Austism Spectrum Disorder, and Benefits of Cannabis Use:

Cannabis & Tech Today

Terpene-Enriched CBD Potentially More Effective Than CBD Alone for Autism

JANUARY 23RD, 2023

One thing that I often point out to people is that the cannabis plant is one of the most dynamic plants on earth, and that in many ways humans are just beginning to scrape the surface of understanding and harnessing its full potential. Now it seems terpene-enriched CBD could help autistic patients more than CBD alone.

The cannabis plant, and wellness products derived from it, can be used to successfully treat a number of health conditions according to an ever-increasing list of peer-reviewed studies, as well as a growing body of patient testimonials.

Research dedicated to specific cannabinoids is becoming more common, thankfully, with research focused on cannabidiol (CBD) being particularly popular these days. One area of CBD-based research that is showing a lot of promise is CBD treatments for autism patients.

Autism spectrum disorder (ASD) is a developmental disability caused by differences in the brain. Tens of millions of people around the world suffer from ASD, including an estimated 1% of all children worldwide.

Cannabis-based treatments are a fairly new thing when it comes to younger ASD patients largely due to prohibition-induced stigma, however, international researchers are exploring CBD and autism more and more thanks to reform victories in various jurisdictions.

A recent example can be found in Italy where a case study was conducted by researchers in Italy and Israel involving a young ASD patient. The patient was first diagnosed in 2008, and after exploring various conventional treatment regimens the patient eventually started to use CBD.

“On August 2018, after contacting a medical cannabis prescribing physician and consulting a specialized laboratory (THC Lab), G was first prescribed a CBD-rich cannabis extract containing 2.5% CBD. This was later exchanged with pure synthetic CBD oil at the same concentration. CBD oil was first administrated at a daily dose of 15 drops (12 mg CBD), corresponding to 0.34 mg CBD/kg bw (body weight) per day. CBD accompanied the Neuleptil treatment. This was found beneficial, completely eliminating aggression and leaving G happy and calm,” researchers stated in an article published by Frontiers in Pharmacology.

The cannabis plant, and wellness products derived from it, can be used to successfully treat a number of health conditions according to an ever-increasing list of peer-reviewed studies, as well as a growing body of patient testimonials.
“CBD treatment was efficient for 3 years, until G turned 16 years old. From April 2021, with puberty, G became highly agitated. In order to control his symptoms, the dose of pure CBD was raised, reaching 27 drops (21.6 mg CBD), corresponding to 0.48 mg CBD/kg bw per day. However, the increased dose did not result in improved efficacy. Aggression had increased, reaching more than two major aggressive events per week. Aggressive events were severe (scored eight to nine on a 0–10 subjective aggressive scale, by

G's parents)," researchers stated.

"G's regular CBD oil (pure synthetic CBD at a concentration of 2.5%) was enriched with one of two proprietary terpene blends, composed of terpenes demonstrated in pre-clinical and clinical trials to produce anxiolytic and calming effects. These included alpha pinene, limonene, linalool, beta caryophyllene and nerolidol. One of these two terpene blends was provided for daily use, and the other – for night use, or for times when G was highly agitated," researchers also stated.

"Since August 2021, G has completed 9 months of treatment with terpene-enriched CBD oil. As can be seen in Table 1 and in Figure 2, aggression was significantly reduced, from two major aggressive events per week during treatment with synthetic CBD oil, to a complete elimination of aggressive events during treatment with the same synthetic CBD oil enriched with the selected terpene blends," researchers observed.

"This case demonstrates the benefit of terpene-enriched CBD oil for treating aggression associated with ASD in an agitated adolescent. Enrichment of CBD with selected terpenes increased CBD potency, providing a therapeutic response wherein CBD alone had insufficient effect," researchers concluded.

This article first appeared on Internationalcbc.com and is syndicated here with special permission.

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(https://www.frontiersin.org/articles/10.3389/fphar.2022.979403/full)

CASE REPORT article
Front. Pharmacol., 28 October 2022
Sec. Neuropharmacology
Volume 13 - 2022 Terpene-Enriched CBD oil for treating autism-derived symptoms unresponsive to pure CBD: Case report

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Cannabidiol (CBD) rich products are successfully used in some countries for treating symptoms associated with autism spectrum disorder (ASD). Yet, CBD provides insufficient intervention in some individuals, or for some characterizing symptoms of ASD, raising the need for improved compositions. The current study presents a case wherein pure CBD was sufficient for treating ASD during childhood and early adolescence. However, it became insufficient during puberty accompanied by increased hyperactivity, agitation, and frequent severe aggressive behavior. Increasing the CBD dose did not result in significant improvement. Enriching the pure CBD with a carefully selected blend of anxiolytic and calming terpenes, resulted in gradual elimination of those aggressive events. Importantly, this was achieved with a significantly reduced CBD dose, being less than one-half the amount used when treating with pure CBD. This case demonstrates a strong improvement in efficacy due to terpene enrichment, where pure CBD was not sufficient. Combined with terpenes' high safety index and the ease with which they can be incorporated into cannabinoid-containing products, terpene-enriched CBD products may

provide a preferred approach for treating ASD and related conditions. The careful selection of terpenes to be added enables maximizing the efficacy and tailoring the composition to particular and changing needs of ASD subjects, e.g., at different times of the day (daytime vs nighttime products).

