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# Cannabis and the Developing Adolescent Brain

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## Abstract

**Purpose of Review:** This review summarizes (1) recent trends in delta-9-tetrahydrocannabionol [THC] and cannabidiol (CBD) content in cannabis products, (2) neurobiological correlates of cannabis use on the developing adolescent brain, (3) effects of cannabis on psychiatric symptoms and daily functioning in youth (i.e., academic performance, cognition, sleep and driving), (4) cannabis products used to relieve or treat medical issues in youth, and (5) available treatments for cannabis use disorder in adolescence.

**Recent findings:** Despite marked increases in THC content and availability of cannabis, there has been a decline in perceived risk and an increase in use of THC extract products among youth in the United States. The primary psychiatric symptoms associated with cannabis use in youth are increased risk for addiction, depressive, and psychotic symptoms. Cannabis alters endocannabinoid system function which plays a central role in modulating the neurodevelopment of reward and stress systems. To date, few studies have examined neurobiological mechanisms underlying the psychiatric sequalae of cannabis exposure in youth. Adolescent cannabis exposure results in impaired cognition, sleep, and driving ability. There are very limited FDA-approved cannabinoid medications, none of them supporting their use for the treatment of psychiatric symptoms. Behavioral therapies are currently the mainstay of treating cannabis misuse, with no pharmacotherapies currently approved by the FDA for cannabis use disorder in youth.

**Summary:** Here, we summarize the most up-to-date knowledge on the neurobiological psychiatric, and daily function effects of the most commonly used cannabinoids, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). We then review FDA approved medical use



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Conflict of Interest

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of cannabinoid treatments as well as pharmacological and psychological treatments for cannabis use disorder in youth. Our current understanding of the effects of cannabis on the developing brain and treatments for cannabis misuse in youth remain limited. Future research aimed at examining the neurobiological effects of cannabis, with objective measures of exposure, over the course of pediatric development and in relation to psychiatric symptoms are needed.

### Keywords

Adolescence; cannabis; delta-9-tetrahydrocannabinol (THC); cannabidiol (CBD); neurodevelopment; cannabis use disorder

## Introduction

Cannabis is the most widely used illicit substance by adolescents and young adults worldwide.[1] An estimated 45% of adolescents have a lifetime history of cannabis use by age 18, with 37% of high-school seniors reporting cannabis use within the past year.[2, 3] In the United States, over 6,000 people are first-time cannabis users per day, over 60% of whom are under age 18.[4, 5] Over the past decade, 4% of college students have consistently been regular cannabis users (i.e., using on 20 or more occasions in the past month), while the rate has doubled from 6% to 13% among same-age non-college *transition-age youth*.[3]

Adolescents tend to use cannabis more frequently than alcohol or other drugs.[6] The Monitoring the Future Study, surveying trends in legal and illicit drug use among approximately 50,000 American adolescents annually, reported a substantial decline in perceived risk associated with regular cannabis use over the past couple of decades, corresponding with increased marijuana use rates.[3] The belief among many teens that marijuana is benign relative to other recreational drugs is in contrast to a preponderance of evidence that adolescent marijuana use is linked to psychiatric symptoms including psychosis and suicidality,[7, 8] as well cognitive impairment in learning, memory, and executive function.[7, 8] Cannabis use also results in compromised motor coordination contributing to an increased risk of motor vehicle collisions, which is a leading cause of morbidity and mortality in adolescents.[9]

## Cannabis ‘Potency’

Marijuana is made from dried flowers and leaves of the *cannabis sativa* plant. Although cannabis contains over 500 identified compounds, delta-9-tetrahydrocannabinol (THC) is the primary psychoactive ingredient of the plant that induces a “high.” While a wide range of potencies are available across cannabis products, the average THC content has significantly increased over the past two decades: In states with legal recreational and medicinal cannabis use, cannabis products contain an average of 16%−35% THC.[10] Conversely, concentrations of cannabidiol (CBD), a component in cannabis found to have antipsychotic properties, has decreased, such that the ratio of THC:CBD has increased 80-fold.[11] Remarkably, THC extract products containing upwards of 60% THC (e.g., “wax,” “crumble, “shatter”) are now easily accessible, especially in states which have legalized marijuana.[12] Purified CBD is also available in a wide array of consumable commercial products, including food products, oils, lotions, balms, bath products, and “vape pen” cartridges.

