Commentaries

The Psychiatric Consequences of Cannabinoids

Joao P. De Aquino MD[1,2,3]; Mohamed Sherif MD, MSc[1,2,3]; Rajiv Radhakrishnan MBBS, MD[1,2,3]; John D. Cahill BMBS, BMedSci[1,2]; Mohini Ranganathan MD[1,2,3]; and Deepak C. D'Souza MBBS, MD[1,2,3]

[1]Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut; [2]Clinical Neurosciences Division, US Department of Veterans Affairs, VA Connecticut Healthcare System, West Haven, Connecticut; and [3]Clinical Neuroscience Research Unit, Connecticut Mental Health Center, New Haven, Connecticut

ABSTRACT

With rising rates of cannabis use in the general population and an increasing number of US states legalizing both recreational and medical cannabis use, it is important to be informed about the adverse consequences of cannabinoids. This Commentary provides an overview of the psychiatric effects of plant-based and synthetic cannabinoids, differentiating acute effects from effects associated with persistent use. Cannabinoids produce multiphasic and dose-dependent effects on anxiety, mood, and perception, in addition to impairing cognition and psychomotor function. Generally, in healthy individuals, the acute negative psychiatric effects of cannabinoids are rated as milder in severity compared with those in individuals with pre-existing psychiatric disorders. With chronic exposure to cannabinoids, the probability of developing tolerance and dependence can increase. A problematic pattern of cannabis use can lead to clinically significant impairment and distress. Cessation of cannabis use in individuals who are tolerant and dependent can lead to a withdrawal syndrome. Studies report long-term cannabis exposure has been linked to psychiatric disorders, such as anxiety, psychotic and mood disorders. Limitations to the existing evidence notwithstanding, the plausibility of a causal relationship between cannabinoid exposure and persistent negative psychiatric outcomes, and the potential for long-term brain changes by regular exposure, especially for adolescents, are sufficient to warrant discussions with clinicians and the public. Implications for clinicians who certify, prescribe, or care for patients receiving cannabinoids are discussed, and a case is made for further research to better understand the impact of legalization on public mental health. (*Clin Ther*. 2018;40:1448–1456) © 2018 Published by Elsevier Inc.

Key words: cannabinoid, cannabis, side effects, medical marijuana, psychiatric.

INTRODUCTION

Since 1992, the proportion of Americans currently using cannabis increased by approximately 60%.[1] International cannabinoid control reform seems to have gained momentum in recent years, with several US states and other jurisdictions in Europe and South and Central America (Portugal, Spain, Belgium Portugal, Argentina, Colombia, Jamaica) moving toward legalization in their cannabis control policies.[2] Given rapid societal changes, elucidating what is known about the consequences of cannabinoid use on mental health takes on heightened public health significance.

Cannabis is a complex and highly variable mixture of approximately 400 or more chemical compounds, including cannabinoids (or phytocannabinoids), terpenoids, and flavonoids that produce individual and interactive effects.[3] Δ-9-Tetrahydrocannabinol (THC) is the principal psychoactive constituent of cannabis. Some of the other 70 currently known phytocannabinoids also have individual effects, and some can modify the effects of THC.[4] For example, cannabidiol (CBD)

Accepted for publication March 23, 2017.
https://doi.org/10.1016/j.clinthera.2018.03.013
0149-2918/$ - see front matter

may have anxiolytic and antipsychotic-like effects that offset THC-induced anxiety and psychotomimetic effects.[5,6] Preclinical studies suggest that the individual effects of phytocannabinoids are multiphasic and dose dependent, which is exemplified by the anxiolytic effects of THC at lower doses and anxiogenic effects at higher doses.[7]

It is also important to note that varieties of cannabis, cannabis-based products, and synthetic cannabinoids (SCs) differ significantly in their cannabinoid content and proportion.[3] It is widely recognized that the THC content (potency) of cannabis in the United States has been steadily increasing over the past 40 years; from 4% in 1995 to 12% in 2014.[8] Some potent forms of cannabis have a THC content of approximately 30%, and other cannabis-based products, such as "earwax" and "shatter," have a THC content of >80%.[9] In comparison, the cannabis made available by the National Institute of Drug Abuse has <4% THC. The THC/CBD ratio has also increased significantly, such that the forms of cannabis that presently dominate the market have very low CBD and high THC content.[8]

This remarkable variability is in contrast with the Food and Drug Administration–approved medications, which have strict guidelines as to the variability in the content of their active moieties, and makes it challenging to compare clinical studies that use different strains or compounds and attributions of positive or negative effects of cannabis with any of its main constituents.

