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Review Article

The Covert Inducer: Narrative Commentary of Marijuana in the 21st Century and its Connection to Psychological Disorders

Michelle R. Dickey*

Veterinary Medical Sciences-Forensic Toxicology, College of Pharmacy, University of Florida, Gainesville, USA

ABSTRACT

Research into *Cannabis* induced psychosis and marijuana's effect on pre-existing mental disorders has been underway for several decades. However, many of these findings have surfaced in the U.S. over the last 15 years. Most of the information includes endogenous cannabinoid receptors in the brain, facts recently discovered, and more scientific evidence is needed to fully understand their role in *Cannabis* induced psychosis. Because cannabinoid receptors are neuromodulators, neurotransmitters are involved and how these are affected has yet to be discovered. Based on current understanding of neurotransmitters, the central nervous system, and mental disorders, this narrative review explores possible mechanisms of *Cannabis* induced mental disorders from a toxicological, pharmacological, and psychological perspective. This review also discusses the myth that no long-term ailments or illnesses arise from *Cannabis* use. It also illustrates why it is important to consider the potential consequences of legalizing *Cannabis* due to costly impacts on society with respect to public health and safety. Additionally, the author shares an experience observing an individual suffering from a mental disorder whose increased marijuana use led to more frequent, and dangerous, manic episodes.

Keywords: *Cannabis*; Marijuana; THC; Psychosis; Mental disorders

INTRODUCTION

Based on my five year, and continued, scholar practitioner work with focus on drug induced mental disorders and crime, a systematic review is almost impossible due to inability to study a living brain. Thus, I have prepared a narrative review using published works, including online articles and physical toxicology, medical, sociological, and pharmacological books. Additionally, my personal experience over the last 15 years dealing with individuals coping with mental disorders and abusing marijuana adds credibility to the literature sources. Such experience with observation of behavioral changes before, during, and after marijuana use, as well as the number of manic episodes coupled with dangers associated with continued *Cannabis* use led to a lengthy case study. The purpose of this narrative review is to propose possible mechanisms of action *Cannabis* has on the human brain that may explain why this substance of abuse is favored among those with mental disorders, as well as how this substance induces mental illness, and to raise awareness to harmful effects of *Cannabis* on public health and safety.

Whether legal or illicit, drug epidemics have plagued America for almost a century due to several reasons; raising awareness, legalization, decriminalization, and in a twisted way, indirect promotion [1]. The latter refers to mindset rather than company promotion whereby human nature urges some individuals to try the forbidden; illegal drugs are attractive because they are illegal [2]. *Cannabis* is a natural occurring plant found in various parts of the world that contains Δ9-tetrahydrocannabinol (THC), a psychoactive substance that leads to various adverse effects such as hallucinations, paranoia, anxiety, mistrust, fear, panic, and extreme sleepiness, to name a few [3]. Interestingly, these same symptoms are evident in various mental illnesses, especially anxiety, paranoia, fear, panic, delusions, and mania; symptoms of Bipolar, schizophrenia, and borderline personality disorder [4].

***Correspondence to:** Michelle R. Dickey, M.S. Veterinary Medical Sciences-Forensic Toxicology, B.S. Criminal Justice, College of Pharmacy, University of Florida, Gainesville, FL 32611, USA, Tel: +704-794-5810; E-mail: phdfny28@gmail.com

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Today, there are two competing epidemics, the opioid crisis and legalizing marijuana, one a legal drug with restrictions and the other an illegal substance with no federally accepted medical use, respectively [3,5]. While opioid overdoses are well-documented, *Cannabis* overdoses are considered rare, however, a procedure known as dabbing with *Cannabis* can lead to death [1,6]. Of major interest is the marijuana induced psychosis more frequently seen in hospital settings in the 21st century but this adverse effect is not new; Mexico and India made the connection between *Cannabis* and schizophrenia in the 20th century [1].

The connection between *Cannabis* and psychological impairments was not as evident as it is today because THC was much lower yet noticeable enough to cause panic leading to the infamous Reefer Madness documentary [1]. Due to various cultivating methods increasing the potency of THC and reducing cannabidiol (CBD), today's marijuana is more addictive and poses a serious public health and safety issue [1,6,7]. CBD is known as THC's counterpart; it is supposed to counteract the psychoactive effects of THC [3]. Thus, when CBD is reduced or eliminated, nothing prevents high potency THC from causing extreme psychosis [1]. Therefore, behavioral effects are the result of THC and today's marijuana has triple the potency with lower or no concentration of CBD, making this drug very dangerous, especially to those with pre-existing mental disorders and adolescents [1,6,7].

Those who suffer from severe neurotransmitter dysregulation or adolescents undergoing brain development are highly susceptible to marijuana's addictive nature and this drug is the number one choice among those suffering from a pre-existing mental disorder [1,6,8,9]. As a result, public health and safety is jeopardized by the inherent rise in cost of additional treatment and emergency room presentations, the imminent danger to law enforcement or other persons present during a manic episode, as well as potential health consequences for the *Cannabis* user, including long-term neuronal impairment and pulmonary illnesses [1,6].

LITERATURE REVIEW

Basic overview of neurotransmitters

Due to the vast array of neurotransmitters and neuromodulators, toxicological interest is narrowed down to the most prominent players in intoxication by various substances [10]. In particular, psychoactive effects of certain drugs are a large area of study because many drugs have the ability to alter neurotransmitter regulation, resulting in a variety of behavioral and toxicological consequences [11]. Even though it is difficult to connect one drug to one effect, where there is understanding of how certain neurotransmitters are supposed to operate, treatment options can be sought to reduce the risk of further complications [10]. Examining the exact roles of each player is beyond the scope of this review, however, a brief description is warranted to provide insight to possible explanations of how *Cannabis* induces and exacerbates psychological disorders.