Moreover, teens perceive vaping these cannabis extract preparations as safer than traditionally smoked joints.[3, 13] Use of cannabis extract products are increasingly popular among youth[3, 14] despite limited understanding of the potential consequences on neurodevelopment. [3, 13]

Information concerning the effects of cannabis use on adolescent health remain limited. The overwhelming majority of prior studies have assessed cannabis effects on health using self-report measures of use (primarily frequency of use), and have *not* incorporated objective measures of potency (i.e., THC content).[15, 16] Studies that included measures of potency have primarily assessed the acute effects of THC administration in adults using standardized cannabis preparations supplied by the National Institute on Drug Abuse which contained much lower THC levels (~3–5%) compared to present-day cannabis formulations.[17] Our limited understanding of the neurobiological and psychiatric sequelae of adolescent cannabis use poses an important public health concern, given the widespread use of cannabis products among youth during a period of brain development.

## Neurobiological Effects of Cannabis Use in Adolescence

Adolescence is a critical period of brain maturation and neurodevelopment that is vulnerable to perturbations induced by cannabis exposure.[18] Cannabis exerts its effects via altering signaling within the endocannabinoid system (ECS), which serves a crucial modulatory role in regulating neurodevelopment of reward and stress circuitry in the brain.[19, 20] The ECS is primarily comprised of two G-protein coupled transmembrane receptors: cannabinoid type 1 receptors (CB1R, primarily expressed in the central nervous system), and cannabinoid type 2 receptors (CB2R, implicated in peripheral immune system function). CB1Rs are located on presynaptic terminals, and modulate GABA, glutamate, and dopamine neurotransmitter release and neuronal firing[21] CB1Rs are dynamically expressed and following activation are internalized into endosomes, such that the balance between rate of expression and internalization regulates the number of active receptors in synaptic membranes.[22] Upon CB1R activation, the receptors' associated G-protein subunits uncouple; these subunits interact with ion channels to modulate cyclic adenosine monophosphate synthesis, downstream protein kinase A (PKA), and extracellular signal–regulated kinase (ERK) pathways. The ion channel modulation allows endocannabinoids to rapidly alter neural signaling.[21]

Anandamide and 2-arachidonoylglycerol (2-AG) are the two primary endocannabinoids that intrinsically activate these cannabinoid receptors.[21] Exogenous THC functions as an allosteric agonist of CB1 Rs. Amongst all G-protein receptors in the brain, CB1Rs are the most abundant, highlighting the widespread effects that exogenous cannabis can have, particularly in the developing brain. The degree to which endogenous and exogenous CB1 receptor agonists induces downstream signaling varies. THC is not as efficacious as anandamide or 2-AG at activating PKA or ERK signaling pathways,[23] but is significantly more effective at receptor internalization, resulting ultimately in tolerance to its effects.[21]

Cannabis may acutely contribute to an increase in pleasure and decrease in perceived stress by increasing dopamine with reward circuitry and decreasing cortisol released by the

hypothalamic-pituitary-adrenal (HPA) axis in response to stress. Chronic cannabis use, however, results in cannabinoid receptor type 1 (CB1-R) downregulation and reductions in endocannabinoids levels [21] that impair sensitivity to reward and stress.[24] In animal models, disruption of ECS signaling results in a depressive phenotype with impaired reward sensitivity.[25, 26] In humans, the CB1-R antagonist rimonabant produced a significant increase in depressive symptoms in individuals with no history of mental illness in a double-blind placebo-controlled clinical trial. Depressive symptoms were so severe that they resulted in withdrawal of this medication from the European market, and prevented FDA approval.[27] The acute psychoactive and rewarding effects of cannabis are largely attributed to its modulatory effects on dopamine (DA) signaling via CB1Rs that are most highly expressed in key regions of meso-cortico-striatal reward circuitry, summarized in Figure 1. CB1R agonist exposure acutely results in alterations in neurotransmitters that are similar to those produced by other drugs of abuse via attenuation of evoked GABA release that results in downstream increases in DA within fronto-limbic brain circuitry, especially within the nucleus accumbens (NAc), a central hub of reward processing.[28] Tolerance that develops with chronic cannabis exposure is attributed to disrupted reward-related signaling mechanisms in this system by reducing DA cell density in the ventral tegmental area (VTA), as well as decreasing VTA DA cell firing and downstream DA release in the NAc and the medial prefrontal cortex (PFC).[21, 29] Reductions in CB1-R expression and function as well as decreased DA are more pronounced with adolescent cannabis use (relative to use in adulthood), contributing to disrupted reward signaling, impaired reward sensitivity, and ultimately depressive symptoms of anhedonia, depressed mood and decreased motivation.

