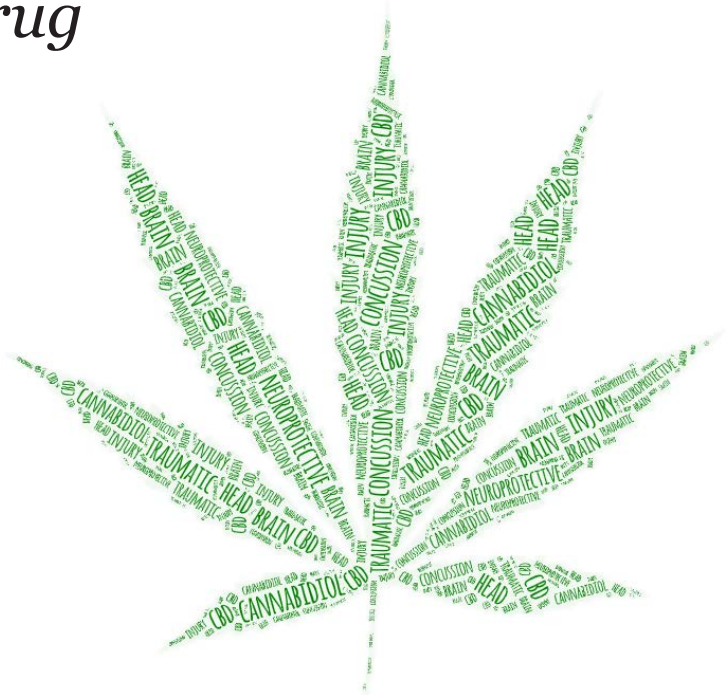
Actually, Say Yes to Dope

A Much-Maligned Drug May be the Key to Saving the Brain from Concussions

by Charles Adams



In what was supposed to be the prime of his career, Calvin Johnson walked away from the sport he loved. While hard work and talent made him one of the most prolific wide receivers in the history of the National Football League (NFL), the years of physical abuse took a toll on his body, and his brain. His team, the Detroit Lions, and the NFL seemed unable or unwilling to properly assist Johnson in managing the damage and the pain. So, he turned to one particular compound after every game, which he claims helped him play for as long as he did. As he confessed to Sports Illustrated, "I had my preferred choice of medicine. Cannabis." Cannabis allowed Johnson to continue to play, and it enabled Johnson to walk away early but mostly whole.[1]

Johnson certainly suffered his fair share of injuries over his nine-year career, from fingers pointing the wrong direction to having at least nine concussions.[1] He needed some way to recuperate, but he found limited viable options. He argues that smoking cannabis was much better than the treatments that he typically saw in the team training room.

"When I got to the league, [there] was opioid abuse,' Johnson says. 'You really could go in the training room and get what you wanted. I can get Vicodin, I can get Oxy[contin].It was too available. I used Percocet and stuff like that. And I did not like the way that made me feel."[1]

Recent evidence suggests that the retired player might have been on to something, especially in the context of concussions and other traumatic brain injuries (TBIs).

Since retiring, Johnson has become a significant advocate of the use of marijuana for medical purposes.[1] He is not alone. Players around the NFL are jumping on the cannabis bandwagon, along with athletes across the professional sports world. Megan Rapinoe, one of the world's highest profile female athletes and member of the United States' Women's National Soccer Team, is a vocal proponent of cannabidiol (CBD) treatment.[2] CBD is one of the major components of marijuana and the subject of

