Medical News & Perspectives

The Path to the First FDA-Approved Cannabis-Derived Treatment and What Comes Next

Rita Rubin, MA

Harvard neurologist Elizabeth Thiele, MD, PhD, is only half-kidding about the surprising direction her research has taken.

"If someone would have said to me 5 years ago that I would be spending most of my time thinking about cannabis, I would tell them they were high," said Thiele, director of the Pediatric Epilepsy Service at Massachusetts General Hospital, Boston.

Thiele was a lead investigator in clinical trials that led to the June 25 US Food and Drug Administration approval of Epidiolex—"the first drug comprised of an active treatment derived from marijuana," as the agency describes it—for patients aged 2 years or older who have Lennox-Gastaut or Dravet syndromes. Each is a rare, severe form of epilepsy with unrelenting seizures that can lead to cognitive impairment and, in the case of Dravet syndrome, a high rate of epilepsy-related death at a young age. Currently, she is leading a placebo-controlled clinical trial of Epidiolex to treat seizures in patients with tuberous sclerosis complex, a rare genetic disorder.

Epidiolex is an oral solution of purified cannabidiol (CBD). The main nonpsychoactive component of cannabis, CBD does not cause a euphoric high, unlike tetrahydrocannabinol (THC), the main psychoactive component.

Besides Epidiolex, cannabis and preparations made from it are largely unproven and unregulated, even though the plant has been used to treat ailments for thousands of years, and 31 states, the District of Columbia, Guam, and Puerto Rico have legalized it for medical use.

"Policy has outpaced science," said Ziva Cooper, PhD, associate professor of clinical neurobiology at Columbia University, who recently published a placebo-controlled, double-blind study that suggested smoking cannabis might decrease the amount of opioid medication needed for pain relief. "Cannabis is a plant that is quite diverse. To say that cannabis as a whole is therapeutic is kind of misleading."

But most manufacturers of cannabis-derived products, in some cases mom-and-pop operations, have neither the wherewithal nor the motivation to conduct clinical trials, and US scientists like Cooper who want to study the plant's therapeutic potential face singular obstacles because of Drug Enforcement Agency (DEA) regulations. Cooper noted that only about 50 pages of the approximately 400 pages in *The Health Effects of Cannabis and Cannabinoids*, a 2017 National Academies report that she helped write, are devoted to therapeutic use.

It took a UK company, GW Pharmaceuticals, to usher Epidiolex through the FDA approval process, but it remains to be seen whether that will loosen restrictions on US scientists who want to study cannabis.

In the Beginning, There Was Sativex

Although Epidiolex is the first cannabis-derived product approved by the FDA, it is GW Pharmaceuticals' second product made from the cannabis plant.

"Back in the late 1990s, there was a lot of discussion within the MS (multiple sclerosis) community in the [United Kingdom] about the needs of patients who were not interested in getting high but were sick and running out of treatment options," said Justin Gover, MBA, who became GW Pharmaceuticals' chief executive officer in January 1999, shortly after the company was founded.

Gover's nascent firm approached the British government about developing a cannabis product that could treat spasticity due to MS. "Patients like this shouldn't have to resort to uncontrolled and unapproved medications," Gover said GW told government officials. The company began cultivating cannabis with varied concentrations of THC and CBD.

In 2010, the United Kingdom approved the company's Sativex, a mouth spray that contains equal parts CBD and THC to treat MS-related spasticity. Absorbed through the lining of the mouth, Sativex does not make users high.

Kathy Young/AP Images

Sativex is now approved in 21 European countries, but GW had never sought FDA approval, although the company plans to discuss the drug with agency officials later this year, Gover said. While GW has published multiple placebo-controlled clinical trials of Sativex, none were conducted in the United States, which the company expects it will have to remedy to earn FDA approval, he said.

"Convincing the medical community and regulators that this is important science that needs to be studied properly has been a constant effort on the part of this company for 20 years," Gover said.

Parents Lobby for CBD

While working on Sativex, GW screened a variety of molecules from the cannabis plant in animal models of epilepsy to identify potential treatments, Gover said. Animal models of epilepsy are particularly good at predicting a drug's effect on humans, he said, and parents of children with Dravet syndrome began reading about GW's promising preclinical work with CBD.

Using cannabis to treat seizures was not a new idea. In fact, a book about epilepsy published in 1881 describes its benefits in patients with the condition. "What we've done at GW is combine empiricism with modern-day science," Gover said.