Cannabidiol (CBD) also interacts with cannabinoid receptors but its mechanism of action is not fully understood, with discrepancies between *in vitro* and *in vivo* studies. CBD has a low affinity for CB1 receptors, [30, 31] and acts as a negative allosteric modulator of CB1R, which may reduce the potency and efficacy of CB1 agonists.[32–34] This interaction is posited to explain the role of CBD in attenuating the psychoactive adverse effects of THC.[35] While 65 discrete molecular targets of CBD have been identified, the majority only interact at supraphysiological concentrations.[36] Adenosine A1, the serotonin transporter (5-HT1a), G protein-coupled receptor 55 (GPR55), peroxisome proliferator-activated receptor (PPAR$\gamma$),[36] and transient potential vanilloid receptor type-1 (TPVR-1) receptor, have been identified as plausible and potential targets in physiologic conditions.[35, 36]

Despite our limited understanding of the neurobiological effects of CBD, CBD products are increasingly marketed for ‘treating’ anxiety and insomnia, further highlighting the need for improved understanding of the neurobiological effects of cannabis exposure, particularly during critical periods of neurodevelopment.

## Adolescent Cannabis Use and Psychiatric Symptoms

The primary psychiatric symptoms associated with adolescent cannabis are increased risk for addiction, depressive symptoms, and psychosis. Despite the significant associations found between adolescent cannabis use and psychiatric symptoms, a causal link between exposure and symptom manifestation is difficult to establish for several reasons: First, common risk factors such as family history of addiction and other psychopathology as well

as environmental stressors may predispose an individual toward both substance use and psychopathology. Second, use may be directly associated with the risk of psychopathology through shared neurobiological mechanisms. Third, youth may be attempting to abate psychiatric symptoms through self-administration of cannabis.[48] Fourth, certain peer groups may influence cannabis use and be linked to psychopathology risk.[49] Regardless of the etiology, the co-occurrence of psychiatric symptoms and cannabis use are well documented, and should be a standard part of patient psychoeducation and motivational interviewing.

### Substance use disorders.

Cannabis use significantly increases risk for addiction,[50] with adolescents being four times as likely to develop cannabis dependence within two years after use onset.[51] About 20% of individuals who start using marijuana in adolescence and up to 50% of teens who smoke marijuana daily will develop an addiction.[9] Moreover, use of cannabis preparations with higher THC content show a dose-dependent increase in risk of developing a substance use disorder.[52] Recent cannabis use trends among adolescents raise concerns because they account for the majority of substance abuse treatment admissions in adolescence.[53, 54] Importantly, adolescent cannabis use also confers increased risk for other substance use disorders. A recent meta-analysis demonstrated significant associations between the frequency of adolescent cannabis use and increased risk of cannabis use disorder (adjusted OR = 4.2 monthly, 8.7 weekly, 17.9 daily use), as well as use of opiates and other illicit drugs (adjusted OR = 2.8, 4.7, 7.8) by young adulthood.[55] Cannabis has recently been proposed as a potential treatment for opioid use disorder based on a study that found that states with medical cannabis laws experienced slower increases in opioid analgesic overdose mortality (−21%).[56] However, the association between legalization of cannabis for medicinal purposes and opioid-related mortality has increased 23% on longitudinal follow up.[57]

### Depression.

While developing a substance use disorder is the most common long-term psychiatric diagnosis associated with adolescent cannabis use,[55] depressive symptoms are the most common psychiatric symptoms associated with cannabis use in adolescence.[58] Depressive symptoms in adolescence are particularly concerning given that suicide, often attributable to depression, is a leading cause of death in this age group.[59] A recent meta-analysis assessing the effects of adolescent cannabis use found an increased risk of major depressive disorder (OR 1.37, 95% CI 1.16–1.62), suicidal ideation (OR 1.50, 95% CI 1.11–2.03) and suicide attempts (OR 3.46 CI 1.53 – 7.83), but not anxiety symptoms by young adulthood.[8] A longitudinal study prospectively followed a community sample of 662 adolescents from 2003–2013 to examine the strength of association between cannabis use frequency and psychiatric symptoms. From ages 15–19 years, more frequent cannabis use lead to greater depressive, but not anxiety or psychotic symptoms, after controlling for age of onset of use, sex, socioeconomic status, and other drug use.[58] Of note, there were no reported changes in anxiety symptoms with more frequent cannabis use.[58] Notably, depressive symptoms during adolescence do not predict subsequent cannabis use in young adults, suggesting that this relation was not simply due to premorbid differences.[4, 60] In addition, reductions in

cannabis use are associated with reductions in depressive symptoms.[61] In Colorado, the rate of increase in cannabis potency directly correlates with increased rates of cannabis related emergency department visits by adolescents.[50, 62] In a study of over 4,000 adolescents who presented for emergency and urgent care visits between 2005 and 2015, the most common ICD codes other than cannabis use were depression (39%) and unspecified mood disorder (22%), with a significant increase in marijuana-related visits following legalization of medicinal and recreational marijuana.[63]