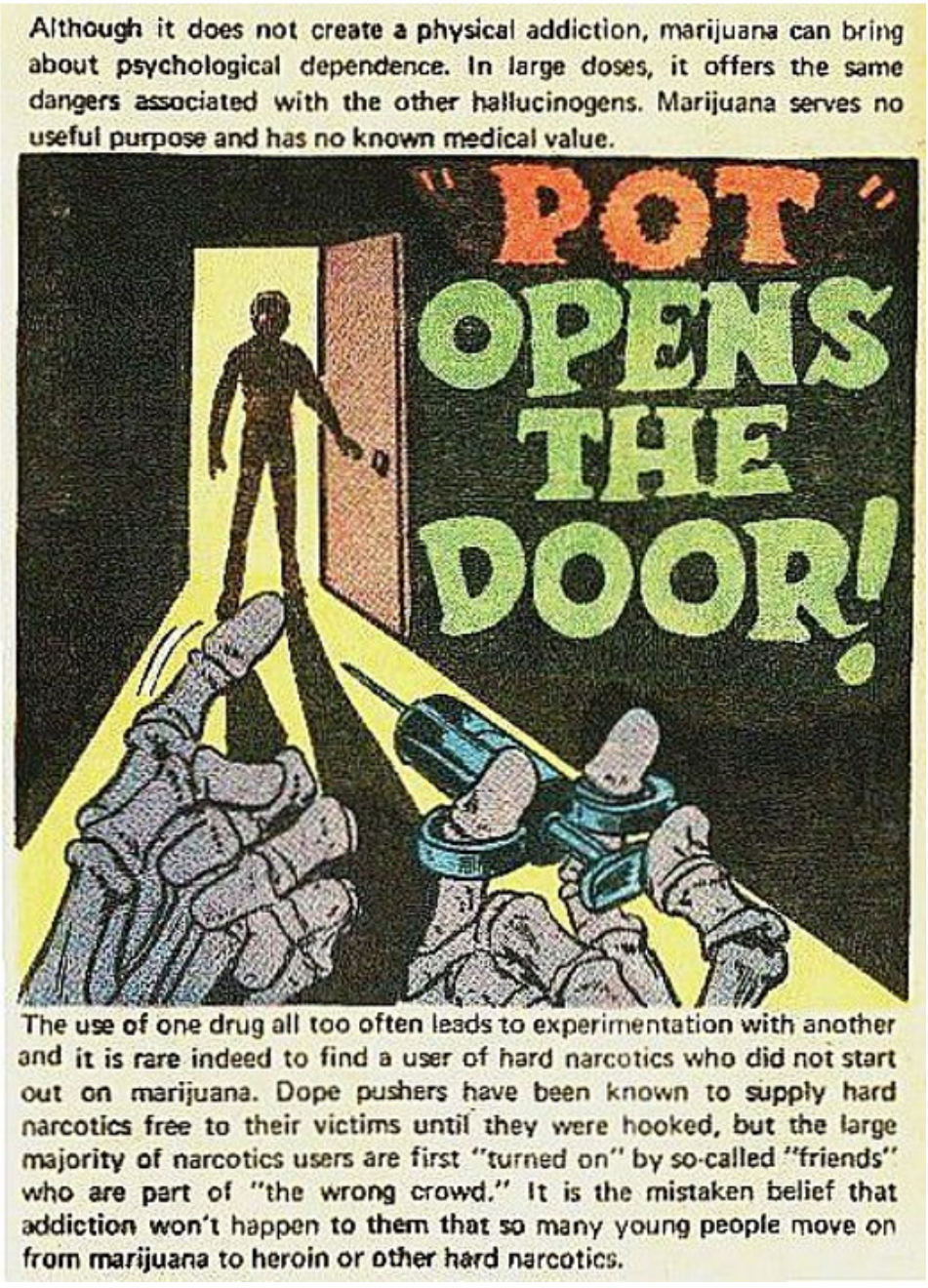
many promising clinical studies. Having suffered multiple severe knee injuries throughout her career, Rapinoe believes that CBD helped with the injury recovery process and with managing pain.[2] If so many athletes tout the restorative properties of the compound, why is it that cannabis and CBD are not widespread treatments? Well, as most people know, cannabis has been demonized for decades, making its use illegal and scientific research nearly impossible.

Sorry Not Sorry: A Little Bit of History

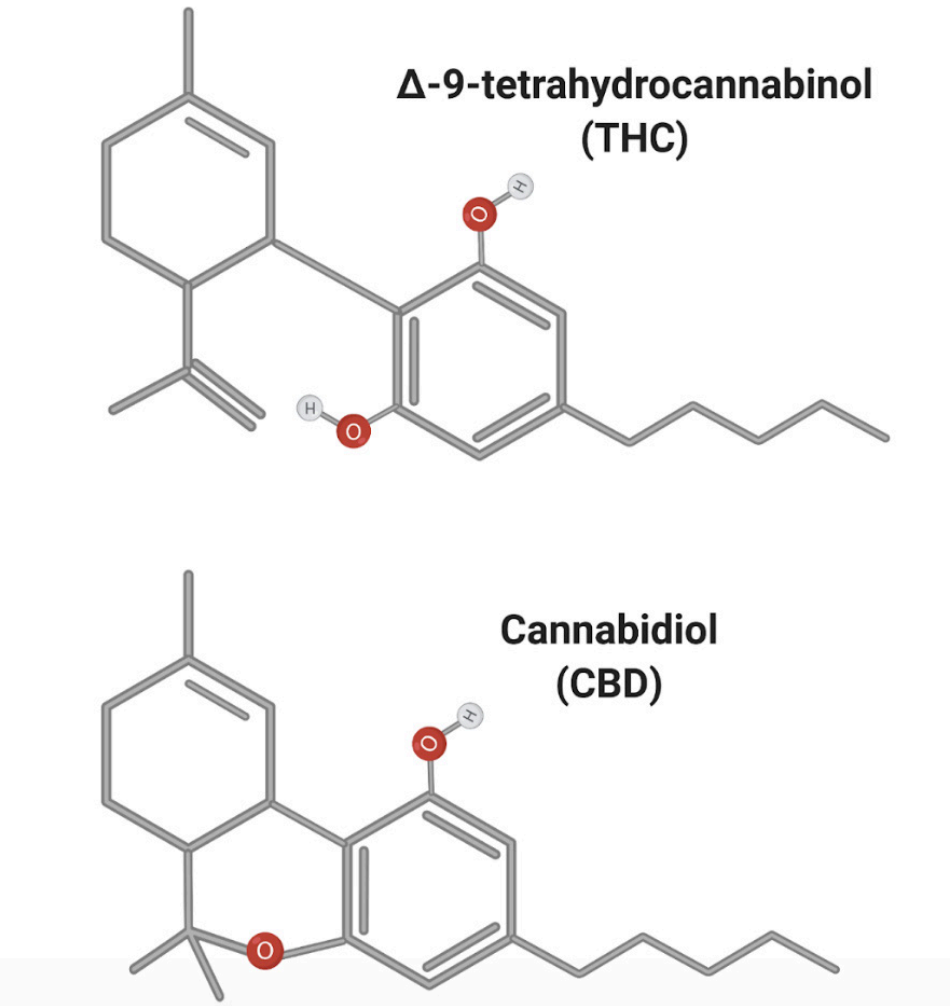
Before getting into the promising research regarding the medical use of marijuana, and, more specifically, CBD, it would be beneficial to go into a brief history of the drug. This will help elucidate the factors that led to many of the policies we see today, including the recently ended NFL practice of suspending players who tested positive for marijuana.[2] Cannabis is one of the oldest plants to be cultivated for non-food purposes, dating as far back as cultures in China in 4000 B.C. In ancient Asian societies, people used the plant to treat a multitude of ailments, including snakebites, malaria, gastrointestinal illness, pain from childbirth, and seizures. Hinduism, Buddhism, and other religious groups included cannabis in their ceremonies. Gradually, the plant spread throughout Asia, the Middle East, and eventually, Europe. People also used the plant as a fiber (for making cloth, paper, and rope), oil, and intoxicating agent.[3]