Common drugs of abuse have been extensively studied and a direct connection to more than one neurotransmitter and cellular communication activities have been documented; however, *Cannabis* is still under investigation [3,10]. Many substances affect acetylcholine (Ach), serotonin (5HT), γ-aminobutyric acid (GABA), dopamine (DA), epinephrine, norepinephrine (NE), glutamate, glycine, adenosine, and γ-hydroxybutyrate (GHB), neurotransmitters and neuromodulators present throughout the entire nervous system [10]. Of note, many of these transmitters play a large role in skeletal muscle responsibilities alongside cognitive and control functions of the brain. Ach mediates activity of skeletal muscle and the nervous system, stimulates the autonomic nervous system and vagus, and is a cardiac depressant, vasodilator, as well as causes muscular contraction via effects in the neuromuscular junction [12].

5HT and GABA

5HT is a strong vasoconstrictor, stimulates smooth muscle contraction in the intestine, and as a neurotransmitter, affects mood, learning, memory, appetite, aggression, emotion, and personality [10,12]. GABA is derived from the brain's excitatory neurotransmitter, glutamate, and is an inhibitor of several central nervous system (CNS) activities whereby under normal circumstances keeps checks and balances between certain neuronal functions. For example, drugs that agonize GABA induce convulsions and excitation whereas substances that antagonize GABA are typically used as an anti-convulsant, sedative-hypnotics, and anxiolytics. Within the spinal cord, GABA mediates skeletal muscle reflexes while working in other areas of the nervous system outside the CNS as a vasodilator and bladder relaxer [10].

DA and NE

DA, perhaps one of the most widely studied neurotransmitters for common drugs of abuse, is typically the reward-pleasure center of the brain and is derived from NE (by which the mechanism is explained later in Possible Link: *Cannabis* and Mental Disorders) [10,13]. DA is the most widely studied due to abundance; it makes up approximately half of every catecholamine existing in the brain and nervous system. Note, catecholamines are various groups of chemical compounds containing an alkyl side chain with an amine in a catechol moiety; many endogenous catecholamines are neurochemicals such as Ach, DA, and NE [11,12].

Thus, it is no coincidence DA is affected by numerous substances, organic or inorganic, exogenous or endogenous, while excessive activity in the frontal cortex and limbic system results in psychosis and paranoia [10]. Excessive activity in the striatum or other areas in the brain caused by anything such as increased receptor activity or inhibited re-uptake results in acute Gilles de la Tourette syndrome and acute choreoathetosis accompanied by cursing, spitting, and tics [10].

Epinephrine's neuronal connection

Epinephrine, or most commonly known as adrenaline, works with NE in the body's normal fight or flight responses, and is an adrenal hormone responsible for mediating pulmonary congestive events (i.e., nasal congestion) [10,12]. NE is largely

known for its anxiety producing behavior, and when coupled with dysregulation of 5HT, DA, and epinephrine, nervousness is inevitable [12]. Like GABA, glycine is a neurotransmitter inhibitor and is predominant in the lower brainstem and spinal cord, and has amino acid receptors [10]. Receptors are made up of various amino acids and each neurotransmitter has an affinity for one or more, some which have multiple subunits (i.e., α, β, 1, 2, etc.) [11]. Neurotransmitter inhibition is, under normal circumstances, required to prevent build-up of a neuron in a given area/organ; hence the importance of understanding to ascertain which drug may have been preventing these workers from doing their job [11].

Neurotransmitter co-dependence

GABA and glycine are the only two inhibitors while many other neurotransmitters are modulators/mediators and adenosine is a modulator of body physiology and brain function [10]. It plays a major role in biotransformation whereas it is responsible for increasing oxygen, reducing oxygen demands, and affiliate (substrate) delivery, as well as limits Ach and glutamate release. The latter is pivotal in brain function to keep excessive neuronal stimulation in the postsynaptic terminal from occurring, like DA in the basal ganglia [10]. GHB has a unique toxicological role and it is debated whether it is a neuromodulator or a neurotransmitter with explained toxicity from exogenous GHB ingestion due to an affinity for GABAβ receptors [10]. Endogenous GHB is prevalent in the brain with high concentrations in the hippocampus, limbic sections, thalamus, cortex, and areas with dopaminergic activity and behavioral effects associated are tremors, agitation, anxiety, paranoia, and hallucinations, to name a few [10].

While much more is needed for a full understanding of GHB, it is believed such behavioral effects are the result of secondary GABA formation [10]. Thus, GABA is supposed to inhibit excessive neuronal build up while GHB induces build-up and with locations in DA regulated areas responsible for effects like paranoia, the correlation is unmistakable. It is important to note that electrolytes ('electrical' channels), calcium (Ca), sodium (Na), potassium (K), for example, work with neurotransmitters at the receptor level; receptors are dependent on these components for normal cellular communications, re-uptake, and transport across neuronal terminals [10,11]. Each neurotransmitter has its own receptor with affinity for one or more electrolytes, for example, Ca and Na are very popular channels receptors rely on to keep normal neuronal regulation under control [11].

Therefore, neurotransmitters and electrolytes are co-dependent whereas an imbalance in either is going to influence the nervous system, some severe and some asymptomatic or non-life threatening where drug use is not the issue. However, when drugs or toxic substances become involved, disruption of these channels often leads to one adverse effect or another whereby over time, if drug abuse is common, depletion or excess of these elements will cause health consequences. Of note, electrolyte depletion or alteration can occur for several reasons from intense exercise to pre-existing conditions, however, many toxic substances play a role in causing adverse effects like appetite suppression (cocaine) or the infamous 'munchies' (marijuana). Thus, when pre-existing mental disorders meet *Cannabis* or *Cannabis* induces psychosis, there are possible explanations for exacerbation of behavioral effects based on various mechanisms of neurotransmitters and neuromodulators occurring simultaneously within the nervous system [11].

