GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

Check for updates

Targeting the endocannabinoid system in the treatment of addiction disorders

David A Dawson * and Clare P Persad

Department of Psychology, Northcentral University, 2488 Historic Decatur Road San Diego, California, USA.

GSC Biological and Pharmaceutical Sciences, 2022, 19(02), 064–074

Publication history: Received on 05 April 2022; revised on 06 May 2022; accepted on 08 May 2022

Article DOI: https://doi.org/10.30574/gscbps.2022.19.2.0175

Abstract

This disquisition provides historical context illustrating the psychosocial, political, and bureaucratic barriers to applying a biomolecular approach to substance use disorders, focusing on what are arguably the most stigmatized molecules in America. It provides a biomolecular treatment strategy designed to mitigate multiple types of addiction by influencing the dopamine and serotonin neurotransmitters' activity through phytocannabinoid supplementation of the endocannabinoid system and proposes a strategy for circumventing the bureaucratic obstacles.

Keywords: Addiction; Cannabinoids; Dopamine; Serotonin; Nutraceutical; Biomolecular Psychology

1. Introduction

Humanity has struggled to understand the nature of drug abuse and addiction for centuries. There have been many false starts and a few successes throughout the years. Despite the traditional resistance to the medical use of botanic cannabinoids, their effectiveness in treating addictive outcomes is beginning to be understood from a biomolecular perspective.

This disquisition consists of two parts. Part I provides historical context illustrating the psychosocial, political, and bureaucratic barriers to applying a biomolecular psychological approach in treating substance use disorders, focusing on what is arguably the most stigmatized substance in America. Part II provides a biomolecular treatment strategy designed to mitigate various types of addiction by influencing the dopamine and serotonin neurotransmitters' activity through phytocannabinoid supplementation of the endocannabinoid system. This section also proposes a strategy for circumventing the bureaucratic obstacles outlined in part I.

Addiction disorders continue to take a toll on public health in most industrialized countries. According to the National Institute of Drug Abuse (NIDA), more people die each year due to the ingestion of prescription medications and legal substances than by illegal ones [1]. Millions Of people die from addiction to tobacco and alcohol every year, and the National Institute of Drug Abuse reveals that currently accepted pharmaceutical treatments for addiction disorders have limited efficacy and application [2]. For these reasons, there is a need to better understand the brain's biomolecular mechanisms in developing new and better-targeted interventions [3].

2. PART I

2.1. Historical, Political, Psychosocial, & Bureaucratic Barriers to Treatment of Addiction Disorders

Psychoactive substances have been used since the earliest human civilizations, but theories of why addiction to these substances occur were not proposed until the scientific renaissance. The etiology of addiction is complex and reflected

* Corresponding author: David A Dawson
Department of Psychology, Northcentral University, 2488 Historic Decatur Road San Diego, California, USA..

in the reoccurring pendulum swings between opposing attitudes concerning the causes of addiction that are still being debated. Views range from whether addiction should be considered a sin or a disease and whether the reason is moral or medical. Consensus has not been achieved within the scientific community concerning whether addiction is caused by the drug, individual vulnerability, or social influences. There is even debate about whether these substances should be regulated or freely available [4].

2.2. Historical, Psychosocial & Bureaucratic Aspects of Illicit Substances in America

In 1784, Dr. Benjamin Rush, a signatory of the Declaration of Independence and founder of the first medical school in the United States, argued that alcoholism was a disease, but he possessed few scientific resources to study the problem. The intricacies of a biomolecular response to a substance would not be understood until the instrumentation was invented to measure a biochemical reaction and integrate this knowledge with complex cellular biochemistry. This instrumentation would not be developed until the 1970s, so psychosocial and cultural explanations predominated. By the late 1700s, unrestrained alcohol use had become a significant public health problem for many Americans. Rush published and frequently presented, correcting erroneous notions about alcohol's presumed medicinal benefits, accurately describing more than a dozen alcohol-related health problems. His speeches and publications launched the beginning of the temperance movement [5].

The temperance movement of the late 19th and early 20th centuries was an organized effort to encourage moderation in consuming intoxicating liquors or press for complete abstinence. During these years, alcohol was blamed for many of society's ills, foibles, and sins, including severe health problems, poverty, and crime. The temperance movement culminated in prohibition from the years 1919 to 1933. The failure of prohibition (repealed by the 21st Amendment) sealed the temperance movement's fate as it lost its steam [6].

In 1930, Harry Anslinger was appointed as the first commissioner of the Federal Bureau of Narcotics. This bureau laid the foundation for the modern-day DEA, and Anslinger was the first architect of the war on drugs. He established the precedent that in the United States, politicians make the medical decisions for the individuals they govern. Anslinger was appointed to the bureau just as alcohol prohibition began to crumble, and he remained in power for 32 years. From the moment he took charge, Harry was aware of the weakness of his new position. Anslinger needed to be able to justify his new bureau's existence financially. He knew he could not keep an entire department alive on narcotics alone. Cocaine and heroin were simply not used enough to sustain a whole bureau. Very few people were using heroin and cocaine [7].

To fund his newly established bureau, Anslinger made it his mission to rid the United States of all drugs except alcohol and tobacco, including botanic cannabinoids, which he pursued with a vengeance. His influence played a significant role in the introduction and passage of the Marijuana Tax Act of 1937, outlawing possessing or selling botanic cannabinoids without a tax stamp, which he ensured would be virtually impossible to obtain [7, 8].

Anslinger claimed that botanic cannabinoid use caused psychosis, insanity, and death. In a radio address, he stated young people are "slaves to this narcotic, continuing addiction until they deteriorate mentally, become insane, turn to violent crime and eventually murder." He had no scientific evidence to support this claim. [9] Anslinger contacted 30 scientists, and 29 told him botanic cannabinoids were not dangerous. He hired the 30th, Dr. James Munch as the U.S government's "official expert" on marijuana [9]. In this position, Dr. Munch was responsible for presenting the scientific evidence indicating that ingesting botanic cannabinoids caused psychosis and, eventually, insanity.