The Brain Endocannabinoid System

The endocannabinoid (eCB) system is one of the most widespread systems in the central nervous system[4] (**Figure**). It consists of receptors, endogenous transmitters or eCBs, and enzymes that synthesize and degrade eCBs. The 2 main receptors are the G-protein–coupled receptors, cannabinoid-1 receptor (CB1R) and cannabinoid-2 receptor (CB2R), but in addition, some cannabinoids also engage transient receptor potential channels, and peroxisome proliferator–activated receptors. The 2 most well-studied eCBs include the lipid ligands anandamide and 2-arachidonoylglycerol. The enzymes involved in the biosynthesis and degradation of anandamide are N-acylphosphatidylethanolamine-selective phospholipase D and fatty acid amide hydrolase, respectively, while the enzymes involved in the biosynthesis and degradation of 2-arachidonoylglycerol are diacylglycerol lipase, monoacylglycerol lipase and 2-arachidonoylglycerol hydrolase.

In contrast to other neurotransmitters, for example, dopamine, that are synthesized ahead of time and stored in vesicles for release, anandamide and 2-arachidonoylglycerol are synthesized on demand from their precursors present in lipid membranes, prompted by activation of G-protein–coupled receptors or by depolarization. After synthesis, eCBs are rapidly released into the extracellular space, where they bind to and activate presynaptic or postsynaptic CB1R or CB2Rs, inhibiting the further release of neurotransmitters.[4] CB1Rs, densely expressed in the brain, are critical to mediating the psychoactive effects of cannabis, as they are the targets of THC, a partial agonist at this receptor. CB2Rs, in contrast, are mostly expressed peripherally (immune, gastrointestinal, and peripheral nervous systems).

Interactions Between Cannabis and the Endocannabinoid System

In contrast to eCBs, exogenous cannabinoids, such as THC, are metabolized over several hours before being excreted. Thus, the duration of effects of THC and eCBs are rather different, with eCBs having brief effects and THC having prolonged effects. The important role of the eCB in neurodevelopment may explain why adolescence is a critical period wherein individuals are particularly susceptible to the effects of exogenous cannabinoids, potentially resulting in the disruption of eCB-mediated processes.[10–12] As reviewed elsewhere, a wealth of preclinical literature supports the notion that activation of CB1-R by exogenous cannabinoids during adolescence leads to persistent and enduring changes in brain function.[10–12] Clinical evidence also supports that young age is a risk factor for conversion to psychiatric disorders with prolonged cannabis exposure, including serious mental illnesses.[13]

The increasing use of cannabinoids, combined with the availability of more potent products, warrants an appropriate understanding of their psychiatric consequences. In this narrative review, which spans the breadth both preclinical and clinical literature, the psychiatric adverse consequences of cannabinoids are summarized, distinguishing their acute effects from effects associated with their persistent use, in order to inform clinicians. As few randomized controlled trials