### Psychosis.

A broad-based literature has established a link between adolescent cannabis use and risk of psychosis. Cannabis use is considered a preventative risk factor for psychotic disorders, including schizophrenia, especially in those with a pre-existing genetic vulnerability.[20] Epidemiological studies have consistently reported an association between cannabis use and schizophrenia in which cannabis use precedes psychosis independent of other substance use.[20] This effect, however, is not immediate with adolescent cannabis use, portending an increased risk of psychotic disorders that manifest primarily in young adulthood.[58] In a sample of 6,534 subjects from the general population Northern Finland Birth Cohort of adolescents that were prospectively followed until age 30, adolescent cannabis use was significantly associated with developing a psychotic disorder after controlling for baseline prodromal symptoms, daily smoking, alcohol and other substance use, with a significant 'doseresponse' effect with respect to frequency of cannabis use (HR = 3.0, 95% CI 1.1–8.0).[64] In a study of over 400 first episode patients with psychosis, adolescents who had started cannabis at age 15 or younger, daily cannabis users, and use of cannabis with higher THC content, significantly advanced the timeline of when they experienced first psychotic episode by 2–6 years.[65] Increasing evidence demonstrates a dose-response relation between cannabis use and risk for psychotic outcomes.[64, 66] In a recent meta-analysis of all available published studies examining the relation between cannabis use and psychosis, regular cannabis users had a 2-fold increased risk, and heavy cannabis users a 4-fold increase in risk, for psychosis relative to nonusers.[7] For a comprehensive meta-analytic review of the association between cannabis use and psychosis, please see Marconi et al. [7]

## Effects of Cannabis on Daily Functioning in Youth

Adolescent cannabis use is also linked to cognitive impairment, sleep disturbance, and increased risk of motor vehicle collisions. Teens who start using cannabis at an earlier age appear to have greater susceptibility to long-lasting consequences of cannabis use than those with a later onset of cannabis exposure.

### Cognition and academic performance.

Although some controversy exists in the adult literature with respect to the lasting effects of cannabis on cognitive function, regular cannabis use in adolescence is significantly associated with cognitive impairment within the domains of attention, processing speed, verbal learning and memory, and executive functioning.[67–69] Longitudinal studies have demonstrated that increased adolescent cannabis use significantly predicts poorer verbal memory[70] and attention.[71] These deficits are also more likely persist following

abstinence with adolescent (as compared to adult) cannabis use.[72] Earlier age of onset of use and heavier use during adolescence are associated with increased rates of cognitive impairment in adulthood.[73] In a prospective longitudinal study of over 1000 youth followed from birth to adulthood, those who regularly used cannabis during adolescence demonstrated the greatest reductions in IQ.[74] Individuals that started using cannabis in early adolescence demonstrated the greatest reductions in IQ (i.e., from 'average' in childhood to 'low-average' in adulthood). Moreover, they did not return to their predicted intellectual trajectory, and cognitive impairments remained evident following over one year of abstinence.[74] It is also important to note that an earlier age of onset has also been associated with greater cognitive impairments even when the total duration of use is relatively short as demonstrated by Solowij and colleagues.[75] Of note, there is some evidence to suggest that greater CBD content may serve a protective role against some THC-induced cognitive deficits.[67] Long term functional consequences include poor educational outcome, with increased likelihood of dropping out of school, and diminished long term academic and occupational achievement.[9]

### Sleep.

While it has been shown that cannabis alters sleep architecture, [76] few studies have examined the effects of cannabis on sleep over the course of adolescent development. Studies examining the relation between sleep quality and substance abuse have demonstrated a bi-directional effect, with sleep disturbance repeatedly linked to substance use in adolescence.[77, 78] Adolescent cannabis use was found to predict subsequent sleep problems in a prospective study of approximately 250 12 year olds that were longitudinally followed until age 18.[78] Whereas lifetime alcohol use was also an important predictor of poor sleep quality at 18 years of age, cannabis showed greater contribution to this outcome. Conversely, shorter sleep duration and poorer quality of sleep in early adolescence is significantly associated with earlier and repeated cannabis (and alcohol) misuse later in adolescence.[77] A separate prospective longitudinal study demonstrated that self-reported 'overtiredness' and 'trouble falling asleep' predicted subsequent cannabis use.[79] This highlights the importance of focusing on educating pediatric patients and their families regarding the importance of good sleep and sleep hygiene as an important and underutilized preventive approach with respect to adolescent substance abuse, especially in light of the fact that almost half of all adolescents report sleep problems reach clinical levels.[80] Longitudinal studies examining the mechanisms linking cannabis use and sleep are warranted.