In the mid-1500s, the Spanish introduced cannabis to the Americas, where it was first grown for manufacturing rope for the navy. Eventually, it became a staple of the American colonies alongside tobacco.[3] Its popularity as a medical and recreational agent continued to steadily grow until the early 20th century, when the Pure Food and Drug Act of 1906 and the Harrison Narcotic Act of 1914 placed constraints on its use and sale.[3,4] These restrictions were not completely effective, however, as there was another spike in use when the Eighteenth Amendment (1920) prohibited the consumption of alcohol.[3]

There are many elements that went into the initial demonization of the compound. One of the major factors was the association of marijuana with Mexican immigrants.[3,4] Xenophobic feelings towards this group translated to a hatred of the compound.[4] Persistent media attacks against cannabis led to the Marijuana Tax Act of 1937, which effectively stopped legal use. The federal government was heavily involved in this propaganda as the first commissioner of the Federal Narcotics Bureau, Harry Anslinger, was the mastermind behind many of these dramatic media assaults. This stigmatization continued to 1970 when the Controlled Substances Act classified marijuana as a Schedule I drug. Cannabis



"Pot Opens The Door" by Michelle Lynne. Available under CC0



Molecular structure of THC and CBD. Original image by Charles Adams. Created in BioRender.

was one of the many compounds that were 'fought' during the War on Drugs.[3] Negative propaganda was (and continues to be, albeit to a lesser extent) rampant. For example, there was a repeated weakly-based claim that marijuana is a 'gateway' drug that would lead to further use of harder, more dangerous compounds. Many of the illustrations and visuals employed in anti-marijuana campaigns were intentionally shocking or unsettling.

Today, despite a swing in public opinion and the advent of new research indicating the potential benefits of the compound, cannabis remains a Schedule I drug. This classification is typically reserved for the most dangerous compounds. The federal government categorizes substances as such because the compounds have no currently accepted medical use, have a high potential for abuse, and create severe psychological and/or physical dependence. Other Schedule I drugs include heroine and lysergic acid diethylamide (LSD). According to the government's classification system, marijuana is more dangerous than cocaine, methamphetamine (meth), and fentanyl, all of which fall under the Schedule II designation. As such, cannabis is federally outlawed for both medical and recreational use.[5] This can and has inhibited research of the compound. CBD is not technically prohibited federally, but it is still derived from an illicit substance, so attempts to perform research on the molecule can be complicated.

Marijuana: A Complex Compound

When I first started researching cannabis and its potential role for treating TBIs, I considered the drug to be a one-trick pony. The only part of the plant that I had ever really heard much about was the primary active molecule, Δ-9-tetrahydrocannabinol (THC). THC is responsible for the majority of the 'high' that is felt as a result of taking the drug.[6] There are, however, many more compounds found within marijuana, including CBD. Both THC and CBD fall under the cannabinoid molecule family.[6,7] This means, despite small differences in the structure, the main backbone of the two molecules is shared. These small variations in structure, however, make a huge difference in how our body reacts to them.

Behaviorally, THC exposure induces anxiety, sedation, dysphoria (a state of unease or generalized dissatisfaction with life), psychotic symptoms, and