These explanations have not yet been scientifically proven and understandably so as *Cannabis* has recently become a major topic of debate. Studies are difficult to conduct on human subjects; therefore, data is collected from hospitalization, institutionalization, and rehabilitation records [1,6,14]. Included with the activities of neurotransmitters are cannabinoid (CB) receptors (CB1, CB2) recently discovered in the brain which are still undergoing research, and CB1 has shown to be the main trigger for marijuana induced psychosis [3,9]. THC has shown the strongest affinity for CB1 and this receptor is prevalent in various parts of the brain, thus explaining the plethora of behavioral symptoms associated with *Cannabis* use [3].

Cannabinoids, neurotransmitters and the CNS

The myth stating *Cannabis* is not dangerous continues to plague society, especially in lieu of medical marijuana, but reality is just beginning to bite in psychological and toxicological disciplines [1,6]. Today's marijuana is up to 30 percent more potent than in 1970 and it cannot be forgotten that street drugs often contain complex mixtures whereby the user is not always aware of what, exactly, they are getting [1,3,5]. Mixtures can obscure neurotransmitter functions either through competitive-binding, induction, or inhibition by one substance or another the same way an active toxic metabolite can, therefore psychotic behavior could be the result of something other than marijuana itself [3,14]. Because THC is the contributor of psychoactive effects that take place mainly in the brain, a deeper look into why it induces psychosis and exacerbates symptoms of mental disorders is warranted and some links have been found during current research.

Like with many drugs, there is a dose-response relationship between *Cannabis* and cannabinoid receptors, but mechanisms that induce psychotic symptoms associated with marijuana use are poorly understood in society due to difficult presentations [3,6]. The nervous system is a complex and busy system with sub-systems all working together simultaneously to control everyday functions from movement, coordination, sleeping, breathing, eating, thought processes, and so on [15]. Marijuana primarily affects the CNS and because this system is the boss of the peripheral nervous system (PNS), which is the boss of the sympathetic and autonomic nervous systems, a trickle-down effect occurs leading to various signs and symptoms of THC toxicity [3,15]. The term 'trickle-down effect' is similar to a domino effect; when toxic substances like THC reach the CNS, which mediates communication with the rest of the nervous systems, impairment to all parts of each system is inevitable. Although there is much left to be researched regarding the effects of marijuana on all aspects of the human body, it is well documented that THC has an affinity for the CNS, the brain in particular [3].

Cannabinoid receptors

As noted previously, the brain is the site of action for naturally occurring CB receptors, CB1 and CB2. These receptors are neuromodulators that prevent adenylate cyclase, an otherwise normal process of cellular communication between pre- and postsynaptic terminals (Lapoint, 2015). This inhibition is dose-dependent and operates in a specific manner designated to promote normal cellular signals and communication; which neurotransmitter and its transporter can travel and when under normal circumstances [3]. The adenylate cyclase process is disrupted by a plethora of drugs and chemicals; therefore anyone is susceptible to some form of neurotransmitter alteration, albeit not severe enough to cause significant damage as cells can and do regenerate after minor exposure to some substances [16]. Such disruption is typically the cause of substances ability to agonize or antagonize a receptor of which THC is considered a CB receptor agonist [3].

While the exact mechanism by which CB receptors exert their psychoactive activities is not fully understood, Huestis notes it was the use of an antagonist on these receptors that revealed marijuana's affinity for CB1. As research continues regarding the effects of *Cannabis*, a plausible theory about how it alters brain activity is proposed. It may be the agonism of CB1 that leads to psychoactive effects, which might explain why THC is coined the psychoactive ingredient of marijuana, whereby more receptors are activated, preventing other neurotransmitters from traversing to the post-synaptic terminal of the neuron for normal regulation [3]. By preventing normal rotation of critical neurotransmitters like DA and 5HT, for example, they linger in the synapse where THC's psychoactive effects pronounce their existence; the pleasurable high smokers experience within minutes of inhalation, or sedation in some users [15]. As with most drugs, the duration of effects depends on the individual (tolerance), dose of *Cannabis*, and amount of exposure as well as pre-existing disease states (health), and THC potency [17].

Effects of *Cannabis* on neurotransmitter regulation

The more potent THC is, there is enhanced prevention of neurotransmitter regulation which maintains the effects longer and can lead to, not just altered mental status, but pure psychosis [1,6]. The mental alterations may be due to neurotransmitters hanging out in the synapse and since these transmitters cannot properly communicate, they cannot move on for normal regulation thereby leading to severe consequences like long-term neuronal impairment [14]. CB1 receptors are in various parts of the brain, explaining why they are involved in mood, behavior, learning (cognitive), and emotional responses [3]. The connection here is each neurotransmitter is responsible for regulating such responses via their modulators, thus explaining the wide variety of, and confusing, symptoms associated with marijuana use/abuse [15,17].

A wide spectrum of behavioral effects are associated with *Cannabis*, as well as other drugs, however, most notably are lack of concentration, decreased learning ability, reduction in memory (temporal degeneration in chronic users), and fluctuations in mood from paranoia, anxiety, to mania [17]. These behavioral responses are still developing in adolescence and marijuana can significantly impact normal development, exacerbating these responses and often leading to a massive manic episodes by the age of 20 if used regularly early in life (this can occur with lower potency THC as well) [1,17]. In those with pre-existing mental disorders, neurotransmitters are already dysregulated, and not necessarily because one or more is missing, but because the one's that do exist are not functioning properly [8]. Therefore, neurotransmitter dysregulation results in various personality and mental disorders exhibiting signs uncannily related to *Cannabis* use. Mood swings, paranoia, psychosis, hallucinations and delusions, anxiety, depression, as well as inability to focus are characteristic of mental disorders and marijuana [8,17].

Possible link: *Cannabis* and mental disorders

As noted, mental disorder characteristics are many, but it is clear they are related to the behavioral spectrum induced or exacerbated by *Cannabis* use. In other words, someone with a pre-existing mental disorder would already exhibit symptoms associated with marijuana use, which is why these individuals are at high risk for increasing the severity of their illness [9,14]. In these individuals, a lack of normal neurotransmitter regulation is the underlying reason for the illness, along with multiple vitamin and electrolyte imbalances [8]. Therefore, smoking a joint provides a sense of being and reward in brain activity for a short time, but as peak concentrations are reached and no additional THC is being administered, a 'freak-out' period ensues, known as a panic attack or paranoia [1,9].