### Driving.

Driving under the influence of cannabis is now more common than driving under the influence of alcohol among adolescent drivers in the United States, [81] and cannabis is the illicit drug most frequently reported in connection with impaired driving and accidents, a leading cause of death in adolescence.[82] Greater THC concentration in blood is directly related to greater impairment in motor coordination.[83] In adults, both immediate and long-term exposure to marijuana are found to impair driving ability.[50, 82] Indeed, meta-analyses have found that cannabis increases collision risk (pooled OR: 1.5 – 2.5). [84, 85] Simulated driving studies have demonstrated that driving under the influence of cannabis

results in significantly poorer lane control and reduced driving speed, similar to effects observed when using a cell phone or texting while driving [85, 86]. This is particularly relevant to young drivers who are more likely to be involved in distraction related motor vehicle accidents. [87] While studies are lacking with adolescent drivers, simulated driving studies of young adult drivers have shown that driving performance in conditions of divided attention and increased driving complexity significantly worsened following cannabis use. Participants were significantly more likely to be classified as having a high crash risk (OR 4.31) after cannabis use lasting up to 5 hours after use. [88] Further research is needed to assess the impact of the cannabis on driving behavior and collision risk in youth, which to date has received little attention.

## Adolescent Use of Cannabis Products to Relieve or Treat Medical Issues

While use of cannabis-derived products are increasingly marketed for medicinal purposes, the few Food and Drug Administration (FDA) approved indications are classified as Schedule I substances by the United States federal government. Some states have laws decriminalizing cannabis and cannabis-derived products such as THC and CBD, but no current regulations with respect to THC and CBD content are in place. In one study, CBD extracts were tested and only 31% were found to actually contain the percentage of CBD advertised. In fact, THC was detected in 21% of the ‘purified’ CBD products.[89] In 2016, the FDA sent warning letters to CBD vendors stating that CBD products are not to be classified as dietary supplements, and therefore cannot make medical claims without FDA approval.[90] This is disturbing in light of increasing rates of use among individuals with psychiatric symptoms of depression, anxiety, post-traumatic stress disorder, and psychosis, who report self-medication of symptoms as a driver of cannabis use.[91].

Currently, two medications containing THC have been approved by the FDA, dronabinol and nabilone. Both are indicated for nausea/vomiting in cancer chemotherapy, and as an appetite stimulant in the setting of weight loss due to AIDS. Outside of the United States, the United Kingdom, Canada, and several European countries have approved the THC and CBDcontaining drug nabiximols (Sativex®) for cancer pain and spasticity caused by multiple sclerosis. The most commonly reported adverse reactions include: central nervous system symptoms including dizziness (~18%), fatigue or drowsiness (~10), confusion (~7%), and psychiatric symptoms including psychotic symptoms, depressed mood and suicidal ideation (~10%); gastrointestinal symptoms including nausea (~10%), vomiting (5%), diarrhea (~7%); cardiovascular symptoms including Hypotension (~5%), palpitations (~1%), syncope (~1%), tachycardia (~1%), and increased risk for substance dependent and abnormal hepatic function (~5%). [92, 93] CBD, in the purified pharmaceutical form Epidiolex, is currently FDA-approved for the treatment of two forms of severe childhood epilepsy: Dravet syndrome and LennoxGaustaut syndrome. Both trials demonstrated efficacy in significantly reducing the number of seizures.[94, 95] These studies also noted CBD-related side effects that included diarrhea, vomiting, fatigue, pyrexia, anorexia, upper respiratory tract infections, convulsions, lethargy, somnolence and abnormal hepatic function.[94 [68] In one study, 12 patients in the CBD group had liver aminotransferase elevations greater than 3 times the upper limit, compared to 1 in the placebo group. {Devinsky, 2017 #67, 95, 96]

These studies, however, are limited to short-term efficacy and do not include the potential longer-term effects of receptor and/or neuronal changes in developing brains. Both Lennox-Gastaut and Dravet syndrome are refractory forms of epilepsy frequently involving severe developmental delays, such that more subtle effects on cognition and perception, for example, are likely to go unnoticed.

Although not FDA approved, three independent RCTs have been conducted on CBD therapy in adults with schizophrenia.[97–99] All three have shown a reduction in psychotic symptoms, but the measures which improved differed in each study. One study conducted an RCT of 88 participants with schizophrenia, randomizing participants to CBD 1000 mg/day or placebo for six weeks of treatment.[97] At the study's end, patients who received CBD showed greater improvement in positive symptoms as measured by the PANSS ($p = 0.019$), but showed no significant differences in the other domains of the PANSS (0.133, 0.196, and 0.965). The CBD group showed greater improvement in cognition, as measured by the BACS composite score ($p = 0.068$), and particularly in motor speed. Finally, a higher proportion (78.6% vs 54.6%) of patients receiving CBD were scored by their physicians as being "improved" on the CGI-I, compared to placebo ($p = 0.018$). A similar six-week study compared 36 stable participants with schizophrenia in an RCT, randomizing them to CBD 600 mg/day vs placebo.[98] The PANSS total score showed a significant decrease over time ($p < 0.0001$), but there was no significant drug × time interaction ($p = 0.18$). The MCCB Composite score showed no main effect from drug or time, but there was a significant drug × time effect ($p = 0.02$). The last study was a four-week double-blind RCT of CBD versus amisulpride in 42 participants with schizophrenia.[99] The dose was started at 200 mg per day and increased stepwise by 200 mg per day up to 800 mg per day. Both groups showed significant improvement from baseline in the PANSS, but there were no significant differences between the two ($p = 0.884$). Non-inferiority of CBD could not be demonstrated ($p = 0.27$). CBD patients did however have significantly fewer symptoms of EPS, less weight gain, and lower prolactin increase.