In 1937, Dr. Munch testified for the Federal Bureau of Narcotics during the Marihuana Tax Act Hearings. His court testimony demonstrates the importance of scientific decisions being based on evidence. America's decision that botanic cannabinoids caused psychosis is primarily based on the findings of the esteemed Dr. Munch. It is appropriate now to introduce the concept of anecdotal evidence. The government's position was (and still is) that botanic cannabinoids use causes psychosis, neuron death, and insanity. Anecdotal evidence does not qualify as scientific evidence because its very nature prevents it from being investigated by the scientific method. Without clinical trials, any success stories of individuals attaining successful medical results from botanic cannabinoid use must be viewed as anecdotal and ignored as unscientific. The personal stories of 4.3 million seniors who claim they are receiving relief from their ailments by supplementing their endocannabinoid system with botanic cannabinoids are not compelling enough to change the evidence the United States has relied on to advance its claim of the dangers of ingesting phytocannabinoids.

The evidence the United States uses to support this claim is based on the research of experts. One of the most notable experts was Dr. Munch, a physiology professor at Temple University in Philadelphia, PA. During the hearing, Munch incorrectly testified that cannabis was introduced into human medicine by William Brooke O'Shaughnessy in 1838. This was 37 years before Louis Pasteur came onto the scene, and Munch testified that before Pasteur, botanic cannabinoids

were used to treat rabies and corns. He correctly stated that synthetic medicines were better options for these conditions and testified that botanic cannabinoids have no medicinal value because there is no established method for standardization of dose that compares to the exacting standards of synthetic narcotics. Dr. Munch further testified, without producing studies, that botanic cannabinoid use causes degeneration of the brain, extreme laziness, violent irritability, and disintegration of personality. In open court, he then stated that he had conducted a series of experiments with cannabis on dogs and had tried the supplement himself for scientific purposes. When asked how botanic cannabinoids affected him, "Dr. Munch testified, under oath, that, after two inhalations of a marijuana cigarette, he was turned into a bat, flew around the room and down a 200-foot-deep inkwell." [10].

Dr. Munch was employed as the U.S government's "official expert" on botanic cannabinoids from 1938 to 1962. By the time Dr. Munch and Harry Anslinger retired from the Federal Bureau of Narcotics in 1962, the paradigm was established. This paradigm was to flourish within the government for the next five decades. In a nutshell, the paradigm is this: Ingesting botanic cannabinoids kills brain cells, causes psychosis, criminal behavior, and insanity. The next step in advancing the paradigm was 1971, when President Richard M. Nixon declared war on drugs, explicitly targeting the biological molecules the cannabis plant produces (phytocannabinoids) and forbidding their study. When he declared war on the biological cannabinoids, no one had a clue that he had effectively targeted the molecules the human body produces naturally. So, the central postulate of the dominant paradigm that is still being promoted as science by the federal government is that the molecules that the human body produces naturally to maintain homeostasis are harmful to humans if produced by a plant.

In the late 1980s and 1990s, technology was developed, which led to the discovery of the endocannabinoid system, a biological system composed of endogenous lipid-based retrograde neurotransmitters that bind to cannabinoid receptors and cannabinoid receptor proteins that are expressed throughout the vertebrate central nervous system and peripheral nervous system. This system plays an essential role in regulating central physiological processes that underlie addiction disorders (Parsons & Hurd, 2015). Because the research of biologic cannabinoids was prohibited in the United States, the National Institute of Health (NIH) provided funding for a trio of researchers at Hebrew University in Jerusalem. This group identified the first endogenous cannabinoid neurotransmitter and gave it the name anandamide[11]. In 1993, a second endocannabinoid, 2-arachidonylglycerol (2AG), was identified [12].

On August 11, 2016, Chuck Rosenberg, the acting head of the U.S. Drug Enforcement Administration, announced it would not change the phytocannabinoids' federal legal status. Their classification would remain Schedule I under the Controlled Substances Act, meaning that they have no currently accepted medical use and a high potential for abuse. He resigned as head of the DEA in September of 2017 after stating President Donald Trump had little respect for the law.

The prohibition on the research of botanic cannabinoid molecules lasted 47 years and ended on December 21, 2018, when Donald Trump ratified the Farm Bill. This legally reclassified phytocannabinoids extracted from *Cannabis sativa* composed of less than 0.3% THC (hemp) as an agricultural product rather than a controlled substance, thereby legally (not scientifically) differentiating them from the molecules produced by cannabis varieties with higher THC content. When Donald Trump signed this bill into law, interstate transportation of the 113 known phytocannabinoid molecules became permitted, provided they originated from *Cannabis sativa* classified as hemp. This concession by the US opened the door to the research of botanic cannabinoids, which scientists in the United States had been prohibited from investigating for more than half a century.

While the prohibition of research on phytocannabinoid molecules has been inadvertently lifted, the paradigm cannabinoid scientists have been mandated to adhere to remains. The paradigm was established 47 years ago and is currently in what Thomas Kuhn [13] termed a state of crisis regarding the potential therapeutic properties of biological cannabinoids (phytocannabinoids & endocannabinoids). The dominant paradigm established and decreed by the DOJ, the DEA, NIH, and NIDA demand acceptance of the proposition that synthetic cannabinoids possess medicinal properties and botanic cannabinoids are dangerous, having none [14]. To ensure their economic security, cannabinoid scientists were forced to accept and promote this view for almost half a century. Until the passage of the Farm Act, studies that might challenge this paradigm were deemed illegal. This five-decade period defined the science of cannabinoids and dictated the methods of solving puzzles that arose. Ironically, this period was a phase Kuhn would have referred to as "normal" science. The established paradigm dictated how observational data was perceived, experiments designed, and results interpreted.