Of note, those with personality disorders often have difficulty remaining inside the realm of 'normal' for any length of time [8]. Therefore, once the high starts to wear off, what is considered normal for these individuals starts to return and with an inability to cope with rapid changes in neurotransmissions, symptoms of their disorder are more pronounced, inducing mania or schizophrenia [8,9]. Stoner, attributes these exacerbated symptoms to downregulation of CB1 receptors in tolerant *Cannabis* users, meaning that manic symptoms are worsened by chronic use even when the person is not under THC's influence. Down-regulation is a reduction in CB1 receptors as THC is an agonist, so when a user stops smoking, for example, fewer receptors are made available to counterbalance adverse effects and causes stress to the neuronal system (aka withdrawal) [9].

Castle notes these individuals do not cope well with stress and the sheer experience of withdrawal sends their nervous system into shock, as most withdrawals from a CNS toxicant often does [8,11]. Stress is one of many nervous system responses regulated by neurotransmitters, thus, elaboration about how DA and NE (aka noradrenaline) may play a major role in marijuana and mental illness is warranted. Dr. D'Adamo and Whitney summarize it best by explaining that DA is converted to NE via an enzyme called dopamine beta-hydroxylase (DBH). Remember, NE is responsible for anxiousness while DA is supposed to be calming and rewarding [13]. So, if normal transport via DBH is blocked from flowing back and forth to produce NE while ridding of excessive DA, both neurotransmitters remain stuck in the synapse after marijuana use [11]. At the same time, CB1

receptors are agonized, blocking other cellular communications between terminals, resulting in temporary relief from stress, albeit stressing out the nervous system in the process [3].

Because DA and NE are catecholamines involved in stress responses, and since their levels are naturally abnormal in those with a mental disorder (among other neurotransmitters and modulators), any additional burden to the CNS will provoke manic responses, especially toxic substances that have an affinity for them [8,11]. Therefore, marijuana induced psychosis may be the result of several mechanisms occurring simultaneously:

- Agonism of CB1 which alters normal cellular communications (i.e., GABA),
- Trapping DA nd other neurotransmitters in the synapse,
- Blocking DBH from eliminating excessive DA, and
- Preventing or altering Ca, Na, K effluxes which in turn further disrupts normal nervous system activity [3,13,11].

Lapoint does point out that responses are dose and experience dependent, yet when speaking of today's high potent THC with little to no CBD counteracting the psychoactive effects, peak concentrations are going to vary greatly among those who use [3].

Electrolyte-neurotransmitter connection

The significance of dose and experience becomes more complex when dealing with those who already have a mental disorder, largely due to the above-mentioned actions having a connection with the disorder itself. When we take electrolytes into consideration, as they play a major role in regulating nervous system functions and are the body's electrical conductors, disruption of any of these can have significant impacts in the CNS [8,12]. For example, Ca is responsible for normal skeletal muscle function, K for skeletal muscle contraction/relaxation, and Na for fluid balance [12]. Therefore, when these conductors are prevented from functioning normally, for example, Ca and K, the relaxed and lethargic state marijuana smokers experience are indications the brain has lost some control over skeletal muscle contractions [11].

The previous statement is based on the understanding of how Ca plays an important role in skeletal muscle function which is known to be impaired by *Cannabis* use; for example, slurred speech associated with smoking marijuana is common and reflects how the drug impairs an important motor skill [3,12]. Lapoint notes that Ca signaling is dependent on GABA receptors for proper transport across the terminal, a pathway that is blocked by increased CB1 [3]. Due to an already imbalanced vitamin and electrolyte condition in mental illnesses, coupled with marijuana's ability to exacerbate the symptoms, it is no surprise that nervous system functions are manipulated, leading to tremors, paranoid thoughts, and erratic behavior [8,17].

The uncanny link between many endogenous components involved in normal nervous system functions that are dependent on neurotransmission and how various substances cause a domino effect among them is astounding. Although these links can be seen with use of other drugs that affect the CNS, *Cannabis* is among the leading substances that cause more severe mania, especially in individuals with pre-existing mental illnesses [18]. Mania, paranoia, and psychosis is often the result of excessive DA activity from inhibition or induction of receptors, re-uptake blockage, or a combination of these activities in conjunction with 5HT, epinephrine, and NE (i.e., 5HT is responsible for hallucinations, delusions, NE for anxiety) [10,12].

Induction of bipolar disorder and schizophrenia

In 1987, Sweden conducted a study of over 40 thousand military personnel who used marijuana frequently and reported the risk for developing schizophrenia or other mental psychosis was six times more likely than in a non-user. These results were presented after outside factors of other health issues and social habits were considered, and other countries like Britain and New Zealand saw similar trends in their studies [6]. Other authors have tuned into the recent interest of *Cannabis* induced bipolar disorder (BD) with and without psychosis in subjects with no family history of mental illnesses, who were otherwise healthy, and found to have a *Cannabis* use disorder (CUD) [9,14].

Kahn and Akella report of a college student who suffered from acute psychosis prior to developing BD after *Cannabis* use. He first tried *Cannabis* at the age of 16 and was an acute user in his early 20's when he presented to the clinic with obvious signs of psychotic behavior [14]. Delusions, internal preoccupation (staring at himself in the mirror and talking to others unseen), and extreme grandiosity appear to be mainstays of *Cannabis*-induced psychosis, as well as fear of being spied on (microphones and bugs planted around the room) [9,14]. Another individual who did not use *Cannabis* as a teen was also affected during college and exhibited the same behavior after using *Cannabis* only a few times [14].