Few studies have examined the therapeutic potential of cannabinoids for the treatment of psychiatric symptoms. A recent meta-analysis and systematic review found insufficient evidence to suggest that cannabinoids improve depressive or anxiety symptoms or disorders, as well as other psychiatric disorders including attention-deficit hyperactivity disorder, Tourette syndrome, post-traumatic stress disorder, and psychosis.[91] Cannabis products may indeed have viable therapeutic potential, and existing clinical trials of CB are encouraging in adults with psychotic disorders.[97, 100] However, there remains inadequate evidence for their use in treating psychopathology. High-quality studies directly examining the effect of cannabinoids on treating mental disorders are needed, and the effects of exogenous cannabinoid administration in pediatric populations remain unknown. Therefore, until further research is available, caution in exposing adolescents and pediatric patients to cannabinoids remains warranted.

## Treatments for Adolescent Cannabis Use Disorder

While cannabis derived products are increasingly used and investigated for therapeutic use, few effective treatments for cannabis use disorder are available to adolescents. Substance use

treatment rates for youth who meet criteria for cannabis (or other substance) use disorder are very low (approximately 5%).[101] Importantly, cannabis use often co-occurs with anxiety and depression in youth, and treating these conditions may be helpful in minimizing cannabis use.[102] The majority of regular cannabis users remain unsuccessful at changing use patterns in the absence of treatment.[103] To date, no Food and Drug Administration approved pharmacotherapies are available for treating cannabis use disorder. Psychotherapy including motivational enhancement therapy (MET), cognitive behavioral therapy (CBT), and contingency management are the mainstay of treatment for cannabis misuse.[104] Randomized controlled trials, open-label trials, case-series, and case reports have been reported. Here we summarize evidence-based treatments for cannabis use disorder in adolescence that are supported by randomized controlled trials.

### Behavioral Therapy.

Behavioral therapies are the mainstay of treating cannabis use disorder in adolescence. Motivational enhancement therapy using educational feedback has been shown to significantly lower cannabis use in a study of approximately 300 non-treatment seeking adolescents at 3 month (21% vs. 8%), but not at 12 month (16% vs 9%) follow-up.[105] Studies comparing the efficacy of CBT and multidimensional therapy (MDT) found comparable decreases in adolescent cannabis use, with approximately 30% reduction in use by 1 year follow up for both interventions. Older adolescents and those with co-occurring psychiatric disorders were significantly more likely to benefit from CBT, whereas younger adolescents were more likely to benefit from MDT.[106] A recent study demonstrated that Approach-Avoidance Training designed to reduce automatic approach bias for cannabis-related cues was effective in reducing cannabis use in 80 non-treatment-seeking adolescents.[107]

Available psychotherapies for cannabis use disorder in adolescence have modest effect sizes in improving abstinence rates, i.e., the primary outcome measure, however the majority of patients in these studies returned to using cannabis within 6–12 months.[101, 108] A greater number of studies have demonstrated reductions in use patterns, which may be a better clinical endpoint for treatment of cannabis misuse in adolescence than abstinence.

### Pharmacotherapy.

A randomized 8 week double-blinded, placebo-controlled clinical trial of 116 cannabis dependent adolescents found that those randomized to receive N-acetylcysteine (NAC) demonstrated a significantly greater likelihood of negative urine toxicology versus placebo (41% versus 27%). While NAC is thought to alter glutamate transmission and reduce oxidative stress, the mechanism by which it may lower cannabis use is not well understood, and abstinence was not sustained at 4-week follow up.[109]

In a randomized double-blinded, placebo-controlled pilot study in adolescents, 66 heavy cannabis users were randomized to MET + topiramate versus MET plus placebo. Adolescents in both treatment arms demonstrated significant reductions in *frequency* of cannabis use during study participation, with no significant advantage of topiramate. Although the overall amount of cannabis that participants smoked was significantly less in

the topiramate group, topiramate was poorly tolerated. Less than half of those randomized to topiramate completed the 6-week trial due to adverse medication side effects.[54]

