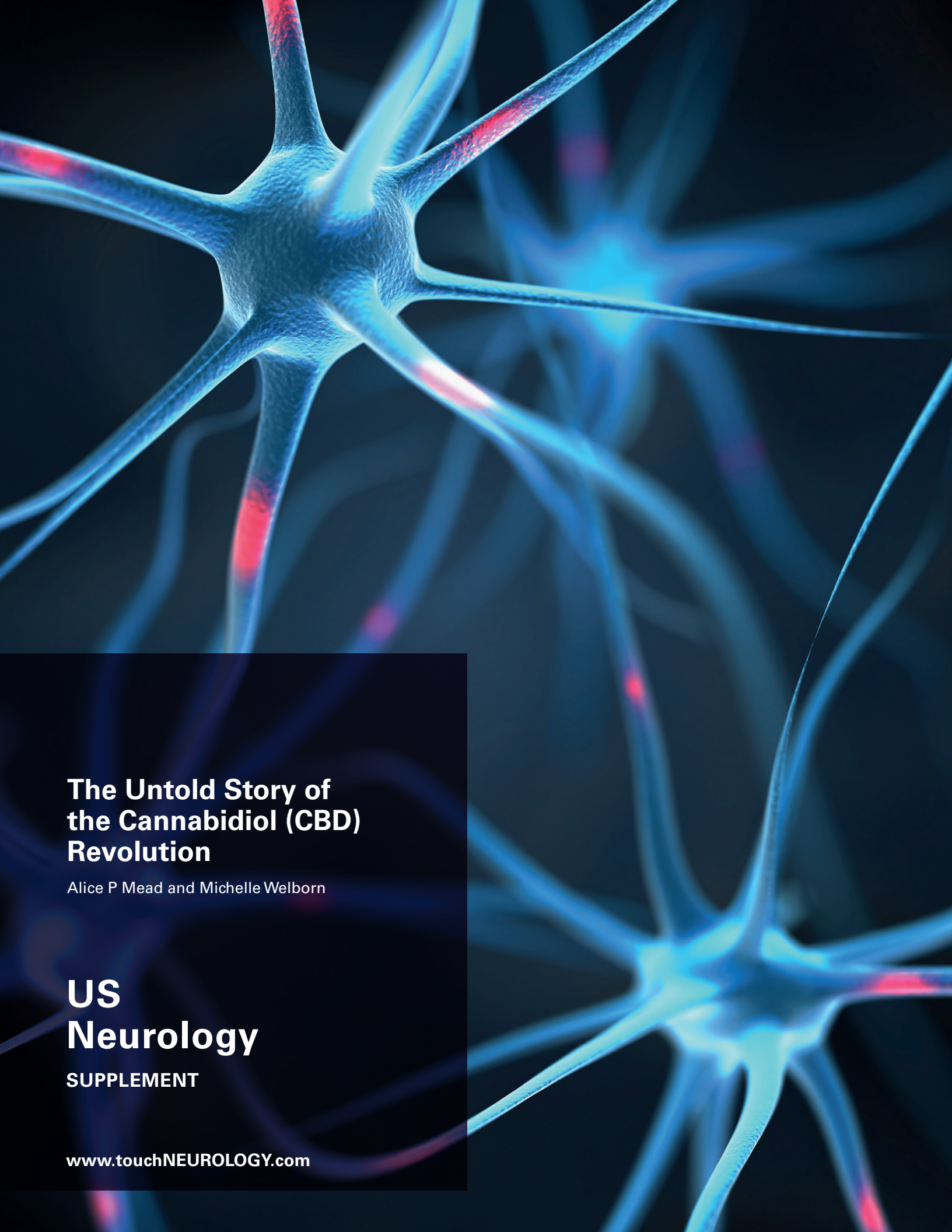

The Untold Story of the Cannabidiol (CBD) Revolution

Alice P Mead and Michelle Welborn

US Neurology

SUPPLEMENT

www.touchNEUROLOGY.com

The Untold Story of the Cannabidiol (CBD) Revolution

Alice P Mead[1] and Michelle Welborn[2]

1. Greenwich Biosciences, Inc., Carlsbad, CA, US; 2. M Welborn Group, LLC, Winston-Salem, NC, US

Dr Sanjay Gupta's 2013 CNN program, entitled "Weed," profiled the case of a little girl with epilepsy whose parents had treated her with cannabidiol (CBD), a substance hitherto unknown to members of the general public. But few people wonder why her parents had been motivated to seek out this particular substance for that therapeutic purpose. This article relates the untold story of the so-called "Cinderella Molecule" (Bailey E. British Firm Holds Hope for Users of Medical Pot. *Los Angeles Times*. February 1, 2004. Available at: http://articles.latimes.com/2004/feb/01/local/me-medpot1 [accessed October 1, 2018]).

Keywords

Cannabidiol, CBD, epilepsy

Disclosures: Alice P Mead is an employee of Greenwich Biosciences, Inc. and stock shareholder of GW Pharmaceuticals plc. Michelle Welborn was a consultant of Greenwich Biosciences, Inc. at the time of writing this article.

Review Process: This historical account is a supplementary piece and, as such, has not been subject to this journal's usual peer-review process. The article was reviewed by an editorial board member before publication.

Authorship: All named authors meet the criteria of the International Committee of Medical Journal Editors for authorship for this manuscript, take responsibility for the integrity of the work and have given final approval for the version to be published.

Received: April 30, 2018

Published Online: October 17, 2018

Citation: *US Neurology*. 2018;14(Suppl. 3):2–8

Corresponding Author: Alice P Mead, Greenwich Biosciences, Inc., 5750 Fleet Street, Suite 200, Carlsbad, CA 92008, US. E: apm@greenwichbiosciences.com

Support: Funding of this article was provided by Greenwich Biosciences, Inc.