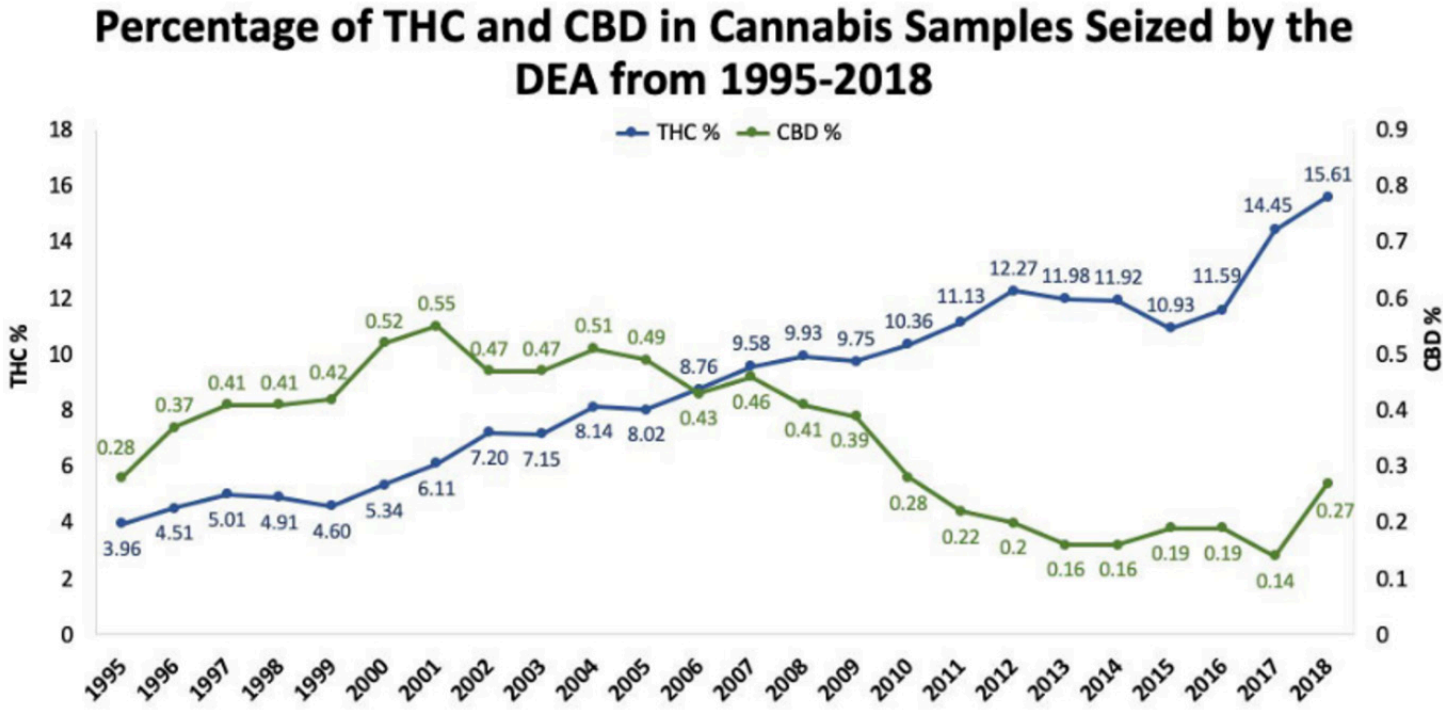
intoxication. These symptoms are heavily subjective from person to person.[6] Alternatively, CBD's only behavioral impact is sedation. In fact, something that I find remarkably interesting is that CBD seems to block some of the effects of THC. Many of the anxiety and psychosis-like effects are significantly diminished when CBD is taken at the same time as THC.[7] Marijuana has curious effects on people, and I think that further research should explore how each molecule in the substance interacts with the body.

While THC and CBD are the main actors found, they make up only a small portion of the overall cannabis plant. The exact percentages vary widely from plant to plant and have been changing throughout years, but the National Institute on Drug Abuse reports that the average percent of cannabis that is THC and CBD is 15.61 and 0.27, respectively (as of 2018).[8] This chemical makeup is the result of a decades-long trend that has seen THC steadily go up in concentration. In 1995, the average amount was 3.96%. CBD has fluctuated throughout these years, with a 1995 concentration of 0.28% and its peak coming in 2001 at 0.55%.[8] These patterns are interesting considering the aforementioned interactions between the two molecules. The rest of the plant consists of hundreds of other molecules. Over 60 of these are additional cannabinoids such as cannabinol (CBN) and tetrahydrocannabivarin (THCV).[9] While we will be looking at recent studies specifically concerning CBD as a candidate for treating TBIs, marijuana is extremely complex and all of its molecular components may be of interest to us, regardless of how "minimal" their effects may seem.

The Not-as-Fun Version of Headbanging

Calvin Johnson and other football players are not the only people who have experienced TBI. Everyone has hit their head at one point in their lives. There are a multitude of dangers for our brains in our everyday lives, whether it is a ball on the soccer field, a car accident, or a low-hanging ceiling on a stairway. After an incident, more often than not, we rub our noggin and walk away. Sometimes we experience a slight feeling of embarrassment if we did something particularly clumsy. We all know major head injuries have lasting consequences, but what can be shocking to most is how little it takes for long-term detrimental brain effects to occur.