In a randomized double-blind placebo-controlled study, 70 adolescents with major depressive disorder and cannabis use disorder were randomized to a 12-week course of MET and CBT plus fluoxetine or placebo. Although fluoxetine was well tolerated, it did not demonstrate greater efficacy than placebo with respect to reduction in depressive or cannabis-use related symptoms.[110]

While no trials have been conducted in adolescents, a 12 week randomized, double-blind, placebo-controlled trial of Gabapentin found statistically significant reductions in frequency and amount of cannabis use, as well as reduction in craving and symptoms of withdrawal in 50 adults with cannabis use disorder.[111]

### Remaining issues in addressing adolescent cannabis use.

No consensus yet defines clinically meaningful reductions in adolescent cannabis use. Key challenges include heterogeneity by which substance use treatment outcomes are measured and reported across studies and limited studies that include both self-report and biological assays to assess change in use. The majority of studies have used self-report measures of cannabis use which presents several challenges, such as obtaining accurate measurements of exposure and route of administration. Improved clinical and functional outcome measures such as assessing change in clinical symptom severity using a dimensional versus categorical DSM or ICD diagnostic approach, as well as assessing ‘functional’ quality of life measures will assist in determining meaningful therapeutic effect in future treatment trials. Further, urine assays of cannabinoid levels are currently the only biological assay that have been employed in treatment trials.[104] Future research that incorporates objective measures of cannabis (e.g. plasma, saliva assays), as well as measures of exposure such as potency (THC) and changes in endocannabinoid levels would provide a more comprehensive understanding of the treatment induced changes with respect to changes in cannabis use and in the endocannabinoid system and help inform treatment development. Integrating neurobiological markers into the design of clinical trials may advance mechanistic understanding of how treatments work and identify focal treatment targets for cannabis misuse in adolescence.

## Conclusions

In recent years, we have observed an increase in youth presenting for consultation and treatment for mood and psychotic disorders in the context of regular high potency cannabis use.[58] Teens report growing popularity of such use among their peers, and the ease of access to which they are able to obtain high potency cannabis preparations. This is consistent with what is being reported in states that have legalized marijuana, that have seen a 25% increase in problematic cannabis use by adolescents relative to states that have not legalized marijuana.[112] Recent surveys have demonstrated a steep rise in the rate of adolescent vaping of cannabis products, and a decline in public perception of harms associated with regular cannabis use.[14] Moreover, cannabinoid products are increasingly

used to ‘self-medicate’ psychiatric symptoms despite available evidence demonstrating that they are ineffective for this indication and can worsen psychiatric symptoms.[91]

The endocannabinoid system (ECS) serves an integral role in regulating neurodevelopment of reward and stress systems during adolescence.[19, 20] Thus, adolescence is a developmental period that is particularly sensitive to perturbations induced by cannabis exposure.[18] Acutely, THC activates CB1R resulting in increased DA synthesis contributing to an increase in perceived pleasure. With chronic use, however, CB1Rs are downregulated and endocannabinoid levels are reduced[21] thereby impairing sensitivity to reward and stress.[24] CBD interacts with cannabinoid receptors are complex, with discrepancies between *in vitro* and *in vivo* studies. Studies suggest the CBD has a low affinity for CB1 receptors, [30, 31] however recent evidence has found that CBD also acts as a negative allosteric modulator of CB1R, and may reduce the potency and efficacy of CB1 agonists. [32–34] This interaction is posited to explain the role of CBD in attenuating or ameliorating the psychoactive adverse effects of THC.[35]

In addition, available diagnostic tools designed to assist in the assessment of cannabis and other substance use disorders may not adequately capture use patterns, including alternative means of cannabis use, such as vaping. Improved diagnostic tools are needed to better capture contemporary problematic substance use and their psychiatric sequelae including longitudinal assessment for progression toward co-occurring disorders in youth. In the context of decreased perceived risk of cannabis use, improved knowledge of the biological effects of cannabis use on neurodevelopment is key, especially with regard to high potency cannabis use. This will assist in identifying novel targets for future prevention and intervention research. We have found that patients often present with severe depressive symptoms, and occasionally psychosis or mania, in the context of regular use of high-potency cannabis. Vaping cannabis products are also increasing in popularity,[113], with approximately 1 in 10 adolescents reporting vaping cannabis.[3] This is concerning given our limited understanding of the effects of vaping high potency cannabis preparations in adolescence. As clinicians, it is important that we continue to educate our patients on the nuances associated with cannabis potency and use, and why cannabis and other substance use is particularly harmful during critical periods of development when the brain is particularly vulnerable to the negative effects of cannabis use.