In 1998, a British physician named Dr Geoffrey Guy heard the knock of opportunity. Always a visionary, he gathered his unique set of skills and experience, and responded. The events that followed contributed significantly to cannabidiol's (CBD's) emergence from relative obscurity into broad public consciousness (personal interview with Guy G, October 31, 2017).[1]

Dr Guy had long been intrigued by the idea that cannabis might be developed into a modern medicine. Since his days in botanical medicines at the French company Pierre Fabre Laboratories, he had been interested in the special properties of botanical extracts. This had led him to wonder, as early as the 1980s, whether the modern regulatory environment and current government attitudes might permit a research and development program to explore the therapeutic potential of cannabis extracts. He had explored this idea with the British Government in the early 1990s, but they informed him that they had no appetite to license such a program. Already the Chairman and founder of another pharmaceutical company, Ethical Holdings plc, he had other fish to fry, so he shelved his idea.

Fast forward to 1997. The endocannabinoid receptor system—a system in the body consisting of receptors, molecules that activate those receptors, and enzymes that synthesize and degrade those molecules—had been discovered.[2,3] This critically important system of receptors and endogenous neurotransmitters both provided a rationale for the action of tetrahydrocannabinol (THC) and offered tools to allow scientists to explore the mechanism of action of THC and other cannabinoids. Preclinical research was blossoming.[4] In addition, a small "medical marijuana"/cannabis legalization movement had developed in the UK. As a result of their using cannabis for symptom relief, patients using cannabis for medical purposes were being arrested by police and subsequently absolved by juries, leading to concerns that seriously-ill patients were not being treated with compassion and that the law was being brought into disrepute. The British Medical Association published a review of the medical and scientific evidence for and against proposals that cannabis should be made available for medical applications.[5]

In 1997, a pivotal meeting relating to the therapeutic potential of cannabis took place at the Royal Pharmaceutical Society.[1] Dr Guy attended and was pleased to see that the audience included eminent scientists and government representatives. They had come together to discuss the plant's therapeutic potential. Dr Guy arose from the floor to describe how cannabis could be developed into a prescription medicine. Subsequently, two Members of Parliament sponsored a formal parliamentary delegation, which included Dr Guy. The delegation made its way to Parliament to ask the government to reschedule cannabis in order to promote research and facilitate medical access.* They were sorely disappointed

*As of the time of writing of this article, cannabis is in Schedule I under UK as well as US law. The US Controlled Substances Act and the UK Misuse of Drugs Regulations 2001 place psychoactive substances in one of five schedules, depending on their accepted medical use in the US and their abuse potential. Schedule I is the most restrictive.

when the presiding government Minister advised that they had no will at that time to reschedule cannabis, but suggested that anyone interested in conducting research should "talk with our Ministry officials." To the assembled group, this was a bitter rejection. To Dr Guy, it was an invitation. Accompanied by another colleague, Dr Brian Whittle, he went to see the Chief Inspector of the drugs branch of the UK Home Office (the equivalent of the US Drug Enforcement Administration [DEA]). As he described the program by which cannabis could become a modern medicine, he warned the Home Office officials that he would need to grow "tons and tons" of plant material, not merely a few plants. Intrigued, the Chief Inspector asked them to prepare a full development plan for cannabis-based medications. Upon receipt of the development plan, the Home Office granted them the necessary licenses, and GW Pharmaceuticals (Cambridge, UK) was born—after 5 months of working with the necessary Home Office lawyers to determine how such a research program could proceed while satisfying the requirements of international drug control treaties.

In parallel to all these events, the UK House of Lords convened a Select Committee on Science and Technology. The Committee was charged with examining the scientific and medical evidence to determine whether there was a case for relaxing some of the restrictions on the medical use of cannabis. The Committee concluded, amongst other things, that clinical trials of cannabis for the treatment of multiple sclerosis (MS) and chronic pain should be mounted "as a matter of urgency," and it "warmly welcome[d]" the fact that Dr Guy had set off down this path. In short, the founding of GW was a direct response to the UK Government's call for research to see if it were possible to develop a modern medication from the cannabis plant.

Procuring the plants

But there was a small issue, Dr Guy had no direct experience cultivating cannabis, so where and how to procure the plants to begin GW's research program? The Chief Inspector of the Home Office alerted Dr Guy to the work of Robert Connell Clarke, Dave Pate and David Watson, Americans who had relocated to The Netherlands in their quest to conduct cannabis breeding and research for the purpose of producing the raw materials for medical products.[6,7] Coincidentally, Dr Guy had met them the previous year. This group, called HortaPharm B.V. (Amsterdam, Netherlands), were fully licensed by the Dutch Government to conduct research into cannabis varieties that might be useful in medical treatment. HortaPharm had collected and analyzed cannabis varieties from all over the world and had also bred new varieties with very defined compositions that were particularly high in CBD, THC, and other cannabinoids. HortaPharm was interested in developing pharmaceutical grade cannabis with controlled cannabinoid ratios that could be evaluated for therapeutic usefulness.[6,7] Based on early research described below, they were particularly interested in the medical potential of CBD and had been breeding plants high in CBD content since the 1980s.[8] Dr Guy worked with HortaPharm to procure its library of cannabis seed varieties, including the CBD- and THC-predominant varieties that they had bred in-house.[9] Thus, GW instantly had the THC-rich and CBD-rich varieties needed to begin its research.