With the methods in place and the assumptions defined, this paradigm flourished. However, deaths and other adverse events resulting from synthetic cannabinoids and an accumulation of anomalies have challenged the dominant paradigm. Thomas Kuhn advanced the notion that the scientist's role is to design studies with the possibility of producing results that challenge the dominant paradigm, and he coined the word "revolution" to describe dramatic

changes in scientific worldviews. Revolutionary science is torturous and painful because it shakes all confidence that science has in its present theories and underlying paradigms. Paradigm shifts occur gradually when the dominant paradigm is termed to be in "crisis. A new paradigm is emerging, which professes botanic cannabinoids have medicinal properties without the adverse effects so often prevalent through intromission of their synthetic counterparts. With changes in state regulations and the Farm Act's implementation, exploring the dominant paradigm's limitations is now possible; this is the nature of science. When too many anomalies appear that current theories cannot explain, a period of "crisis" results, and political and economic events fuel the search for new understandings. This is the stage we are in with respect to phytocannabinoid-based medicines. Studies are only now beginning to be proposed, which might subvert the accepted assumptions. History has demonstrated that whether the opposition to attaining and disseminating scientific knowledge is politically or religiously motivated, humanity has the potential to ensure this knowledge is eventually acquired [15].

3. Part II

The historical analysis described above illustrates the convoluted nature of the construct of illicit substances and the political, cultural, psychosocial, and bureaucratic influencers that brought about this convolution. The paradigm describing the nature of addiction has changed, and our understanding of the mechanism that causes someone to become addicted to a substance has evolved. The next section of this presentation is designed to explain this evolution.

3.1. Models of Addiction: Assertations Which Shape Our Views

The biological mechanism causing addiction is rarely adequately addressed, and at the time these models were conceived, the mechanism of addiction was not yet known. Still, politicians elected to make medical decisions rely on at least one of these addiction models. As is typical for all psychological constructs, many different models have been developed to understand and explain the nature of substance abuse and addiction. There is tremendous variation in assertions of causes of addiction, ranging from blaming the individual to purely medical explanations. The following is an examination of three of the most common explanatory models proposed by psychologists in their attempts to understand and explain the nature of drug abuse and addiction.

3.2. Moral Model of Addiction

The easiest to understand and most traditional approach to addiction in America is the Moral Model. This model focuses on the idea that addiction is indicative of an individual's moral failures, and the legal system should be employed to punish drug users for their indecency. Addiction in this model is viewed as a result of poor life choices by an individual. Nearly 300,000 people currently incarcerated in prison are serving time for drug-law violations [16].

Despite the propaganda promoting a subsequently disproved economic justification of this model by politicians and leaders in the law enforcement industry, the moral model has fallen into disrepute in academia. In June of 2017, analysts for Pew Charitable Trust released a study designed to evaluate imprisonment effectiveness for drug-related offenses. The study analyzed state-by-state data on drug offender incarceration rates alongside illicit drug use, overdose deaths, and arrests. The analysis found no statistically significant relationship existed, indicating incarcerating drug addicts is not an effective strategy in the nation's war against drugs. If incarcerating addicts were effective, states would experience reduced drug abuse rates. Instead, they found higher imprisonment rates did not correlate with lower drug abuse rates, drug arrests, or drug fatalities. These findings add to mounting evidence demonstrating that incarceration is not a viable solution for addiction. Still, in 2018, the most significant politician in America promoted the Moral Model of addiction. On Monday, March 19, 2018, President Donald Trump called for harsher prison sentences when he announced his program to combat the opioid epidemic [17].

3.3. Medical Model of Addiction

A position diametrically opposed to the Moral Model of Addiction is the Medical Model, which views the construct as a disease. The Medical Model considers addiction analogous to any other illness and the predisposition to contracting an addiction disorder as outside the individual's control. Animal studies support this position. C57 genotype mice are often used in addiction experiments because their genetic makeup makes them more sensitive to the rewarding effects of morphine, cocaine, and alcohol than other genotypes in the same way genetic factors predispose a person to addiction [18, 19, 20, 21].

Essentially, the Medical Model proclaims addiction is a disease, not a sin, as claimed for more than two centuries, beginning with the Declaration of Independence signer and physician Benjamin Rush in the early 1800s. Alcoholism was declared a disease by the American Medical Association in 1956, and the organization classified other drug

addictions as diseases in 1989. While the American Medical Association is an established bureaucratic authority, if politicians that make medical decisions for the population accepted addiction as a disease, the assertation would not *need* to be continuously reasserted. In the context of addiction, "disease" is viewed entirely differently from the word "disease" used for any other condition. It has not been necessary for the American Medical Association to repeatedly declare that AIDS or diabetes are diseases. While a segment of the population and certain politicians became convinced that COVID-19 was a hoax, no one has ever asserted that it is not a disease.

Despite the American Medical Association's repeated proclamations, many people do not accept addiction as a genuine medical condition. A 2010 study examined Americans' perceptions about alcoholism, finding that 65 percent of 630 people polled in a general population sample felt the condition was due to "bad character," while 47 percent viewed it as a problem of brain chemistry or genetics [22]. Four years later, a study found a robust moral stigma associated with addiction. Seventy-eight percent of responding participants stated they did not want to work with someone with an addiction disorder, and ninety percent said they would not want someone with an addiction to marry into their family. These rates are significantly higher than those who would similarly reject someone with diabetes [23].

The prejudice is ongoing. If addiction is truly a disease, it is the only one that can get the sufferer arrested simply for displaying symptoms. Punitive incarceration for being addicted undermines the disease model. Images of arrests and police officers standing in front of large quantities of drugs promote the idea that drug use is criminal and undermines the medicalization model. Drug users are viewed as sinful by nature. No other disease exists for which a judge can deny medical treatment [24]. While advances in neuroscience provide compelling evidence to support a medical perspective of problematic substance use and addiction, the science is still in its early stages, and theories about how addiction emerges are neither universally accepted nor completely understood [25].

