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Cannabidiol oil has purported health benefits, including helping to relieve chronic pain.

DRUG REGULATION

From menace to medicine

Cannabidiol could offer an effective treatment for a variety of conditions. But the substance's uncertain legal status is stalling serious investigation.

BY MICHAEL EISENSTEIN

Cannabidiol (CBD) is an illegal drug with no redeeming value. It is also a useful prescription medicine for epilepsy, with considerable potential for treating numerous other conditions. And it is a natural dietary supplement or 'nutraceutical' with countless evangelists in the health and wellness community. Although contradictory, all three statements are true from different perspectives, and clinical researchers are frustrated.

"In New York City, you can go to a latte shop and get a CBD product, but if I want to do a clinical trial, I've got to get a 2,000-pound safe and go through six months of paperwork and licensing," says Orrin Devinsky, director of the NYU Langone Comprehensive Epilepsy Center in New York City. Like the cannabis plant from which it is derived, CBD, a type of cannabinoid, is classified by the US Drug Enforcement Administration in the same way as are heroin and lysergic acid diethylamide (LSD) — schedule 1 substances with "high potential for abuse" and "no currently accepted medical use".

This flies in the face of current evidence. Numerous studies have shown that CBD is a safe and non-habit-forming substance that does not produce the 'high' associated with tetrahydrocannabinol (THC), the main psychoactive component of cannabis[1]. In 2018, the US Food and Drug Administration (FDA) determined that Epidiolex — a purified CBD product developed by GW Pharmaceuticals in Histon, UK — effectively reduces the frequency of seizures in certain rare forms of paediatric epilepsy. This approval has heartened the cannabinoid research community, which has long recognized the medicinal potential of CBD but come up against scepticism and regulatory constraints on the road to the clinic.

But at the same time, the many manufacturers that promote CBD-laden oils, lotions and foods as a panacea for various health issues, often with minimal regard for local laws or medical evidence, are putting CBD's medical advocates in an uncomfortable position. "I get calls and e-mails all the time — not just from families, but from physicians who have no clue how to address the requests they get from patients," says Yasmin Hurd, director of the Addiction Institute of Mount Sinai in New York City. "It's a real problem."

STUCK IN THE WEEDS

The breakthrough approval of Epidiolex was driven by strong investment from GW Pharmaceuticals, as well as vigorous advocacy from families of children with epilepsy who had heard tantalizing anecdotes about CBD's effects from jurisdictions in which medical cannabis is legal. "About eight years ago, a patient's father said he was hearing stories about families in Colorado and California who use high-CBD strains for their kids' epilepsy," says Devinsky. "He asked me to do a trial." As a medical student, he had been taught the history of medicinal cannabis, including well-documented uses of the plant by nineteenth-century physicians to treat seizures. Indeed, cannabis has been part of the clinical armamentarium for epilepsy for more than 4,000 years.

Research on CBD in the 1970s and 1980s focused on its interplay with other cannabinoids, and particularly THC. "Whereas THC can induce psychotic symptoms, impair cognition and make people anxious, CBD appears to do the opposite," says Philip McGuire, a psychiatrist at King's College London.

The first clues that CBD might suppress epileptic episodes came from a small clinical trial[2] in 1980. It was led by Raphael Mechoulam, a chemist at the Hebrew University of Jerusalem, whose work on the synthesis and biochemical characterization of cannabinoids in the 1970s had led researchers to begin to explore the medicinal properties of CBD. A number of other trials that explored the compound's pharmaceutical properties followed, although scientists conducting early forays into CBD clinical research faced an uphill battle. F. Markus Leweke, a psychiatrist who specializes in mental illness at Sydney Medical School, Australia, recalls struggling for seven years to publish findings from a randomized controlled trial that demonstrated that CBD might offer an effective treatment for psychotic symptoms in schizophrenia[3]. "We got about 15 rejection letters," says Leweke. "And this is a paper that has since been cited almost 500 times."

Forty years on from Mechoulam's initial work, extensive randomized controlled trials have decisively shown that this purified cannabinoid can profoundly benefit children with certain epileptic disorders. "Over those

trials, we saw about a 26–28% reduction in frequency over placebo in all convulsive seizures for Dravet syndrome and drop seizures for Lennox–Gastaut syndrome," says Devinsky, who has led several such studies[4,5]. "Some of the patients became, and remain, seizure-free."