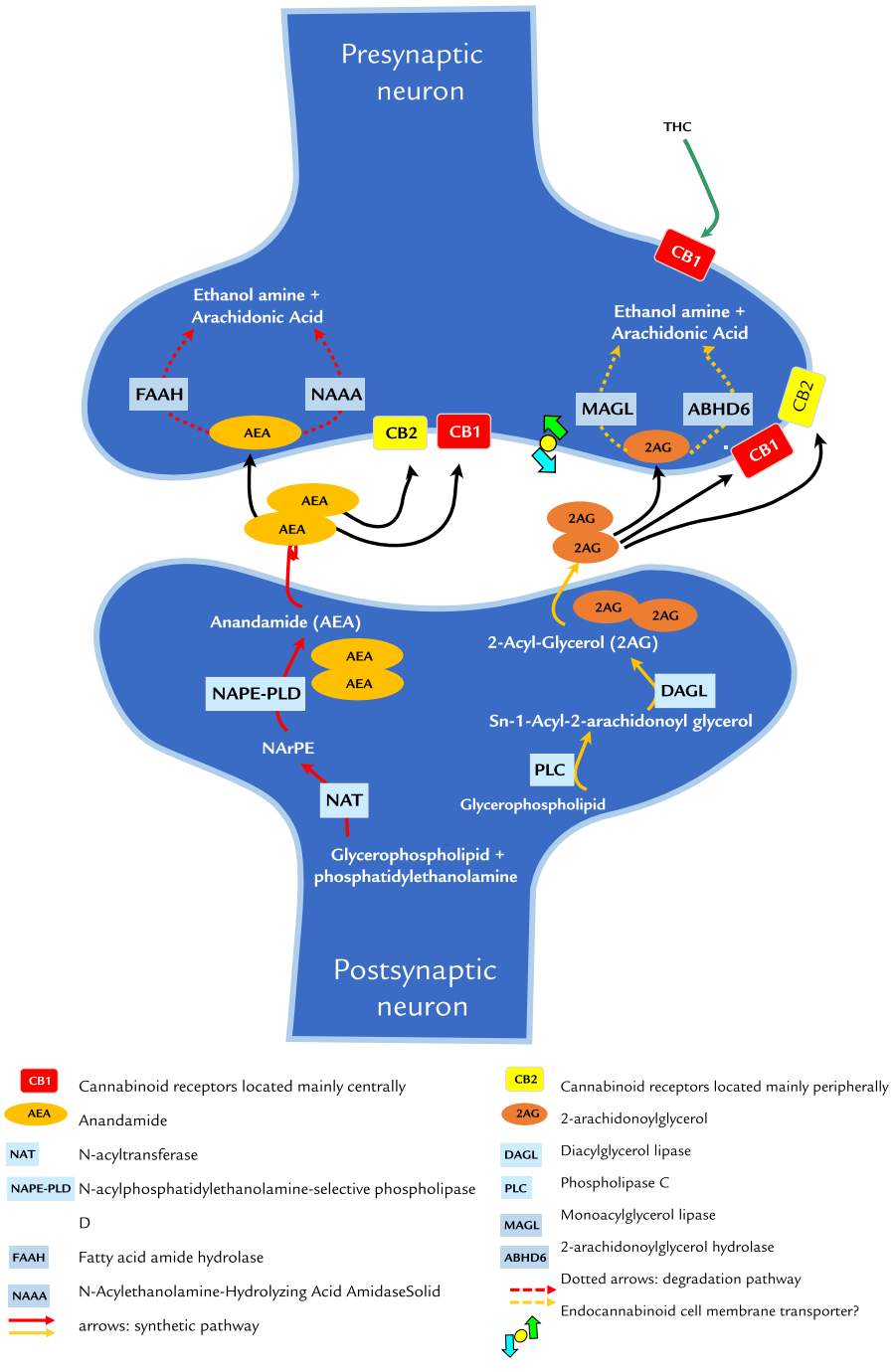

Figure. The endocannabinoid system. ABHD6 = 2-arachidonoylglycerol hydrolase; AEA = anandamide; 2AG = 2-arachidonoylglycerol; CB1 = cannabinoid receptors located mainly centrally; CB2 = cannabinoid receptors located mainly peripherally; DAGL = diacylglycerol lipase; FAAH = fatty acid amide hydrolase; MAGL = monoacylglycerol lipase; NAAAN = acylethanolamine-hydrolyzing acid amidase; NAPE-PLD = N-acylphosphatidylethanolamine-selective phospholipase D; NAT = N-acyltransferase; PLC = phospholipase C. Solid arrows = synthetic pathway; dotted arrows = degradation pathway.

have specifically assessed the safety of herbal cannabis, most of the data on safety are derived from randomized controlled trials with cannabinoids (eg, dronabinol and nabilone) or from data on cannabis use. Clinical implications are discussed subsequently.

Acute Effects

The onset of cannabinoid effects depends on the route of administration, with effects emerging within a few minutes with the inhaled route, but taking much longer (60–90 minutes) after oral consumption.[14] The duration of these effects are highly variable, but typically last for 2 (inhaled) to 4 hours (oral).[14,15] The acute psychiatric effects of cannabinoids have greater likelihood of occurrence and severity with higher doses and higher THC/CBD ratio and full agonists, such as SCs. Why some healthy individuals are more vulnerable than others to acute psychiatric effects of cannabinoids is not entirely clear. Individuals with pre-existing psychiatric disorders may be more prone to experience acute psychiatric effects of cannabinoids. Individuals who use cannabinoids regularly may show blunted responses to some of the acute effects of cannabinoids, which may be related to development of tolerance.[16]

Behavioral Effects

Mood

Cannabis has commonly been reported to have acute transient effects on mood. The "high" produced by cannabis includes, but is not limited to, a combination of effects reported as relaxation, euphoria, relaxed inhibitions, and a sense of well-being. Although cannabis generally reduces anxiety, especially at lower doses, the higher concentration of THC found in cannabis in recent years may be related to the increase in reports of panic-like effects.[17] THC has been reported to increase anxiety when administered alone, especially at high doses administered under conditions of stress.[18] Conversely, co-administration with CBD can counter THC-induced anxiety.[5,6]

Consistent with the notion of a biphasic influence of cannabinoids on anxiety-like behavior, genetic studies in mice found that, by selectively knocking down CB1Rs in either GABAergic or glutamatergic neurons, the anxiolytic effect of cannabinoids at low doses depends on CB1R activation of cortical glutamatergic neurons (therefore decreasing the release of this excitatory neurotransmitter), whereas the anxiogenic effect at high doses is related to CB1R activation of forebrain GABAergic neurons (therefore decreasing the release of this inhibitory neurotransmitter).[18]

Emerging preclinical data suggest that a deficit in eCB signaling can contribute to the etiology of depression.[19] There are observational reports of elevated mood and reduced depressive symptoms after short-term consumption of cannabis, which are blocked by CB1 receptor antagonists.[19] These effects are likely confounded by euphorigenic effects associated with intoxication.

