Cannabis as a Gateway Drug for Opioid Use Disorder

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Introduction

The pace of cannabis policy reform in the United States has continued to rapidly increase since the late 1990s.[1] Billions of dollars in private investment have expanded legal markets for both the medical and recreational sale of whole plant cannabis and related extracts in the majority of states. While most media coverage has emphasized potential benefits such as improved symptom relief for patients, decreased rates of arrest and incarceration of people of color, and increased tax revenues, there is growing alarm among healthcare professionals, especially addiction specialists, about looming risks to population health and underappreciated societal costs.[2] Among top concerns are increasing rates of daily heavy use and the development of cannabis addiction,[3] earlier age of initiation of regular cannabis use and impact on cognitive functioning and psychological development, worsening courses of severe mental illness among those with certain familial predispositions (i.e. for schizophrenia), and the use of cannabis as a gateway to more serious and risky subsequent drug use.[4]

This article will focus on the latter concern — that cannabis use among adolescents can act as a gateway to harder drugs such as opioids. Long derided by drug policy reformers,[5] the "gateway hypothesis" posits that a drug, such as cannabis, could "lower the threshold for addiction" to other substances, such as opioids.[6] Behaviorally and developmentally it is clear that many of the shared root causes (e.g. genetic predisposition, trauma, unstable psychiatric symptoms, thrill seeking, impulsivity, delay discounting, environmental exposures) that increase an individual's likelihood of using cannabis also increase the same individual's likelihood of opioid use.

For instance, one study published by the American Academy of Pediatrics documents findings from one analysis that adolescents who use cannabis are *104 times more likely* to use cocaine than adolescents who never use cannabis.[7] There are significant differences between these two populations of adolescents predating the onset of cannabis use. These observations are often used by proponents of cannabis legalization to disregard the possibility that the adolescent use of cannabis may, in and of itself, create *de novo* risk for the use of opioids or other drugs that otherwise would not exist. This review discusses recent scientific discoveries that address neuropathophysiological mechanisms whereby cannabis use could biologically introduce additional risk for the likelihood of opioid initiation, dose escalation, and OUD that otherwise might not occur within the same individual.

Development and Pathology of Opioid Use Disorder (OUD)

The horrors of the opioid epidemic extend beyond the estimated ~ 45,000 annual deaths from opioid overdose. Firstly, for every fatal opioid overdose there are many more *non-fatal* overdoses, some of which inevitably lead to hospitalization, intubation, coma, and permanent disability. Additionally, common sequelae afflicting the roughly 2.1 million people with OUD spans infections such as hepatitis C, HIV/AIDS, abscesses, and endocarditis (a bacterial infection of the heart tissue that can quickly lead to sepsis, heart failure, and death), trauma and injury, worsening of following self-administration of highly potent addictive substances greatly surpasses that from natural pleasurable activities such as eating rich foods, social activity, sex, and adventure sports. Thus, it has been postulated that some individuals are at risk for overlearning the habitual use of drugs. It is thought this occurs among approximately 15–25% of regular users of any given class of intoxicants (e.g. alcohol, cannabis, opioids, nicotine, stimulants).[12]

Recent discovery stemming from the boom in neuroimaging in the 1990s has added much more nuance to the dopamine-hijacking-the-brain hypothesis. There is now greater appreciation for disruptions between neural circuits in the frontal lobes that control executive functioning, inhibition and impulse control, and higher-level reasoning and the aggressive emotional circuits of the lower brain (sometimes referred to as the psychiatric conditions such as anxiety and depression, job loss and decreased worker productivity, child custody cases, relationship instability, and criminal justice involvement.[8] As a result, it is estimated that the current epidemic costs the nation hundreds of billions of dollars a year.[9]

