabinoids in the United States

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ABSTRACT

The role of cannabis in medicine is rapidly evolving. Medical cannabis is now legal in a majority of states, and THC and CBD, the prominent cannabinoids found in cannabis, have both been utilized in the development of FDA-approved drugs. Due to the complicated legal status of cannabis and cannabinoids, as well as regulations that vary from state to state, the appropriate use of these substances for both patients as well as clinicians is often unclear. Advancements in the understanding of the pharmacology of cannabis have led to numerous proposed uses of these drugs, including as antidepressant or analgesic agents. However, clinical trial data for these substances suggests that many purported indications of cannabis and cannabinoids are not supported by good clinical data. Furthermore, cannabis and several cannabinoid-based medications have potentially concerning side effect profiles that may limit their use in certain patient populations. As the legal status and clinical database of these medications continue to evolve, physicians will need to continue to balance the real potential of these compounds with their limitations and adverse effects.

1. Introduction

Though the role of cannabis in society has evolved over several millennia, it may be going through its most rapid period of change to date. In 1996, California became the first state to legalize the use of cannabis with the approval of a physician, known widely as “medical marijuana.” As of January 2020, 33 states and the District of Columbia have legalized the use of cannabis for medical purposes, and 12 states and DC have gone a step further to legalize the recreational use of cannabis [1].

In addition to the sociocultural, legal, and economic impacts of these legislative changes, the widespread expansion of cannabis and cannabis-related products has had a marked impact on the medical field. Recently, cannabis has been perceived as being safer and use of the drug has increased [2]. Approximately 10% of cannabis users in the United States use the drug to treat a medical condition [3]. Cannabis now occupies a unique position as both a schedule I narcotic (indicating that there are no acknowledged medical uses of the drug), as well as a substance with various purported health benefits (such as antidepressant, hypnotic, and analgesic effects) that clinicians may indirectly offer to patients through certification.

Further complicating the picture, the Food and Drug Administration (FDA) has approved three medications based on compounds contained in cannabis for various indications [4]. Additionally, CBD (cannabidiol; a cannabinoid found in cannabis) is now widely available in non-medical settings, such as coffee shops and tobacco stores, in several US states. CBD has been advertised to treat a wide array of medical conditions, and sales of CBD-related products continue to grow rapidly [5].

These rapid changes are not unique to the United States. The majority of European Union member-states have authorized the use of cannabis-derived medications [6]. However, laws can vary widely between nations with respect to legal status and insurance coverage [7,8]. Furthermore, even within countries there can be gaps between the legal status of a drug and its actual availability to patients [6].

These developments present a unique challenge to physicians. Clinicians now face the dual task of avoiding harms related to the most widely-abused drug in the United States [2], as well as identifying appropriate and evidenced-based indications for the use of cannabis or cannabis-related products. This is further complicated by patients often receiving misinformation from parties with vested interests in the debate over these substances. State-level regulations provide little clarity as there are over 50 medical conditions that various states list as appropriate indications for cannabis despite little evidence to support such prescribing practices [9].

This review will attempt to clarify the science behind the use of cannabis and cannabis-related drugs, and provide guidance for the clinician attempting to safely balance the risks and benefits that these drugs carry.

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This manuscript primarily focuses on recent developments in the appropriate use of cannabis and cannabinoid-based medications. Relevant studies were identified by reviewing the available medical literature in PubMed for between 1948 and October 2019 pertaining to the medical use of cannabis and cannabinoids, with a focus on meta-analyses and randomized clinical trials.

2. Pharmacology

Cannabis comes from the *Cannabis sativa* plant and contains over 140 pharmacologically-active cannabinoids [10]. The two most prominently-studied cannabinoids, as well as the two thought to be most pharmacologically-relevant compounds are delta-9-tetrahydrocannabinol (THC) and CBD. THC and CBD share several pharmacologic properties, such as poor bioavailability and high lipophilicity [11]. However, the receptor profile of these compounds differs markedly, and their divergent physiologic effects are explained in large part by their interaction (or lack thereof) with the endocannabinoid system.

Endocannabinoid receptors are G-protein-coupled receptors that interact with endogenous cannabinoids (*endocannabinoids*) [12]. These receptors, named CB1 and CB2, are differentially found primarily in the basal ganglia, hippocampus, cerebellum, cerebral cortex, and peripheral nervous system (CB1), or on cells in the immune system (CB2) [13]. These receptors have effects on multiple downstream neurotransmitters including serotonin, acetylcholine, dopamine, glutamate, and GABA, as well as NMDA and opioid receptor systems [14].