Accordingly, treatment of healthy individuals with a CB1R antagonist (eg, rimonabant) increases indices of anxiety, depression, and suicidal ideation.[20] Nonetheless, the evidence for antidepressant effects of herbal cannabis remain contradictory, with reports of chronic, high-dose exposure resulting in depressive symptomatology.[17] Brief, self-limiting dysphoric reactions are also well-recognized consequences of acute cannabis use. For instance, oral THC administration to depressed individuals can result in dysphoria, especially in those who are naïve to the psychoactive effects of cannabis.[17]

Psychosis

Cannabis intoxication is associated with transient psychosis-like or psychotomimetic effects that include depersonalization, de-realization, ideas of reference, grandiose and paranoid delusions, flight of ideas, disorganized thinking, and auditory and visual hallucinations.[21] Such effects have been increasingly reported with high THC-containing strains of cannabis and SCs.[22] SCs, sold as "spice," "K2," and "kush," are more potent than THC and have a mixture of constituents that are generally CB1R and CB2R full agonists. This pharmacologic profile of SCs confers their much higher risk of inducing acute psychosis, disorganized behavior, and even catatonic-like reactions.[23]

Individuals with an established psychotic disorder may be more vulnerable to these effects. For example, in a survey of ultra-high-risk and recent-onset first-episode psychosis patients, 37% reported that their first psychotic symptoms appeared during cannabis intoxication.[24]

Cognitive Effects

Evidence has accumulated indicating that, among non-daily users, cannabis and its constituent

cannabinoids can acutely impair several domains of cognition.[25] However, daily users of cannabis can have blunted responses to the cognitive impairing effects of cannabis, and abstinence from cannabis can be associated with cognitive impairment.[16] The acute effects of cannabis on cognition might depend on the THC/CBD ratio, with higher concentrations of CBD "protecting" against cognitive impairments.[5,6]

Attention

Many attentional processes are acutely impaired by cannabis use. Deficits on selective, focused, and divided attention tasks; allocation of attention (P300); and signal detection have been found after acute administration of both cannabis and THC to healthy individuals.[21] Impaired performance on a divided attention task after a high dose (500 μg/kg) of THC was shown in occasional, but not heavy users, suggesting tolerance.[26]

Memory

Among the memory domains affected by acute cannabis use are spatial working memory, procedural memory, verbal learning and recall, and associative learning.[27] Deficits in verbal learning and memory are perhaps the most robust impairments associated with acute cannabis use.[25] THC was shown to interfere with encoding, but not retrieval, of verbal memory, suggesting that learning information before using cannabinoids is not likely to disrupt recall of that information. Whether THC impairs encoding of non-verbal information and memory consolidation remains unclear.[28] The activation of CB1Rs, especially in the hippocampus, might interfere with short-term memory, and might impair the consolidation of memories that are being processed currently.

Inhibitory Control

Impairment of inhibitory control is evident after acute cannabis intoxication, though impulsive responding, matched by attenuated activation in the right interior frontal and anterior cingulate cortex[29] and opposing effects of THC and CBD in the hippocampus after "go/no go" tasks.[30] It has been suggested that the eCB system may modulate dopaminergic tone in the prefrontal cortex and nucleus accumbens, contributing to incentive salience to specific stimuli and impulsivity, and that THC disrupts such physiologic mechanisms underlying inhibitory and decision-making processes.[29]

Effects on Driving Ability

Consistent with the known distribution of CB1Rs in areas that subserve cognitive and motor processes, driving simulation studies collectively suggest that cannabinoids produce acute impairments in a number of driving outcomes.[4,31] Emerging data suggest that driving impairments may be more than additive while under the influence of both alcohol and cannabis, or prescribed drugs (ie, benzodiazepines or opioids).[32]

Acute Psychiatric Emergencies

Between 2007 and 2011, cannabinoid-related visits to emergency departments increased by >50%, accounting for almost 40% of all, and 75% of adolescent, visits involving illicit substances in 2011. Reasons for emergency department visits include acute anxiety, psychotic, and manic symptoms, which are up to 30 times more common after exposure to SCs compared with cannabis.[22]

Effects Associated with Persistent Use

Cognitive Effects

The chronic cognitive effects of cannabinoids are more complex and controversial than their acute effects, appearing to be related to the dose of exposure (frequency, duration, amount) and age of onset of use.[33] Both adult and adolescent cannabis users have been reported to perform worse than non-using controls on the memory tasks when not acutely intoxicated.[27] The evidence is stronger for impairments in verbal learning and memory, working memory and attention, with mixed evidence for effects on decision making.[27,34] Whether these impairments remain has been disputed.

