Medical News & Perspectives

Cannabidiol Products Are Everywhere, but Should People Be Using Them?

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General internist Brent Bauer, MD, sees patients at the Mayo Clinic in Rochester, Minnesota, one of the most esteemed medical centers in the world.

And yet, some of his patients have sought relief from a variety of ills with ubiquitous, unregulated products they can pick up at 7/Eleven or order online (although not from Amazon, whose selling guidelines prohibit them).

The products' labels say they contain cannabidiol, or CBD, 1 of more than 100 identified compounds in the cannabis plant, commonly known as marijuana. Unlike tetrahydrocannabinol (THC), the other well-known cannabinoid in cannabis, CBD doesn't make users high. Bauer's patients take CBD products to reduce pain, sleep better, and ease anxiety.

"Right now we have [CBD] popping up everywhere," said Bauer, director of research for Mayo's Integrative Medicine program. "I've heard it described as the Wild West meets Wall Street. There's tons of money to be made."

No question, the CBD market has exploded in recent months, with products ranging from bath salts to coffee and tea to maple bacon–flavored dog biscuits. In fact, it surpassed turmeric in 2018 as the top-selling herbal dietary supplement in US natural- and health-foods sales channels, according to a recent report from the American Botanical Council.

Sales of CBD products in those channels in 2018 totaled $52.7 million—more than triple the amount sold in 2017, according to the report. (CBD products have not yet placed in the top 40 for herbal dietary supplement sales in mass-market channels such as mainstream grocery and drug stores.)

"This idea that anybody and everybody can just go out and buy as much [CBD] as they want is very worrisome to me," Bauer said.

Despite the flood of products claiming to contain CBD, research suggests that many actually do not. And the compound's murky status raises a host of questions: Is it safe? Is it effective? Is it legal? Is it a dietary supplement or a drug?

Is It Safe?

Even with pharmaceutical-grade CBD, potentially dangerous adverse events can occur. With unregulated CBD products, the adverse events are unpredictable, in part because their ingredients might not be the same as those listed on the package.

In June 2018, Epidiolex became the first and so far only approved drug in which CBD is an active ingredient. Clinical trials of Epidiolex, indicated for the treatment of intractable seizures in patients with 2 rare epilepsy syndromes, found that adverse events included elevated liver enzymes, diarrhea, somnolence, and decreased appetite. The US Food and Drug Administration (FDA) has required GW Pharmaceuticals, the UK-based company that markets it, to conduct postmarket studies to assess the drug's impact on the liver.

But patients and their families know what they're getting with Epidiolex, emphasizes Stephen Schultz, GW Pharmaceuticals' vice president of investor relations. "Because it's an FDA-approved product, it's exactly the same every time you take it," Schultz said. "It is our belief that physicians and patients want a cannabidiol medicine that they can trust."

A recent letter to the editor of *Clinical Toxicology* highlighted the safety concerns associated with unregulated CBD products. It described the case of an 8-year-old boy with a known seizure disorder who had started using CBD oil his parents had purchased from an online distributor in Colorado. After 9 seizure-free days on the oil, the boy was brought to the emergency department because he had experienced more than 14 tonic-clonic (formerly known as grand mal) seizures in the previous 24 hours. Analysis of the CBD oil he had been taking revealed it also contained AB-FUBINACA, a synthetic cannabinoid whose adverse effects were consistent with the boy's symptoms.

A California cannabis-testing company, CannaSafe, recently conducted a blind analysis of 20 popular CBD products and found that only 3 of them contained what their labels said, *Business Insider* reported. And 8 of the products contained less than 20% of the amount of CBD they claimed, including 2 that contained none. The analysis

also found high levels of solvents and dangerous gases in some of the products, according to the report.

In a recent review article entitled "Clinicians' Guide to CBD and Hemp Oils," Bauer and his coauthors included a section on "finding a quality product."