THC is a partial agonist at both CB1 and CB2 receptors [15]. THC is thought to be predominantly responsible for the psychotropic effects of cannabis, and agonism at the CB1 receptor is the likely mechanism for its pro-psychotic and euphoric effects [15]. In addition to psychiatric properties, some evidence suggests that THC may also have analgesic and anti-inflammatory properties [12]. Notably, the concentration of THC in *Cannabis sativa* has been increasing over time (4% in 1995 to 12% in 2014) [16].

In contrast, CBD is a CB1 antagonist and CB2 negative allosteric modulator, and generally has a low level of activity at these receptors compared to THC [17]. The contrary receptor profiles of THC and CBD have been found to correspond to opposing functional MRI blood oxygenation signatures in several basal ganglia and cortical areas during cognitive tasks [18]. This same study also found that pretreatment with CBD ameliorated THC-induced psychotic symptoms, further suggesting that the THC-based agonism of CB1 is counteracted by the negative allosteric of CBD at this receptor.

In addition to cannabinoid receptor-dependent properties (such as possible anti-inflammatory effects from CB2 negative allosteric modulation), CBD has many cannabinoid receptor-independent properties. CBD is also a capsaicin analog and agonist at the TRPV1 receptor [17]. Furthermore, CBD has agonist properties at the 5HT1A receptor, which are thought to perhaps facilitate the anxiolytic properties of CBD [19]. Lastly, CBD has physiologic properties that are not yet clearly related to a specific mechanism, such as antioxidant, anticonvulsant, analgesic, and immunomodulatory functions [20].

Given that CBD and THC, the predominant cannabinoids found in cannabis, display distinct and often opposite physiologic properties, it should not be surprising that the two have very different therapeutic indications and adverse effect profiles (Table 1). For this reason, cannabis and medications containing THC are discussed separately from medications containing only CBD.

3. Cannabis and THC analogs

3.1. Indications

Estimates suggest that over two million Americans utilize cannabis for medical purposes [30]. There are many proposed medical uses of cannabis; internationally, the most uses include post-injury pain, depression, sleep disorders, multiple sclerosis (MS), and back pain [15]. This represents only a small fraction of suggested medical benefits of cannabis. Several of these indications are supported by good scientific evidence, but many are not.

Despite its medicalization and legalization, cannabis remains a schedule I narcotic. Medical cannabis is, therefore, not prescribed by physicians, but rather obtained at dispensaries after a physician has licensed its use for a given indication. Notably, medical cannabis is not a “special” or even standardized form of cannabis, meaning that the THC and CBD content of cannabis obtained for a medical indication is completely unstandardized [13]. In other words, medical cannabis and recreational cannabis are not meaningfully distinct terms from a pharmacologic perspective.

State rules on medical cannabis vary widely and include indications with high-quality as well as low-quality evidence. Indications range from post-traumatic stress disorder to hepatitis C, and states also differ on the quantity of cannabis that patients may have at a given time [13]. The best evidence exists for the role of cannabis in alleviating pain and spasticity due to MS. A 2018 meta-analysis examined 17 randomized clinical trials (RCTs) of both cannabis in standardized dosages and relative THC:CBD ratios as well as cannabinoid-based medications for this use [31]. Totaling over 3000 patients, aggregate data showed modest, though statistically significant, positive effects on pain, spasticity, and bladder dysfunction. In 2014, the American Academy of Neurology published a set of specialty guidelines that identified nabiximols, a combination THC-CBD medication, as having the highest level of empirical evidence for the treatment of pain and spasticity associated with MS [26]. Notably, nabiximols (trade name Sativex®) is available in many European countries for the treatment of neuropathic pain due to MS, though is not approved in the US [32].

In addition to medical cannabis, there are two FDA medications that act as THC analogs. Nabilone (trade name Cesamet®; [23]) and dronabinol (trade name Syndros® or Marinol®; [22]) have both received FDA approval for chemotherapy-induced nausea and vomiting, as well as cachexia related to HIV or cancer. Though neither medication is typically believed to be a first line option, society guidelines now identify these agents as reasonable for symptoms refractory to first-line agents [21].