Early interest in cannabidiol

By this time, Dr Guy had read extensively about the medicinal use of cannabis in the historical literature and especially the reports in Europe and North America dating from the mid-1850s. During that time, Dr William B O'Shaughnessy had returned from India and published his observations and studies on the effects of cannabis extracts and tinctures.[10] Dr Guy also examined the likely cannabinoid content of the imported hashish materials that many UK patients—largely patients with MS—were using at that time, and he determined that CBD represented a significant, if not dominant, component of these materials.[11]

Dr Guy began to speak about the potential of CBD with colleagues at research centers and scientific meetings. By 1998, cannabis grown in North America had been primarily bred for its psychoactive properties, and, as a result, CBD-rich strains had been discarded. Therefore, most of the modern research—exploring either the harmful effects or (less so) the potential therapeutic properties—would have focused almost exclusively on THC. Indeed, at a scientific conference in New York, a well-respected researcher chided Dr Guy for being interested in CBD, with the query: "Doesn't Dr Guy know that CBD is an inert component of the cannabis plant and all of the pharmacological and therapeutic properties of cannabis can be attributed to THC?" While this may have been true of modern street cannabis, Dr Guy and his expanding team were certain that CBD had great potential.

Armed with very defined CBD- and THC-rich varieties, GW immediately developed three whole plant extracts: one in which THC was the predominant cannabinoid, one that was predominantly CBD, and one in which the first two extracts were blended to produce a third extract with a 1:1 ratio of CBD:THC. GW moved rapidly into clinical research with these different cannabinoid formulations and ratios to identify their different therapeutic properties and safety profiles.[12,13] The company explored a number of ways to deliver the cannabinoid formulations, but, for the 1:1 product, decided on a sublingual (later oromucosal) spray, which allowed patients to take the product in small aliquots, thus enabling individualized titration (gradual adjustment) of dose. The oromucosal route also allowed THC to be absorbed by the body at a slower rate than what would occur with smoking or other forms of inhalation. All of this helped to reduce the THC-related intoxicating effects (GW Pharmaceuticals, data on file). The product, called nabiximols (Sativex®, GW Pharmaceuticals, Cambridge, UK [this product is not US Food and Drug Administration (FDA) approved]), was formulated by blending the THC- and CBD-rich extracts to give a 1:1 ratio of CBD:THC, but also retained the minor cannabinoids, terpenes and flavonoids of a whole extract.

Dr Guy also believed that CBD had therapeutic properties that were independent of its effect on THC and sought to confirm this with data. In a sleep study, THC was sedating, whereas CBD was alerting.[14] In double-blind, placebo-controlled studies in which patients served as their own controls (n-of-1 studies),[15] patients often responded only to the CBD-rich extracts, and not the 1:1 or THC-rich extracts. He continued to believe that, for some conditions, there may be a synergistic effect of all the components of the cannabis plant—later dubbed the "entourage effect,"[16] after a concept describing the synergistic interactions of the components of the endocannabinoid system—but recognized that, for other medical conditions, a more highly purified cannabinoid might be preferable.

He was certainly not alone in believing that CBD had significant potential. Professor Raphael Mechoulam, the Israeli chemist who had elucidated the structure of THC and identified it as the primary psychoactive component of cannabis,[17] had also isolated CBD and a number of other cannabinoids.[18,19] He shared these materials with interested researchers. A group of these researchers in Brazil and elsewhere had

conducted small human trials with CBD in psychosis, epilepsy, and other conditions.[20–22] At the University of California, San Francisco (UCSF), pharmacologist Dr Lester Bornheim was studying the metabolism of CBD, particularly its effect on the "super family" of P450 enzymes.[23] In 1998, Dr Aidan Hampson at the National Institute on Drug Abuse discovered that cannabinoids, including THC, CBD, and the synthetic compound HU-211, have antioxidant properties. A patent was granted on this work by the US Patent and Trademark Office in 2003.[24] The patent claimed a method of treating diseases caused by oxidative stress, such as neurodegenerative or ischemic disease, by the administration of cannabinoids. Professor Pertwee published a seminal paper on the mechanisms of action of CBD, which cited preclinical research from the 1980s indicating that CBD could have an anti-convulsant effect.[25] These studies provided tantalizing signals of CBD's anti-convulsant and other potential benefits, but none were robust enough to galvanize the wider scientific and medical communities, much less the general public.

Indeed, scientific reports that were published in the late 1990s acknowledged CBD but viewed it as a molecule of little importance.[21,26–29] The esteemed Institute of Medicine (IOM)[26] of the National Academy of Sciences wrote in *Marijuana and Medicine: Assessing the Science Base* "Cannabidiol (CBD) does not have the same psychoactivity as THC, but it was initially reported to attenuate the psychological response to THC in humans; however, later studies reported that CBD did not attenuate the psychological effects of THC… The most important effect of CBD seems to be its interference with drug metabolism, including delta-9-THC metabolism in the liver."[27] With regard to epilepsy, the IOM reported that "The potential antiepileptic activity of CBD has been investigated but is not promising." Leslie Iversen, PhD, in his review entitled *The Science of Marijuana,* concluded in his discussion of epilepsy "Attempts to follow up on these potentially useful findings [animal studies and one small placebo-controlled trial], however, failed to confirm any positive effect of this dose (200–300 mg) on seizure frequency, although a single patient treated with a higher dose of cannabidiol (900–1200 mg per day) seemed to benefit… It is difficult to see epilepsy as a high priority area for research on the potential use of cannabis or cannabinoids."[28] In *Marijuana Myths, Marijuana Facts,* John Morgan, MD, and Lynn Zimmer, PhD, stated "Delta-9-THC is probably responsible for most of marijuana's therapeutic effects, but one of marijuana's other cannabinoid constituents—cannabidiol—appears to be useful as an anticonvulsant."[29] To support this statement, they cited early small clinical trials from the 1980s.[21,30]

It was against this background that Dr Guy persevered in pursuing the therapeutic potential of CBD. He recognized as early as 1998 that CBD and other cannabinoids might have an important role to play as an anticonvulsant.[31] With enthusiasm, he explored the idea with researchers and other interested parties, and inquired of scientists such as Dr Mechoulam about the importance of CBD:THC ratios. One of these interested parties was Fred Gardner, a journalist who recognized that cannabis and cannabinoids might soon become important tools in the physician's armamentarium. The fact that a true pharmaceutical company was seeking to develop the world's first cannabis-derived prescription medication captured Gardner's interest. And the additional fact that this company believed in the therapeutic importance of CBD, a little-known component of the plant, garnered even more attention and particularly intrigued Gardner. In 1999, he began to publish information about GW's research in *Synapse*, the UCSF weekly.[31]