Given these widely publicized and dramatic risks and outcomes, it is striking how so many individuals have nonetheless developed OUD in the past two decades. Although much remains to be discovered about addiction, scientific researchers have determined several key pathways involved in the development of "substance use disorders" as they are called in the field of psychiatry's *Diagnostic and Statistical Manual,* 5th edition (DSM-5). Since the 1970s, the centrality of dopamine release in reward pathways has been emphasized as a critical step for intoxicating substances that hijack the brain,[10] especially among persons with low basal levels of dopamine activity.[11] Dopamine release in the Central Nervous System reptilian brain as it is structurally shared across most non-human animal species) that regulate drives for survival such as hunger, defense, and procreation.[13] With longer periods of frequent heavy drug use, top-down control by the frontal lobes (e.g. orbitofrontal cortex, anterior cingulate, dorsolateral prefrontal cortex) over circuitry associated with strong drives (e.g. limbic system including the ventral tegmental area (VTA) and the striatum) weakens.[14] As a result, many individuals experience increasingly strong drives to continuously use a substance while becoming less inhibited and less aware of mounting consequences.[15] Over time, use can become compulsive and uncontrollable. The role of dopamine release and impairments in top-down control are thought to be involved in the development of addiction, spanning all major classes of drugs.[16]

Who is at risk? In some ways this question has been answered. Individuals with family histories of drug addiction are clearly at risk, such as members of families with intergenerational alcoholism or someone with multiple biological siblings with nicotine use

disorder.[17] These individuals would clearly be at increased risk of developing, respectively, alcohol use disorder or nicotine use disorder with repeated exposure. Largely, this shared risk among family members reflects gene activity, likely impacting the structure and distribution of relevant cell surface receptors and signaling molecules (i.e. glutamate transmission or nicotinic acetylcholine receptors) encoded by those regions of DNA. For instance, epidemiological studies in monozygotic (i.e. identical) and dizygotic (i.e. fraternal) twins have shown that genetic factors account for ~ 60% of the variance of drug abuse and addiction.[18]

Beyond what are likely combinations of high-risk genes that actively increase risk of uncontrollable use of a given class of drug, there are other risk factors that have been repeatedly associated with the development of substance use disorders including biological characteristics, psychological traits and symptoms, and social determinants of health.[19] Foremost is trauma and early adverse childhood events. Especially among women with substance use disorders, rates of early life trauma are high.[20] In addition to the profound and sometimes lifelong psychological disruptions from experiencing trauma, it is now increasingly appreciated that early life adversity can change neurochemical messaging and network activity in the brain.[21] As a result, affected individuals may have greater mood reactivity, lower distress tolerance, increased difficulty attaching to others in healthy ways, and be more prone to outbursts of anger and mood lability.[22] Relatedly, individuals, especially adolescents, with untreated psychiatric disorders such as anxiety and depression have higher rates of substance use and addiction treatment admissions.[23] Such psychiatric symptoms can both contribute to, and be exacerbated by, personality traits such as thrill seeking, externalizing behaviors, delay discounting (over valuing short term rewards above long-term satisfaction), and impulsivity.

Individual risk factors for developing a substance use disorder (i.e. OUD), such as genes, family history, trauma, psychiatric conditions, and personality traits can be amplified by certain environmental factors. For instance, individuals predisposed to addiction have much worse outcomes when they live in environments with easy access to intoxicating substances (i.e. ubiquitous prescription of opioids, advertisement of pharmaceuticals, cheap black market prices) and minimal constraints on their use (societal acceptability, peer pressure, lack of employment opportunities).[24]

Cannabis as a Gateway Drug

While gateway theories about cannabis can be dated back to the Reefer Madness of the 1920s and beyond, contemporary work on the gateway hypothesis is largely attributable to Eric and Denise Kandel's pioneering investigations spanning lines of animal, human, and epidemiological research. In a seminal article in the *New England Journal of Medicine* (2014), the Kandels demonstrate how "one drug affects the circuitry of the brain in a manner that potentiates the effects of a subsequent drug."[25] In this case, the Kandels showed in early work how administering nicotine to mice for seven days before exposing them to cocaine changed (i.e. amplified) their response to subsequent cocaine administration. How could this be possible?