Beyond these indications, the evidence for the use of cannabis or THC-based cannabinoids ranges from equivocal to very weak [13]. One oft-cited indication is chronic pain. Theoretically, given that endocannabinoids modulate pain and CB1 receptors are present in nociceptors on peripheral nerves, cannabis appears to be promising analgesic [33]. However, a 2017 meta-analysis of 27 studies examining the effectiveness of cannabis in treating chronic pain found only weak evidence that cannabis alleviates neuropathic pain, and no evidence suggesting that cannabis was useful in other types of pain [34]. Another meta-analysis specifically examining the use of cannabis to treat non-cancer related chronic pain found that the number needed to treat to achieve a 50% reduction in pain was 24, whereas the number needed to harm for any adverse effect of cannabis was only 6, suggesting that the benefits of cannabis use were outweighed by possible harms [35]. One theory posits that the therapeutic window for the analgesic properties of cannabis is relatively narrow [33]. It should be noted, however, that some professional organizations have been more receptive to the use of cannabis as an analgesic—in their 2017 report on cannabis, the National Academies of Sciences, Engineering, and Medicine found a clinically significant (albeit modest) effect of cannabis and cannabinoids on chronic pain [[28]].

Many states identify glaucoma as an approved condition for medical cannabis [13]. However, while there is some evidence for cannabis use leading to a decrease in intraocular pressure, this effect is quite ephemeral, lasting only three to 4 h [36]. The American Academy of Ophthalmology released a position statement in 2014 stating that the risks associated with chronic use of cannabis outweighed the benefits, and thus they did not recommend the use of cannabis for glaucoma

Table 1
Summary of the pharmacologic, legal, and clinical differences between THC and CBD.

	THC	CBD
Receptor profile and notable physiologic properties	Partial agonist at CB1 and CB2 receptors. Noted to have anti-inflammatory, analgesic, psychotomimetic, and euphoric properties.	CB1 antagonist, CB2 negative allosteric modulator, capsaicin analog, TRPV1 agonist. 5HT1A agonist. Noted to have anti-inflammatory, immunomodulatory, antioxidant, anticonvulsant, analgesic effects.
Legal status in the United States	THC (and thus cannabis) is still considered a schedule I substance in that it has no officially recognized medical use. Specific laws vary from state to state with respect to medical or recreational usage.	CBD without THC is available without a license or prescription and can easily be obtained at grocery stores, restaurants, and other non-medical businesses.
Pharmaceuticals based on active ingredient and FDA indication	Nabilone (Cesamet®) and dronabinol (Syndros®, Marinol®); chemotherapy-induced nausea and vomiting [21–23], cachexia related to HIV or cancer [22].	Epidiolex®; seizures associated with Dravet or Lennox-Gastaut syndromes [24,25].
Investigational uses supported by high-quality clinical evidence	Pain and spasticity related to MS [26,27], possibly other forms of chronic pain [28].	Other types of treatment-resistant epilepsy [29].
Notable adverse effects associated with use	Acutely, tachycardia, euphoria, impaired judgment and concentration, psychosis. Chronically, chronic bronchitis (if smoked), risk of abuse and dependence, possibly an increased risk of developing a chronic psychotic or depressive disorder, lower IQ.	Acutely, somnolence, diarrhea, fatigue, and anorexia. May inhibit CYP450 isozymes. No known chronic adverse effects. Generally well-tolerated.

5HT1A, serotonin 1A receptor; CB1, cannabinoid receptor type 1; CB2, cannabinoid receptor type 2; CBD, cannabidiol; CYP450, cytochrome P450; HIV, human immunodeficiency virus; IQ, intelligence quotient; MS, multiple sclerosis; THC, delta-9-tetrahydrocannabinol; TRPV1, transient receptor potential cation channel subfamily V member 1.

[36].

A comprehensive 2015 systematic review and meta-analysis that examined 79 RCTs and a total of 6462 for a variety of physical and mental health conditions well demonstrates many of the challenges of making clear recommendations for the medical use of cannabis and cannabinoids [27]. Notably, only 4 of these RCTs were judged as having a low risk of bias. Many of the included RCTs suffered from small sample size, inadequate randomization and blinding, and other methodological issues. The small sample sizes are particularly challenging as the use of cannabis in treating several indications (such as pain and spasticity) showed some possible benefit that did not reach statistical significance. Furthermore, heterogeneity in specific pharmacologic agent, dose, and route of administration complicates straightforward comparison and data aggregation. Ultimately, the study found moderate-quality evidence of cannabinoids for neuropathic and cancer pain as well as spasticity in MS, and low-quality evidence for other conditions (including nausea and vomiting due to chemotherapy, sleep disorders, and several mental health conditions).