With the passing of California's 1996 Proposition 215 (also known as The Compassionate Use Act), interest in CBD would shift to the US west coast. Word of what was happening in the UK disseminated through some of the earlier publications to cannabinopathic medicine. *O'Shaughnessy's,* a California publication named after the Irish physician credited with bringing cannabis to western medicine, was among the first to credit GW Pharmaceuticals for being able to select and isolate CBD varieties.[32] GW's research also elicited considerable interest among both preclinical and clinical researchers, as well as within the cannabis advocacy community (due largely to Gardner's writings). GW shared its extracts with external researchers, and the International Cannabinoid Research Society (ICRS) annual meetings bristled with posters and conversations about possible medical applications of the burgeoning preclinical research, and interest in CBD grew.

In 2000, discussion of the therapeutic properties of cannabis burst into the hallowed halls of medical science in the US. In that year, the first-ever continuing medical education (CME) conferences on the medical potential of cannabis were held at UCSF and the University of Washington. Dr Guy was one of the speakers, and these conferences gave him the opportunity to showcase the GW program and to stress the importance of CBD.[33] Looking back, these were pivotal events that elevated discussion in the US about the medicinal use of cannabis and the importance of CBD and CBD:THC ratios. In the years that followed, GW continued to research different cannabinoids and cannabinoid ratios and to develop nabiximols, securing its first regulatory approval in Canada in 2005.[34] At that moment, nabiximols became the first complex botanical extract ever to be approved as a prescription medication under modern regulatory requirements. At numerous scientific conferences, Dr Guy and others in GW continued to stress the therapeutic potential of CBD, and Gardner continued to report on these and other scientific studies in various publications, including *O'Shaughnessy's*.[8,32,35]

2007 proved, in hindsight, to have been an important year for CBD. That year, GW and a US development partner sponsored extensive preclinical research conducted by Professor Ben Whalley and his colleagues. This research examined a number of cannabinoids, including CBD and cannabidivarin (CBDV), in various animal models of human disorders, including epilepsy. In many different animal models, both CBD and CBDV had anti-convulsant effects.[36,37] GW had a great interest in epilepsy and had spent quite a lot of time studying CBD in other medical conditions. While the company was contemplating whether to lead with CBD or some other cannabinoid in a formal development program, something was happening in the US that was entirely unexpected. The animal research was presented at scientific conferences, such as ICRS, and then published in peer-reviewed journals.[36–38] Gardner followed these studies closely and began urging cannabis cultivators to take an interest in CBD and in these results.[31] On the heels of this research, Gardner and another journalist, Martin Lee, began a small nonprofit called Project CBD to educate the cannabis community and the outer world about CBD research, particularly GW's. As one writer stated "Cannabis growers were surprised about these findings. Most cannabis varieties in North America had been bred to express high levels of THC, and those with lower levels of THC (and higher levels of CBD) had been discarded."[39] However, even if growers were now getting interested in CBD's potential, they had no way to know whether any CBD-rich varieties still existed.[35]

Fortunately, at about that time, Harborside Health Center, a large cannabis dispensary in Oakland, CA, had become frustrated because no DEA-registered analytical laboratory would test its cannabis samples for cannabinoid content, mold, or heavy metals. Therefore, its founder, Steve DeAngelo, went about setting up his own analytical lab,[40] Steep Hill Laboratory, with the capability of testing cannabis samples for both potency and contaminants. Gardner had been telling them about the potential of CBD, so they tested for CBD, along with THC and cannabinol (CBN—a result of THC degradation). Over the next few years, Steep Hill identified a number of CBD-rich varieties. As one journalist opined: "The credit to this moment can be traced back to 1998 in Britain with Geoffrey Guy, MD, and the foundation of GW Pharmaceuticals."[32]

It was still a hard sell for certain cultivators and manufacturers.[32] The consumer demand primarily focused on THC-rich products. Nevertheless, a few were interested in CBD's medical potential. Project CBD gathered CBD clones and seeds from various sources and provided them to willing growers. Gardner developed a questionnaire to be filled out by Harborside patients purchasing CBD buds or products, with the hope that they could develop a database indicating which varieties or ratios were helpful for which medical conditions. Growers began to cultivate CBD-rich chemovars and some CBD extracts were produced. Harborside carried these products.[32] A few families of children with devastating types of epilepsy, who had been connected on Facebook to support one another and share information, read *O'Shaughnessy's*,* spoke with Harborside or other dispensaries, or even read GW's preclinical research directly, and began to take an interest in such extracts.

In 2011, a Discovery Channel program—which primarily profiled Harborside—included a segment on Jason David, a father who was treating his epileptic son with a CBD extract in glycerin that he had obtained through Harborside.[41] Steve DeAngelo, at the end of the segment, stressed the importance of CBD and spoke of his involvement with Project CBD.[42] David thanked Harborside for their assistance.[41] Other families, who had watched or learned of this program, sought to find CBD extracts. However, many of these extracts lacked good quality control and batch-to-batch consistency.