3.4. The Discovery of Dopamine and its Role in Addiction

A significant event occurred in biomolecular psychology in the 1970s when a mechanism of addiction was identified. It was found rats would repeatedly and willingly electrically self-stimulate areas in the brain, which were subsequently demonstrated to comprise a set of dopamine neurons.[26]. This experiment was used to explain the finding of an earlier study, which showed that stimulants enhanced this neurotransmitter's actions [27].

A subsequent series of experiments demonstrated that blocking dopamine receptors with neuroleptic drugs impaired the reinforcing effects of addictive drugs in rats and primates. These studies placed dopamine as the central neurotransmitter in addiction and indicated that it played a critical role in reward, motivation, and incentive behavior. [28, 29] The following conceptual breakthrough coincided with the development of microdialysis sampling techniques pioneered by a group of researchers in Sardinia, Italy. Microdialysis sampling produced conclusive evidence that drugs of abuse release dopamine in the basal forebrain, a preoptic area of the hypothalamus known as the nucleus accumbens. This resulted in a general theory of addiction in which addictive drugs release dopamine, but non-addictive substances do not. [30]. from this point, the field developed rapidly, with replications of the early animal findings of dopamine being released by 'addictive' drugs and confirmations in humans using neurochemical imaging. These studies' results led to immense investment in research to alter dopamine neurotransmitter function to treat addiction. Positron imaging tomography (PET scans) and single-photon emission computed tomography (SPECT scans) provided critical breakthroughs in our understanding of the human dopamine system and its role in addiction when it was demonstrated these technological innovations could be used to measure dopamine release in the human striatum [31,32]. It was later demonstrated the magnitude of this increase could predict the euphoria or 'high' produced by a drug [33]. This proved that in humans, the feeling of pleasure produced by addictive drugs is mediated by striatal dopamine release by the same mechanism as in animals [30], and addiction has come to be viewed as a disorder of the dopamine neurotransmitter system [3].

3.5. Psychoactivity and its Relationship to the Moral Model of Addiction

The dopamine theory of addiction has generated acceptance by biomolecular psychologists because drugs that induce dopamine release repeatedly correlate with feelings of pleasure or euphoria. This sensation of joy or bliss is indicative of psychoactivity. According to the moral model of addiction, psychoactivity should only be induced by legal chemicals like alcohol, tobacco, caffeine, or physician-prescribed pharmaceutical medications [34].

The development of the technology capable of analyzing neurotransmitters and applying the results to the dopamine theory of addiction profoundly affected the creation of synthetic drugs designed to target the brain. Pharmaceutical companies used ventral striatal dopamine release assays to estimate the abuse potential of new medicines, rejecting compounds if they were determined to be psychoactive, as determined by increased dopamine levels. It might be argued this was a concession to the moral model of addiction, that anything that results in a pleasurable sensation should be

illegal. Still, this view is disconcerting because animal studies conclusively demonstrate that dopamine activity in the ventral striatum is critical in resistance to depression [35]. As already implied, the Moral Model of addiction has produced barriers to cultural and political acceptance of cannabinoid-based medicines. This model also affected where botanic cannabinoids would fall when the Controlled Substances Act was created.

3.6. The Relationship of Controlled Substance Schedules to Biologic Cannabinoids

The United States Drug Enforcement Administration (DEA) classifies chemicals, drugs, and certain substances used to make drugs into five categories or schedules depending upon the abuse or dependency potential and acceptability as medicine. The potential for abuse is the determining factor in scheduling a drug. Schedule I drugs have a high potential for abuse and create severe psychological and physical dependence. The lower the substance appears on the Schedule, the less potential the drug has to be abused. [36] Legal drugs like alcohol and tobacco do not appear on the Schedule, meaning the DEA considers them outside their purview as the paramilitary division tasked with adjusting the Schedule and enforcing it upon the citizenry [37].

Unable to provide the studies the DEA claimed to have that demonstrate the abuse potential of biological cannabinoids, the justification for them to remain Schedule I became based on claims that particular phytocannabinoids are psychoactive and, therefore, pleasure-inducing. A compound's psychoactive nature is considered indicative of its potential for abuse. In 1971, the United States declared a 'War on Drugs,' mainly targeting the entirety of the known botanic cannabinoids. Research of these cannabinoids was prohibited in 1972, and research universities were mandated to forbid biological cannabinoid study, and conducting such research could jeopardize their federal funding. At the time, the only known biologic cannabinoids were the phytocannabinoids, the cannabinoids derived from the *Cannabis sativa* plant. These non-synthetic molecules were classified as Schedule I drugs, the category reserved for the most dangerous substances humans can ingest. This classification for the biologic cannabinoids worked well for the next two decades because it fit perfectly into the moral model of addiction, which fueled the drug war. The DEA flourished during this time through asset forfeitures and massive budgeting allocations provided to ensure the Judicial System punished Americans for possessing botanic cannabinoids produced through biologic synthetization.

3.7. Endocannabinoid/Phytocannabinoid Equivalents

Things became problematic for the law enforcement agency in 1992 when the United States funded a trio of researchers at Hebrew University in Jerusalem. This group identified the first endogenous biologic cannabinoid (endocannabinoid) and named it anandamide [11]. Shortly thereafter, the National Institute of Drug Abuse declared anandamide and Trans-Δ^9-tetrahydrocannabinol (THC) to be the same molecule and justified this position with the image provided in Figure 1. Suddenly, it could reasonably be argued all Americans were in possession of an illicit substance merely by being alive [38].