Preclinical data from rodent and cell-culture studies have hinted at the possible benefits of using CBD to help treat disorders that range from Parkinson's disease to chronic pain. The range of conditions in which CBD is being tested might seem diverse, but it is a compound with far-reaching, if poorly understood, physiological effects. Antonio Zuardi, a psychiatrist at the University of São Paulo in Brazil, notes that something on the order of 20 possible mechanisms of action have been described to date for CBD. "These multiple pharmacological effects may justify the wide range of possible therapeutic activities."

The mechanism of CBD's action on cannabinoid receptors, at least, is well understood. CBD can bind to the cannabinoid receptor CB_1, which is the same receptor that THC seeks out in the brain. Unlike THC, however, CBD restrains rather than activates CB_1 signalling, and therefore doesn't induce the psychoactive effects of its cannabinoid cousin.

But CBD wears many hats. It seems to mediate its antiepileptic effects by binding to a protein called GPR55, which can otherwise trigger the onset of seizures by promoting the hyperactivation of neurons[6]. In addition, CBD acts on receptors that mediate pain signalling and inflammation, as well as at least one receptor for the neurotransmitter serotonin, 5-HT_{1A}[7]. Gabriella Gobbi, a psychiatrist and neuroscientist at McGill University in Montreal, Canada, has found that CBD's physiological effect on the brain resembles that of selective serotonin reuptake inhibitor (SSRI) drugs[8], which are used to treat clinical depression. "After a few days, you get this desensitization of 5-HT_{1A}, like you would with an SSRI, and increased serotonin signalling," she says. Further experiments in rats failed to capture an antidepressant effect, but her team found that CBD-mediated modulation of 5-HT_{1A} could relieve neuropathic pain in the animals.

MULTITASKING MOLECULE

Beyond epilepsy, clinical data to support the medicinal benefits of CBD are more limited, mainly due to the small scale and inconsistent design of trials. "We have very few double-blind, randomized placebo-controlled trials," says Gobbi. But exciting progress is being made towards treating several conditions.

Psychosis — particularly in the context of schizophrenia — is one such area of promise. In 1995, Zuardi and Mechoulam reported the case of a person with schizophrenia who experienced meaningful relief from their symptoms when treated with high doses of CBD[9]. Several subsequent small-scale clinical studies detected similar hints of efficacy. In their groundbreaking trial[3], Leweke and his colleagues put the compound through a particularly rigorous test by comparing its effects with those of amisulpride, a potent medication for schizophrenia. "We saw a significant decrease in symptoms over time for both compounds, and CBD beat amisulpride in terms of side effects, by far," Leweke says. The team also found a clue to the mechanism by which CBD might exert its antipsychotic effects: treatment with CBD was associated with elevated levels of anandamide, a cannabinoid produced by the body that seems to offer protection from psychosis.

McGuire and his colleagues conducted a randomized controlled trial that showed that CBD can have an additive effect when used with conventional antipsychotic drugs[10]. Together, they were better able to control symptoms such as hallucinations and delusions than could conventional medication alone. His team has received funding for a large, international trial to test whether CBD can be developed as a licensed medicine for treating psychosis.