One family's quest to help their son

One California family (Evelyn Nussbaum and Fred Vogelstein) had been using artisanal CBD products to try to help their son, Sam, who had a severe, intractable type of epilepsy. They were frustrated to discover that a first batch initially seemed to help their son, but the next batch brought his seizures galloping back. Tinctures from three different dispensaries didn't work. Then they reviewed the GW-sponsored animal research and realized that GW must have a standardized CBD product that had been used in the animal research. So, the family embarked on a quest to contact GW. On behalf of the family, a member of the House of Lords—who was acquainted with Sam's grandfather—sought to contact Dr Guy through a mutual colleague, Sir Michael Rawlins, then-Chairman of NICE (The UK National Institute for Health and Care Excellence). Dr Guy spoke with Evelyn and then asked GW's US representative, Alice Mead, to follow up in more detail with the family to inquire how GW could help. The family explained that their son Sam (who was about 10 years old) was having up to 120 seizures a day, that his condition significantly impeded his ability to participate in normal childhood activities, such as play, reading, conversation, etc., and that he would probably never lead an independent life. Dr Guy sympathized with the family's plight but helping would be a challenge. The situation involved a child, and CBD was a Schedule I substance with "no currently accepted medical use" under the federal Controlled Substances Act. Mead undertook research to try to identify a regulatory pathway by which GW could come to the aid of this family. This research revealed that the FDA had promulgated "expanded access" regulations, which were lodged in a little-used section of its website.[43] These regulations allowed a patient (presumably including a child) who 1) had a serious or life-threatening condition, 2) did not respond to available therapies, and 3) could not be enrolled in a formal clinical trial, to obtain access to an investigational product (presumably including a Schedule I substance).

Dr Guy traveled to the US and met with the family and their pediatric epileptologist, Professor Roberta Cilio, at a leading pediatric hospital in San Francisco, to explore whether Sam might be an appropriate candidate for CBD. Expanded access appeared to be a promising regulatory vehicle. However, particularly since CBD was a Schedule I substance, the assembled group recognized that it might be challenging for Professor Cilio to obtain FDA and DEA approval for a single-patient expanded access program (EAP), without some evidence—from a properly-monitored medical setting—that GW's CBD would not harm and might help the child. So, the family agreed to travel to the UK, where highly purified CBD was not a controlled substance. But before that could happen, it was essential to identify a UK specialist in childhood epilepsy and for Professor Cilio to discuss the case with him or her. Sir Michael Rawlins recommended a well-known pediatric epileptologist, Professor Helen Cross of a leading hospital in London. Dr Guy spoke with Professor Cross and also provided her name to Evelyn so the UK and US physicians could speak. Professors Cilio and Cross had known one another for many years, but it was a still long shot; Professor Cross was not familiar with CBD. However, GW had produced preliminary safety and toxicology data on CBD as part of its nabiximols program (unpublished data, GW Pharmaceuticals) and was able to provide the data to Professors Cross and Cilio. The two epilepsy specialists discussed the case and evaluated the safety and potential efficacy of the purified CBD. Professor Cross agreed to see Sam.

Another question arose: what form of CBD should GW provide if Professor Cross deemed it appropriate to go forward? GW had previously researched CBD in other medical conditions, but the company did not currently have any CBD from those programs on the shelf. Clearly, in order to respond to the child's medical need, the company was going to have to make up a formulation just for him. The company was aware of preclinical research indicating that chronic exposure to THC may be damaging to the young developing brain.[44,45] There was also some evidence from animal studies that THC could cause seizures.[46] Therefore, the company decided to provide pure CBD to Sam—rather than a CBD-rich "whole plant" extract, which contained larger amounts of THC and other cannabinoids.

Evelyn, Sam and his sister arrived over the Christmas holiday, 2012. Sam was having many dozens of seizures a day upon arrival; subsequently, following 2 weeks of treatment, he showed a markedly positive response.** This extraordinary result captured everyone's attention. By prior agreement, the

*Harborside distributed 5,000 copies and there were another 20,000 copies distributed within California.

**Note that individual results may vary; please see prescribing information for benefit/risk information.[55]

family returned to the US without the CBD (since it would have been illegal to bring it with them) but was determined to seek FDA authorization for Sam to use GW's CBD in the US.

The genesis of the expanded/compassionate access program

In early January 2013, Professor Cilio submitted a protocol to the FDA for a single-patient access to CBD under the expanded access regulations. By this time, GW had been researching nabiximols in the US for 7 years. Therefore, the FDA already had the same safety and toxicology data that GW had provided to Professors Cilio and Cross. The FDA agreed to the EAP application, and the DEA provided Professor Cilio with a Schedule I research registration (license). This was the first ever protocol for the use of pharmaceutical grade CBD in pediatric epilepsy, the approval of which was the result of long back-and-forth discussions with the FDA. Sam became the first ever patient to receive what would become known as Epidiolex® (CBD; GW Pharmaceuticals, Cambridge, UK).

Also, in January 2013, Dr Orrin Devinsky, of New York; Evelyn Nussenbaum, the mother of the first patient; and Catherine Jacobson, the mother of a child who would become the second patient to receive CBD through an investigational new drug (IND) EAP, arranged a small meeting in New York. Several prominent epileptologists, representatives of the National Institutes of Health, epilepsy advocacy organizations, Dr Marlene Hafner (former Director of the FDA's Office of Orphan Drug Products), and GW came together to explore possible steps forward. It was clear that one-by-one single patient expanded access applications to FDA and DEA were far too cumbersome. Dr Michelle Welborn, a regulatory consultant, founder of an epilepsy advocacy organization, and mother of a child with Dravet syndrome, suggested that larger EAPs might be possible. Word spread among the families connected on Facebook, as well as among their pediatric neurologists and epileptologists, that it was possible to open these EAPs with GW's CBD. The company was now aware that there were thousands of children with devastating epilepsies in the US and elsewhere, and, without hesitation, GW still wanted to help. Dr Welborn and Dr Devinsky developed a protocol for an "intermediate size" expanded access IND, covering up to 25 patients, and, with fingers crossed, submitted it to the FDA; the FDA granted it.[47]

The decibel level of discussion among families and their physicians escalated further, and three more physicians stepped forward to ask GW if the company would supply its CBD for 25-patient programs, and FDA if it would permit such programs. Dr Eric Marsh of Children's Hospital of Philadelphia, Dr Elizabeth Thiele of Massachusetts General Hospital, and Dr Linda Laux of Lurie Children's Hospital in Chicago, along with the family's doctor and Devinsky, were known within GW as the "founding five." GW continued to want to help families, so the company agreed, as did the FDA and DEA. Continuing to say yes was a hard decision for the company. GW had not yet embarked on a formal clinical trial program in childhood epilepsy with CBD, and they were making the product in small batches that were expensive to manufacture. US regulations would have allowed the company to impose a charge for its manufacturing, administrative, and shipping costs. However, GW realized that, by doing so, the only families who would be enrolled in the programs would be those who could pay these costs out-of-pocket (health insurance typically does not cover the costs of investigational drugs). Hence, GW took a deep breath, and agreed to provide Epidiolex® without charge.