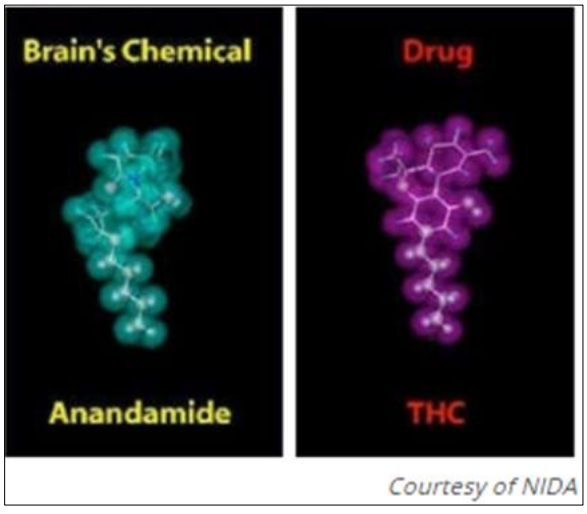

Figure 1 Endocannabinoid/Phytocannabinoid Equivalents

Cannabidiol was determined to be the phytocannabinoid equivalent to the endocannabinoid 2-arachidonoylglycerol (2-AG) because each act on the body's receptors in the same ways, and other biologic cannabinoid equivalents quickly followed [39]. Still, the DEA refused to deschedule botanic cannabinoids and categorize them as no-risk drugs like alcohol and tobacco. Instead, politicians admitted the war against the 113 known phytocannabinoids was lost and

shifted the attack to THC by misappropriating the term psychoactive. THC would remain the botanic cannabinoid with the most destructive potential due to its purported psychoactive nature. This psychoactive property comes from its ability to release dopamine by activating the CB1 receptor the same way anandamide does, thereby providing the sense of pleasure abhorrent to the moral model of addiction. Cannabidiol was claimed to be non-psychoactive and, therefore, the 'safe' cannabinoid.

In a classic bit of hypocrisy, at the same time the United States was claiming cannabidiol had no medicinal properties and great potential for abuse, they filed patent number 6630507, claiming the rights to the use of a non-psychoactive phytocannabinoid to treat neurological conditions resulting from concussion or stroke, and its use in the treatment of Alzheimer's, Parkinson's, autoimmune diseases, in addition to HIV dementia [40].

Somehow, the patent survived the application process. The federal government now holds the license on an illegal, unpatentable, natural form of non-psychoactive cannabidiol to treat Alzheimer's disease, Parkinson's disease, human immunodeficiency virus dementia, Down's syndrome, and heart disease. Within the patent application, it is repeatedly stated that the cannabidiol being patented has no psychoactive properties. One of the most significant differences between science and politics is that terms must be defined in science. In the patent application, the term "non-psychoactive" is undefined. Thus, the standard definition must apply. For this definition, we look to the World Health Organization; "Any substance that affects mental processes when ingested" is considered to be psychoactive [41]. All forms of cannabidiol have been demonstrated to alter serotonin levels, which affects the mental process by providing a sense of contentment [42, 43]. If the government has patented a form of cannabidiol that does not alter serotonin levels when intromitted, it is unique in the cannabinoid world. It is more likely the government has claimed a patent on a non-psychoactive form of cannabidiol, which does not, in reality, exist [44].

While the United States holds a patent on a unique form of cannabidiol purported not to affect brain chemistry, research is progressing on existing cannabidiol compounds that activate the 5-H1A (serotonin) and TRPV-1 receptors and inverse-agonize the CB1 receptors, thereby contributing to the treatment of opiate addiction, cocaine addiction, nicotine addiction, heroin addiction, Ecstasy addiction, THC addiction, and methamphetamine addiction [45, 46, 47, 48].

4. Part II

4.1. Targeting Dopamine & Serotonin Neurotransmitters to Treat Substance Abuse Disorders

The preceding discussion provided a necessary explanation of the Dopamine Theory of Addiction. This theory views addiction as a disorder of the dopamine neurotransmitter system and is, by definition, a medical issue. As with the array of endocannabinoid deficiency disorders, neurotransmitter disorders are not yet recognized as a disease. Although not officially a disease and, therefore, not technically a primary condition, neurotransmitter disorders can effectively be treated by nutraceutically manipulating the system that oversees the biomolecular mechanism responsible for the neurotransmitters' production. While addiction has come to be viewed as a disorder of the dopamine neurotransmitter system, targeting this neurotransmitter has not led to new treatments [3]. Dopamine deficiency has been demonstrated to have a significant role in susceptibility to addiction, but these effects are mediated by the activation of the serotonin neurotransmitters [49].

4.2. Targeting the Serotonin Receptors by Modulating the Endocannabinoid System

As with most biomolecular psychology concepts, the simplest way of reaching the target is to modulate the endocannabinoid system. The cannabinoid receptors and their endogenous agonists and antagonists (endocannabinoids) are ubiquitously distributed throughout the central nervous system. They have a critical role in the regulation of neurotransmitter production and excitability. 2- arachidonoylglycerol (2-AG) plays an essential role in regulating stress-related behaviors and the mood-elevating and euphoric effects resulting from the intromission of dopamine-enhancing drugs [50,51]. The two most critical endocannabinoids with regard to addiction are anandamide and 2-AG. Anandamide is the endocannabinoid that agonizes the CB1 receptors responsible for activating dopamine neurotransmitters. This results in the sense of pleasure referred to as psychoactivity. The bliss resulting from dopamine activation is considered the biomolecular mechanism that makes psychoactive drugs addicting [11]. 2AG is the endocannabinoid responsible for serotonin activation, the neurotransmitter that provides a sense of happiness, contentment, and well-being. [12] For these reasons, from a biomolecular perspective, addiction treatment is more likely to be effective by activating serotonin while repressing dopamine. The most useful phytocannabinoid for accomplishing this task is cannabidiol. CBD inverse agonizes the CB1 receptor [52], Blocking its access and thereby mitigating the effects of addictive drugs. Simultaneously, it agonizes the CB2 receptors, which activate the serotonin neurotransmitters. This biomolecular mechanism explains how CBD's intromission demonstrates efficacy in treating

every substance abuse disorder studied. Biomolecular manipulation of the endocannabinoid system is expected to compliment the Matrix Model, an integrative therapeutic approach incorporating the most efficacious aspects of behaviorism, person-centered therapies, cognitive behavioral therapy, the twelve-step approach, and motivational interviewing [53,54].