Much of the explanation lies in learning and memory formation at the molecular level. In short-term memory, an external stimulus, such as painful shock to a rodent's tail, causes the sensory neuron detecting the stimulus to send information in the form of neurochemical signals across the synapse to a motor neuron which instructs the rat's tail to move out of the way in order to reduce pain. In short-term (i.e. temporary) memory, the structure of neither cell is changed. In long-term memory however, such as with repeated stimuli, a gene transcription factor, cyclic AMP (cAMP) response-element-binding protein (CREB), is activated to turn on downstream genes, resulting in the growth of new synapses in the sensory cell, thus strengthening its connection with motor neurons.[26] This long-term memory is also referred to as long-term potentiation and in the case of facilitating a rodent's ability to avoid pain would be considered adaptive.

Long-term potentiation is relevant to nicotine's gateway effect on cocaine use because nicotine directly impacts CREB's ability to turn on downstream genes. The Kandels explain (2014):

Genes associated with long-term memory have two regions: a regulatory (promoter) region and a coding (early genes and late genes) region. Early genes refer to genes that are turned on early in the process of switching on longterm memory and in turn lead to the activation of late genes, which encode for proteins essential for the growth of new synaptic connections. DNA is wrapped around nucleosomes (octamers of histones). The combination of DNA and nucleosomes is called chromatin. The nucleosomes cluster around the promoter region and need to be modified (acetylated) for the transcription factors to bind to the promoter regions so that memory is stored. This modification is referred to as the acetylation of chromatin structure.[27]

In summary, they demonstrated in animal models how exogenous chemicals (in this case nicotine) can alter gene expression affecting long-term potentiation in response to other drugs of abuse (in this case cocaine) through increased global acetylation of chromatin in the striatum, the same region of the brain directly implicated in the development of addiction.[28] The Kandels found in their studies that nicotine changed the ability of cocaine to affect gene expression based on its impact on CREB activity. In follow up studies, they further showed that this robust effect was minimized among mice bred with genetic mutations leading to the under production of CREB.

While their work is convincing that nicotine can serve as a gateway drug to cocaine in mice models, it cannot speak directly to the possible role of cannabis as a gateway drug for opioids in adolescent humans. However several lines of research are suggestive that similar processes may occur for a subset of individuals with genetic risk. For instance, the adolescent brain is on an ongoing state of pruning and remodeling. And it is known that the endocannabinoid system plays a pivotal role in adolescent brain developmental phases through action on neurotransmitter systems regulating neurogenesis, differentiation, and synaptogenesis.[29] These critical stages of pruning and remodeling strategically reduce the number of neurons and shape their connections during adolescence, a process that does not fully mature until around age 24. It is these processes and the extended period of time it takes for a human brain to fully myelinate that are thought to confer additional risk for

addiction with younger ages of trauma exposure, adverse events, and drug use-because the brain is still actively developing and more vulnerable to environmental exposures.

Cannabis and cannabinoids impact adolescent neurodevelopment through many different mechanisms including the regulation of synapse plasticity, modification of adolescent emotion and cognition circuits, the reduction of whole dendrites, reduction in postsynaptic glutamate A2 AMPA receptors, disruption of signaling and impaired neurogenesis, spinogenesis and NMDA-receptor mediated memory formation, and regulation of CREB which directly regulates histone deacetylases controlling gene expression as detailed in the prior section on nicotine and cocaine.[30]

For instance, cannabinoid-opioid interactions have been detailed by studies showing that developmental exposure to cannabinoids among rodents increases subsequent heroin-induced conditioned place preference,[31] a classic hallmark of addiction severity. Pistis and colleagues have also shown that adolescent rodent exposure to novel cannabinoid agonists has been reported to induce tolerance to morphine.[32] In part this could be explained by the central role of pruning of excitatory synapses in adolescence for fortifying executive functioning, inhibition, and impulse control in adulthood-processes that underlie drug self-administration and the development of addiction.