Ultimately, 22 EAP sites were opened, involving over 1,000 patients, mostly children. As of November 2017, the company had also responded to 29 emergency INDs, involving critically ill children who were in pediatric intensive care units. Eight state governments asked if they could initiate EAP programs in their states to ensure that their citizens would have access to quality-controlled, standardized CBD medication. GW continued to provide the product without charge to the EAP sites and the state programs, with new programs now in New South Wales and Queensland.

Dr Sanjay Gupta and Charlotte's Web

In August 2013, as the CBD EAPs were getting underway, Dr Sanjay Gupta of CNN, presented a program entitled "Weed," in which he profiled Charlotte, a young girl with Dravet syndrome.[48] Charlotte was having hundreds of seizures a week,[49] and her parents feared that she might die. They had watched a video of the Discovery Channel program "Weed Wars" and had seen Mr David administering a CBD-predominant extract to his son Jayden.[48,49] Encouraged, they began to search for CBD. Word about GW's CBD research had already traveled from California to Colorado, and they were able to find a CBD-rich strain at a Denver dispensary—R4, said to be low in THC and high in CBD. Charlotte's mother was only able to buy about two ounces. Charlotte had an astonishing response, becoming seizure-free for seven days. After their supply was used up, they contacted a group of brothers (the Stanleys), who were cultivating various types of cannabis. Charlotte's mother inquired about CBD.

The Stanleys had acquired some CBD-rich varieties,[31] and one of these varieties was prepared into an extract for Charlotte. As with her prior experience with CBD, Charlotte was a "super-responder"—on television it seemed like a miracle. She went from having 300+ seizures a week to having only a few seizures a month, and then usually at night.[48] A wildfire was ignited among the families with children with similarly devastating epilepsies. Many moved to Colorado, desperate to obtain access to the strain that the Stanleys subsequently-named "Charlotte's Web." Others went to their state legislatures, seeking access to CBD, and bringing their children in wheelchairs to legislative hearings. Sixteen states passed CBD-access laws in less than 2 years. Suddenly, the world—and not just preclinical researchers and California cannabis advocates—were aware of the therapeutic potential of CBD in epilepsy. But it all really started in 1998.

The need for a formal clinical development program

The company did not anticipate the impact that the CNN program would have. More physicians began to contact GW, requesting access to EAPs. GW realized it just did not have the ability at that time to fulfill every request, but also recognized the extent of the medical need among these children with devastating, childhood-onset epilepsies. A formal clinical development program would be necessary to ensure that CBD would be available by prescription in pharmacies around the country, and not only in the specific locations of the physicians at the EAP sites. Hence, in the spring of 2014, the company opened its own IND program with FDA to conduct four large, randomized, placebo-controlled clinical studies.[50–53] Based on advice from epilepsy experts and the results of a survey conducted with families of patients with intractable epilepsies,[54] the company studied two rare childhood-onset epilepsies: Dravet syndrome and Lennox-Gastaut syndrome. Almost immediately, physicians at the EAP sites stepped up to become investigators in the controlled studies required by the FDA (as well as to continue as EAP sites), and some of them participated in the protocol

development for the studies. Patients flooded into the studies. In a little over 2 years, three of four studies had been completed, and had positive results, making it possible for the company to seek FDA approval.

In October 2017, GW and its US subsidiary Greenwich Biosciences, completed the process of applying to the FDA for marketing approval for Epidiolex®, and on June 27, 2018, the FDA approved the product, making Epidiolex® the first cannabis-derived medication ever to be approved as a prescription medicine in the US.[55] The FDA then transmitted a rescheduling recommendation to the DEA. On September 28, 2018, the DEA moved the product to Schedule V.

Obtaining FDA approval and DEA rescheduling were not the only steps that the company had to take to make it possible for Epidiolex® to be dispensed to patients. US states have their own controlled drug laws that mirror the federal Controlled Substances Act. Under these laws, marijuana is a Schedule I substance. The definition of "marijuana" includes derivatives like CBD. Even US states with "medical marijuana" or "adult use" marijuana laws have not, for the most part, rescheduled marijuana. Hence, even after FDA approval and DEA rescheduling, CBD could not be dispensed by pharmacies in a state until the product was rescheduled or some other change to state law takes place. US states do not automatically reschedule a new product because the DEA has done so. This state process can take as long as 2 years. Hence, approximately 2 years before FDA approval, GW embarked on a project to try to ensure that patients in every state would have access to Epidiolex® at the point when (or shortly after) it was approved by FDA and rescheduled by DEA. This project has created a new legal pathway for prescription CBD products like Epidiolex® but does not affect existing pathways under state law allowing lawful access to non-FDA approved cannabis products for medical and/or adult use.