In one of the largest and longest prospective studies controlling for premorbid function, Meier et al,[35] reported that cannabis use before the age of 18 years resulted in greater decline in intelligence by age 38 years, persisting even after cessation or reduction of use in the past year.[35] Other studies show that deficits in neuropsychological functioning can resolve over time; recovery times can vary from 1 week to 2 years of abstinence.[27,36] A recent meta-analysis suggests that only small-magnitude effects are apparent in the first few weeks of abstinence (of the order of d = 0.25−0.35), and these become smaller and nonsignificant with extended abstinence (to around d = 0.15).[37]

Some of the mixed findings on the cognitive effects of cannabinoids are likely due to the use of differences

in cognitive measures used, study design, varying extents of cannabinoid exposure and potency, imprecise estimates of cannabinoid, and co-occurring drug and alcohol exposure. Confounding of residual effects of cannabis on IQ test performance remains a possibility, and quantification of cannabinoid in hair samples has been proposed as more precise estimation of exposure.[37,38]

Cannabis Use Disorder

Cannabis use disorder (CUD) is the most prevalent substance use disorder (SUD) in the general US population after alcohol and nicotine use disorders.[1] In DSM-5, the diagnostic criteria for CUD were revised to combine dependence and abuse criteria into a single disorder; drop the legal problems criterion; and add craving, withdrawal, and a severity metric.[39]

In the National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III), the 12-month prevalence of DSM-5 CUD was 2.54% and the lifetime prevalence was 6.27%. This represents an increase from the first NESARC (2001–2002) study, in which the 12-month and lifetime rates were 1.5% and 8.5%, respectively.[40] The lifetime rates of CUD in those who begin use in adolescence have also been reported to be close to 17%.[40] Importantly, participants in the NESARC-III with CUD experienced considerable disability across a variety of domains. Their level of disability correlated with the frequency of cannabis use and was greater than the corresponding levels of disability associated with alcohol use disorder in the same study.[40] Although the risks of CUD might decrease during a 10-year period, people who use cannabis at least 5 times per year are likely to continue the same level of use for at least 10 years. Similarly, cannabis is currently the primary illicit substance responsible for first-time admission to specialist SUD treatment across various European countries, with up to 43% more admissions between 2006 and 2015.[41]

Accumulating preclinical and clinical evidence indicates that exposure to CB1R agonists is accompanied by CB1R down-regulation,[42] with changes related to the duration and magnitude of exposure. While tolerance to some of the somatic effects of CB1R agonists appears to develop within days, tolerance to the cognitive and mood-altering effects may take longer to develop.[43] It is unclear whether medical cannabis is associated with lower or higher levels of CUD, although some evidence suggests the latter, as states where medical cannabis is legal had higher rates of CUD diagnoses among veterans in 2002, 2008, and 2009.[44]

Cannabis Withdrawal Syndrome

Now recognized in DSM-5 as a distinct entity, cannabis withdrawal syndrome is characterized by anger, aggression, appetite change, weight loss, irritability, anxiety, restlessness, sleep disturbance, cannabis craving, and physical discomfort.[45] Less common symptoms include chills, depressed mood, stomach pain, and diaphoresis. Most symptoms appear within 1 day of abstinence, peak within 2 to 3 days, and resolve within 1 to 3 weeks. However, other studies suggest that withdrawal symptoms can persist longer than 4 weeks, and specifically sleep disturbances can persist longer.[46] Both animal and human studies showed that with abstinence there is recovery in the number and function of CB1Rs, as early as 2 days in humans.[47–49]

Substance Use Disorders

Some evidence suggests that regular cannabinoid use might be implicated in the development of SUDs other than CUD. Approximately 1 in 10 adult cannabis users develop an SUD, and this number is higher among adolescents.[50] In a large, nationally representative sample, cannabis use was prospectively associated with increased prevalence and incidence of alcohol and other SUDs, after adjusting for several covariates that predicted cannabis use.[40] It has been hypothesized that the neurocircuitry involved in mediating the effects of cannabis overlaps with that involved in other substances, and that overlap might contribute cross-sensitization to substance use.[51]

Other Psychiatric Disorders

Psychotic Disorders

Transient, cannabis-induced psychosis, often clinically indistinguishable from schizophrenia, can outlast the period of acute intoxication and can persist for as long as 30 days.[52]

Drawing on observational data, the relationship between cannabis and persistent psychosis fulfills many but not all of the standard criteria for causality. Although most people who consume cannabis do not experience psychosis, the cannabis–psychosis link may occur in those with predisposing genetic[53] and environmental factors.[54] Like other negative effects of

cannabis, the risk of psychosis appears to be heightened by heavy and early use.