"Weed," a 2013 CNN documentary by Sanjay Gupta, MD, that featured a 5-year-old with Dravet syndrome who experienced 2 seizures an hour before she started using CBD oil extracted from cannabis plants low in THC, helped spread awareness and boost demand, Gover said.

Lobbying by parents over the past few years spurred 17 states that had not legalized medical marijuana to specifically legalize the use of CBD oil by children with intractable epilepsy. Some of the laws are named for affected children, such as "Harper Grace's Law" in Mississippi.

Orrin Devinsky, MD, director of the NYU Langone Comprehensive Epilepsy Center, said he understands why state legislators, confronted by desperate parents of children having multiple seizures daily, would want to legalize CBD. "It's reasonable in the short-term, but it's a terrible long-term policy," Devinsky said. "We as a society need to do the scientific studies."

Although some state CBD laws call for the collection of outcomes data and allow their public universities and medical schools to conduct research into the compound, little is known about the safety and effectiveness of the various products that claim to contain it.

Because such products are not regulated, consumers can't even be sure they contain CBD. In 2015 and 2016, the FDA tested CBD products sold online and found that some had no CBD but did contain THC, which their labels failed to mention. And in a recent study in *JAMA*, researchers bought and analyzed 84 CBD products sold online. They found that only 26 had accurate CBD content labeling. In addition, THC was detected in 18 of the products.

"It's been a frustrating thing for the medical community and the parent community," Thiele said of the dearth of information about CBD therapy for refractory epilepsy and the lack of consistency in CBD products. "We don't prescribe it. We don't know how to dose it. In 2018, parents are put in a position of figuring out their own kid's doses. That's wrong. Some parents say they feel they're experimenting with their own child."

The Epidiolex Epic

Sam Vogelstein's parents had tried treating his intractable epilepsy with tinctures of CBD bought in their hometown of Berkeley, California, but laboratory tests revealed that, despite their claims, the products contained little or no CBD.

When Sam was 11 years old, his mother, Evelyn Nussenbaum, read a 2012 article about the anticonvulsant effects of GW's CBD product in rodent models of epilepsy. As Nussenbaum recounted at an April FDA advisory committee meeting at which panelists voted unanimously for Epidiolex's approval, she "pursued" Geoffrey Guy, MBBS, GW founder and chair, seeking his company's CBD for Sam.

Because Sam, who has absence epilepsy, not Dravet syndrome or Lennox-Gastaut, had responded well to CBD extracted in a California laboratory, Guy was open to letting the boy try his company's experimental CBD drug, Nussenbaum said. Guy felt US anticannabis sentiment was too strong, so in December 2012, Sam, his mother, twin sister, and aunt flew to London for 2 weeks, where he could become the first person to try GW's pharmaceutical-grade CBD, legal to use in the United Kingdom under a physician's supervision. With FDA and DEA permission, he has been taking Epidiolex at home since mid-2013.

Before Epidiolex, Sam had tried 2 dozen medications, the ketogenic diet, and corticosteroids to control his seizures, which numbered as many as 100 a day. After 3 days of treatment with Epidiolex, Sam had only 1 seizure in a day. Sam, who is now 17, told the FDA panel that he had been seizure-free for more than 2 years and hoped to become a neurologist to help others with epilepsy.

Sam's success with Epidiolex in 2013 spurred GW officials to meet with Thiele, Devinsky, and epilepsy specialists from 3 other institutions to map out US clinical trials, launched in 2014 in parallel with an expanded access program. "Epidiolex development was very much led by the US medical community," Gover said.

The 5 academic sites represented at the initial planning meeting each asked the FDA for permission to allow 25 of their patients to take Epidiolex through the expanded access program, Thiele said. To help make their case, the scientists submitted biographies of the patients they had in mind. Many of Thiele's had tried brain surgery, special diets, and numerous medications to control their seizures. "All of them were still having an incredible seizure burden," she said. "We had to demonstrate that this was a population that deserved the opportunity" to try a pharmaceutical made from cannabis.

Thiele's first patient to receive Epidiolex through expanded access began taking the drug in April 2014. The program expanded to 7 more sites that year, and the original 5 sites each added 25 more patients.

Clinical trial results were published in May 2017 and in March and May of this year. Participants had continued the antiepilepsy medications or nondrug interventions they took before enrollment. In the Dravet trial, the average number of convulsive seizures per month fell from 12.4 to 5.9 in participants who received Epidiolex compared with a decline of 14.9 to 14.1 in the placebo group.