Scientific research and public awareness of various cannabis preparations, potencies, and risk of psychiatric sequelae are needed due to increased availability, prevalence, and shifting perceptions of cannabis use. Studies to date have characterized the effects of cannabis according to self-report measures or acute effects of much lower potency preparations in adult samples. Future research is needed to examine the neurobiological effects of cannabis exposure, with objective measures of potency, and over the course of pediatric development and transitions into adulthood. The increase in cannabis potency and reliance on self-report assessments that do not incorporate quantifiable measures of potency may contribute to our limited understanding of the complex relation between the effects of cannabis on developing neurobiological symptoms modulated by the endocannabinoid system and psychiatric symptom onset and severity in adolescence. Future work examining biological effects of increasingly potent cannabis exposure in adolescence will help identify ‘bottom up’

neurobiologically informed treatment targets, as well as inform public policy and prevention to mitigate access to high potency cannabis and develop other harm reduction approaches.

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## Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

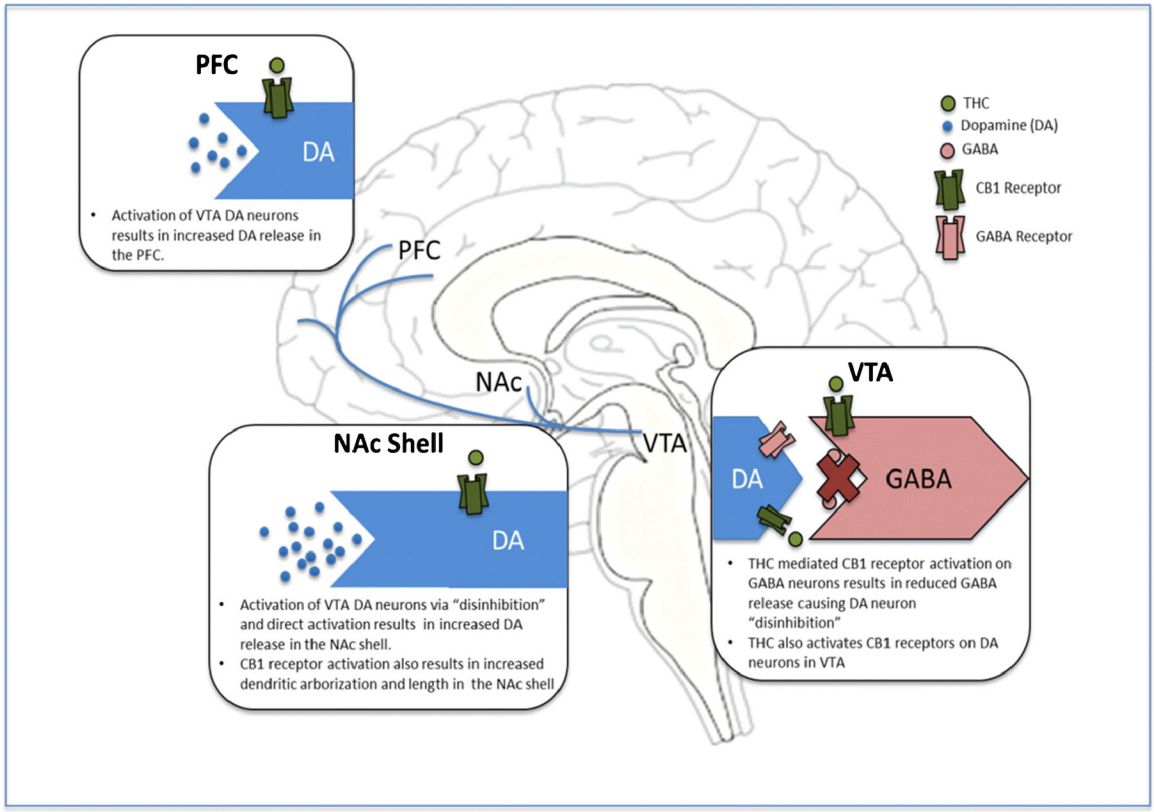


**Figure 1: Modulatory effects of THC on dopamine signaling within brain reward circuitry**

Figure Legend: Neuromodulatory effects of THC on dopamine signaling within key regions of brain reward circuitry. Acutely, THC increases DA synthesis within the VTA and downstream release within brain reward centers (i.e., NAc and PFC), similar to other drugs of abuse. With Chronic use, CB1-R expression and function decreases and DA release and cell density is reduced (more pronounced with adolescent exposure) resulting in disrupted reward signaling and impaired reward sensitivity and motivation. DA: dopamine, GABA: gamma-aminobutyric acid, VTA: ventral tegmental area, NAc: nucleus accumbens, PFC: prefrontal cortex.