Observational studies of patients with psychotic disorders indicate that those with a history of cannabis use have an earlier age of onset of illness by approximately 2.7 years.[55] Cannabis use has also been shown to exacerbate the course of illness in individuals with established psychotic disorders, and its psychotomimetic effects typically are not offset by traditional antipsychotic medications.[21,52] With the rising potency of cannabis strains and more frequent use, there is some evidence that age at onset of first-episode psychosis is decreasing.[56] Consistent with this, SC users are generally more frequently diagnosed with psychotic disorders.[57]

Anxiety Disorders

Long-term cannabis use can worsen anxiety and even promote panic attacks and exacerbate the neuroendocrine response to stress.[7] While individuals with anxiety disorders report a high incidence of cannabis use, whether cannabis is used to self-medicate anxiety or it contributes to anxiety disorders can be difficult to discern clinically. Cannabis use has also been associated with social anxiety disorder.[40]

Mood Disorders

Cannabis use is associated with worse clinical course, including more frequent hospitalizations, higher number and longer manic episodes, and greater prevalence of psychotic symptoms in individuals with bipolar disorder.[58] There is also preliminary evidence of cannabis use conferring a higher risk for bipolar disorder.[13] Similarly, chronic cannabis use can result in increased risk for depressive disorders.[59]

DISCUSSION

Clinicians who certify, prescribe, or care for patients receiving cannabinoids need to be aware that the most of the safety data are derived from studies conducted with less-potent compounds compared with some of the currently available products. While medical use of cannabinoids may benefit a selected group of patients, systematic scientific evidence supporting most claims remains fairly limited. Conversely, the ample psychiatric consequences of cannabinoids have been documented extensively. As with all drugs prescribed by physicians, the overall value of a drug is the balance between efficacy and adverse effects, and clinicians should engage in evidence-based discussions with patients who are using or requesting to use cannabinoids.

Clinicians need to be mindful that because of tolerance, over time patients may require more cannabinoids to achieve a desired effect; that abrupt discontinuation may precipitate cannabis withdrawal syndrome; and, that in patients who have been abstinent for weeks, lower doses of cannabinoids are advisable if they are to be resumed. Further, clinicians should be aware that cannabinoids may impair cognition on their own; when combined with other prescribed medications (eg, opioids or benzodiazepines) or other substances, including alcohol; or when used by those with neurocognitive disorders.

In addition to individual with major psychiatric disorders, adolescents may be more prone to developing psychiatric consequences of cannabinoids. Early initiation of cannabis use may also sensitize individuals to other SUDs. Given that medical cannabis is mostly prescribed for chronic conditions, and that chronicity heightens the risk of psychosis in cannabis use, psychosis represents a real risk, especially in individuals at risk for psychotic disorders. The plausibility of a causal relationship between adolescent cannabis use and negative psychiatric outcomes is enough to warn the public about the potential for long-term brain changes with regular exposure. New onset of worsening of anxiety, mood disturbance, cognitive impairment, or psychosis might prompt clinical evaluation of whether cannabinoids are a contributing factor. As states continue to proceed with legalization of cannabinoid use, educational campaigns regarding the potential psychiatric consequences of cannabinoids use may help limit the consequences of exposure. Continued surveillance of several trends is necessary to monitor the balance of social costs and benefits and the needs for treatment. These include whether there will be an increase in psychiatric disorders related to cannabinoid use, the relationship between cannabinoids and other substances (especially alcohol and opioids), and the relationship between acute cannabinoid intoxication and driving abilities. In light of the rapidly shifting legal landscape, more research is needed to better understand the impact of cannabinoid use on public mental health.

ACKNOWLEDGEMENTS

This research project was funded in part by grants from the National Institute of Mental Health (R25

MH071584 to JPD). We also acknowledge support from the 1) Department of Veterans Affairs, 2) National Institute of Drug Abuse, 3) National Institute of Alcoholism and Alcohol Abuse.

CONFLICT OF INTEREST

Deepak Cyril D'Souza has received in the past 3 years and currently receives research grant support administered through Yale University School of Medicine from Pfizer Inc. All other authors report no biomedical financial interests or potential conflicts of interest.