Background

Autism spectrum disorder (ASD) is a group of heterogeneous neurodevelopmental disorders, commonly characterized by an early-onset impairment in social interactions and communications, accompanied by restricted or repetitive patterns of behavior. Approximately 50% of ASD children and adolescents demonstrate behavioral difficulties, including aggression, self-injury, tantrums and hyperactivity. Anxiety disorders are highly prevalent, ranging between 42–79% of the ASD population (Kent and Simonoff, 2017). Sleep disorders, gastrointestinal disorders and immune dysfunction are also quite frequent. The incidence of ASD is about 1–2.5% (Aran and Cayam-Rand, 2020; Su et al., 2021).

Currently, no established pharmacological treatment for the core symptoms of ASD is available. Some medications were approved by the United States Food and Drug Administration (FDA) to treat associated symptoms, including irritability, aggression and behavioral disorders. Commonly used medications include psychotropic drugs (such as atypical antipsychotics), selective serotonin reuptake inhibitors (SSRI's), stimulants or anxiolytics. However, long-term use of these drugs may cause serious side effects, including sedation, apathy and weight gain. Additionally, these medications are frequently insufficient to provide a significant improvement. The most common treatment for ASD nowadays comprises behavioral and educational therapies; however, these are inadequate or unsuitable for many ASD individuals (Canitano and Scandurra, 2008; Wink et al., 2010; Quintana et al., 2021).

An increasing number of studies has pointed to the potential role of cannabidiol (CBD), the second most abundant cannabinoid in the cannabis plant, in treatment of multiple symptoms associated with ASD (Gu, 2017; Aran et al., 2019a; Bar-Lev Schleider et al., 2019; Barchel et al., 2019; Su et al., 2021). Accordingly, CBD-based products are increasingly prescribed for relieving ASD-associated symptoms. Yet, a considerable variation between countries exists. Epidolex, a pure CBD preparation was recently approved by FDA for treating seizures associated with Lennox-Gastaut syndrome, Dravet syndrome or tuberous sclerosis complex. Given their comorbidity with ASD, CBD is currently used for treating a sub-population of the ASD patients.

The endocannabinoid system in ASD

The endocannabinoid system (ECS), the endogenous target of cannabis active pharmaceutical ingredients (APIs), plays an important role in central nervous system (CNS) development, in synaptic plasticity, and in the response to endogenous and environmental insults. The ECS has a major role in controlling and regulating multiple physiological systems. Particularly, the ECS has been shown to participate in the regulation of social reward behavior, plausibly by oxytocin-dependent activation of the ECS (Wei et al., 2015), and was suggested, by both animal models and clinical studies, to be a potential target for the treatment of autism. (Aran et al., 2019b; Su et al., 2021; Zou et al., 2021).

The ECS comprises cannabinoid receptors, endocannabinoids as ligands, and enzymes responsible for the synthesis and degradation of these endocannabinoids. 2-Arachidonoyl glycerol (2-AG) and arachidonoyl ethanolamine (Anandamide, AEA) are the best-studied endocannabinoids. They have different synthesis and degradation conducted by different enzymatic pathways and impart distinct physiological and pathophysiological roles. The ECS involves multiple cannabinoid receptors, the most common being cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2), which are mostly expressed in the central nervous system and throughout the immune system, respectively. Other

receptors include the transient receptor potential (TRP) channels, and the peroxisome proliferator activated receptors (PPAR's). In addition to their activation by endogenous cannabinoids (endocannabinoids), the ECS receptors are responsive to exogenous cannabinoids, which could be of two types, phytocannabinoids - extracted from the cannabis plant, and synthetic cannabinoids (e.g. (Pacher et al., 2006; De Petrocellis and Di Marzo, 2009; Lu and MacKie, 2016)).

Studies have pointed to a possible deficiency of the ECS in ASD, which is plausibly involved in known ASD comorbidities, including anxiety, cognitive impairments and sleep disturbances. Alterations of the ECS have been demonstrated in several animal models of ASD. In some of these models, activating the ECS reversed the social deficits. Recent studies have demonstrated lower serum levels of AEA (Zamberletti et al., 2017; Karhson et al., 2018; Aran et al., 2019b), as well as of PEA (N-palmitoylethanolamine) and OEA (N-oleoylethanolamine); two endocannabinoid-like compounds in children with ASD as compared to controls. These may suggest that impaired signaling of AEA (and possibly of their associated compounds) is involved in the pathophysiology of ASD. However, further studies are required to support such claims (Aran et al., 2019b)
(https://cannatechtoday.com/terpene-enriched-cbd-potentially-more-effective-than-cbd-alone-for-autism/)

Athletic Medicine and Benefits of Cannabis Use:

Darren McCarty knew how to beat any drug test. Now his marijuana brand is on the market
Evan Petzold
Detroit Free Press - July 2, 2020.