In 2013, a study indicated that a significant portion of individuals who experienced a single traumatic brain injury were at an increased likelihood to exhibit symptoms of dementia and Alzheimer's disease. Symptoms included neuroinflammation (increase in the inflammatory response in the brain) and neurodegeneration (deterioration of the brain and nervous system). The presence of extensive and densely packed activated microglia (the brain's frontline immune defense cells)



Graph of the concentration of THC and CBD in marijuana from 1995-2018. Figure adapted from 'Marijuana Potency,' by the National Institute of Drug Abuse, 2020, retrieved from https://www.drugabuse.gov/drug-topics/marijuana/marijuana-potency8. Available under public domain.

within brain tissue served as an indicator of this neuroinflammatory response. This pattern of reactive microglia was exhibited in over a quarter of cases in which the subject survived more than a year after the initial trauma. Sometimes, they were still present in cases up to 18 years later.[10] This is a long time after just one injury and speaks to how important it is to find potential long-term treatments.

In the same study, the researchers found the injuries people endured led to a decrease in overall white matter integrity in the brain for many subjects. Since the tissue makes up a majority of brain mass and plays a pivotal role in the transmission of brain signals, white matter is a crucial component of the nervous system. The effect was most pronounced in cases where the elevated microglia response was also present. This leads to questions regarding the relationship between an extended neuroinflammatory response and long-term brain health. The scientists also observed a 25% reduction in the overall thickness of the corpus callosum, a portion of white matter that connects the left and right sides of the brain and is known to be heavily affected by trauma in the average one-year post-injury subject.[10] These are scary results, especially considering there are those who experience more than one TBI during their lifetime. Research into potential solutions is crucial for these people.

National CTE League

Sports can be punishing on the body, especially high-contact sports like football. High speed collisions between players are in the very nature of the game and occur on every single play. For too many of these athletes, concussions (a form of TBI) are a way of life. It therefore makes sense that the body of the football athlete deteriorates more distinctly and rapidly than normal. There are long-term consequences for participating in such a violent sport, especially for your brain and central nervous system.

The long-term brain health outcomes for football players are not good, to put it mildly. Research has indicated that the vast majority of these athletes develop chronic traumatic encephalopathy (CTE). CTE is a neurodegenerative disorder that is associated with people who have experienced TBIs. It is often correlated with dementia and symptoms like difficulty thinking, memory loss, and an increase in aggressive and depressive behaviors. Results of one study concluded that, in a sample of 202 deceased players across all levels of competition, CTE could be diagnosed in 87% of cases. The numbers are even more disheartening for former NFL players. Over 99% (110 of the 111) of these athletes showed CTE pathology. One, one, person's brain did not show signs of the condition.[11] Granted, these brains were donated to research for the purpose of looking at brain health, so there may be the confounding variable that the donors suspected they might have an issue. However, 99% is still 99% no matter how you look at it.

Football players, although likely the most well-known sufferers, are not the only ones that have to deal with CTE. Anyone who has experienced multiple concussions (diagnosed or undetected), are at an increased likelihood of developing the condition. These include people who have been in multiple car accidents and people who have served in the military.[10] In 2014 alone, the CDC reported that there were about 2.87 million TBI-related emergency department visits, hospitalizations, and deaths in the United States.[12] CTE is a disease that could potentially affect millions of people. There is a clear problem and there are few viable options for treatment.

Unfortunately, many of the physiological indicators required to diagnose CTE are only discovered after death. These markers include the aforementioned decrease in white matter volume and increase in inflammation in the brain.[10] On a more molecular level, an effective gauge for the progression of the disease is the concentration of hyperphosphorylated tau protein aggregates (HTPA, sometimes referred to as phosphorylated tau immunoreactive neurofibrillary tangles, but I will stick with HTPA).[13] HTPA are abnormal accumulations of naturally occurring proteins. In healthy cells, these tau proteins are involved in the assembly and stabilization of microtubules, which are basic structural components of the nervous system.[14] When they are hyperphosphorylated (extra phosphate group molecules are added to the basic structural makeup of the protein) this causes HTPA to form, leading to numerous unwanted consequences. HTPA are a hallmark of other related neurological conditions, like Alzheimer's disease, generally known as tauopathies.[15] The specific molecular composition of HTPA varies depending on the condition, but they are usually related in