REFERENCES

1. Abuse S. *Results from the 2012 National Survey on Drug Use and Health: Summary of national findings, in NSDUH Series H-46, HHS Publication No.(SMA) 13-4795*. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013.
2. Fischer B, Kuganesan S, Room R. Medical Marijuana programs: implications for cannabis control policy–observations from Canada. *Int J Drug Policy*. 2015;26:15–19.
3. ElSohly M, Gul W. Constituents of cannabis sativa. In: Pertwee R, ed. *Handbook of Cannabis*. Oxford, UK: Oxford University Press; 2014:1093.
4. Mechoulam R, Parker LA. The endocannabinoid system and the brain. *Annu Rev Psychol*. 2013;64:21–47.
5. Englund A, et al. Can we make cannabis safer? *Lancet Psychiatry*. 2017;4:643–648.
6. Boggs DL, et al. clinical and preclinical evidence for functional interactions of cannabidiol and delta(9)-tetrahydrocannabinol. *Neuropsychopharmacology*. 2018;43:142–154.
7. Rey AA, et al. Biphasic effects of cannabinoids in anxiety responses: CB1 and GABA(B) receptors in the balance of GABAergic and glutamatergic neurotransmission. *Neuropsychopharmacology*. 2012;37:2624–2634.
8. ElSohly MA, et al. Changes in cannabis potency over the last 2 decades (1995-2014): analysis of current data in the United States. *Biol Psychiatry*. 2016;79:613–619.
9. Giroud C, et al. E-Cigarettes: A Review of New Trends in Cannabis Use. *Int J Environ Res Public Health*. 2015;12:9988–10008.
10. Renard J, Rushlow WJ, Laviolette SR. What Can Rats Tell Us about Adolescent Cannabis Exposure? Insights from Preclinical Research. *Can J Psychiatry*. 2016;61(6):328–334.
11. Rubino T, Parolaro D. The impact of exposure to cannabinoids in adolescence: insights from animal models. *Biol Psychiatry*. 2016;79(7):578–585.
12. Schneider M. Puberty as a highly vulnerable developmental period for the consequences of cannabis exposure. *Addict Biol*. 2008;13(2):253–263.
13. Starzer MSK, Nordentoft M, Hjorthùj C. Rates and predictors of conversion to schizophrenia or bipolar disorder following substance-induced psychosis. *Am J Psychiatry* 2017; Nov 28 [Epub ahead of print].
14. Cahill JD, et al. Psychotomimetic and cognitive effects of Δ 9-tetrahydrocannabinol in laboratory settings. In: Compton MT, Manseau MW, eds. *The Complex Connection Between Cannabis and Schizophrenia*. London: Elsevier; 2018:75–128.
15. Heishman SJ, et al. Acute and residual effects of marijuana: profiles of plasma THC levels, physiological, subjective, and performance measures. *Pharmacol Biochem Behav*. 1990;37(3):561–565.
16. D'Souza DC, et al. Blunted psychotomimetic and amnestic effects of Delta-9-tetrahydrocannabinol in frequent users of cannabis. *Neuropsychopharmacology*. 2008;33:2505–2516.
17. Patel S, Hill MN, Hillard CJ. Effects of phytocannabinoids on anxiety, mood, and the endocrine system. In: Pertwee R, ed. *Handbook of Cannabis*. Oxford, UK: Oxford University Press; 2014:189–207.
18. Lutz B, et al. The endocannabinoid system in guarding against fear, anxiety and stress. *Nat Rev Neurosci*. 2015;16:705–718.
19. Hill MN, et al. The therapeutic potential of the endocannabinoid system for the development of a novel class of antidepressants. *Trends Pharmacol Sci*. 2009;30:484–493.
20. Christensen R, et al. Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. *Lancet*. 2007;370(9600):1706–1713.
21. Sherif M, et al. Human laboratory studies on cannabinoids and psychosis. *Biol Psychiatry*. 2016;79:526–538.
22. Manseau MW, et al. Clinical characteristics of synthetic cannabinoid use in a large urban psychiatric emergency setting. *Subst Use Misuse*. 2017;52:822–825.
23. Adams AJ, et al. "Zombie" outbreak caused by the synthetic cannabinoid AMB-FUBINACA in New York. *N Engl J Med*. 2017;376:235–242.
24. Peters BD, et al. Subjective effects of cannabis before the first psychotic episode. *Aust N Z J Psychiatry*. 2009;43:1155–1162.
25. Ranganathan M, D'souza DC. The acute effects of cannabinoids on memory in humans: a review. *Psychopharmacology (Berl)*. 2006;188:425–444.
26. Ramaekers JG, et al. Neurocognitive performance during acute THC intoxication in heavy and occasional cannabis users. *J Psychopharmacol*. 2009;23:266–277.
27. Broyd SJ, et al. Acute and Chronic Effects of Cannabinoids on Human Cognition-A Systematic Review. *Biol Psychiatry*. 2016;79:557–567.
28. Ranganathan M, et al. Tetrahydrocannabinol (THC) impairs encoding but not retrieval of verbal information. *Prog Neuropsychopharmacol Biol Psychiatry*. 2017;79:176–183.