As a harm reduction strategy, phytocannabinoid supplementation is supported by evidence demonstrating its efficacy for pain relief and as a substitution for multiple illicit drugs, alcohol, tobacco, and pharmaceuticals. Animal models show that phytocannabinoids reduce withdrawal, which contributes to drug-seeking behavior, but statistically significant human clinical trials are lacking [55]. With few exceptions, all animal trials involved the addictive drug is administered intravenously, followed by the animals receiving a CBD systemic injection. While this methodology is deemed acceptable for rats and mice because they are excluded from the Animal Welfare Act, it rightly would not pass IRB scrutiny for human clinical trials in any industrialized nation.

The FDA has rejected nearly all ingestion methods of phytocannabinoids, but transdermal drug delivery methods developed by the pharmaceutical industry have made an essential contribution to medicine. They can easily be appropriated to deliver specific doses of phytocannabinoids into the bloodstream through a porous membrane. Transdermal delivery also provides steady and consistent permeation of a drug through the skin, leading to more constant plasma supplement levels, which is usually therapy's goal. The absence of peaks and troughs in plasma concentration levels results in significant improvement compared to traditional methods of ingestion of nutraceuticals. Intromission through a transdermal patch has FDA approval, and CBD ingestion does not result in dopamine activation, so the detestable pleasurable sensation is avoided. Still, serotonin levels are enhanced, providing the subject with a sense of contentment and well-being.

4.3. Training and Ethical Issues

The endocannabinoid system has been called the single most important scientific medical discovery since the recognition of sterile surgical techniques. As our understanding of its complexities expands, it becomes increasingly evident that the endocannabinoid system controls all physiological and psychological processes [56]. Still, creating and conducting human clinical trials to test this methodology in the United States is problematic. Many American scientists are ignorant of even the endocannabinoid system's existence and would likely need to be trained if the trial were conducted in America. Physicians associated with hospitals are still forbidden to learn about or discuss the endocannabinoid system because doing so could jeopardize the hospital's federal funding [57]. The historical timeline provided in Section I of this disquisition illustrates the breaches of ethics the United States government has committed to ensure knowledge of botanic cannabinoids is repressed. Given these conditions, it could be argued that the United States should be eliminated as a potential country to conduct human clinical trials to test the efficacy of treating addiction disorders by targeting the endocannabinoid system. If a clinical trial of this nature is to occur, it will likely be more advantageous to conduct it in a more scientifically advanced country and one more conducive to innovative approaches.

5. Conclusion

Biomolecular psychology experiments conducted in the 1980s identified dopamine as the central neurotransmitter responsible for addiction disorders. This review article integrated existing biomolecular psychology research to explain the demonstrated efficacy of botanic cannabinoid medicines in alleviating every substance use disorder studied. It proposed a rudimentary treatment strategy designed to mitigate multiple types of addiction disorders by influencing dopamine and serotonin neurotransmitters' activity through phytocannabinoid supplementation of the endocannabinoid system. Given the extent of addiction to pharmaceutical and legal and non-legal substances throughout the industrialized world, it could be reasonably argued an efficacious biomolecular treatment strategy of this nature would benefit humanity.

Compliance with ethical standards

Acknowledgments

Gratitude, respect, and appreciation to Spectral Analytics and CannaCare Medical Foundation for their support and assistance in the creation of this work.

Disclosure of conflict of interest

Authors David A Dawson and Clare P Persad declare they have no conflicts of interest to disclose.

References

[1] NIDA Overdose Deaths. [Internet]. 2020a. Available from Overdose Death Rates | National Institute on Drug Abuse (NIDA)

[2] NIDA How effective is drug addiction treatment? 2020b. [Internet] Available from https://www.drugabuse.gov/publications/principles-drug-addiction-treatment-research-based-guide-third-edition/frequently-asked-questions/how-effective-drug-addiction-treatment on 2020

[3] Nutt, D. J., Lingford-Hughes, A., Erritzoe, D., & Stokes, P. R. A. The dopamine theory of addiction: 40 years of highs and lows. (2015). *Nature Reviews Neuroscience*, *5,* 305.

[4] Crocq M. A. Historical and cultural aspects of man's relationship with addictive drugs. (2007). *Dialogues in clinical neuroscience*, *9*(4), 355–361.

[5] Katcher, B. S. Benjamin Rush's educational campaign against hard drinking. (1993). *American Journal of Public Health, 83*(2), 273–281.

[6] Webb, H. Temperance movements and prohibition. (1999). *International Social Science Review, 74*(1/2), 61.

[7] Musto, D. F. *The american disease: Origins of narcotic control*. (1999). Oxford University Press.

[8] Nicholas, P., & Churchill, A. The federal bureau of narcotics, the states, and the origins of modern drug enforcement in the united states, 1950-1962. (2012). *Contemporary Drug Problems, 39*(4), 595-640.

[9] Kinder, D. C., & Walker III, W. O. Stable Force in a Storm: Harry J. Anslinger and United States Narcotic Foreign Policy, 1930-1962. (1986). *Journal of American History, 72*(4), 908–927.

[10] Booth, M. *Cannabis: A History*. (2004). New York, Picador Press.

[11] Devane, W. A., Hanus, L., Breuer, A., Pertwee, R. G., Stevenson, L. A., Griffin, G., Gibson, D., Mandelbaum, A., Mechoulam, R., & Etinger, A. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. (1992). *Science, 5090*, 1946

[12] Mechoulam, R., Ben-Shabat, S., Hanus, L., Ligumsky, M., Kaminski, N. E., Schatz, A. R., Gopher, A., Almog, S., Martin, B. R., Compton, D. R., & et. al. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. (1995). *Biochemical Pharmacology, 50*(1), 83–90.