If patients want to try CBD, the authors recommended, they should use products imported from Europe, because it has more stringent limits for THC in CBD products (0.2% vs 0.3% in the United States) as well as a more established regulatory system for industrial hemp, the variety of cannabis that is the main source of CBD.

And as with other herbal supplements, the authors wrote, patients should make sure CBD products are certified as organic by the US Department of Agriculture and have been tested for pesticides and herbicides. In addition, patients should use only CBD products whose manufacturers meet certain quality standards, such as Current Good Manufacturing Practices certification from the FDA.

Is It Effective?

In a perfect world, Bauer says, he'd be able to direct patients who ask about CBD to a dozen studies of its effectiveness in treating their complaint.

However, "Since we lack those studies, the market is light years ahead of the science," he said. "That's why it's such a frustrating area."

Much of the literature about the therapeutic benefits of CBD involves preclinical research. Other than the work in intractable seizures, randomized controlled trials are sparse and small. For example, in a 6-week exploratory trial involving patients with schizophrenia, published in 2018, participants randomized to CBD were more likely to be rated improved by their treating physician than those randomized to a placebo.

And a recent systematic review and meta-analysis of 81 studies, including 40 small randomized controlled trials, of any type of medicinal cannabinoid for the treatment of a range of mental disorders concluded that evidence of effectiveness was scarce. The studies examined the effect of medicinal cannabis (THC with or without CBD) as well as pharmaceutical CBD.

"Although 16 trials are underway to examine the effectiveness of pharmaceutical CBD for specific conditions, including seven in psychosis, few or no clinical studies to date have examined the effectiveness of CBD for depression, anxiety, Tourette syndrome, or ADHD [attention-deficit/hyperactivity disorder]," the authors noted.

When patients say they want to try CBD, Bauer's first question is "Why?" "Unless you have no other good options, I'm not sure you should rush out and start using it," he said. Children, pregnant women, and people taking multiple medications should not use it at all, he added. "We just don't know enough."

Acknowledging the evidence gap, the National Institutes of Health (NIH) in September announced that it had awarded 9 grants totaling approximately $3 million for research into the potential pain-relieving properties of CBD and other cannabis compounds besides THC.

For now, though, data from randomized controlled trials are lacking. The most he can do, Bauer said, is encourage patients to at least talk to him if they're considering trying or have already tried CBD. That way, Bauer says, he can direct them toward products that appear to be safer. And he can monitor their liver function and potential interactions between CBD and other drugs they're taking.

"They're going to do the experiment, unfortunately, no matter what I say," he said. "I want them to feel free and comfortable to call me."

Is It Legal?

The 2018 Farm Bill, signed into law by President Donald Trump last December, removed cannabis with extremely low concentrations of THC, commonly known as industrial hemp, from the definition of marijuana in the Controlled Substances Act.

Marijuana and industrial hemp are cultivated from the same species. Industrial hemp is a high-fiber plant used to make a variety of products, including textiles and biodegradable plastics.

"Hemp is exactly the same plant as recreational cannabis," from which CBD can also be extracted, said Pieter Cohen, MD, a Harvard Medical School internist who studies dietary supplements. "What happens when you're growing the plant for stalks is you have very small leaves. There's very little THC in those leaves."

A total of 33 states, the District of Columbia, Guam, Puerto Rico, and the US Virgin Islands have legalized medical marijuana, and another 13 states allow the use of low THC, high CBD products for specific indications, such as intractable seizure disorders, according to the National Conference of State Legislatures.

However, the Drug Enforcement Administration (DEA) still considers cannabis or cannabis products—including those claiming to contain CBD—with concentrations of THC higher than 0.3% to be Schedule 1 controlled substances. Such substances "have no currently accepted medical use in the United States, a lack of accepted safety for use under medical supervision, and a high potential for abuse," according to the DEA.

The Farm Bill expanded the definition of hemp, Cohen noted. Industrial hemp used to be only the stalky cannabis plants with small leaves. Now it's any cannabis plant that contains less than 0.3% THC.