Drug tests were like a circus for former Detroit Red Wing Darren McCarty during his playing days.

With cannabis in his system from the night before (smoking helped him sleep), he'd pass the random test through manipulation, or fail. He once used synthetic urine and broke the testing machine. That cost him a $20,000 fine from the NHL.

"That's just the way it is, bro," he said. "What are you gonna do? Life's about consequences — positive and negative. I'm the market. I'll go first because what's the worst thing that could happen? They kill me. But once they get by me, dude, you guys are on your own. I'm off to another place anyway."

He'd typically pass by tampering with the test, but he's not quite ready to give up those secrets from his playing days, which span from 1993 to 2009 and include four Stanley Cups with the Red Wings.

Former Detroit Red Wings player Darren McCarty has created his own brand of medical marijuana products.
What he will unveil, however, is the Darren McCarty Pucker Up pre-rolls. Featuring a 5-to-1 THC-to-CBD ratio, McCarty's brand of medical marijuana will be available for purchase at 10 a.m. Thursday at Pincanna, a dispensary in Kalkaska.

[As he joins the pot business, memorable moments from Darren McCarty's career]

At some point, the product will be available at three other locations, ranging from the Bay City area to

Negaunee in the Upper Peninsula. Ideas for future include CBD and hemp products, new marijuana strains and a high-potency chocolate peanut-butter candy bar infused with marijuana.

"I love this plant," McCarty said. "When I retired, I took that Red Wing off and put the cannabis plant on the chest of my jersey. I will protect it as much as I protected any of my Red Wing teammates. It's just the right thing."

The "Brawl in Hockeytown" on March 26, 1997 at Joe Louis Arena is the signature moment of the bloody Red Wings-Avalanche rivalry that lasted for about a decade. Here, Darren McCarty punishes Claude Lemieux.
When he had a sports hernia in 1999, the doctor gave him pills for the pain, but it became tough for him to sleep. One night, he decided to smoke some weed.

"My body was like, 'What the hell? Wait, hold on, somebody is lying to you,' " said McCarty, who was 27 at the time. "So the fact that I put my mind to something, then I got educated because it saved my life. I came to it later, but the education is there. It's always been there. I'm glad everybody's sort of catching up to the reality of it."

He went back and forth on how to utilize marijuana because it wasn't (and still isn't) allowed in the NHL. He didn't share it with his teammates, using it only when he was with a different group of friends outside of hockey, and also to help him sleep.

[Sober again: 'This is a different Darren McCarty']

"I wasn't the weed warrior that I am now," he said. "Now I know the truth."

On Nov. 11, 2015, McCarty quit drinking alcohol after a near-death experience. He had been to rehab four times, spent more than $1 million on therapy, went through more substance-abuse programs than he can count, and believed his life was on the line.

Former Detroit Red Wings player Darren McCarty has created his own brand of medical marijuana products.
That's when he found cannabis. He hasn't consumed alcohol since.

McCarty smokes every day. He takes CBD, hemp topicals and a couple of grams of weed each morning. Then, depending on what he has going on, he'll take an edible or smoke again. At night, he usually enjoys a pot brownie.

"I'm never high," he said. "I'm fully medicated."

As an advocate for marijuana legalization, McCarty wants NHL players to be able to use weed in certain situations rather than turn to pills or shots that could become addicting. He's calling for people to become educated about the benefits of marijuana, which he said includes healing of the body.

Darren McCarty with his then 5-year-old son, Griffin on his shoulders raises the Stanley Cup during post game celebrations after their Game 5 win over the Carolina Hurricanes in 2002.
Right now, all marijuana use, including medical, is illegal in 11 states. Marijuana is fully legal in 11 states, plus the District of Columbia. Even the NFL has changed its marijuana testing policy.

McCarty used to stay quiet about his marijuana use, but he's now an advocate for its legalization across the board.

[Former Red Wing Darren McCarty joins marijuana company, says pot saved his life]

"I believe there's more people like me that have suffered for so long, so that's why having my own brand is so important," he said. "It gives me a bigger platform to talk about it. I'm not just talking about it, I am about it.

"That's what I do. March 26, 1997. It's the same thing: vulnerable truth with integrity. Get on board. That's my march, and this is what I'm doing."

And if you remember March 26, 1997, then you know McCarty won that fight.

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(https://www.freep.com/story/sports/nhl/red-wings/2020/07/02/detroit-red-wings-darren-mccarty-marijuana-brand/5357920002/)

OPINION- Tampa Bay Times
Guest Column
Denise Vidot
With so many concussions in the NFL, we need to respect cannabis for treatment, recovery | Column.
Cannabis has been shown to reduce inflammation and assist in rebuilding connections within the brain (neuroplasticity) that were damaged via concussion or during recovery.
Medical staff tend to Miami Dolphins quarterback Tua Tagovailoa during a game against the Cincinnati Bengals in September. He was unconscious after being thrown to the ground and says he doesn't remember being carted off the field.