[13] Kuhn, T. S. *The structure of scientific revolutions, 3rd ed*. (1996). Chicago, IL: University of Chicago Press.

[14] [14] Drug Enforcement Administration. Schedules of controlled substances: Placement of FDA-approved products of oral solutions containing Dronabinol-delta-9-trans-tetrahydrocannabinol (delta-9-THC)] in Schedule II *Federal Register* (2017). Available from https://www.federalregister.gov/documents/2017/11/22/2017-25275/schedules-of-controlled-substances-placement-of-fda-approved-products-of-oral-solutions-containing

[15] Dawson D.A. The psychosocial and biological aspects of synthetic and natural FAAH inhibitors. (2019). *Edel J Biomed Res Rev 1*, 6-11.

[16] Carson, A. & Anderson, E. Prisoners in 2015. (2016). US *Department of Justice, Bureau of Justice Statistics,* https://www.bjs.gov/content/pub/pdf/p15.pdf

[17] Lopez, G. Trump's criminal justice policy, explained. (9/11/2020). *Vox* Retrieved from https://www.msn.com/en-us/news/politics/trumps-criminal-justice-policy-explained/ar- B18R8nt

[18] Elmer, G. I., Pieper, J. O., Hamilton, L. R., & Wise, R. A. Qualitative differences between C57BL/6J and DBA/2J mice in morphine potentiation of brain stimulation reward and intravenous self-administration. (2010). *Psychopharmacology, 208*(2), 309–321

[19] Freet, C. S., Arndt, A., & Grigson, P. S. Compared with DBA/2J mice, C57BL/6J mice demonstrate greater preference for saccharin and less avoidance of a cocaine-paired saccharin cue. (2013). *Behavioral Neuroscience, 127*(3), 474–484.

[20] Griffin, I. W. C., Randall, P. K., & Middaugh, L. D. Intravenous cocaine self-administration: individual differences in male and female C57BL/6J mice. (2007). *Pharmacology, Biochemistry and Behavior, 87*(2), 267–279.

[21] Thompson, K. J., Nazari, S. S., Jacobs, W. C., Grahame, N. J., & McKillop, I. H. Use of a crossed high alcohol preferring (cHAP) mouse model with the NIAAA-model of chronic-binge ethanol intake to study liver injury. (2017). *Alcohol & Alcoholism. Supplement, 52*(6), 629–637.

[22] Pescosolido, B. A., Martin, J. K., Long, J. S., Medina, T. R., Phelan, J. C., & Link, B. G. "A disease like any other"? A decade of change in public reactions to schizophrenia, depression, and alcohol dependence. (2010). *American Journal of Psychiatry, 11*, 1321.

[23] Barry, C. L., McGinty, E. E., Pescosolido, B. A., & Goldman, H. H. Stigma, discrimination, treatment effectiveness, and policy: public views about drug addiction and mental illness. (2014). *Psychiatric services (Washington, DC)*, *65*(10), 1269–1272.

[24] *People in prison are denied medication for addiction treatment.* (December 19, 2019). Available from https://www.aclum.org/en/news/people-prison-are-denied-medication-addiction-treatment

[25] Buchman, D. Z., Skinner, W., & Illes, J. Negotiating the relationship between addiction, ethics, and brain science. (2010). *AJOB neuroscience*, *1*(1), 36–45.

[26] Crow, T. J. A map of the rat mesencephalon for electrical self-stimulation. (1972). *Brain Research, 36*(2), 265–273.

[27] Stein, L. Self-stimulation of the brain and the central stimulant action of amphetamine. (1964). *Federation Proceedings, 23*, 836–850.

[28] Robinson, T. E., & Berridge, K. C. The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Research.* (1993). *Brain Research Reviews, 18*(3), 247–291.

[29] Wise, R. A., & Bozarth, M. A. A psychomotor stimulant theory of addiction. (1987). *Psychological Review, 4*, 469.

[30] Di Chiara, G., & Imperato, A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. (1988). *Proceedings of the National Academy of Sciences of the United States of America, 85*(14), 5274–5278

[31] Laruelle, M., Abi-Dargham, A., van Dyck, C. H., Rosenblatt, W., Zea-Ponce, Y., Zoghbi, S. S., Baldwin, R. M., Charney, D. S., Hoffer, P. B., King, H. F., & Innis, R. B. Spect imaging of striatal dopamine release after amphetamine challenge in humans: Relationship between subjective effects and dopamine release. (1995). *Schizophrenia Research, 15*(1), 89–90.

[32] Volkow, N. D., Wang, G. J., Fowler, J. S., Logan, J., Schlyer, D., Hitzemann, R., Lieberman, J., Angrist, B., Pappas, N., MacGregor, R., & et al. Imaging endogenous dopamine competition with [11C]raclopride in the human brain. (1994). *Synapse (New York, N.Y.), 16*(4), 255–262.

[33] Volkow, N. D., Wang, G.-J., Fowler, J. S., Logan, J., Gatley, S. J., Wong, C., Hitzemann, R., & Pappas, N. R. Reinforcing effects of psychostimulants in humans are associated with increases in brain dopamine and occupancy of D_2 receptors. (1999). *The Journal of Pharmacology and Experimental Therapeutics, 291*(1), 409–415.

[34] Urban, N. B. L., Kegeles, L. S., Slifstein, M., Xu, X., Martinez, D., Sakr, E., Castillo, F., Moadel, T., O'Malley, S. S., Krystal, J. H., & Abi-Dargham, A. Sex differences in striatal dopamine release in young adults after oral alcohol challenge: A positron emission tomography imaging study with [^{11}C]raclopride. (2010). *Biological Psychiatry, 68*(8), 689–696.