Similarly, a 2019 systematic review and meta-analysis specifically sought to evaluate the evidence for cannabis and cannabinoids in treating mental health conditions such as depression, anxiety, post-traumatic stress disorder (PTSD), psychosis, and attention-deficit hyperactivity disorder (ADHD) [37]. This study also noted a lack of high-quality randomized clinical trials, small sample sizes, and the difficulty of standardizing across studies. The meta-analysis found only very low-quality evidence for the use of cannabinoids in treating anxiety disorders in patients with other medical conditions, and no evidence for the other indications studied. The authors succinctly summarized their findings in concluding their study: “In light of the paucity of evidence and absence of good quality evidence, and the known risk of cannabinoids, the use of cannabinoids as treatments for mental disorders cannot be justified at this time” [37].

The largely negative results seen in trials of using cannabis to treat a variety of conditions likely reflects a number of challenges in adapting cannabis for medical usage. First, as mentioned previously, medical cannabis is simply recreational cannabis that has been licensed by a physician for a given use. This means that two patients using medical cannabis may be utilizing very different drugs depending on the THC and CBD content of their two marijuana strains [39]. Although advertisers have attempted to capitalize by marketing certain strains as being specially formulated for different causes, this approach is not backed by hard science [13]. Furthermore, dosing is also complicated by the inexactitudes of prescribing a given amount of cannabis. If, for example, cannabis does have a narrow therapeutic range as an analgesic, clinicians may be at a loss as to pick the appropriate dose not knowing how this corresponds to a quantity of the active cannabinoid of interest.

All the above raises the question of how a clinician can responsibly assess a patient for medical cannabis [13]. Clinicians should use a standardized approach to identify patients that are more likely than not to benefit from such treatment and unlikely to experience serious adverse effects. First, such patients should be identified as having a condition where there is high-quality evidence that cannabis or cannabis-based medications have been found to be useful. Additionally, the treatment history should be investigated to see if patients have first undergone adequate trials of FDA-approved medications for these conditions. Clinicians should complete a thorough medical and psychiatric evaluation to identify risk factors that may place patients at greater risk of adverse effects (such as psychotic or substance use disorders; see ‘Adverse Effects’ below). If after an interview and history the physician determines that a patient may benefit from cannabis, they should then discuss the scientific evidence that does or does not support the usefulness of these substances. Beyond medical decision-making, physicians should also discuss legal and logistical concerns with using cannabis, including that it is not available at pharmacies (needs to be obtained at dispensaries), and is rarely covered by insurance (though FDA-approved cannabinoids often are). Lastly, patients who use medical cannabis can also face challenges when they are hospitalized. While rules vary by state and across different healthcare systems, many forbid the use of cannabis while inside hospitals [39]. After collectively deciding to initiate treatment with cannabis or a cannabinoid, close follow-up is strongly recommended.

3.2. Adverse effects

Cannabis use is increasingly seen as being relatively harmless [2]. Cannabis and cannabinoid medications containing THC are discussed together here as the adverse effects of cannabis are similar to those of THC alone, and THC is thought to be responsible for the majority of the adverse effects of cannabis [15]. Notably, the effects of cannabis are not limited to the individual directly smoking the drug—second-hand cannabis smoke can produce effects even with second-hand ingestion [40].

Short-term effects of cannabis use include tachycardia, hypotension, xerostomia, xerophthalmia, euphoria, as well as impaired attention, coordination, and judgment [12,15,41]. Notably, respiratory depression, a major overdose concern with the use of opioids or benzodiazepines, is not an effect of cannabis use as CB1 receptors are not located in the midbrain [12]. Furthermore, there is virtually no risk of lethal overdose with cannabis, as even regular heavy users of cannabis use consume doses of THC that are orders of magnitude smaller than the

theorized lethal dose of approximately 4 g for a 70 kg human [15]. However, cannabis may indirectly have acute lethal effects, as it has been found to double the risk of motor vehicle accidents [42]. At higher doses, cannabis use may also result in psychosis and paranoia [41].

At lower doses the acute side effects of cannabis use may be relatively mild, but chronic adverse effects can be more pronounced. These adverse effects may be conceptually broken into neuropsychiatric and systemic side effects.

