

We're Not on OxyContin Anymore, Toto

By Rebecca Flint Marx, from *California*

Can cannabinoids help alleviate America's opioid crisis?

Perry Solomon is used to people extolling the virtues of medical cannabis.

Dr. Solomon is the chief medical officer of HelloMD, a website that bills itself as one of the nation's largest online medical cannabis communities. Over the past five years, the site has issued more than 70,000 recommendations for patient cannabis use in the state of California alone. And 65 percent of those recommendations, Solomon says, have been for pain.

"Just yesterday, my cell phone rang,

and it was a gentleman whose wife was using Vicodin for her fibromyalgia, and he wanted to know how to get her off of it," Solomon reports. "We get questions like that all the time."

So last year, HelloMD and the University of California, Berkeley, decided to conduct a survey of HelloMD patients to see how well cannabis worked as a substitute for opioid- and non-opioid-based pain medications. Solomon was expecting positive results; similar earlier studies had shown that between 40 and 60 percent

of participants were able to reduce their opioid use with medical cannabis.

But, he recalls, "I was shocked."

When Solomon and his co-authors looked at the results of the study—the largest patient survey ever conducted on the topic—they found that 97 percent of the survey's 2,897 respondents reported that they had decreased their opioid use while taking cannabis. "That's almost everybody who uses cannabis," Solomon says. "It's an exit drug for the vast majority of patients."



That may be overstatement. The study had its flaws, after all: Patients were self-reporting, and, as HelloMD members, they were already biased towards medical cannabis. Still, Solomon finds the results convincing. “It was statistically significant that so many people were affected in a positive way. The validity was in that large number.”

On the topic of numbers, those that illustrate prescription opioid abuse in this country are sobering. According to the Centers for Disease Control and Prevention, deaths from opioid overdoses have risen exponentially since 1999. In February 2017, the agency reported that more than 183,000 Americans died from prescription opioid-related overdoses in the last 16 years, with an average of 115 deaths every day. Factor in deaths from heroin overdoses—of which there were 13,000 in 2015 alone—and the total number grows even more daunting.

Over the past decade, as prescription drug overdoses have claimed celebrities such as Heath Ledger, Michael Jackson, Prince, and Tom Petty, public awareness of the opioid epidemic has grown. Journalist John Temple recently noted that in 2017, the terms “opioid” and “prescription drug overdose” appeared in 42,456 newspaper stories. That rising awareness happens to dovetail with the growing number of states—29, including California—that have legalized the use of medical cannabis.

And this is where people like Solomon see further support for the idea that cannabis might offer a solution to the opioid problem. They can tell you, for example, that last year researchers at UC San Diego found that, in states with legal cannabis, opioid abuse rates dropped by 23 percent, while opioid overdose cases fell an average of 13 percent. They

can point you to another study, which found that, in states with legal cannabis, a typical doctor prescribes 1,826 fewer painkiller doses to Medicare patients in a given year because those seniors prefer to medicate with pot.

Unlike opioids, medical cannabis has few serious side effects and doesn't pose the risk of fatal overdose. Amanda Reiman is one of the HelloMD study's co-authors and a former lecturer at Berkeley's School of Social Welfare.

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In various studies she has conducted over the past 15 years, she found that subjects substituted cannabis for other medications for similar reasons: less potential for addiction and withdrawal, and effectiveness equal to if not greater than those other medications. And that has particularly important implications for aging patients, who, Reiman says, “are more vulnerable to drug dependence and interactions because we have a different metabolism as we age.”

USE OF THE CANNABIS plant as medicine goes back a very, very long time: Recorded instances can be traced to 2737 B.C. when the Chinese emperor Shen Neng was prescribed cannabis tea for a host of ailments that included gout and rheumatism. In the United States, late-18th-century medical journals recommended hemp seeds and roots for numerous treatments. And Irish doctor William O'Shaughnessy first popularized the use of medical cannabis in 18th-century America and England.

But at the end of the 19th century, an epidemic of addiction to another opioid, morphine, led to the 1906 Pure Food and Drug Act, which in turn created the Food and Drug Administration. Chemical substances were now being regulated, and in 1914 the Harrison Narcotics Act made drug use a crime. In 1937, passage of the Marijuana Tax Act made it illegal to possess and sell cannabis; and, although the act was later deemed unconstitutional, the Controlled Substances Act of 1970 classified cannabis as a Schedule 1 drug, meaning it was considered highly addictive and having no accepted medical use.

The country's only legal source of cannabis today is the National Institute on Drug Abuse, and to date, there are only two FDA-approved cannabis-derived pharmaceutical products available in the United States: dronabinol (Marinol) and nabilone (Cesamet), which have been used to treat chemotherapy-induced nausea and vomiting and AIDS-related wasting since 1985. As a result, says Donald Abrams, a professor at the UCSF School of Medicine and a general oncologist at Zuckerberg San Francisco General Hospital, oncologists have “a lot of familiarity” with the potential

of cannabis to treat certain conditions. Abrams himself led a 2011 study that found chronic pain patients who took medical cannabis in conjunction with their opiate medication had greater pain relief, suggesting that such patients could take lower doses of opiates for longer periods of time if used in conjunction with cannabis.

But when asked about the potential of cannabis as a viable alternative to opioid painkillers, Abrams demurs. Because of all of the restrictions placed on researching cannabis, the question “is sort of hard to answer without data,” Abrams says. “Medicine is quite evidence based. In absence of such evidence, it’s not going to make a lot of change in people’s prescribing habits.”