[35] Tye, K. M., Mirzabekov, J. J., Warden, M. R., Ferenczi, E. A., Tsai, H.-C., Finkelstein, J., Kim, S.-Y., Adhikari, A., Thompson, K. R., Andalman, A. S., Gunaydin, L. A., Witten, I. B., & Deisseroth, K. Dopamine neurons modulate neural encoding and expression of depression-related behaviour. (2013). *Nature, 7433*, 537.

[36] Kenny, B. J., & Zito, P. M. Controlled substance schedules. (2022). *StatPearls* Available from https://www.ncbi.nlm.nih.gov/books/NBK538457/

[37] Robbins, I. P. Guns N' ganja: How federalism criminalizes the lawful use of marijuana. (2018). *U.C. Davis Law Review, 51*(5), 1783-1826. Available from https://search.ebscohost.com/login.aspx?direct=true&AuthType=sso&db=edshol&AN=edshol.hein.journals.davlr51.55&site=eds-live&scope=site&custid=s1229530

[38] NIDA. How does marijuana produce its effects? (April 8, 2020). Available from https://www.drugabuse.gov/publications/research-reports/marijuana/how-does-marijuana-produce-its-effects on 2020

[39] Dawson D.A. Synthetic cannabinoids, organic cannabinoids, the endocannabinoid system, and their relationship to obesity, diabetes, and depression. (2018). *Mol Biol 7*: 219.

[40] United States Department of Health and Human Services (2003). *Patent # 6630507 Cannabinoids as antioxidants and neuroprotectants.* Washington, DC, USA. World Health Organization (1994). *Lexicon of alcohol and drug terms.* Available from file:///C:/Users/dad83/Downloads/9241544686_eng.pdf

[41] Linge, R., Jiménez-Sánchez, L., Campa, L., Pilar-Cuéllar, F., Vidal, R., Pazos, A., Adell, A., & Díaz, Á. Cannabidiol induces rapid-acting antidepressant-like effects and enhances cortical 5-HT/glutamate neurotransmission: role of 5-HT1A receptors. . (2016). *Neuropharmacology, 103*, 16–26.

[42] Sartim, A. G., Guimarães, F. S., & Joca, S. R. L. Antidepressant-like effect of cannabidiol injection into the ventral medial prefrontal cortex—Possible involvement of 5-HT1A and CB1 receptors. (2016). *Behavioural Brain Research, 303*, 218–227.

[43] Russo, E. B. Forum: Cannabidiol Claims and Misconceptions. (2017). *Trends in Pharmacological Sciences*, *38*, 198–201.

[44] Hurd, Y. L., Yoon, M., Manini, A. F., Hernandez, S., Olmedo, R., Ostman, M., & Jutras-Aswad, D. Early Phase in the Development of Cannabidiol as a Treatment for Addiction: Opioid Relapse Takes Initial Center Stage. (2015). *Neurotherapeutics: The journal of the American Society for Experimental NeuroTherapeutics*, *12*(4), 807–815. https://doi.org/10.1007/s13311-015-0373-7

[45] Luján, M. Á., Castro-Zavala, A., Alegre-Zurano, L., & Valverde, O. Repeated Cannabidiol treatment reduces cocaine intake and modulates neural proliferation and CB1R expression in the mouse hippocampus. (2018). *Neuropharmacology, 143*, 163–175.

[46] Morgan, C. J. A., Das, R. K., Joye, A., Curran, H. V., & Kamboj, S. K. Cannabidiol reduces cigarette consumption in tobacco smokers: Preliminary findings. (2013). *Addictive Behaviors, 38*(9), 2433–2436.

[47] Shannon, S., & Opila-Lehman, J. Cannabidiol oil for decreasing addictive use of marijuana: A case report. (2019). *Alternative Therapies in Health & Medicine, 25*, 40–43.

[48] Vicky, K., Ilektra, A., & George, P. Cannabidiol inhibits the reward-facilitating effect of morphine: involvement of 5-HT1A receptors in the dorsal raphe nucleus. (2013). *Addiction Biology, 18*(2), 286–296.

[49] Tanimura, A., Yamazaki, M., Hashimotodani, Y., Uchigashima, M., Kawata, S., Abe, M., Kita, Y., Hashimoto, K., Shimizu, T., Watanabe, M., Sakimura, K., & Kano, M. The endocannabinoid 2-arachidonoylglycerol produced by diacylglycerol lipase α mediates retrograde suppression of synaptic transmission. (2010). *Neuron, 65*(3), 320–327.

[50] Viveros, M. P., Marco, E. M., & File, S. Endocannabinoid system and stress and anxiety responses. . (2005). *Pharmacology, Biochemistry and Behavior, 81*(2), 331–342.

[51] Thomas, A., Baillie, G. L., Phillips, A. M., Razdan, R. K., Ross, R. A., & Pertwee, R. G. Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. (2007). *British journal of pharmacology*, *150*(5), 613–623.

[52] Christian, P. M. & Judith R. H. The role of serotonin in drug use and addiction. (2015). *Behavioural Brain Research, 277 Suppl C,* 146–192.

[53] Prud'homme, M., Cata, R., & Jutras-Aswad, D. Cannabidiol as an intervention for addictive behaviors: a systematic review of the evidence. (2015). *Substance Abuse: Research and Treatment, 33.*

[54] Siklos-Whillans, J., Bacchus, A., & Manwell, L. A. A scoping review of the use of cannabis and its extracts as potential harm reduction strategies: Insights from preclinical and clinical research. (2020). *International Journal of Mental Health and Addiction,* 1.

[55] Allen, D. Survey shows low acceptance of the science of the ECS (Endocannabinoid System) at American medical schools. (2016). *Outworld*. Available from http://www.outwordmagazine.com/inside-outword/glbt-news/1266-survey-shows-low-acceptance-of-the-science-of-the-ecs-endocannabinoid-system

[56] Hatzenbuehler M. L. Structural stigma: Research evidence and implications for psychological science. (2016). *The American psychologist*, *71*(8), 742–751. https://doi.org/10.1037/amp0000068