Published Nov. 19, 2022
How many concussions do we need to witness before a treatment regimen that includes cannabis takes hold?

Despite the NFL's $1 million investment in studying cannabis' potential for improving post-concussion outcomes — and the conclusive evidence of its benefits — the league has yet to implement comprehensive policies allowing for its use in treatment and recovery, even though the incidence of concussions continues to rise.

Denise C. Vidot
Denise C. Vidot [Provided]
Recently, Miami Dolphins fans and millions on television watched as star quarterback Tua Tagovailoa lay motionless for several minutes after a crushing tackle that caused a concussion. On another week, six NFL players suffered concussions.

I run the Sports Medicine Subdivision of the Global Cannabis and Psychedelics Laboratory at the University of Miami School of Nursing and Health Studies.

After witnessing this unsettling increase in concussions in the NFL, my team and I asked the question: When is it enough before a treatment regimen that includes cannabis is taken seriously?

And it's not just the NFL. The World Cup — soccer's premier event — is set to begin Sunday in Qatar. Those who play soccer, or that other "football" sport, also suffer a staggering number of concussions — second only to American football.
For the NFL, 26 of its 32 teams are located in states that have legalized cannabis.

Yes, there have been revisions to the cannabis use policy after negotiations with the NFL Players Association. These revisions allow for more leniency in testing limits, but still hold potential for fines and suspensions after consecutive positive tests. Specific to Tagovailoa's situation, what is the implementation of cannabis allowance after a player concusses? There is emerging evidence, especially over the past 5 years, showing improvements in post-concussion outcomes among those who consume cannabis compared to those that do not. Will Tua and other recent players who have suffered concussions in the game be offered cannabis as part of their short- and long-term recovery?

Cannabis has been shown to reduce inflammation and assist in rebuilding connections within the brain (neuroplasticity) that were damaged via concussion or during recovery. There are ongoing studies funded by the NFL and National Institutes of Health (NIH) to study cannabis, concussions, and concussions' side effects.

One of the biological reasons cannabis can influence our health, especially after concussions, is because of its near-perfect match with a vital system within the human body — the endocannabinoid system — responsible for maintaining the body's balance. Imagine all the organs in our body have a puzzle piece (receptor) waiting for a matching puzzle piece, and cannabis has over 180 of them called cannabinoids. CBD and THC are the most well-known and studied cannabinoids in the United States and have both been shown to impact inflammation and neuroplasticity along with other health benefits, leading to significant shifts in the acceptance of cannabis use in our national society.

Of course, there is a portion of the population that may not experience the benefit of cannabis. Though studies are still being conducted for validation, it is possible that this may be due to a person's baseline endocannabinoid system. If the baseline is already in balance, introducing cannabis may over-supplement the endocannabinoid system and cause imbalance, leading to negative health impacts. Since most receptors for THC, the psychoactive component of cannabis, are in the brain, over-supplementation may lead to mental health imbalances in some consumers. Therefore, it is critical to recognize that "not all cannabis is created equal." Additionally, most to-date research on the potential benefits of cannabis have been related to CBD, thus support for additional studies on other cannabinoids and their potential health benefits is more important than ever.

Our sports medicine laboratory is focused on providing evidence on the potential of cannabis and psychedelics to improve the negative mental and physical health status of NFL and NCAA players before, during and after the game. Our team, which provides lectures, workshops, and seminars at conferences, includes Tywan G. Martin, associate professor in the University of Miami Department of Kinesiology and Sport Sciences, and former NFL stars Mike James (Detroit Lions and Tampa Bay Buccaneers) and Boo Williams (New Orleans Saints).

Science has provided evidence on the potential benefit of cannabis use for post-concussion, post-

traumatic brain injury and also, independent of injury, as part of wellness treatment to reduce inflammation.

It is well past time that policies be changed in professional sports to allow players the freedom of choice to obtain the health care resources and best options available to facilitate their recovery.

Denise C. Vidot is a cannabis epidemiologist and associate professor at the University of Miami School of Nursing and Health Studies.

(https://www.tampabay.com/opinion/2022/11/19/with-so-many-concussions-nfl-we-need-respect-cannabis-treatment-recovery-column/)

Long Overdue, Cannabis Needs to Have a Place in Professional Sports
Ohio State Legal Studies Research Paper No. 692
Drug Enforcement and Policy Center, No. 45, March 2022
15 Pages Posted: 22 Mar 2022
Caroline M. Rice
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Date Written: March 9, 2022

Abstract
Although most professional sport leagues amongst the Big Four (National Football League, National Basketball Association, Major League Baseball, and National Hockey League) have restrictions on athletes' use of cannabis, many professional athletes have spoken out about turning to cannabis as relief for the chronic pain caused by playing professional sports. This paper explores how as a result of cannabis being wrongly classified as a Schedule I drug on the Controlled Substances Act, professional leagues followed suit restricting cannabis use and leaving athletes with rigid marijuana testing policies and an overuse of prescription painkillers. This paper then analyzes the medicinal benefits of marijuana use for professional athletes, and subsequently argues for further use of cannabis in professional sports in the United States.