Both were diagnosed bipolar with psychotic features; the first patient was admitted for four months and treated with divalproex sodium and olanzapine, leaving the researchers to conclude his *Cannabis* use did affect the neurochemical system that will leave him with long-term consequences [14]. Stoner reiterates the significance of early onset of BD in long-term marijuana users who begin using during adolescence and many will have their first manic episode by age 20 [9]. Castle notes that those who are bipolar will also have their first manic episode by 20 and this is without the use of marijuana [8]. These two revelations are correlated so tightly due to the developing brain and how stress, upbringing, and societal influence are major components in both development of BD as well as *Cannabis* use [8,9]. In addition, Rubin and Zorumski found that acute psychosis induced by marijuana may very well predict future mental illnesses [18].

A 1994 to 2014 study of individuals with no previous history of psychotic illnesses was conducted and those who exhibited marijuana-induced psychosis for more than 48 hours were diagnosed. A 20 year follow up was conducted and 41 percent developed schizophrenia and 47 percent became bipolar or schizophrenic; those with BD within approximately three years and those with schizophrenia within approximately four years [18]. Of note, this long-term study occurred during the critical

time period Berenson and Sabet mention the increase in THC potency. In addition, the study included individuals who experienced psychotic episodes after taking opioids, amphetamines, hallucinogens, alcohol, sedatives, and cocaine, but the most dramatic episodes occurred in those who used *Cannabis* [1,6,18]. Thus, a major concern for today's youth is on the rise as more adolescents are using *Cannabis*, particularly marijuana cigarettes and vapes due to the impact on developing brains as well as increased risk for inducing BD or schizophrenia [1,19].

The developing brain versus chronic adult *Cannabis* use

Of most importance are studies involving the developing brain and marijuana's effect on cognitive impairment, which is nothing new [19]. However, in lieu of new evidence connecting *Cannabis* to mental disorders, focus remains on the young who begin using early because those who do, often use more frequently [20]. Interestingly, among teens, those who do use heavily are the ones with no plans to attend college and while the number of teen drug abuse has not grown significantly, the issue lies within the addictive quality of new marijuana products [6,20]. It is also relevant that heavy users at younger ages tend to drop out of high school due to the developmental aspects involved with learning, memory, and motor skills [2,20].

In short, adolescents are under a lot of stress, from parents, peers, and teachers, as well as to learn what is considered normal and accepted versus what is considered deviant and rejected [2]. Because young brains are under development, from childhood to approximately age 25, it is crucial to point out the brain's sensitivity to not only marijuana, but to many drugs and substances that can alter neurotransmitter regulation and development [11,20]. For example, in the hippocampus, the region for learning, memory, and motor skills, it was once believed that neurons do not regenerate (neurogenesis) like they do in other parts of the brain after childhood [21].

However, new studies are emerging that show it is, after all, possible for neurons to regenerate in the hippocampus during adulthood, yet this depends on several factors such as pre-existing disease and lifestyle (i.e., exercising promotes neurogenesis in the hippocampus) [21]. Although this has yet to be demonstrated in humans, the major connection here is marijuana's effect on the exact same characteristics-learning, memory, and motor skills, thus reiterating Lapoint's account of CB1 receptors prominence in areas of the brain associated with emotional and cognitive functions. In other words, it is known that marijuana affects the hippocampus in animals and the drug impairs cognitive function in humans [3,19].

Then it comes as no surprise Kalin notes a surge in substance abuse among those with pre-existing mental illnesses and severe cognitive consequences in adolescents who use *Cannabis* [22]. As mentioned previously, stress is perhaps one of many triggers that makes *Cannabis* attractive, thus possibly explaining the need to self-medicate with marijuana after developing BD or schizophrenia [9]. This need to self-medicate arises later in life, during adulthood, by those who started using *Cannabis* during adolescence; perhaps another reason marijuana is the number one drug of choice among those who suffer from BD and schizophrenia [1,6,9,18]. Where stress appears to be the main ingredient for marijuana smoking, adolescents are likely turning to this drug as a stress reliever and in turn, reduces the ability to learn how to cope with stress later in life and increasing risk of developing a mental disorder [1,6,20].

This does not discount the college student who did not use *Cannabis* until in his 20's while in college who also developed BD, but there is no conclusion as to whether he continues to use and if so, why. What it does illustrate is the possibility of developing marijuana-induced psychosis later in life when no use occurred during adolescence (Rubin & Zorumski, 2018). It is important to remember that many mental illnesses go undiagnosed, untreated, and often ignored, the latter due, in large part, to the environment a sufferer is in-surrounded by like-minded individuals (Berenson, 2019; Kendall, 2015; Castle, 2003). Additionally, drug use in adolescence is not uncommon as many will experiment with different things for several reasons, thus making the distinction between normal teenage behavior and drug-induced behavior very difficult [18]. Hence why *Cannabis* induced BD and psychosis may go unrecognized until later in life and unfortunately, once the development of a mental illness has occurred, there is no known reversible treatment [1,6,8]. An illustration of how such events can go unnoticed is provided by the authors own observation of an elderly man who admitted to life-long marijuana smoking.

Case study of Mr. Z (April 2017-November 2018)

The subjects name is kept confidential per APA guidelines. Launching her own investigation into unusual behavior exhibited by Mr. Z, Ms. Dickey wanted to understand why he increased his marijuana use and resorted to additional illegal behavior. With knowledge his criminal behavior would be somewhat difficult to prove without physical evidence (much was cyber-related/electronic manipulation), she went into observation mode for one year and seven months to piece together a puzzle that fits with emerging evidence of *Cannabis* and mental illness. Mr. Z admitted to using marijuana from adolescence through adulthood and was age 69-70 during observation.

It was during April of 2017 that signs of bipolar disorder in Mr. Z began to emerge. With extensive knowledge about the disorder due to education, Ms. Dickey conducted research on the various types of mental illnesses for a deeper understanding of their characteristics. She observed an increase in marijuana smoking and became concerned as she watched a rapid decline in Mr. Z's short-term memory ensue. Signs of BD he exhibited were mild; typical mood changes, inability to make decisions, inability to focus, and unstable behavior patterns, until he increased his marijuana intake [8]. She watched these symptoms go from mild to severe manic episodes where Mr. Z claimed feeling suicidal, had low-toned, and slurred/incoherent speech.