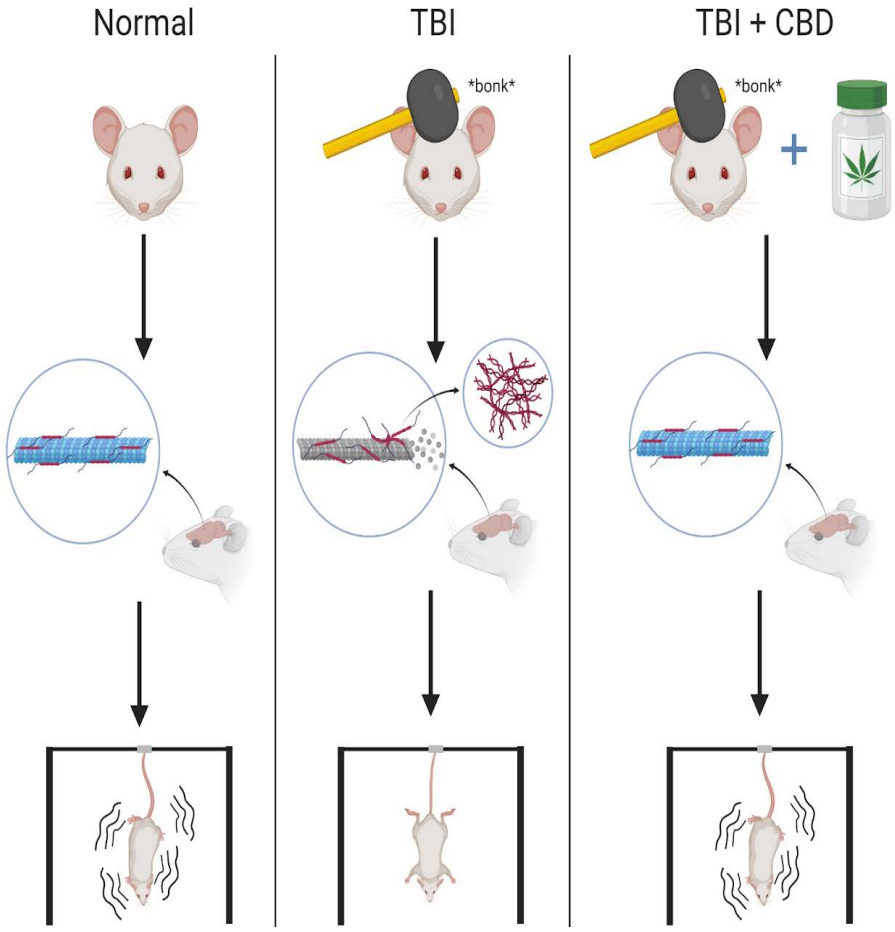
Original image by Charles Adams. Created in BioRender.

general structure. Regardless of ailment, higher concentrations of HTPA are correlated with higher severity disease states.[15,16] Although there is an apparent lack in truly effective treatments for these tauopathies, there is promising research revolving around the use of CBD, especially concerning its use in alleviating the long-term neurodegenerative effects of CTE.

CBD: A Rising Star

We all have that one friend who will not stop talking about the various vitamins and supplements that they take. They tout the wondrous things the vitamins do for their health and how the supplements 'make them feel years younger'. Usually these 'wonder' remedies are little more than placebos at best, and actively detrimental to your health at worst. Recently, one of these supplements that seems to be hooking peoples' attention is CBD. The only difference is CBD might actually have the science to back it up.

Numerous recent studies have supported the use of the drug as a treatment for several different ailments and diseases. A 2012 study indicated that, in lieu of the typical treatment for schizophrenia, a routine CBD dose helped alleviate subjects' psychotic symptoms.[17] In another arena, work in rats suggests that CBD can prevent inflammation and thus, pain and nerve damage associated with osteoarthritis.[18] Of course, there is always the worry that a potentially effective treatment will pair badly with existing medication, but preliminary evidence seems to suggest that this might not be the case for CBD. Research with mice found that CBD inhibited chemotherapy-induced pain without diminishing chemotherapy effectiveness or otherwise reducing the function of the nervous system. In fact, in some cases, researchers found an increase in the efficacy of the chemotherapy when paired with CBD treatment.[19] These are good signs for the future therapeutic role of this molecule and more studies should definitely be performed.



CBD prevents TBI-induced neurodegeneration. In normal mice, microtubules (blue bar) are stabilized by tau proteins (pink strands), and the mice will struggle when suspended upside down. In mice that suffer a TBI, microtubules will fall apart (gray bar) as tau proteins become less effective. This also leads to HTPA (pink tangle) in the brain and a lack of struggle in the mice when suspended (they are more depressed). When treated with CBD, mice with TBI do not experience these detrimental neurological effects. Original image by Charles Adams. Created in BioRender.

An Extra Layer of Padding

There are promising results concerning CBD and its use to fight against CTE. CBD might be an effective combatant against HTPA. A study found that PC12 cell cultures (representative of rat neuronal brain cells), when treated with CBD, show a decrease in the HTPA formation due to β-amyloid stimulation. β-amyloid stimulation is what causes the tauopathy patterns found in Alzheimer's disease.[20] This is a really exciting finding for all tauopathy treatment research, not just with Alzheimer's, because the molecular markers of these conditions are related.[15,16] Since CBD can help prevent HTPA in one disease, then there is a chance that it can be used in the fight against other related disorders. More research is needed to see if CBD can prevent the HTPA connected with CTE.

CBD may help with the negative behavioral aspects of CTE as well. Depression, increased feelings of pain, and aggression are all characteristic of the behavioral profile of many pre- and post-retirement contact sport athletes, like football players.[21,22] In a 2019 study involving a mouse model of mild TBI, researchers found that CBD treatment alleviated many of these symptoms and more. TBI-

induced mice acquired chronic pain and exhibited aggressive, depressive, and anxious behaviors. The combination of these factors probably led to the observed decrease in the sociability of these animals. When regularly treated with CBD after they received their TBI, these characteristics did not develop.[23] These are unbelievably exciting results, and I cannot wait for more related research to come out.