Note:
Funding Information: None.

Declaration of Interests: No financial or non-financial competing interests to report.
Keywords: Athletes, Professional Sports, Professional Athletes, Pain, Public Opinion, Painkillers, Medicinal Benefits, Marijuana, Cannabis, League Cannabis Policies

Suggested Citation:
Rice, Caroline M., Long Overdue, Cannabis Needs to Have a Place in Professional Sports (March 9, 2022). Ohio State Legal Studies Research Paper No. 692, Drug Enforcement and Policy Center, No. 45, March 2022, Available at SSRN: https://ssrn.com/abstract=4053967 or http://dx.doi.org/10.2139/ssrn.4053967

(https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4053967)

Alzheimers, and Cannabis Use-

In the lab
A key hallmark of Alzheimer's disease is the build up of clumps of a protein, called amyloid, in the brain. Some studies have shown that components of cannabis, including THC, appear to remove this protein from nerve cells grown in the lab.

Another study that gave both THC and CBD oil to mice with symptoms of Alzheimer's disease showed an improved in learning and had less evidence of amyloid clumps in their bodies.

Research continues to better understand the effects of CBD oil on the brain. Some early evidence suggests that CBD oil may reduce inflammation in the brain, although this has yet to be proven in people. (https://www.alzheimers.org.uk/)

Grant Will Fund MedPharm Study of Cannabinoids' Effects in Alzheimer's
Mary Chapman avatar
by Mary Chapman | July 26, 2022

cannabinoids Alzheimer's | Alzheimer's News Today | illustration of medical cannabinoid treatments
Cannabis researcher MedPharm has been granted funding to study the effect of phytocannabinoids — naturally occurring chemicals, called cannabinoids, from marijuana plants — on Alzheimer's disease, with the ultimate aim of treatment development.

The new funding comes from the Colorado State University Institute of Cannabis Research (ICR). It was awarded to MedPharm for its proposal, titled "Isolation and Pharmacological Evaluation of Phytocannabinoids for Alzheimer's Disease."

MedPharm, which specializes in neuropharmacology with a focus on Alzheimer's and dementia, is expected to launch its study Oct. 1.

Phytocannabinoids are naturally occurring cannabinoids found in cannabis (marijuana) plants. Cannabinoids are chemicals derived from cannabis.

"The study results will allow MedPharm to further develop innovative, bioavailable, and bioequivalent dosage forms," said Scott Karolchyk, MedPharm's director of formulation and development, in a press release. "These are important elements in support of Investigational New Drugs (INDs) and New Drug Applications (NDAs) for future FDA-approved products."

Cannabinoid-based therapy, agitation
July 15, 2021 News by Margarida Maia, PhD
New Study Will Test Cannabinoid-based Therapy for Agitation
Early research has suggested that phytocannabinoids may be able to mitigate the psychological and behavioral symptoms of dementia in Alzheimer's disease. Such products, if developed, could potentially help to erode the abnormal accumulation of amyloid, the protein that's linked to disease progression in Alzheimer's.

In particular, the phytocannabinoid cannabidiol (CBD) has been shown to have anti-inflammatory, antioxidant, and neuroprotective properties, with no psychoactive or cognition-impairing elements.

Still, there has been a dearth of large, well-controlled clinical studies that have measured the effect of cannabis or its compounds on Alzheimer's symptoms, according to the researchers.

"It's by pursuing this one-of-a-kind study in an area where research is really needed that sets MedPharm apart from other cannabis research and development companies," said Albert Gutierrez, MedPharm president. "Alzheimer's is a terrible brain disease. Any way we can provide therapies to help treat it, such as doing a pharmacological evaluation to find out what a certain compound can do, we know helps us close in on a better understanding of Alzheimer's, and perhaps a pathway to greater and more helpful cannabis-based therapies down the road."

The grant announcement comes as Alzheimer's researchers are actively seeking sources of additional funding. In June, the U.S. House Appropriations Health and Human Services subcommittee proposed a $200 million hike in federal Alzheimer's and dementia research funding.

"This is a big win for not only our team, but the entire cannabinoid research community," Duncan Mackie, PhD, MedPharm's director of pharmacology and experimental therapeutics, said about the grant. "The completion of this project will provide the first clear mechanistic and cellular evidence for the application of cannabis and cannabinoid-based natural products for the treatment of Alzheimer's disease, Parkinson's disease, and other neuroinflammatory diseases."

Gutierrez said the ICR grant will allow MedPharm to further understand the medicinal effect of cannabis compounds on the human body.