He often claimed he didn't know why he was shaking (tremors), why he couldn't sleep, why he couldn't focus, and why he kept forgetting daily chores. While this sounds like onset of dementia, the more logical explanation became more evident as his manic episodes increased. Mr. Z became extremely erratic around the house, running around in frantic circles looking for

something he misplaced, was easily agitated, his face was always flushed, and he could not make proper eye contact during conversations. Aside from lying, his facial expressions said more than a thousand words when casually informed of how chronic marijuana use can lead to temporal disintegration; he gazed out a window, sighed, and denied that was the reason for his behavior.

Each manic episode entailed a plethora of behavioral patterns, none consistent, and to anyone else it would have looked like Mr. Z was having a complete meltdown. What he was experiencing was massive manic episodes after smoking marijuana-he could not cope with the coming down period that follows cessation of *Cannabis* use. Ironically, advocates for marijuana legalization believe there is no such 'withdrawal'; however, more research is emerging with evidence that says otherwise [1]. Mr. Z would express paranoia about being hacked, believed he was hearing high pitched whistling sounds, was irritable, restless, and extremely narcissistic.

He spent more time on his appearance than necessary, always combing his hair and staring at himself in the mirror. Mr. Z often accused the author of being paranoid; he accused her of feeling things he was feeling like obsessed, judgmental, crazy, and out of touch with reality. Ms. Dickey never said or did anything out of the ordinary that would indicate such feelings, which upset Mr. Z because she would not reinforce his behavior. Castle notes that individuals with personality disorders will deflect what they are feeling or seeing onto someone else, and, in fact, they often see their own emotions and behavior being carried out in others (delusions and hallucinations) [8]. It became extremely difficult for Ms. Dickey to differentiate between the disorder and *Cannabis* use, so she closed the case.

The experience watching someone with a pre-existing mental disorder, who increased his marijuana use that led to frequent manic episodes, and even schizophrenia type behavior, illustrates this danger to public health and safety. Thus, it really is complex for those with pre-existing mental disorders and is one major reason legalizing recreational marijuana warrants a lot more research and medical use is just as controversial.

Legalization versus medical marijuana

Public health and safety should be at the forefront of the legalization debate, a component rarely discussed by advocates who lack a full understanding of potential dangers associated with psychological disorders induced by many drugs, not only *Cannabis* [1,6]. However, this does not stop lobbyist from using the traditional myths surrounding 1970's *Cannabis*; nonaddictive, safer than alcohol, no long-term complications, and no one gets violent on pot [6]. These myths are being debunked as the days go forward and additional studies emerge; after all, if *Cannabis* can induce psychological disorders like schizophrenia, how would one explain the violent, angry behavior associated with this mental disorder? [1]. Thus, whether *Cannabis* use is secondary to psychosis or psychosis is secondary to *Cannabis* use, it still equals potential for violent and criminal behavior [1,6].

Dickey explains the impact of such behavior resulting in an arrest due to the nature of psychotic episodes rather than possession of a small amount of marijuana [7]. For example, someone suffering from BD or schizophrenia under the influence of THC would become erratic just from being pulled over in a routine traffic stop, thus leading to an arrest and/or possible mandatory admission to a mental facility. The arrest might include possession of marijuana if later found during a legal search, however, due to decriminalization, it would not be the main cause of arrest [1]. Even though no massive catastrophe, other than an increase in car crashes, has yet occurred when someone is high on *Cannabis*, this does not mean it won't ever happen when THC levels continue to increase and therefore, increasing risk for addiction [1,6,17]. The main issue here is finding ways to be proactive, not reactive, and a very important step is bringing the issue of marijuana's role in mental disorders to the forefront [6].

Complexities with intervention

Society often talks of intervention to cease drug addiction, but very little is discussed about intervention for mental illnesses; this is conflicting due to various drugs playing a role in mental illnesses in the first place. Therefore, it can be inferred when discussing intervention for drug addiction it can include such for mental illness as the two are highly correlated. Next, the financial cost to society for treatment of such disorders and addiction whereby a rise in healthcare plans for those suffering from a diagnosed mental disorder is discouraging [6]. In addition, danger for the public stems from the knowledge drug addicts will go through great lengths to obtain their drug of choice and no one can confirm marijuana smokers do not steal to obtain their drug [6,7].

Personal experience has proven that items around the house accessible to a *Cannabis* user can and do go missing, and not necessarily cash, but rather, something of value that can be sold or pawned for the cash. Why do robberies and burglaries occur in the first place; cash, and what is the cash needed for? The number one suspect is drugs; therefore, it is erroneous to assume a marijuana smoker would never rob someone of their money or possessions to obtain that joint. Interestingly, it is no coincidence that studies have shown high correlation with drug use, intelligence, impulsivity, and psychopathy among those arrested in forensic and psychiatric populations. Evans et al. note that drug use and impulsivity are highly indicative of criminal and psychotic behavior, meaning where drug use and psychological disorders meet, there will be crime [24].

In other words, where psychological problems exist, so does drug abuse in populations left undiagnosed and untreated. The cost of such actions to a victim can be devastating (i.e., filing a police report, filing a claim with insurance companies, emotional distress, etc.), and dangerous if the perpetrator is high with psychotic features and approaches a victim on the street [23]. In addition, if a *Cannabis* user is suffering from a pre-existing mental disorder, anyone who resides in the same environment who does not share those characteristics is also in harm's way for becoming the object of deflection (the one who is believed to be conducting wrongful acts when it is the *Cannabis* user actually

doing so) [8]. Another aspect to public health and safety is financial repercussions whereby emergency rooms and treatment facilities become inundated with individuals exhibiting high potency THC symptoms [1,6].