You may be wondering how in the world someone can do research on subjective feelings, like depression, in animals, and you would not be in the wrong to question the validity of the results. It is difficult to understand just how mice and rats are feeling, as they do not usually speak any English, but there are some methods that are employed as stand-ins for trips to the psychiatrist. For instance, in the experiment mentioned above, the scientists suspended the mice upside down by their tail and they measured how long the mice remained still during a set period of time. Immobility is considered "giving up" and a measure of hopelessness (a symptom of depression) in mice. In this study, control animals who did not receive treatment were still for a longer period of time than their CBD medicated counterparts. This means that the non-CBD treated mice should be considered more 'depressed.' It also means that CBD helped prevent neurobehavioral degeneration after TBI.[23] These findings are extremely encouraging, and I think that CBD treatment should be further explored in this arena.

Hold On: There Are No Cure-Alls Here

To produce many of the wonderful studies and discoveries regarding CBD, much of the research was conducted with animals. While they are immensely helpful and can lead to many great breakthroughs, animal studies are no substitutes for human trials. Many promising animal studies in the past have not translated well to people. The results we do have are promising, but there is a limited number of studies in humans on the effects of CBD treatment. While anecdotal evidence may seem appealing, more experimentation is needed before it can be definitively stated that CBD is a miracle drug that heals all bumps and bruises.

It should also be noted and made clear that I am not advocating for the use of marijuana. I am merely a major supporter of the study of the molecules that are found within the substance. The compound is still a drug. The component parts may not be as dangerous as the component parts of other drugs, but they should still be administered with caution. For instance, smoking is still smoking, and no matter what, there are inevitable health-related consequences of the practice. Laws and rules on the use of the drug and the molecules cultivated from it vary from state to state and organization to organization, so proper knowledge on how the use marijuana and CBD will affect your legal life is always good information to have.

It is also worth reminding you that CBD, while not technically federally prohibited, is derived from a Schedule 1 substance in the United States. Setting aside the serious socio-economic effects marijuana-related laws have had on the country and the people who live within it, this classification has and continues to make research difficult. Laws may be more lenient depending on the area of the country in which you live, but it makes receiving federal funding a lot harder for anything related to marijuana. These difficulties are especially disheartening considering all of the encouraging TBI- and other health-related findings regarding the compound.

A High Time for Change

I love the game of football. I deeply appreciate the sense of community it brings and the opportunities and chances it provides for thousands of people who would not have had anything else. I also am grateful for all of the sacrifices that veterans and active-duty military personnel have made to keep us safe. These people should not be forced to suffer for the rest of their lives just because they wanted to make ours better. CTE and other brain disorders are devastating, and their prevalence is a problem that affects millions of people. I believe that every avenue should be explored when trying to find a solution. One of these potential paths involves the much ostracized and demonized drug cannabis and the molecule CBD that is found within it. There are promising preliminary results regarding the compound and molecule and I think that they should be studied further.

Calvin Johnson walked away from the sport he loved in order to survive. Controlled use of medically researched CBD could have extended his career while maintaining his quality of life. Whether it be football players, people in the military, or any other victims of TBI, everyone deserves a chance at living a healthy and happy life. Marijuana may provide this chance. ■