"Helping people live better, happier, and more productive lives has always been the focus of MedPharm," he added.

The amount of the grant was not disclosed.
(https://alzheimersnewstoday.com/news/medpharm-studying-cannabinoids-effects-alzheimers-new-grant/)

Addictions to Opioids, Alcohol Abuse and Benefits of Cannabis Use:

Could pot help solve the U.S. opioid epidemic?
Hints are emerging that cannabis could be
an alternative to opioid painkillers
3 NOV 2016 BYGREG MILLER
Jars full of medical marijuana are seen at Sunset Junction medical marijuana dispensary.
For researchers, marijuana is tightly regulated, but some patients can easily buy it at dispensaries like this one.
In the mid-19th century, some European doctors became fascinated with a plant-derived drug recently imported from India. Cannabis had been used as medicine for millennia in Asia, and physicians were keen to try it with their patients. No less an authority than Sir John Russell Reynolds, the house physician to Queen Victoria and later president of the Royal College of Physicians in London, extolled the medical virtues of cannabis in The Lancet in 1890. "In almost all painful maladies I have found Indian hemp by far the most useful of drugs," Reynolds wrote.

Like other doctors of his day, Reynolds thought cannabis might help reduce the need for opium-based

painkillers, with their potential for abuse and overdose. "The bane of many opiates and sedatives is this, that the relief of the moment, the hour, or the day, is purchased at the expense of to-morrow's misery," he wrote. "In no one case to which I have administered Indian hemp, have I witnessed any such results."

More than 125 years later, the misery caused by opioids is clearer than ever, and there are new hints that cannabis could be a viable alternative. Some clinical studies suggest that the plant may have medical value, especially for difficult-to-treat pain conditions. The liberalization of marijuana laws in the United States has also allowed researchers to compare overdoses from painkiller prescriptions and opioids in states that permit medical marijuana versus those that don't. Yet following up on those hints isn't easy. Clinical studies face additional hurdles because the plant is listed on Schedule I, the U.S. Drug Enforcement Administration's (DEA's) list of the most dangerous drugs.

Some researchers worry that rigorous research is being outpaced by informal experimentation, as millions of people with access to medical marijuana treat themselves. "It's clear that the policy has gone way out in front of the science in terms of allowing access to products that haven't been through the standard clinical trials process," says Mark Ware, a pain specialist at McGill University in Montreal, Canada.

quotation mark
It's mind-boggling that we have millions of people in the U.S. using cannabis for medicine and we not only don't have the proper data to help them take it appropriately, we're not doing a good job of collecting it.

RYAN VANDREY, BEHAVIORAL PHARMACOLOGIST, JOHNS HOPKINS UNIVERSITY
Nearly 2 million Americans were addicted to or abusing prescription opioid drugs in 2014, according to the Centers for Disease Control and Prevention, and the Kaiser Family Foundation estimates that more than 21,000 died from overdoses.That same year, a study published in JAMA Internal Medicine hinted that medical marijuana could make a dent in that alarming toll. The researchers, led by Marcus Bachhuber, then at the Philadelphia Veterans Affairs Medical Center in Pennsylvania, examined death certificates in all 50 states between 1999 and 2010. They found that the annual rate of deaths due to overdose on an opioid painkiller was nearly 25% lower in states that permitted medical marijuana. In 2010, that translated into 1729 fewer deaths in those states. The researchers also found that the effect grew stronger in the 5 to 6 years after the states approved medical marijuana.

More recently, David Bradford, a health economist at the University of Georgia in Athens, and his daughter Ashley, a master's student there, sought to investigate whether marijuana was supplanting conventional drugs in states where it's legal. Analyzing Medicare drug prescription data from 2010 to 2013, they found a significant difference in the number of prescriptions for several conditions, including anxiety and nausea, in states with medical marijuana. But one condition stood out from the rest: "The effect for pain was three to four times larger than all of the others," David Bradford says. In medical marijuana states, each physician prescribed an average of 1826 fewer doses of conventional pain medication each year, they reported in the July issue of Health Affairs. That translates into many millions of doses per year in those states.

The Bradfords haven't yet analyzed how many of those doses were opioid drugs versus other painkillers, but David Bradford suspects it's a large chunk. "It's suggestive evidence that medical marijuana might help divert people away from the path where they would start using [an opioid drug], and of course if they don't start, they're not on that path to misuse and abuse and potentially death."

In a follow-up study, the Bradfords analyzed prescription data from Medicaid recipients, a younger population than the Medicare enrollees in their previous study. So far, the reduction in pain prescriptions appears to be even more dramatic in this group, David Bradford says.

A rising toll

Statistics from the Kaiser Family Foundation show a growing epidemic of opioid abuse in the United States over the last 15 years. In the cartogram below, the size of each state reflects the total number of prescription opioid overdose deaths from 1999–2014. Darker colors indicate more overdose deaths relative to the state's population in 2014.