Chronic cannabis usage puts patients at risk of multiple neuropsychiatric conditions. Cannabis use has been associated with both depression and anxiety [43]. It has long been known that cannabis use can not only lead to a brief psychotic episode, but may also increase the risk of developing schizophrenia. Current estimates suggest that the risk of schizophrenia in chronic cannabis users is approximately double that of the rest of the population, though the causality of the relationship between cannabis use and the development of psychotic disorders remains controversial [15,44].

Cannabis exposure can be especially detrimental to brains still undergoing development. Prenatal and adolescent exposure to THC can lead to impaired neural connectivity [45]. Some of this impaired neural connectivity has been found to occur in the hippocampus, potentially explaining an association between adolescent cannabis use and decreased IQ [41]. Some preclinical research has suggested, however, that detrimental developmental effects from cannabis smoking may instead be related to non-cannabinoid contaminants [46].

Cannabis is an abusable substance. Given evidence of physiologic dependence and tolerance, as well as documented withdrawal syndromes (occurring in up to 1/3 of chronic users), the 5th Edition of the Diagnostic and Statistical Manual recognizes the diagnosis of cannabis use disorder (CUD) [47]. Among users of cannabis, estimates are that approximately 10% meet criteria for CUD [15]. Concerningly, cannabis abuse is a predictor for future abuse of illicit drugs [41]. As with other consequences of cannabis use, risks associated with CUD are most pronounced in adolescent patients. This may be because in adolescence the endocannabinoid and mesolimbic reward systems, which are affected by cannabis use, continue to actively development until approximately age 21 [41,48,49].

Finally, multiple organ systems outside the central nervous system can be affected by chronic cannabis use. Chronic smokers of cannabis are at increased risk for developing chronic bronchitis, cannabis use mildly increases the risk of myocardial infarction, and there is a moderately increased risk of testicular cancer [15].

4. CBD

4.1. Indications

Preliminary studies of CBD have identified several therapeutically useful properties of the chemical, including anti-inflammatory, antioxidant, antiapoptotic, neuroprotective, analgesic, oncolytic, and immunomodulatory effects [17]. Despite this, there is only one currently FDA-approved CBD-based product, Epidiolex® [50]. Epidiolex® has been approved by the FDA to treat two rare conditions: drug-resistant seizures due to either Dravet syndrome or Lennox-Gastaut syndrome (LGS), or as an add-on therapy for LGS [24,25,51].

Beyond these, CBD has no current FDA-approved uses, though both preclinical and clinical evidence point to possible future uses of the drug. One area of intense interest is the use of CBD to treat psychosis. Preclinical data supports the possible use of CBD to counteract psychogenic properties of THC [18]. Additionally, a 2018 neuroimaging study examining patients at high risk of psychosis showed that CBD normalized fMRI signatures in regions associated with psychosis [52]. Other preclinical work has suggested several mechanisms through which CBD may exert anti-psychotic properties, including antagonism of CB1 receptors, modulation of dopamine signaling, and decreasing neuroinflammation [53,54]. Follow-up RCTs examining the effectiveness of CBD in psychotic disorders has shown mixed results [54]. A 2012 double-blind RCT reported that CBD was as effective as amisulpride, an antipsychotic commonly used to treat schizophrenia, in treating both positive and negative symptoms of schizophrenia and had fewer associated side effects, including extrapyramidal symptoms, hyperprolactinemia, and weight gain [55]. Another RCT comparing CBD with placebo showed a significant improvement in positive symptoms without any difference in adverse effect reporting compared to placebo [56]. However, a 2018 RCT comparing CBD to placebo did not show any significant change in positive or cognitive symptoms [57]. A review of available studies suggests that the opposing effects seen in these studies could be related to dosing of CBD (timing and quantity) as well as the stage of schizophrenia being studied [54]. Therefore, while preliminary evidence has suggested a possible role for CBD as an antipsychotic, the specifics of how—and in whom—the drug should be used are still unclear.

CBD has been tested in mental illness other than schizophrenia as well. It has been found to decrease reported anxiety in patients with social phobia when subjects were exposed to a simulated public speaking exercise [58]. Another study examining patients with social anxiety disorder found that CBD ameliorated symptoms of anxiety and these symptomatic changes corresponded to altered cerebral blood flow on SPECT imaging in anxiety-associated limbic and paralimbic areas [59]. Lastly, some case reports have found that CBD may be useful in treating cannabis withdrawal, though evidence for using CBD for CUD itself is mixed [54].