Conclusion

In 1998, Dr Guy's willingness to listen to patients, his vision and entrepreneurial spirit drove him to form GW Pharmaceuticals. GW, along with its physician-investigators, collaborating scientists, and patients, embarked on an ambitious program to investigate the therapeutic potential of cannabis, at a time when cannabis still carried a significant stigma and barriers to research were formidable, especially in the US. His attention to patient reports and exhaustive review of historical literature led him to believe in the importance of CBD and cannabinoid ratios, despite the fact that many scientists at the time believed that CBD was of little value, and it had all but disappeared from modern cannabis strains. GW Pharmaceuticals' research with both THC:CBD ratios, and with CBD itself, resulted in awareness—in the cannabis community (through Gardner), and consequently in families with children with epilepsy—that CBD could have important therapeutic action, particularly in epilepsy. As Gardner so cogently says: "Without Geoffrey Guy [and GW Pharmaceuticals], there would be no CBD" (personal interview with Gardner F, October 7, 2017). GW has now been successful in securing FDA approval for Epidiolex®, Dr Guy's vision has been fulfilled, and patients with Dravet and Lennox-Gastaut syndromes now have access to a medication that can be prescribed by their doctors and dispensed by specialty pharmacies, free of legal uncertainty and stigma. GW and Greenwich continue to advance research in cannabinoids to identify and study other potential therapeutic uses for CBD, as well as other cannabinoids. ❑

1. Crowther SM, Reynolds LA, Tansey EM (eds). *The Medicalization of Cannabis.* London, UK: The Wellcome Trust Centre for the History of Medicine at University College of London. 2010; 106 pp, ISBN: 978-085484-129-5. Available at: http://discovery.ucl.ac.uk/20363/1/20363.pdf (accessed August 29, 2018).
2. Pertwee RG. The pharmacology of cannabinoid receptors and their ligands: an overview. *Int J Obes.* 2006;30 Suppl 1:S13–8.
3. Griffing GT, Thai A. Endocannabinoids. 2015. Available at: https://emedicine.medscape.com/article/1361971-overview (accessed July 20, 2018).
4. Pacher P, Batkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacol Rev.* 2006;58:389–462.
5. Ashton CH, Holdcroft A, Mars S, et al. *Therapeutic Uses of Cannabis.* Amsterdam, The Netherlands: Harwood Academic Publishers. British Medical Association. 1997; 142 pp, ISBN: 978-9057023187.
6. Breen B. Dr. Dope's Connection. 2004. Fast Company. Available at: www.fastcompany.com/48172/dr-dopes-connection (accessed July 20, 2018).
7. Pate DW. Development of cannabis-based therapeutics. 1998. Available at: www.internationalhempassociation.org/jiha/jiha5113.html (accessed July 20, 2018).
8. Gardner F. Who's Afraid of Cannabidiol? 2007. Available at: www.counterpunch.org/2007/07/14/who-s-afraid-of-cannabidiol/ (accessed July 20, 2018).
9. GW Pharmaceuticals. Details released of collaboration between GW Pharmaceuticals and Hortapharm medicinal cannabis. 1998. Available at: www.gwpharm.com/about-us/news/details-released-collaboration-between-gw-pharmaceuticals-and-hortapharm-medicinal (accessed July 20, 2018).
10. O'Shaughnessy WB. On the preparations of the Indian hemp or gunjah. *Prov Med J Retrosp Med Sci.* 1843;5:363–9.
11. Potter D, Clark P, Brown MB. Potency of delta-9-THC and other cannabinoids in cannabis in England in 2005: implications for psychoactivity and pharmacology. *J Forensic Sci.* 2008;53:90–4.
12. Guy GW, Flint ME. A single centre, placebo-controlled, four period, crossover, tolerability study assessing pharmacokinetic effects, pharmacokinetic characteristics and cognitive profiles of a single dose of three formulations of cannabis based medicine extracts (CBMEs) (GWPD9901), plus a two period tolerability study comparing pharmacodynamic effects and pharmacokinetic characteristics of a single dose of a cannabis based medicine extract given via two administration routes (GWPD9901 EXT). *J Cannabis Ther.* 2003;3:35–77.
13. Guy GW, Robson P. A phase I, double blind, three-way crossover study to assess the pharmacokinetic profile of cannabis based medicine extract (CBME) administered sublingually in variant cannabinoid ratios in normal healthy male volunteers (GWPK02125). *J Cannabis Ther.* 2003;3:121–52.
14. Nicholson AN, Turner C, Stone BM, Robson PJ. Effect of delta-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults. *J Clin Psychopharmacol.* 2004;24:305–13.
15. Notcutt W, Price M, Miller R, et al. Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 'N of 1' studies. *Anaesthesia.* 2004;59:440–52.
16. Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Br J Pharmacol.* 2011;163:1344–64.
17. Mechoulam R, Gaoni Y. The absolute configuration of delta-1-tetrahydrocannabinol, the major active constituent of hashish. *Tetrahedron Lett.* 1967;12:1109–11.
18. Adams R, Pease DC, Clark JH. Isolation of cannabinol, cannabidiol and quebrachitol from red oil of Minnesota wild hemp. *J Am Chem Soc.* 1940;62:2194–6.
19. Adams R. Marijuana. *Bull N Y Acad Med.* 1942;37:168–97.
20. Carlini EA, Cunha JM. Hypnotic and antiepileptic effects of cannabidiol. *J Clin Pharmacol.* 1981;21 (S1):417S–427S.
21. Cunha JM, Carlini EA, Pereira AE, et al. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. *Pharmacology.* 1980;21:175–85.
22. Ames FR, Cridland S. Anticonvulsant effect of cannabidiol. *S Afr Med J.* 1985;*69*:14.
23. Bornheim LM, Everhart ET, Li J, Correia MA. Characterization of cannabidiol-mediated cytochrome P450 inactivation. *Biochem Pharmacol.* 1993;45:1323–31.
24. Hampson AJ, Axelrod J, Grimaldi M. US Patent No. 6630507. Washington, DC, 2003: United States Patent Office.
25. Pertwee RG. The pharmacology and therapeutic potential of cannabidiol. In: Di Marzo V, *Cannabinoids.* New York, US, Kluwer Academic/Plenum Publishers 2004;32–83.
26. The National Academies. Press Release: Institute of Medicine to Become National Academy of Medicine. 2015. Available at: www.nationalacademies.org/hmd/Global/News%20Announcements/IOM-to-become-NAM-Press-Release.aspx (accessed July 23, 2018).
27. Joy JE, Watson SJ, Benson JA, eds., Cannabiods and Animal Physiology. In: Institute of Medicine, *Marijuana as Medicine: Assessing the Science Base.* Washington DC, US, The National Academy Press, 1999;36.
28. Iversen L. Is Cannabis Safe? In: Iversen L. *The Science of Marijuana*. New York, US, Oxford University Press, 2000;170.
29. Zimmer L, Morgan J, Marijuana as a Medicine. In: Zimmer L, Morgan J, *Marijuana Myths, Marijuana Facts.* New York, US, The Lindesmith Center. 1997;17.
30. Consroe P, Snider SR. Therapeutic Potential of Cannabinoids in Neurological Disorders. In: Mechoulam R, *Cannabinoids as Therapeutic Agents.* Boca Raton, US, CRC Press. 1986;21–50.
31. Bienenstock D. A Comprehensive History of Marijuana's Epilepsy-Treating Compound, CBD. 2014. Available at: www.vice.com/en_uk/article/mv53yp/desperately-seeking-cbd (accessed July 23, 2018).
32. Bennett P. The History and Emergence of the CBD Cannabis Strains. 2017. Available at: www.leafly.com/news/cannabis-101/cbd-marijuana-strains-history (accessed July 23, 2018).
33. Guy, Geoffrey W. The Future of Cannabis as a Prescription Medicine: Progress Toward Cannabis Extracts and Nonsmoking Delivery Devices. Presented at: Cannabis Therapy: Science, Medicine And The Law Conference, June 10, 2000, The University of California San Francisco School of Medicine, San Francisco, CA.
34. Government of Canada. Fact Sheet: SATIVEX. 2005. Available at: www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions/fact-sheet-sativex.html (accessed July 23, 2018).
35. Gardner F. Molecule of the year: cannabiodiol. 2007. Available at: www.counterpunch.org/2007/12/22/molecule-of-the-year-cannabiodiol/ (accessed July 23, 2018).
36. Jones NA, Hill AJ, Smith I, et al. Cannabidiol displays anti-epileptiform and anti-seizure properties in vitro and in vivo. *J Pharmacol Exp Ther.* 2010;332:569–77.
37. Jones NA, Glyn SE, Akiyama S, et al. Cannabidiol exerts anti-convulsant effects in animal models of temporal lobe and partial seizures. *Seizure.* 2012;21:344–52.
38. Hill AJ, Mercier MS, Hill TDM, et al. Cannabidivarin is anticonvulsant in mouse and rat in vitro and in seizure models. *Br J Pharmacol.* 2012;167:1629–42.
39. Potter D, Clark P, Brown M. Potency of delta 9–THC and other cannabinoids in cannabis in England in 2005: implications for psychoactivity and pharmacology. *J Forensic Sci.* 2008;53:90–4.
40. Harborside. Steve DeAngelo: Leading the Way. Available at: www.shopharborside.com/about/ourteam.html (accessed July 23, 2018).
41. Weed Wars. Dir. Alex Braverman. Perf. Steven DeAngelo. Braverman Productions Inc. 2011. Documentary.