In the cartogram below, the size of each state reflects the total number of prescription opioid overdose deaths from 1999–2014. Darker colors indicate more overdose deaths relative to the state's population in 2014.

(GRAPHIC) J. YOU/SCIENCE; (DATA) KAISER FAMILY FOUNDATION/U.S. CENSUS BUREAU

Additional evidence about whether cannabis can reduce opioid use could come from Canada, which legalized medical marijuana in 2001 and might legalize recreational use as soon as next year. In Quebec, researchers established a patient registry in 2015 to collect demographic data on patients who use medical marijuana, the type and dose they take, and the conditions they're seeking treatment for, along with self-reports on benefits and adverse outcomes. McGill's Ware, who is leading the effort, says the registry is also collecting data on opioid use. "We'll certainly be looking at whether patients who manage their pain with cannabis can reduce their opioid doses over time or even wean themselves off opioids entirely," he says.

Yet in the United States, where 25 states and Washington, D.C., have legalized medical marijuana, there are no state-wide efforts to collect data on how patients are using cannabis or on whether they have been affected for good or ill, in part because marijuana is still illegal at the federal level. That's a huge missed opportunity, says Ryan Vandrey, a behavioral pharmacologist at Johns Hopkins University in Baltimore, Maryland. "It's mind-boggling that we have millions of people in the U.S. using cannabis for medicine and we not only don't have the proper data to help them take it appropriately, we're not doing a good job of collecting it."

Researchers have good reason to think marijuana might relieve pain. Tetrahydrocannabinol, or THC, the plant's main psychoactive ingredient, binds to a class of receptors on neurons that are involved in mediating pain, appetite, and mood, among other things. "It's working directly on pain pathways in the brain, spinal cord, and periphery," says Ethan Russo, a neurologist and medical director of Phytecs, a Los Angeles, California–based company developing therapies based on compounds isolated from marijuana. Previously, Russo oversaw international clinical trials for Sativex, an oral spray made by GW Pharmaceuticals in Salisbury, U.K., that has been approved in 27 countries for treating spasticity caused by multiple sclerosis and in Canada for certain types of pain. Sativex combines THC with cannabidiol, another compound in marijuana that may counteract the anxiety and cognitive side effects associated with THC and that appears to have antiinflammatory effects.

But few marijuana-based therapies have gone through clinical trials. A metaanalysis published last year in the Journal of the American Medical Association found just 28 randomized clinical trials investigating cannabis for chronic pain. (Sativex accounted for nearly half of them.) The authors concluded there was "moderate quality evidence" to support its use. Part of the reason for the scarcity of cannabis trials is that whole plants and natural extracts aren't patentable, giving pharmaceutical companies little incentive to pursue them.

Recently, however, some states that have legalized medical marijuana have begun to fund clinical studies. California, which in 1996 became the first U.S. state to legalize medical marijuana, led the way with its Center for Medicinal Cannabis Research, which has done several placebo-controlled studies on pain. Barth Wilsey, a pain management physician at the University of California in San Diego, led two of them. The first, published in 2008, found that smoking marijuana reduced pain caused by nerve damage in 38 patients, with minimal side effects. The second, published in 2013, found that vaporized cannabis, even in low doses, relieved pain in a similar group of patients who hadn't responded to traditional medications, including opioid analgesics.

A trial just getting underway at the University of Colorado (CU) Anschutz Medical Campus in Aurora will be the first to directly compare cannabis and opioid painkillers in patients with back and neck pain. "There's definitely emerging evidence in the literature for [using cannabis to treat] neuropathic pain, but there's hardly anything for chronic back and neck pain, which is one of the most common reasons people go see their doctor," says neurobiologist Emily Lindley, who will run the CU study.

Hers is one of nine medical marijuana research grants funded so far by the state of Colorado with a total of $9 million from tax collected on marijuana sales. The impetus for the study was a survey done a few years ago at CU Hospital's Spine Center. Nearly one-fifth of the 184 patients with chronic back and neck pain who responded to the survey reported using marijuana to treat their pain. Of those, 86% reported that it "moderately" or "very much" relieved their pain, and 77% said marijuana provided as much or more relief than their opioid prescription painkillers. "We expected to see some positive effects regarding pain control but not quite to that extent and not with that many patients," says Vikas Patel, chief of orthopedic spine&surgery at CU.

Now, Lindley's study will enroll 50 patients with back and neck pain, who will visit the university three times and receive either vaporized cannabis, the opioid drug oxycodone, or a placebo. (In the case of cannabis, the placebo is marijuana with the THC chemically extracted; for oxycodone, the placebo is a pill.) At each visit, the patients will be given a battery of tests to assess their pain levels and look for side effects like impairments of memory, attention, and concentration.

But such research faces regulatory obstacles, because DEA still classes marijuana as a Schedule I drug: the most dangerous drugs with no known medical benefits. It has taken Lindley nearly 2 years from the time she received her grant to start her study. Getting the required Schedule I license from DEA took about 6 months. Prior to that, the university spent tens of thousands of dollars to install secure narcotics cabinets to meet DEA's requirements and a new ventilation system to comply with its own no smoking policy.