Cannabinoid-opioid interactions are likely mediated by activation of cannabinoid type-1 (CB1) and μ-opioid receptors within synaptically-linked (or possibly even the same) neurons and afferent axons in the nucleus accumbens (NAc) shell. Co-expression of receptors suggests convergent actions of cannabinoids and opioids on downstream neural activity. For example, when naloxone and anandamide are co-administered (i.e. in the same NAc microinjections), endocannabinoid "liking" was muted in the presence of naloxone, hedonic response to cannabinoids may require concurrent endogenous opioid signaling on some level.[33]

Additionally, rodent investigations exploring the potential gateway effects of cannabis (studies examining adolescent rodent exposure to cannabinoid agonists or THC) provide evidence of enhanced opioid intake and adult sensitivity later in life to opioids.[34] Hurd and colleagues developed an experimental rodent model that could mimic periodic adolescent use of cannabis use, finding that adult male rats with low to- moderate THC exposure during adolescence exhibited enhanced heroin self-administration.[35]

As the endocannabinoid system is dynamically altered during adolescence in brain areas central to reward, decision-making, and motivation (e.g. the limbic system VTA and striatum, mentioned earlier) suggests that cannabis use during these critical developmental phases may impact long-term potentiation in the mesocorticolimbic system (spanning the mesocortex in the frontal lobes and the limbic system), impacting later-life drug use and addiction proneness.

Additional studies on genetic variation suggests these effects may be more likely among an undetermined subset of the population with genes controlling relevant pathways involved in the tightly linked opioid and endocannbinoid systems (such as Penk genes, the expression of FosB, and other messengers in the striatum) vulnerable to cannabis exposure. For instance,

Cadoni and colleagues found that adult Lewis and Fischer rats differentially responded to heroin when pre-exposed in adolescence to THC (typically the most abundant and reinforcing cannabinoid in the cannabis plant). Lewis rats developed stronger conditioned place preference to heroin and resistance to decreasing use compared with Fischer rats when first exposed to THC.[36] In other words, THC exposure induced strain-specific changes in the impact of heroin on conditioned place preference and in resultant behaviors provoked by subsequent heroin use. In conclusion, Hurd writes that, "vulnerability involves a delicate balance between factors that promote and protect against disease, and adolescent cannabis use, an environmental factor, may tip this balance in teens with high-risk genotypes and behavioral traits."[37]

In summary, several converging lines of inquiry have shown that adolescent and young adult (i.e. through age 24) brain development is key to executive functioning and behavioral control, that cannabis can change adolescent gene expression and alter these key periods of neurodevelopment, that genes can predict the priming impact of cannabis on opioids and that there is likely individual variation in the risk of cannabis use in adolescence having a deleterious effect on adolescent brain maturation and downstream vulnerability to opioid exposure and addiction.

Population-Level Studies

Although the prior section largely drew from animal lab studies, consistent findings exist in the human literature at the population level, highly suggestive of interactions between the endogenous opioid and endocannabinoid systems. For instance, it has long been known that there are high rates of cannabis use among methadone patients with OUD. Human clinical trials have shown that intermittent cannabis use has been associated with attenuated opioid withdrawal, that medical cannabis participants report reduced use of prescription opioids, and innovative human lab studies have shown that low dose cannabis and low dose opioids when co-administered can provide superior analgesia than the use of either alone at higher doses.[38] These findings have prompted some advocates and policymakers to push for the availability of medical cannabis for patients with OUD.[39] It is premature, however, to suggest there is conclusive evidence for cannabis benefiting patients with OUD or the risk for developing OUD.[40] Further, with increasing prevalence of high potency cannabis, up to 90+% for concentrates, it is unclear what population-level effects will be observed in the coming years.[41]