In 1 Lennox-Gestault trial, patients randomized to receive 20 mg of Epidiolex per kilogram of body weight had an average each month of 43.9% fewer "drop seizures"—a sudden loss of muscle tone that usually results in a fall—than at baseline compared with a decrease of 21.8% in the placebo group. In the other Lennox-Gastaut trial, participants randomized to 20 mg of

Epidiolex per kilogram of body weight had an average of 41.9% fewer drop seizures, while those who received a 10-mg dose had a 37.2% decline compared with an average decrease of 17.2% in the placebo group.

The most common adverse events among patients in the CBD groups in all 3 trials included diarrhea, somnolence, and abnormal results on liver function tests.

GW included some Western European sites in the phase 3 Epidiolex clinical trials and submitted an application at the end of 2017 to the European Medicines Agency to market the drug in Europe, said Gover, adding that he expects approval there in early 2019. Gover said GW also expects to seek approval for other epilepsy indications for Epidiolex and, likely, other indications for Sativex.

In addition, he said, GW is screening cannabinoids in animal models of autism because it has received reports from the Epidiolex expanded access program that suggested the drug improves autistic behaviors and cognition independent of seizure control in patients with both epilepsy and autism. The company is planning clinical trials to look at the effect of Epidiolex on behavior in children on the autism spectrum with and without epilepsy, Gover said. GW is also studying the use of CBD in treating schizophrenia and neonatal hypoxic-ischemic encephalopathy.

On Scheduling

Although the majority of states have legalized medical marijuana and 8 have legalized recreational use, the DEA still classifies it as a Schedule I drug, defined by the 1970 Controlled Substances Act as a drug with a high potential for abuse and no accepted medical use. The DEA has licensed only 1 source of marijuana for research purposes, a University of Mississippi farm funded through a contract with the National Institute on Drug Abuse (NIDA).

The DEA has 90 days from the FDA's approval of Epidiolex to decide how it will be scheduled. Gover said he expects Epidiolex to be classified as Schedule IV or Schedule V, similar to other epilepsy drugs, such as pregabalin (Lyrica) and lacosamide (Vimpat). At a conference call with analysts in August, Gover said GW expects to begin selling Epidiolex in the fall. The list price will be about $32 500 a year, said Julian Gangolli, GW president, North America.

Whether rescheduling 1 cannabis-derived product will have much of an impact on research into therapeutic uses of the plant depends on who is asked.

"This approval by the FDA for Epidiolex has catapulted this field forward because A, it's a new indication; B, it's CBD-based so it doesn't have psychoactive effects; and C, it's plant-derived and not synthetic," Cooper said.

The FDA-approved drugs Marinol and Syndros contain dronabinol, a synthetic version of THC, while a third FDA-approved drug, Cesamet, contains nabilone, a synthetic compound whose chemical structure is similar to that of THC. All 3 are last-resort treatments for nausea and vomiting related to cancer chemotherapy, while the first 2 are also approved to treat lack of appetite associated with weight loss in people with AIDS.

Daniele Piomelli, MD, PhD, director of the new Institute for the Study of Cannabis at the University of California (UC), Irvine, is not as optimistic as Cooper. "I think the whole situation is going to stay pretty much the same," Piomelli said. While the DEA could even decide that Epidiolex is not a controlled substance, given that it has virtually no potential for abuse, the agency "will continue to crack down on the use of any other form of CBD, including the CBD coming from the plant and the CBD being used for research," he said.

As a California-based scientist, Piomelli finds the tension between state law and federal law especially ironic, not to mention antiscience.

In 1996, California became the first state to legalize medical marijuana. Recreational use became legal January 1 of this year, making California home to the country's largest legal marijuana market, according to the *Los Angeles Times*.

That means everyone in California can now use marijuana grown in California except scientists who, with federal government funding, want to study it, not smoke it, Piomelli noted. Californians aged 21 years or older can buy and possess up to 28.5 g of marijuana, up to 8 g of cannabis concentrate, and up to 6 live plants. When Piomelli gets cannabis from the DEA-approved farm in Mississippi, though, "I have to account for every single milligram," he said. "I have to treat this as if it is a dangerous compound. That is the absurdity of it all."

Piomelli's cannabis institute involves UC Irvine's law school as well as its medical school. "We created it to have a place for not just high-quality scientific research … but also a place where that research could be made more relevant by interacting with legislators, by interacting with lawyers."

Meanwhile, Piomelli said, studying cannabis "takes a lot more energy than it should. The energy should go to more productive endeavors. If anything, the government should ease [restrictions on] research in an area in which research is so urgently needed." ■

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