References

1. Rosenberg, M. (2019, September 23). Calvin Johnson Doesn't Regret a Thing. Sports Illustrated. Retrieved November 23, 2020, from https://www.si.com/nfl/2019/09/20/calvin-johnson-lions-big-interview
2. Peterson, A. M. (2020, October 9). Rapinoe among athletes touting CBD's benefits for pain. AP News. Retrieved November 23, 2020, from https://apnews.com/article/megan-rapinoe-womens-soccer-nhl-portland-soccer-50d2ceb1d8ccd836a12201acb99fdb25
3. Advokat, C. D., Comaty, J. E., & Julien, R. M. (2019). Cannabis: A New Look at an Ancient Plant. In Julien's primer of drug action: A comprehensive guide to the actions, uses, and side effects of psychoactive drugs (14th ed., pp. 292-294). New York, NY: Worth.
4. Little, B. (2017, August 04). Why the US Made Marijuana Illegal. Retrieved November 23, 2020, from https://www.history.com/news/why-the-u-s-made-marijuana-illegal
5. Drug Scheduling. (n.d.). Drug Enforcement Agency. Retrieved November 23, 2020, from https://www.dea.gov/drug-scheduling
6. Martin-Santos, R., Crippa, J. A., Batalla, A., Bhattacharyya, S., Atakan, Z., Borgwardt, S., . . . Mcguire, P. K. (2012). Acute Effects of a Single, Oral dose of d9-tetrahydrocannabinol (THC) and Cannabidiol (CBD) Administration in Healthy Volunteers. Current Pharmaceutical Design, 18(32), 4966-4979. doi:10.2174/138161212802884780
7. Freeman, A. M., Petrilli, K., Lees, R., Hindocha, C., Mokrysz, C., Curran, H. V., . . . Freeman, T. P. (2019). How does cannabidiol (CBD) influence the acute effects of delta-9-tetrahydrocannabinol (THC) in humans? A systematic review. Neuroscience & Biobehavioral Reviews, 107, 696-712. doi:10.1016/j.neubiorev.2019.09.036
8. National Institute on Drug Abuse. (2020, July 08). Marijuana Potency. Retrieved November 23, 2020, from https://www.drugabuse.gov/drug-topics/marijuana/marijuana-potency
9. Auda, B. S., Ofojekwu, P. C., Ujah, A., & Ajima, M. N. (2014). Phytochemical, proximate composition, amino acid profile and characterization of Marijuana (Cannabis sativa L.). The Journal of Phytopharmacology, 3(1), 35-43.
10. Johnson, V. E., Stewart, J. E., Begbie, F. D., Trojanowski, J. Q., Smith, D. H., & Stewart, W. (2013). Inflammation and white matter degeneration persist for years after a single traumatic brain injury. Brain, 136(1), 28–42. https://doi.org/10.1093/brain/aws322
11. Mez, J., Daneshvar, D. H., Kiernan, P. T., Abdolmohammadi, B., Alvarez, V. E., Huber, B. R., . . . McKee, A. C. (2017). Clinicopathological evaluation of chronic traumatic encephalopathy in players of american football. JAMA: The Journal of the American Medical Association, 318(4), 360-370. doi:10.1001/jama.2017.8334
12. TBI-related Emergency Department Visits, Hospitalizations, and Deaths (EDHDs). (2019, March 29). Retrieved November 24, 2020, from https://www.cdc.gov/traumaticbraininjury/data/tbi-edhd.html
13. McKee, A. C., Stern, R. A., Nowinski, C. J., Stein, T. D., Alvarez, V. E., Daneshvar, D. H., Lee, H. S., Wojtowicz, S. M., Hall, G., Baugh, C. M., Riley, D. O., Kubilus, C. A., Cormier, K. A., Jacobs, M. A., Martin, B. R., Abraham, C. R., Ikezu, T., Reichard, R. R., Wolozin, B. L., Budson, A. E., … Cantu, R. C. (2013). The spectrum of disease in chronic traumatic encephalopathy. Brain: a journal of neurology, 136(Pt 1), 43–64. https://doi.org/10.1093/brain/aws307
14. Mietelska-Porowska, A., Wasik, U., Goras, M., Filipek, A., & Niewiadomska, G. (2014). Tau Protein Modifications and Interactions: Their Role in Function and Dysfunction. International Journal of Molecular Sciences, 15(3), 4671-4713. doi:10.3390/ijms15034671
15. Roberson, E. D., Scearce-Levie, K., Palop, J. J., Yan, F., Cheng, I. H., Wu, T., . . . Mucke, L. (2007). Reducing endogenous tau ameliorates amyloid -induced deficits in an alzheimer's disease mouse model. Science (American Association for the Advancement of Science), 316(5825), 750-754. doi:10.1126/science.1141736
16. Woerman, A. L., Aoyagi, A., Patel, S., Kazmi, S. A., Lobach, I., Grinberg, L. T., McKee, A. C., Seeley, W. W., Olson, S. H., & Prusiner, S. B. (2016). Tau prions from Alzheimer's disease and chronic traumatic encephalopathy patients propagate in cultured cells. Proceedings of the National Academy of Sciences, 113(50), E8187–E8196. https://doi.org/10.1073/pnas.1616344113
17. Leweke, F. M., Piomelli, D., Pahlisch, F., Muhl, D., Gerth, C. W., Hoyer, C., Klosterkötter, J., Hellmich, M., & Koethe, D. (2012). Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. Translational Psychiatry, 2(3), e94. https://doi.org/10.1038/tp.2012.15
18. Philpott, H. T., O'Brien, M., & McDougall, J. J. (2017). Attenuation of early phase inflammation by cannabidiol prevents pain and nerve damage in rat osteoarthritis. PAIN, 158(12), 2442–2451. https://doi.org/10.1097/j.pain.0000000000001052
19. Ward, S. J., Mcallister, S. D., Kawamura, R., Murase, R., Neelakantan, H., &Walker, E. A. (2014). Cannabidiol inhibits paclitaxel-induced neuropathic pain through 5-HT 1A receptors without diminishing nervous system function or chemotherapy efficacy. British Journal of Pharmacology, 171(3), 636-645
20. Esposito, G., De Filippis, D., Carnuccio, R., Izzo, A. A., & Iuvone, T. (2005;2006;). The marijuana component cannabidiol inhibits β-amyloid-induced tau protein hyperphosphorylation through wnt/β-catenin pathway rescue in PC12 cells. Journal of Molecular Medicine (Berlin, Germany), 84(3), 253-258. doi:10.1007/s00109-005-0025-1
21. Lemieux, P., McKelvie S. J., & Stout, D. (2002). Self-reported hostile aggression in contact athletes, no contact athletes and athletes. The Online Journal of Sport Psychology, 4(3), 42-56.
22. Schwenk, T. L., Gorenflo, D. W., Dopp, R. R., & Hipple, E. (2007). Depression and Pain in Retired Professional Football Players. Medicine & Science in Sports & Exercise, 39(4), 599-605. doi:10.1249/mss.0b013e31802fa679
23. Belardo, C., Iannotta, M., Boccella, S., Rubino, R. C., Ricciardi, F., Infantino, R., . . . Guida, F. (2019). Oral Cannabidiol Prevents Allodynia and Neurological Dysfunctions in a Mouse Model of Mild Traumatic Brain Injury. Frontiers in Pharmacology, 10. doi:10.3389/fphar.2019.00352

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