For instance, what if the use of cannabis actually worsens outcomes among these populations of interest? Large national studies suggest this may be the case, or at least that the many touted protective benefits of cannabis for people using opioids may be overblown in the media. Olfson and colleagues found that among NESARC respondents in waves I and II (the same group of roughly 35,000 individuals were re-interviewed three years apart in 2001–2002 and 2004–2005) that cannabis users were less likely to decrease opioid use than non-users.[42] In part due to these findings and other studies, Humphreys and Saitz recently cautioned in *JAMA* that, "aggregate population associations (eg, between medical cannabis and opioid overdose) may be opposite of those seen within individuals.[43] In the only individual-level analysis, which included 57,146 people aged 12 and older, of a nationally

representative sample, medical cannabis use was positively associated with greater use and misuse of prescription opioids.[44] Their suggestion is that while states with medical cannabis programs may have been associated with slower increases in rates of opioid overdose following their implementation,[45] that this may be an ecological fallacy unrelated to individuals' experiences with cannabis and the progression of opioid use and OUD. For instance, a recent analysis that replicated Bachhuber's design[46] found negative associations casting doubt on the earlier publication.[47]

Additional concerns regard the impact of adolescent cannabis use on psychiatric symptomatology. Among addiction specialists, long-term and high potency use of cannabis is well known to cause or worsen symptoms of anxiety, psychosis, depression, and PTSD.[48] Cannabis withdrawal can also cause protracted symptoms of anxiety, irritability, insomnia, and pain,[49] all of which can be associated with opioid self-administration. A recent systematic review and meta-analysis in *JAMA Psychiatry* (2019) of 11 studies including more than 23,000 individuals, found that adolescent cannabis consumption was associated with *increased* risk of developing depression and suicidal behavior later in life, even in the absence of a premorbid condition.[50] Although this association did not replicate for subsequent anxiety disorders, their findings are certainly not suggestive of a protective effect of cannabis on psychiatric comorbidity. Given high rates of psychiatric conditions, especially depressive disorders, among patients with OUD, if cannabis has a gateway effect on subsequent opioid use or the development of OUD it may be indirectly mediated by worsening mental health burdens (e.g. depressive symptoms) among already at risk adolescents.

Conclusion

The risk of developing OUD is multifactorial and often driven by genetic and familial risk factors, environmental risk factors (trauma history, social networks, other exposures), and untreated psychiatric comorbidity. Neurodevelopment of the adolescent brain continues through young adulthood with ongoing pruning and remodeling which is affected by cannabis use and directly implicates key pathways that are also involved in the neuropathophysiology of substance use disorders. Cannabis use affects adolescent emotion and cognition circuits through disruption of signaling, decreased neurogenesis, and impaired memory formation during key periods of development. Genetic studies have found that genes can predict the impact of cannabis use on subsequent heroin in animal models and that cannabis can also change adolescent gene expression suggesting individual variation in risk of cannabis' effects on adolescent brain maturation based on gene by environment interactions. Finally, there are many reasons to believe endogenous cannabinoid and opioid systems interact in complex ways; there may be multiple mechanisms by which the use of one class of substances could affect self-administration of the other. Population-level epidemiological studies of cannabis use on opioid outcomes have observed that frequent cannabis users are more likely, rather than less likely, to escalate opioid use and subsequently meet criteria for OUD. Additionally, cannabis can worsen mental health outcomes for some people-especially anxiety, depression, cognitive deficits, and psychosis-all of which can increase risk for opioid use and substance use disorders.

In conclusion, for some at risk individuals, through a combination of genetic and environmental factors, it is highly likely that adolescent cannabis use can meaningfully increase risk of the initiation of opioid use and development of OUD. Much more research is needed, particularly to identify which adolescents are most at risk and to develop interventions addressing trauma and psychiatric comorbidity while designing protective and nurturing environments to minimize harm.

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