Commentary

The Psychiatric Consequences of Cannabinoids

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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;▮:▮▮▮–▮▮▮) © 2018 Published by Elsevier HS Journals, Inc.

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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,

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cannabidiol (CBD) 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