Beyond utilizing CBD for psychiatric conditions, researchers have also attempted to leverage the neuroprotective effects of CBD in neurodegenerative diseases. In Alzheimer's Disease, promising results have been found in preclinical studies showing CBD promoting neuronal survival and decreasing neuroinflammation, though clinical evidence is lacking at this time [17]. For Parkinson's Disease (PD), clinical studies thus far have shown that CBD may be useful for improving overall well-being and treatment of comorbid psychiatric symptoms [17]. One study of PD patients taking CBD in addition to dopamine-replacement therapy showed a decreased in psychotic symptoms as well as overall decreased in psychiatric symptomatology [60]. Treatment of PD patients with CBD has also been found to reduce the frequency of aggressive behaviors [61]. Notably, however, a double-blind study investigating the effect of CBD on motor symptom severity in PD patients did not show any effect [62]. Similarly, a randomized crossover of patients with Huntington Disease did not show any benefit of CBD in reducing chorea severity [63].

The broad set of potentially beneficial properties of CBD have also led researchers to examine its effects outside the central nervous system. Despite efficacy in a mouse model of inflammatory bowel disease (IBD), a randomized controlled trial examining the effect of CBD in IBD patients did not identify any change in disease severity [64]. However, a phase II clinical trial investigating the use of adjunctive CBD to prevent graft-versus-host disease (GVHD) found CBD may be a useful adjunctive medication to standard immunosuppressive therapies [65].

In sum, evidence suggests that CBD may prove to be a valid therapeutic option for several conditions, though many areas thought to be particularly promising have shown mixed results, emphasizing that further research will need to investigate the therapeutic effects of CBD in rigorous clinical studies.

4.2. Adverse effects

As opposed to THC, which may cause several acute and chronic adverse effects, CBD is notable for having a comparably good safety profile. Most notably, as CBD does not agonize CB1 receptors, it is devoid of the psychotropic side effects associated with THC [17]. Reported short-term side effects of CBD use include somnolence, diarrhea, fatigue, and anorexia [15]. Additionally, there is evidence from animal

studies that CBD may inhibit several cytochrome P450 proteins, raising a possible concern for patients on medications dependent on hepatic metabolism [66–68]. Evidence suggests that CBD, through interactions with the 3A4 and 2C19 P450 isozymes, increases blood levels of clobazam, and has been found to alter blood levels of several other antiepileptics [20,69]. Given that CBD also has been found to interact with the p-glycoprotein drug transporters, it is very possible that other, currently unknown drug interactions exist [20]. Lastly, one notable indirect adverse effect from a public health perspective is that off-label use of CBD may preclude patients receiving evidence-based treatments.

Notably, studies examining the abuse potential of CBD have not identified any evidence of tolerance or physical dependence [15]. Indeed, some have even suggested that CBD's ability to therapeutically modulate dopaminergic neurotransmission in the mesolimbic pathway supports its role as a treatment for other substance use disorders [70]. Due to these findings, a World Health Organization report recommended that CBD not be labeled as a scheduled substance [15].

5. Conclusion

The medicalization of cannabis and cannabinoids presents several opportunities as well as challenges for medical professionals. From the perspective of researchers, studying cannabis is complicated by inadequate blinding, limited funding, charged political views, stigma, complicated legal status, and lack of standardization [38,71]. Clinicians attempting to safely use these substances for their patients encounter many of these issues as well as misinformed patients and an ever-evolving base of literature pointing to possible therapeutic indications. To sort through these possible indications, however, physicians and researchers should both expect the gold standard of randomized, double-blind, placebo-controlled clinical trials.

Whether under medical guidance or self-prescribed, patients will continue use these substances. In either case, physicians will need to be prepared to educate patients regarding the risks and benefits of these compounds. As the use and ubiquity of these substances continues to grow, the need to distinguish between high-quality clinical evidence, potentially promising preclinical data, and mere conjecture will only grow more important.

In the meantime, clinicians are best served by adhering to FDA-approved indications for CBD- and THC-based medications and restricting the use of medical cannabis to those few conditions supported by robust clinical data (such as pain or spasticity related to MS and possibly other forms of chronic pain). All patients being considered for these medications should undergo a thorough and complete medical and psychiatric evaluation to identify possible contraindications and should be followed if a cannabinoid-based medication is started.

Declarations of Competing Interest

None.

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