ABRAMS IS CORRECT to point to a dearth of peer-reviewed research about the potential of cannabis as an alternative to opioids. But that hasn’t stopped a number of companies from developing cannabidiol-based drugs (cannabidiol, or CBD, is a nonpsychoactive chemical compound found in cannabis). Given that the global pain market is expected to reach \$52 billion by 2022, there is great incentive to learn more about how the body responds to cannabis. As pointed out by David Presti, professor of neuroscience, biology, and cognitive science at Berkeley, “lots of careers can be built on better understanding the genius of the cannabis plant.”

Costa Mesa-based Nemus Bioscience has managed to find its way around one obstacle to researching and developing its roster of cannabinoid-based drugs: by teaming up with the University of Mississippi, which happens to be the only entity in the U.S. licensed by the federal government to research and cultivate cannabis legally.

But Nemus CEO Brian Murphy says that the biggest challenge to making cannabinoid-based drugs isn’t the government. It’s turning cannabinoids—the molecules that interact with cannabinoid receptors located throughout the body’s endocannabinoid system (which is in turn involved with regulating processes such as appetite and pain sensation)—into drugs that can enter the body in a reliably consistent way that achieves predictable blood levels. Cannabinoid molecules are fat soluble, Murphy explains, which means they don’t cross cellular membranes very well. “If you consume cannabinoids orally, the amount absorbed can vary and be uneven, as can be the rate the molecule is metabolized by the liver. This variation can impact blood levels that at times can lead to too much exposure, and other times, not enough,” he says.

The cannabis plant has more than 100 types of cannabinoid molecules. Nemus, with UMiss, is focused on bioengineering six key molecules from the plant to make them more amenable to absorption, so that they can cross membranes more effectively. One of the drugs in the Nemus pipeline is targeted at pain syndromes, potentially as a safer substitute for opioids. Murphy says these molecules, unlike THC, “have been shown not to possess psychogenic side effects”—and thus mediate the perception of pain without altering a patient’s sense of reality.

Another company to watch in the burgeoning market for cannabinoid-based drugs is GW Pharmaceuticals, the British manufacturer of Epidiolex, a cannabinoid-based epilepsy drug that is undergoing application for approval by the FDA. If approved, Murphy says, “we expect it to be a major positive for the

cannabinoid biotech industry, and good in a way that will hopefully get clarity from regulatory agencies on the handling and classification of the drug.”

With all of the drug manufacturers now eager to add cannabinoid-based medications to their arsenals, “this is like the tech boom in the late ’90s,” Murphy adds. “There are tons of small companies. Ultimately, it’s either go big or go home.”

Regardless of whether companies manage to bring their cannabinoid-based drugs to market, it’s still far too early to know how effective they could be as an alternative to opioid painkillers. Even putting aside the relative scarcity of research into cannabinoids and government restrictions on their development, there are plenty of obstacles to contend with. A big one is social acceptance.

Living in the Bay Area, it’s easy to forget the stigma that still exists around cannabis. Amanda Reiman reports, “I hear people say, ‘I would use cannabis, but’—and the ‘but’ is usually, ‘I don’t want people to know I use cannabis.’” She adds that the stigma is particularly strong towards women and people of color who admit to cannabis use. And those negative perceptions extend to assumptions about the safety of the drug itself. “There’s a weird arbitrary line we draw between illegal and legal that somehow equates to ‘safe’ and ‘not safe,’ even though cannabis is way safer than most drugs.” As an example she points to Tylenol, which is easily accessible and considered safe despite the fact that, if taken in high doses, it can cause liver damage and even death.

And even if medical cannabis does prove to be as effective in treating pain as opioid medications, it’s not likely to help reduce opioid addiction, says

Tomás Aragón, health officer for the San Francisco Department of Public Health and assistant adjunct professor of epidemiology at Berkeley. “The treatment of pain and the treatment of addiction are two separate things,” Aragón points out, adding that “once someone is addicted to opioids, I don’t think cannabis is going to help them get off [them].” And while having more options to address pain is “fantastic,” he continues, all of the options in the world won’t solve the larger underlying issue: Big Pharma.

“They basically lied and distorted to make physicians believe that you can manage chronic pain with opioids,” Aragón says. “That’s the biggest driver [of the crisis]. Once people are addicted, they’re still going to have pain,

but also the pain of withdrawing from opioids. If they can learn to manage their pain early on so they don’t have to be exposed to opioids, that would be ideal.” And medical cannabis may well offer a hopeful alternative for that early pain management. As David Presti says, “there’s lots and lots of hints and clues and indications that there is so much that is useful here, and that should really be explored.” But, he warns, further exploration will have to somehow overcome considerable legal restrictions and pushback from the pharmaceutical industry.

And that could take a while.

In the meantime, proponents of medical cannabis envision a world of greater possibilities. Amanda Reiman sees a growing role for other cannabis products, such as topical creams, and teas for general wellness and as alternative sleep aids.

“My hope,” she says, “is that we move cannabis to being an over-the-counter medication so that different individuals will learn other ways to incorporate it into their lives in a way that’s not just about intoxication.” 

Rebecca Flint Marx has been an editor and writer for several publications including *Entertainment Weekly*, *New York, Elle*, and *The Village Voice*. Reprinted from *California* (Spring 2018), a quarterly publication of the Cal Alumni Associate at University of California, Berkeley. www.californiamag.org



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