In August, DEA rejected two petitions to remove marijuana from Schedule I. The decision was made after a scientific review by the Food and Drug Administration (FDA) concluded that the evidence for the medical benefits of marijuana did not meet their standards for new drug approval.

FDA noted that most cannabis studies to date have been fairly small—with a few dozen participants, not hundreds—and they've followed patients for a few hours, not the 12 weeks or more that's typical in the clinical trials pharmaceutical companies conduct. Another complication is the variation in how cannabis is delivered. Patients in many early studies smoked it, and people ingest varying amounts of THC per puff. Newer delivery systems, such as vaporizers and edible products, add still more uncertainty about the doses patients actually receive. Then there's the natural variation in the concentration of THC and

other cannabinoids in different strains of marijuana.

Even scientists who are bullish on the potential for medical marijuana acknowledge that consistent dosing is an issue. Yet many researchers see the situation as a Catch-22: The Schedule I listing and other restrictions on marijuana research hinder the type of studies that are needed to convince regulators to loosen those restrictions.

Two bills introduced in Congress this year aim to lower some of these hurdles. The bills would limit the time that DEA spends reviewing proposed research studies (just as FDA has 30 days to review drug studies). They would also restrict DEA's role in making sure listed drugs are stored securely. Now, DEA also has to weigh in on changes of scientific protocol, and that can really slow things down, says Vandrey of Johns Hopkins, who is collaborating on a study there to compare the analgesic effects of cannabis and the opioid drug hydrocodone in healthy subjects.

A third bill, introduced in July, aims to ease research with cannabidiol and other chemical components of marijuana. "The current interpretation [of the Controlled Substances Act] is that anything in the plant is Schedule I," Vandrey says. Even though there is no evidence that cannabidiol is prone to abuse, researchers interested in studying it have to jump through the same hoops as if their study involved whole-leaf marijuana. "That, in my mind, is just silly," Vandrey says. Research on terpenes, still another group of cannabis compounds that may have analgesic effects, faces the same hurdles.

"With changing attitudes and changing policy, I'm hopeful that research can proceed with fewer barriers," McGill's Ware says. He and others hope they'll soon be able to firm up the case for marijuana as an effective pain treatment. "I'd hate to think we're still asking the same questions 10 years from now," Ware says.
(https://www.science.org/content/article/could-pot-help-solve-us-opioid-epidemic)

Cannabis use during treatment for alcohol use disorders predicts alcohol treatment outcomes
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PMID: 27865015 PMCID: PMC5339049 DOI: 10.1111/add.13693
Free PMC article
Abstract
Aims: To compare post-treatment alcohol use between those who use cannabis and those who abstain during treatment for alcohol use disorders (AUD); and to examine potential cannabis use thresholds by comparing post-treatment alcohol use between four frequency groups of cannabis users relative to abstainers.

Design: Secondary analyses of the Combined Pharmacotherapies and Behavioral Interventions (COMBINE) Study, a randomized control trial of AUD treatments. The current study compares longitudinal drinking data between those who used cannabis versus those who abstained during COMBINE treatment.

Setting: The COMBINE Study treatments were delivered on an out-patient basis for 16 weeks. The current analyses include 206 cannabis users and 999 cannabis abstainers.

Participants: All participants met diagnosis of primary alcohol dependence (n = 1383).

Measurements: Primary exposures were any cannabis use and quartiles of cannabis use (Q1: 1-4 use days during treatment, Q2: 5-9 days, Q3: 10-44 days, Q4: 45-112 days). Outcomes were percentage of days abstinent from alcohol (PDA), drinks per drinking day (DPDD) and percentage of heavy drinking days (PHD), all measured at treatment end and 1 year post-treatment.

Findings: Compared with no cannabis use, any cannabis use during treatment was associated with 4.35% [95% confidence interval (CI) = -8.68, -0.02], or approximately 4 fewer alcohol abstinent days at the end of treatment. This association weakened by 1 year post-treatment (95% CI = -9.78, 0.54). Compared with no cannabis use, only those in the second quartile of cannabis use (those who used once or twice per month during treatment) had 8.81% (95% CI = -17.00, -0.63), or approximately 10 fewer days alcohol abstinent at end of treatment, and 11.82% (95% CI = -21.56, -2.07), or approximately 13 fewer alcohol abstinent days 1 year post-treatment. Neither any cannabis use nor quartiles were associated with DPDD or PHD at either time-point.

Conclusions: Among individuals in alcohol treatment, any cannabis use (compared with none) is related to a significantly lower percentage of days abstinent from alcohol post-treatment, although only among those who used cannabis once or twice per month.

Keywords: Alcohol; alcohol dependence; alcohol use disorders; cannabis; marijuana; treatment.

Conflict of interest statement
The authors have no conflicts of interest to declare.
(https://pubmed.ncbi.nlm.nih.gov/27865015/)