29. Madeo G, et al. Dopamine-dependent CB1 receptor dysfunction at corticostriatal synapses in homozygous PINK1 knockout mice. *Neuropharmacology*. 2016;101:460–470.
30. Borgwardt SJ, et al. Neural basis of Δ-9-tetrahydrocannabinol and cannabidiol: effects during response inhibition. *Biol Psychiatry*. 2008;64:966–973.
31. Ronen A, et al. Effects of THC on driving performance, physiological state and subjective feelings relative to alcohol. *Accid Anal Prevent*. 2008;40:926–934.
32. Dubois S, et al. The combined effects of alcohol and cannabis on driving: Impact on crash risk. *Forensic Sci Int*. 2015;248:94–100.
33. Solowij N, Battisti R. The chronic effects of cannabis on memory in humans: a review. *Curr Drug Abuse Rev* 2008;81–98.
34. Grant I, et al. Non-acute (residual) neurocognitive effects of cannabis use: a meta-analytic study. *J Int Neuropsychol Soc*. 2003;9:679–689.
35. Meier MH, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proc Natl Acad Sci U S A*. 2012;109 E2657-E264.
36. Pope Jr. HG, et al. Cognitive measures in long-term cannabis users. *J Clin Pharmacol*. 2002;42(Suppl):41S–47S.
37. Schreiner AM, Dunn ME. Residual effects of cannabis use on neurocognitive performance after prolonged abstinence: a meta-analysis. *Exp Clin Psychopharmacol*. 2012;20:420–429.
38. Curran HV, et al. Keep off the grass? Cannabis, cognition and addiction. *Nat Rev Neurosci*. 2016;17:293–306.
39. Hasin DS, et al. DSM-5 criteria for substance use disorders: recommendations and rationale. *Am J Psychiatry*. 2013;170:834–851.
40. Blanco C, et al. Cannabis use and risk of psychiatric disorders: prospective evidence from a US national longitudinal study. *JAMA Psychiatry*. 2016;73:388–395.
41. Freeman TP, Winstock AR. Examining the profile of high-potency cannabis and its association with severity of cannabis dependence. *Psychol Med*. 2015;45:3181–3189.
42. Clapper JR, Mangieri RA, Piomelli D. The endocannabinoid system as a target for the treatment of cannabis dependence. *Neuropharmacology*. 2009;56(Suppl 1):235–243.
43. Ranganathan M, et al. The effects of cannabinoids on serum cortisol and prolactin in humans. *P*sychopharmacology (Berl). 2009;203:737–744.
44. Bonn-Miller MO, Harris AH, Trafton JA. Prevalence of cannabis use disorder diagnoses among veterans in 2002. 2008, and 2009. *Psychol Serv*. 2012;9:404–416.
45. Budney AJ, et al. Oral delta-9-tetrahydrocannabinol suppresses cannabis withdrawal symptoms. *Drug Alcohol Depend*. 2007;86:22–29.
46. Bonnet U, Preuss UW. The cannabis withdrawal syndrome: current insights. *Subst Abuse Rehabil*. 2017;8:9.
47. D'Souza DC, et al. Rapid changes in CB1 receptor availability in cannabis dependent males after abstinence from cannabis. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2016;1:60–67.
48. Hirvonen J, et al. Reduced cannabinoid CB1 receptor binding in alcohol dependence measured with positron emission tomography. *Mol Psychiatry*. 2013;18:916–921.
49. Sim-Selley LJ, et al. Prolonged recovery rate of CB1 receptor adaptation after cessation of long-term cannabinoid administration. *Mol Pharmacol*. 2006;70:986–996.
50. Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. *Lancet*. 2009;374(9698):1383–1391.
51. Baker TE, et al. Individual differences in substance dependence: at the intersection of brain, behaviour and cognition. *Addict Biol*. 2011;16:458–466.
52. Ranganathan M, Skosnik PD, D'Souza DC. Marijuana and madness: Associations between cannabinoids and psychosis. *Biol Psychiatry*. 2016;79:511–513.
53. Caspi A, et al. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. *Biol Psychiatry*. 2005;57:1117–1127.
54. Vinkers CH, et al. The effect of childhood maltreatment and cannabis use on adult psychotic symptoms is modified by the COMT ValMet polymorphism. *Schizophr Res*. 2013 Oct;150 (1):303–311.
55. Large M, et al. Cannabis use and earlier onset of psychosis: a systematic meta-analysis. *Arch Gen Psychiatry*. 2011;68:555–561.
56. Di Forti M, et al. Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. *Schizophr Bull*. 2014;40:1509–1517.
57. Bassir Nia A, et al. Psychiatric comorbidity associated with synthetic cannabinoid use compared to cannabis. *J Psychopharmacol*. 2016;30:1321–1330.
58. Strakowski SM, et al. Effects of co-occurring cannabis use disorders on the course of bipolar disorder after a first hospitalization for mania. *Arch Gen Psychiatry*. 2007;64:57–64.
59. Lev-Ran S, et al. The association between cannabis use and depression: a systematic review and meta-analysis of longitudinal studies. *Psychol Med*. 2014;44:797–810.

Address correspondence to: Deepak C. D'Souza MBBS, MD, Yale University, VACHS Psychiatry 116A, 950 Campbell Avenue, West Haven, CT 06516. E-mail: deepak.dsouza@yale.edu