Comorbidity in treatment

Berenson and Sabet note there has been an increase in hospital admissions by those suffering from marijuana's psychoactive effects including hallucinations, delusions, tachycardia, anxiety, and paranoia. While many other drugs also cause such symptoms, it is important to note these authors are referring to patients with high levels of THC and is not due to more users, per se, but as the result of increase in potency. Another aspect to consider is CBD products; even though this component in *Cannabis* counteracts psychoactive effects of THC and is credited for the pain relieving properties of the drug, it is still highly controversial. Currently, a major trend in CBD products is hitting many health markets as an herbal supplement that is confusing to the uninformed consumer who may associate CBD with THC, believing they are okay because both come from the same plant [1,6].

The fact is, CBD may or may not work to relieve pain or induce other acclaimed health benefits in everyone [1,3]. In addition to the lack of understanding THC versus CBD, medical marijuana has planted a no nonsense line of thinking in segments of society whereby mentally, it is assumed that *Cannabis* must be safe or it wouldn't be used in medicine, right? Wrong. The reason *Cannabis* has not been approved by the FDA to treat any medical condition is because it does not meet necessary requirements, and the DEA leaves it as a schedule I drug for the same reason. Even the National Academy of Medicine (NAM) reported absolutely no evidence *Cannabis* is of any use to treat glaucoma, epilepsy, Parkinson's disease, ALS/Lou Gehrig's disease, dementia (marijuana actually increases risk for development-impairs memory and inhibits ability to learn anything new), or irritable bowel syndrome [1].

On the other hand, *Cannabis* has been shown to reduce suffering and side effects of chemotherapy induced emesis and spastic muscles (multiple sclerosis), while CBD, not THC, has been approved for some forms of epilepsy, a condition for which the FDA has approved CBD use [1]. While this is an improvement in finding a little evidence for only a few medical conditions, it by no means makes it universal; healthcare is not a universal, one-size-fits all entity and the use of *Cannabis* in medicine is still in its infancy.

Therapeutic versus health consequences

Another component in the misunderstanding of *Cannabis* use lies within the knowledge it is being used, experimentally, for therapeutic purposes but nothing conclusive has been ascertained or observed [17]. Hence the inability to connect therapeutic outcomes with behavioral effects; however, it is important to note that legitimate medical marijuana prescribed by a licensed doctor does not contain high quantities of THC, if at all [1]. While *Cannabis* has been used as an analgesic, treatment of AIDS, multiple sclerosis, and as an anti-emesis agent post chemotherapy, there have been other drugs found to be more effective in treating these conditions [17]. Long-term treatment with *Cannabis* has yet to be examined and therapeutic effects have not been successfully separated from behavioral effects [17].

In addition, many have believed that smoking marijuana is safer than smoking regular cigarettes, however, tobacco of any kind is a known carcinogenic [25]. It is ludicrous to think smoke inhalation of any kind would not introduce possible consequences; the human lungs are not designed to have smoked circulating inside the body. After all, marijuana smokers tend to hold in the smoke whereas cigarette smokers do not and the American Lung Association notes that marijuana smokers report more respiratory ailments and take more sick days than do traditional smokers. Ironically, tobacco companies are salivating over the prospect of marketing marijuana cigarettes; they should have the same Surgeon General's warning on a pack of those like they do a pack of regular cigarettes [1,6].

Empirical evidence of *cannabis* induced illnesses

The FDA could not approve the use of marijuana cigarettes because there are too many various chemicals in *Cannabis* to conduct a human study for medical approval [1]. Sabet notes a 2002 Yale study that found an increase in airway obstruction, bronchitis, and immune system impairment in those who smoked marijuana regularly [6]. The Yale School of Medicine conducted a similar study in 2005 which yielded the same results and concluded that marijuana smoking does have significantly similar consequences of regular tobacco smoking [6]. In addition, scientist in New Zealand conducted another study in 2007 that reiterates findings from both Yale studies; marijuana smoking does have adverse effects on the pulmonary system, in particular, obstruction of airways and overall lung [6].

In 2009, scientists in Canada conducted a study on individuals with a history of smoking tobacco and marijuana who were over 40 years of age and concluded these individuals showed an extremely higher risk for developing chronic obstructive pulmonary disorder (COPD) and other severe respiratory symptoms [6]. Therefore, the myth about marijuana smoking being less harmful than tobacco has been debunked and another area of concern is *Cannabis*'s effects on reproductive health.

Sabet notes chronic *Cannabis* use does impair reproductive qualities in men and women with decreased fertility as one of many symptoms [6]. In men, this is thought to be related to *Cannabis*'s role in reducing sperm count as well as testosterone levels while in pregnant women who smoke, THC is passed through the placenta to the developing fetus [3,6]. Although more research is needed to understand more about marijuana smoking during pregnancy, several observations have been made regarding babies born to these mothers. Studies show that babies born to mothers who smoked marijuana during pregnancy have higher-pitched cries, problems with visual stimuli, and have increased tremors, which doctors indicate could be related to problems with neurological development [6].

Additional studies have shown an increased risk for development of breathing problems like wheezing and asthma,

as well as development of chronic chest infections during the first six months of the baby's life [6]. This information illustrates another issue with the cost of healthcare; children born to mothers who smoked marijuana while pregnant are at a higher risk for lifetime chronic pulmonary illnesses [6]. Another health concern is the cardiovascular system, which is of major concern for a variety of drugs and lifestyle characteristics but is an area regarding the myth *Cannabis* is 'better' for you than any other substance. Lapoint and Sabet note that after inhalation of marijuana smoke, the heart speeds up (tachycardia), eyes turn red (decreased flow of oxygen [the eyes are most delicate because circulation is already poor]), and expansion of blood vessels occurs. Evidence from emergency room admissions shows marijuana related cardiovascular problems, however, further studies are needed to conclude these complications were solely caused by the drug itself [3,6].