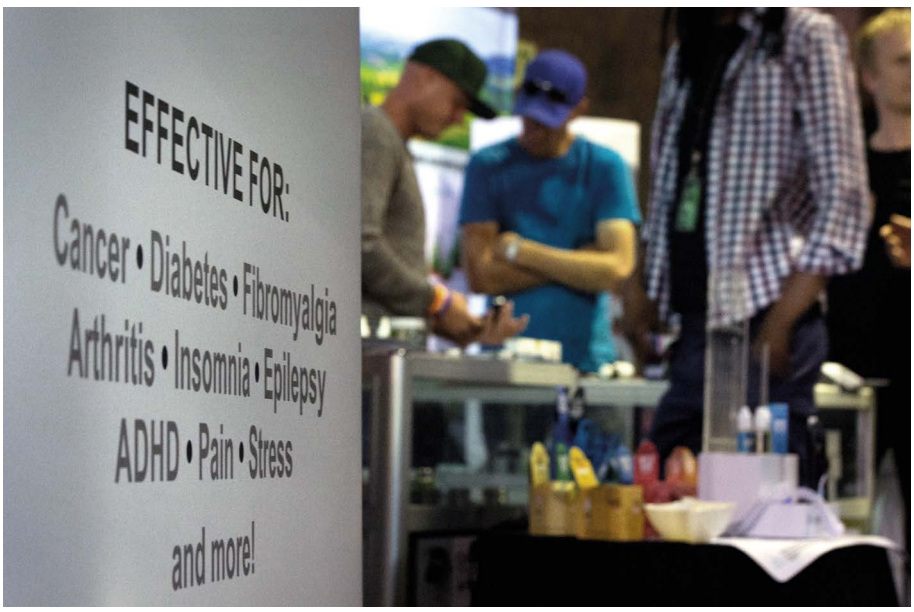
"We have very few double-blind, randomized placebo-controlled trials."

Anxiety disorders are another mental-health condition that CBD has been shown to help alleviate. Zuardi and his colleagues used a test that simulates speaking in public to show that pretreatment with a single dose of CBD can reduce the associated discomfort in people with social anxiety disorder[11]. A similar effect has been observed in healthy people in anxiety-inducing situations[12], and several researchers are exploring CBD as a means of soothing social stress in people with autism spectrum disorder. Devinsky notes that many of his patients with epilepsy have also been diagnosed with autism spectrum disorder, and he is involved in two clinical trials that aim to test whether CBD can meaningfully reduce the irritability and anxiety of those with autism. "Many parents wanted to keep their children on it even if the seizures didn't improve, because they're calmer and sleeping better," he says.

And although cannabis been demonized as a gateway to more dangerous substances, Hurd has found that it might actually contain an effective antidote for potentially deadly addictions. After observing that rats with a heroin addiction were less likely to seek out the opioid when treated with CBD, she began to investigate whether CBD might have the same effect on people with an opioid dependency. On the basis of an encouraging pilot study, Hurd and her team conducted a randomized controlled trial in 42 abstinent heroin users, who had avoided taking the drug for up to three months after years of routine or heavy use[13]. The researchers then exposed the participants to drug paraphernalia and videos that showed heroin use — cues that normally provoke strong cravings in people with a dependency — and then measured participant-reported responses and physiological indicators of stress and anxiety. "Cue-induced craving is associated with increased cortisol levels and increased heart-rate, and CBD reduced those," she says. Participants receiving CBD also reported lower levels of drug craving and anxiety relative to placebo group, and Hurd notes that the beneficial effects persisted for a week after the final administration of CBD.

A DIFFICULT DELIVERY

Despite its promise, CBD's impact as a drug has been mixed. Importantly, it is relatively safe. The side effects most commonly associated with a high dose of Epidiolex include digestive problems, rash and drowsiness, as well as the potential for liver damage in patients taking certain other medications. For example, Devinsky notes that patients who are receiving valproic acid to treat seizures or migraines might be at



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Claims about the health benefits of cannabis are often overstated and lack supporting evidence.

ERIK S. LESSER/EPA/SHUTTERSTOCK

Campaigners show support for legalizing cannabis for medical use in Atlanta, Georgia.

an elevated risk. But in many of the CBD trials conducted so far — particularly in the realm of antipsychotic drugs, which are known for their strong side effects — CBD has proved more tolerable than existing alternatives. "The side effects weren't significantly worse than with placebo," says McGuire of his 2018 study of CBD in people with schizophrenia[10].

This is important because people typically require large doses of the drug to experience a clinical benefit — in many studies, the doses used are as high as 1 gram or more. This is because CBD is poorly absorbed by the body, with most of every dose being excreted before it can take effect. "If you take it orally, the bioavailability is in the range of 4–6%, which is terrible," says Devinsky. "If you take it after a fatty meal, you can get that up to 16–20%." Zuardi notes that his group routinely observes a bell-shaped dose–response curve for CBD. For example, whereas 300 milligrams of CBD might reduce a person's anxiety, the same person might not get any relief from a dose of either 100 milligrams or 900 milligrams. To complicate matters further, this sweet spot for CBD dosing can differ not only between symptoms, but also between patients.