42. About Project CBD. Project CBD. 2018. Available at: www.projectcbd.org/about/about-project-cbd (accessed July 23, 2008).
43. US Food and Drug Administration. Expanded Access (sometimes called "Compassionate Use"). 2018. Available at: www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.html (accessed July 23, 2018).
44. Volkow ND, Baler RD, Compton WM, Weiss SRB. Adverse health effects of marijuana use. *N Engl J Med.* 2014;370:2219–27.
45. Campolongo P, Trezza V, Ratano P, et al. Developmental consequences of perinatal cannabis exposure: behavioral and neuroendocrine effects in adult rodents. *Psychopharmacology.* 2011;214:5–15.
46. Whalley BJ. Cannabis in the management and treatment of seizures and epilepsy: a scientific review. American Herbal Pharmacopoeia: Therapeutic Compendium. 2014. Available at: www.alchimiaweb.com/blogfr/wp-content/uploads/2015/11/AHP-Therapeutic-Compendium-Cannabis-Epilepsy-and-Seizures-Scientific-Review.pdf (accessed August 22, 2018).
47. Devinsky O, Marsh E, Friedman D, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. *Lancet Neurol.* 2016;15:270–8.
48. Cable News Network (CNN). Young S. Marijuana stops child's severe seizures. 2013. Available at: www.cnn.com/2013/08/07/health/charlotte-child-medical-marijuana/index.html (accessed July 23, 2018).
49. Maa E, Figi P. The case for medical marijuana in epilepsy. *Epilepsia.* 2014;55:783–6.
50. Devinsky et al. Trial of cannabidiol for drug resistant seizures in Dravet syndrome. *N Engl J Med.* 2017;376:2011–20.
51. Devinsky O, Patel AD, Cross HJ, et al. Effect of cannabidiol on drop seizures in the Lennox–Gastaut syndrome. *N Engl J Med.* 2018;378:1888–97.
52. Thiele EA, Marsh ED, French JA, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet.* 2018;391:1085–96.
53. ClinicalTrials.gov. GWPCARE2 A Study to Investigate the Efficacy and Safety of Cannabidiol (GWP42003-P) in Children and Young Adults With Dravet Syndrome. 2016. Available at: https://clinicaltrials.gov/ct2/show/NCT02224703 (accessed August 6, 2018).
54. Porter B, Jacobson C. Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. *Epilepsy Behav.* 2013;29:574–7.
55. Epidiolex Prescribing Information. 2018. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf (accessed August 29, 2018).

The White House
Mill Road
Goring-On-Thames
RG8 9DD
UK

Tel.: +44 (0) 207 193 5482
E-mail: info@touchmedicalmedia.com
www.touchNEUROLOGY.com

touchmedical media®

www.touchmedicalmedia.com