Just because industrial hemp is no longer considered to be a controlled substance doesn't necessarily mean that CBD products are legal as long as they contain less than 0.3% THC, though. They no longer violate the Controlled Substances Act, but they do violate the Food, Drug, and Cosmetic (FD&C) Act, according to the FDA.

"At present, any CBD food or purported dietary supplement products in interstate commerce is in violation of the FD&C Act," Amy Abernethy, MD, PhD, principal deputy FDA commissioner, told the Senate Committee on Agriculture, Nutrition, and Forestry in late July.

Epidiolex is the reason such products violate the FD&C Act. Under the act, it is illegal to sell across state lines a product that contains an active ingredient in an approved drug. Because of the FDA's stance, some states, such as North Carolina and Ohio, as well as New York City, have restricted the sale of CBD products, although it is not clear how strict enforcement has been.

So on the one hand, cannabis with a THC concentration lower than 0.3% is no longer a controlled substance regulated by the DEA. But on the other hand, the FDA considers products that contain CBD to be unapproved new drugs that violate the FD&C Act, even if such products claim to be dietary supplements. In other words, in the FDA's eyes, the same compound cannot be both a dietary supplement and a drug.

The boom in the CBD market, apparently, has spurred the FDA—which declined to comment for this story—to try to figure out how best to classify and regulate the

compound. In late May, the agency held a public hearing to gather information about the safety, manufacturing, product quality, marketing, labeling, and sale of products containing cannabis or cannabis-derived compounds such as CBD.

It also created a docket that collected more than 4000 public comments on the topic, many from people who say CBD has helped relieve their aches and pains and improved their sleep.

Is It a Dietary Supplement or a Drug?

Considering how many products claim to contain CBD, trying to rid the market of them seems like an unwinnable game of whack-a-mole.

The FDA says it considers many factors, including agency resources and the threat to public health, in deciding whether to initiate an enforcement action against makers of products adulterated with approved drugs such as CBD. The agency appears to be enforcing the FD&C Act mainly in cases where manufacturers claim their products prevent, diagnose, treat, or cure serious diseases, such as cancer, or are marketed for use in infants or children.

For example, the FDA sent a warning letter in late July (as of mid-November, 1 of 47 it sent in 2019 regarding CBD products) to the president of Curaleaf Inc, in Wakefield, Massachusetts, about the company's claims that its CBD products can treat attention-deficit/hyperactivity disorder (ADHD), chronic pain, Parkinson disease, Alzheimer disease, and anxiety.

Those conditions are no longer mentioned on the Curaleaf website, although the company still sells topical creams, gels, and lip balms that contain CBD. Without any health claims, those products appear to fit the FDA's definition of cosmetics, in which the agency allows cannabis and cannabis-derived ingredients, unless they are found to injure users.

Meanwhile, many other companies continue to make health claims about a range of products purported to contain CBD. "Unbeknownst to clinicians and the public, [dietary] supplements have become a back-door [way of] introducing drugs to US consumers without FDA approval," Cohen said.

"This is unbelievable to physicians," he continued. "You isolate CBD, and you use a number of different loopholes in the law to sell a drug directly to consumers, either as a supplement or in food. CBD is the most dramatic example. I've never seen any new drug take off like this."

Cohen and former FDA deputy commissioner Joshua Sharfstein, MD, now a vice dean at the Johns Hopkins Bloomberg School of Public Health, recently coauthored an article that suggested a way to help weed out bad actors, namely manufacturers whose products contain less CBD or more ingredients—such as THC or pesticides—than they claim on the label.

Congress could pass a law that waives the prohibition against CBD products that was triggered by Epidiolex's approval, Cohen and Sharfstein wrote. In conjunction with that move, they wrote, Congress should "create clear, reasonable pathways for low-dose CBD and other new substances to be safely introduced into supplements and food."

In the meantime, though, Bauer said, "What I really need is a couple of good companies to come along to do really good studies." ■

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