Summary of health consequences

Based on emerging health studies, it is safe to infer that smoking marijuana can, and does, lead to potentially severe pulmonary illnesses and complications with a plausible increased risk for cardiovascular issues. When coupled with the neurological ailments induced or exacerbated by *Cannabis* use, there is much more to consider before rendering marijuana safe for recreational use. In addition, the subject of direct marijuana overdoses has yet to surface; however, there have been cases of dabbing overdoses [6]. Dabbing is inhalation of extremely high concentrations of marijuana oils and waxes after being heated and overdose occurs from passing out [6]. NORML (National Organization for the Reform of Marijuana Laws) has even admitted to an increase in 911 teams being dispatched to *Cannabis* overdose situations in the last couple of years [6].

It is important to point out that heating these oils involves butane, a highly flammable substance that leaves toxic residues on the marijuana oil being used, thus, an individual is not only inhaling high concentrates of marijuana, but also toxic fumes from the butane. Dabbing is essentially a way for users to obtain an extremely intense and rapid 'high' where consequences of death are unintentional. With these potential health consequences, it is no surprise NAM published a 2017 report that contradicts the legalization advocates message that *Cannabis*, as a whole, is a medicine. *Cannabis* as a cure for cancer is another myth being torn down by studies conducted in other countries pointing out that marijuana smoke contains more chemicals than tobacco. Therefore, marijuana and tobacco do have carcinogenic properties; marijuana smokers will hold in multiple chemicals longer than regular tobacco smokers and not necessarily less frequently [1,6].

In 2008, the European Respiratory Journal published an article concluding that some of the chemicals found in *Cannabis* are known carcinogens that can induce molecular changes indicative of cancer. While the lung cancer debate continues, as there are competing studies, it can be inferred that both tobacco and marijuana increase the risk of lung cancer in some individuals. However, neck and head cancer, as well as oral lesions, were noted in a 2002 study by the Journal of Clinical Pharmacology [6]. It is of great intrigue that many individuals associate health problems with almost every drug, legal and illegal, but when it comes to *Cannabis*, it is somehow difficult to equate this substance as a 'drug'. In addition, addiction is associated with various drugs, but *Cannabis* seems to be the exception; however, in toxicology and pharmacology, there is evidence that anything which produces pleasurable effects to instant gratification, from pain relieve to euphoria, is, in fact, addictive [11,26].

DISCUSSION

With evidence emerging of how *Cannabis* plays a major role in mental disorders and other potential health problems, it is difficult to ignore toxicological consequences of legalizing recreational use, and in some cases, medical use depending on how it is manufactured. As continued methods of cultivating *Cannabis* reduces or eliminates CBD and increases THC, it is only a matter of time before overdose cases apart from dabbing occur. Indirect accidents are already on the rise due to *Cannabis* use from vehicular crashes to bodily injury, and to a lesser extent, suicide in those who already suffer from mental disorders that include depression, anxiety, and/or mania [1,6]. The healthcare cost of treatment for mental disorders caused by *Cannabis* and the rising number of emergency room presentations from today's THC toxicity are just the beginning of a new type of drug epidemic [1,6,14].

It will not be just a drug epidemic; it will be a drug abuse and mental disorder epidemic coupled with medical consequences of other potential health issues, largely due to pharmacodynamics of high potency THC yet to be discovered. Although much of the mechanism of actions surrounding *Cannabis* is still not fully understood, these studies, among others, and personal experience witnessing such effects tell a much more dangerous story. Of note, much of the same possible consequences have been shown with use of other psychoactive substances like cocaine, amphetamines, and hallucinogens [11]. However, the major difference with marijuana lies within two important facts; the FDA has not approved *Cannabis* for treatment of any medical condition and the DEA has not removed as a Schedule 1 substance [1,6]. This also applies to non-medical CBD products and consumers should be skeptical of the origins from which the ingredients were derived [1].

As noted, another difference is that *Cannabis* is the number one drug of choice by those who already suffer from BD or other mental disorder, despite claims these individuals also abuse ethanol [9]. Castle debunks the abuse of alcohol by those with BD due to the side effect of headaches after one or two drinks [6]. This is likely due to neurotransmitter dysregulation whereby DA and 5HT play major roles indicating a BD sufferer does not experience the same initial 'alertness', but rather, the complete 'downer' effect associated with alcohol [8,27]. The significance of this point lies within an already depressed mood non-treated BD sufferer's deal with daily and marijuana helps them escape those feelings even if it is short lived. Headaches are uncomfortable-BD makes them uncomfortable in their own skin, and marijuana relieves those feelings while alcohol exacerbates them [8,9].

Aside from various drug debates, marijuana as the number one drug of abuse among this population raises the notion this is one finding that can help explain the difficulties in recognizing mental illness at its core. In other words, too often are there cases where someone suffering from a psychological disorder goes unnoticed until they reach a breaking point that leads to a criminal act; individuals who knew the person claim they had no idea about the illness [24]. It is plausible to think marijuana use has, for a period, masked the mental illness, allowing that person to appear normal until either increased use or cessation has induced a manic episode. Tolerance to drugs is not new and plays a major role in how a *Cannabis* user will react when THC intake is stopped or increased. This is no different than the concept of too much or too little causing the same side effects; there is a point at which a substance reaches equilibrium, but it becomes difficult or impossible when the substance is chronically abused [3,11].

CONCLUSION

In conclusion, the United States Justice Department and other researchers report that many individuals who would have been placed in hospitals are currently in prison and have been diagnosed with psychotic disorders. It is has been concluded that marijuana causes psychosis and violence, largely due to the fact that individuals with psychosis under the influence of drugs are 10 times more likely to commit violent crime whereas those with psychosis and no drug use are only twice as likely. What would these numbers look like if every state legalizes recreational use of marijuana? Schizophrenia is largely correlated with violent crime (i.e., homicide) and *Cannabis* can induce schizophrenia, therefore more research is needed to identify those who are at greater risk when using *Cannabis*. Additional research is also warranted into the relationship between *Cannabis* and neurological activity to gain a better understanding of how to combat mental illnesses and drug abuse. While all neurotransmitters play roles in behavioral effects and many substances induce similar symptoms as *Cannabis*, the main point is the juxtaposed nature by which marijuana affects critical players that can induce mental illness and exacerbate symptoms of pre-existing disorders.

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