This is one of several reasons why researchers caution against self-medication with CBD products targeted at consumers. CBD is available in shops worldwide, but the legality of such sales varies widely. In Canada, selling cannabis and its derivatives is legal, whereas the European Union authorizes the sale of CBD derived from hemp (low-THC varieties of cannabis) but not from marijuana (high-THC cannabis). In the United States, the latest Farm Bill, which was enacted in 2018, potentially legalizes the production of CBD from hemp under certain conditions — although the sale of CBD products generally remains ostensibly illegal. Regardless of the legal situation at the federal level, CBD commercialization remains something of a free-for-all in the United States — individual states are making their own laws, and the FDA has taken only limited action to enforce federal laws on CBD. "They've sent some notices to companies that have made medical claims, but that's about it," says Marcel Bonn-Miller, a psychologist at the University of Pennsylvania, Philadelphia, and global scientific director at Canopy Growth Corporation, a cannabis company in Smiths Falls, Canada. (An FDA spokesperson responded that the agency "is working quickly to continue to clarify our regulatory authority over products containing cannabis and cannabis-derived compounds like CBD".)

Many such claims lie beyond the bounds of medical evidence — including that regarding CBD preparations that purport to prevent cancer or to treat Alzheimer's disease. However, even products that make more modest claims could be problematic. In 2017, Bonn-Miller and his colleagues performed chemical analyses on 84 products purchased online from 31 companies, and found that only 31% were accurately labelled with regard to CBD content[14]. What's more, many commercially available preparations have been found to be contaminated with intoxicating doses of THC, heavy metals and pesticides, as well as toxic solvents from the CBD extraction process. In a case reported by the US Centers for Disease Control and Prevention, up to 52 people in Utah became seriously ill or were hospitalized after using a CBD oil that contained an intoxicating synthetic cannabinoid drug. The possibility of such contamination is concerning to all potential users, and especially to people who are seeking relief from the effects of a health condition. "It's one thing if you've got too much THC in gummy bears you're using with friends, but something entirely different if it's a kid you're giving CBD for medical reasons," says Bonn-Miller. "I don't trust any CBD product until I've done the tests."

BETWEEN TWO WORLDS

The regulatory disconnect that surrounds CBD creates an odd situation in which the public can self-medicate using a potentially questionable product, while scientists face a struggle to perform high-quality clinical trials. "The fact that CBD remains schedule 1 in the United States is unconscionable," says Devinsky. That restrictive classification, he says, "is impairing research".

Obtaining sufficient quantities of pharmaceutical-grade CBD to conduct a well-powered clinical trial is already difficult. "It's extremely expensive," says Leweke. "You need about one gram a day, and the list price is about 60 euros [US$67] per gram." This is because the process of extracting CBD from the cannabis plant is complex and arduous — and when the goal is to obtain CBD for use in people, the substance must meet the high bar set for clinical-grade preparations, under which only minimal quantities of THC or other contaminants are permissible. Several companies have developed strategies for manufacturing fully synthetic CBD, an approach that essentially eliminates concerns about purity. But synthetic CBD still falls under the schedule 1 classification in the United States, which creates extra economic and bureaucratic hurdles for clinical trials. Even in Canada, where recreational cannabis has been legalized, Gobbi describes a complex application process and a more than six-month wait to obtain government authorization to conduct a CBD study in people or animals.

Unfortunately, if studies such as these are not done — or not done properly — then consumers will be left to fend for themselves in a poorly monitored marketplace. In that scenario, the signal of true clinical benefit would almost certainly be drowned out by the noise from personal anecdotes and the placebo effect, which could jeopardize the future of a potentially valuable medicine. "Humans are notoriously bad when they think they see patterns," says Devinsky. "When everyone is convinced that they're right with no data, I call that religion — and CBD is currently religion for the average person." ■

Michael Eisenstein *is a freelance writer in Philadelphia, Pennsylvania.*

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CORRECTION

This Outlook article misstated a quote from Gabriella Gobbi. It should have said that 5-HT_{1A} is desensitized in response to cannabidiol, not sensitized.