

## REVIEW ARTICLE

C. Corey Hardin, M.D., Ph.D., *Editor*Cannabis-Related Disorders  
and Toxic Effects

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CANNABIS (SOMETIMES CALLED MARIJUANA) IS A BROAD TERM THAT CAN refer to a specific plant (genus *Cannabis*), the chemicals contained in the plant, their synthetic counterparts and analogues, and products derived from any of these things. The cannabis plant contains more than 500 identified chemicals, many of which are not well characterized pharmacologically,<sup>1</sup> including more than 125 phytocannabinoids. The most studied phytocannabinoids are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is considered the primary psychoactive compound in cannabis, responsible for many of its psychological and physiological effects. CBD is also psychoactive (anxiolytic, analgesic, and possibly antipsychotic) but is not euphorogenic. Dozens of terpenes and flavonoids are also present. Terpenes confer the distinctive odor emitted by cannabis buds.

Cannabis has a dichotomous legal status in the United States.<sup>2</sup> The cannabis plant and all the compounds and products derived from it (with one exception) are classified in Schedule I of the Controlled Substances Act. This classification renders them illegal at the federal level. The 2018 Farm Bill removed cannabis plants containing less than 0.3% THC from the jurisdiction of the Controlled Substances Act and defined them as hemp. The CBD products now widely available in the United States are presumably derived from hemp. In contrast, as of November 8, 2023, under state law, cannabis was legal for medicinal use in 38 states, the District of Columbia, and 3 territories and for recreational use (so-called adult use) in 24 states, the District of Columbia, and 2 territories. An additional 9 states allow medicinal use of cannabis products with low THC and high CBD content. Thus, only 3 states (Idaho, Kansas, and Nebraska) have no form of legalized cannabis product.

This article reviews the diagnosis and treatment of the seven cannabis-related disorders defined in the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition, text revision (DSM-5-TR)<sup>3</sup> (Table 1). Some of the toxic effects that are associated with long-term cannabis use are reviewed here and in the Supplementary Appendix, available with the full text of this article at NEJM.org.

## EPIDEMIOLOGY AND BURDEN OF ILLNESS

Cannabis is one of the most commonly used psychoactive substances globally, trailing only caffeine, alcohol, and tobacco (nicotine). Worldwide, an estimated 209 million persons 15 to 64 years of age used cannabis in 2020, representing about 4% of the global population in that age group.<sup>4</sup> In the United States, an estimated 52.4 million persons 12 years of age or older used cannabis in 2021, representing 18.7% of the community-dwelling population in that age group,<sup>5</sup> and 16.2 million persons met the diagnostic criteria for cannabis use disorder, which has as its core feature the use of cannabis despite adverse consequences. Cannabis use disorder occurs in all age groups but is primarily a disease of young adults. The median

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**Table 1. Cannabis-Related Disorders Listed in DSM-5-TR.\***

Acute disorder (typically lasting <24 hr)
Cannabis intoxication
Subacute disorders (lasting <1 mo)
Cannabis-induced anxiety disorder
Cannabis-induced psychotic disorder
Cannabis-induced sleep disorder
Cannabis-induced delirium
Cannabis withdrawal
Cannabis use disorder

\* DSM-5-TR denotes *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition, text revision.<sup>3</sup>

age at onset is 22 years (interquartile range, 19 to 29).<sup>6</sup> In the United States, the percentage of 18-to-25-year-old persons with current (past-year) cannabis use disorder in 2021 was 14.4%.<sup>5</sup> Younger age at initiation of cannabis use is associated with faster development of cannabis use disorder and more severe cannabis use disorder.<sup>7</sup>

Cannabis use disorder often occurs alongside other psychiatric conditions, including other substance use disorders. About two thirds of persons given a diagnosis of cannabis use disorder have at least one other current substance use disorder, most commonly alcohol or tobacco.<sup>8,9</sup> Almost half the persons with a diagnosis of cannabis use disorder have a current psychiatric disorder that is not a substance use disorder — most commonly major depression, post-traumatic stress disorder, or generalized anxiety disorder.<sup>9</sup> The presence of a coexisting psychiatric disorder is associated with more severe cannabis use disorder and poorer response to treatment.

Cannabis use poses a global disease burden, albeit substantially less than that posed by other psychoactive substances such as alcohol, tobacco (nicotine), opioids, and stimulants.<sup>10</sup> The Global Burden of Disease project calculated that cannabis use in 2016 was responsible for an estimated 646,000 years of healthy life lost to disability, an age-standardized rate of 8.5 years per 100,000 persons. Cannabis use is most strongly associated with an increased risk of motor vehicle crashes, suicidality, and cardiovascular and pulmonary disease.<sup>11</sup> Most other cannabis-associated conditions and death are probably due to coexisting

psychiatric disorders and substance use, rather than to cannabis itself.<sup>12</sup> Cannabis use was associated with an estimated 10% of drug-related emergency department visits in the United States in 2021.<sup>13</sup> Whether cannabis use is significantly associated with increased all-cause mortality remains unclear.<sup>14,15</sup>

#### PATHOPHYSIOLOGY AND PHARMACOLOGY

The major effects of cannabis are generated by the interaction of THC with the endogenous cannabinoid (endocannabinoid) system. The endocannabinoid system comprises at least two cell-surface receptors — cannabinoid receptors type 1 (CB<sub>1</sub>) and type 2 (CB<sub>2</sub>) — and endogenous ligands for those receptors.<sup>16</sup> CB<sub>1</sub> receptors are found on both neurons and glia throughout the brain, especially in regions that are thought to mediate prominent effects of THC, such as the hippocampus (memory), basal ganglia and cerebellum (motor coordination), and cerebral cortex (subjective experience and executive function).<sup>17</sup> Adults who use cannabis over the long term have downregulation of brain CB<sub>1</sub> receptors.<sup>18</sup> CB<sub>1</sub> receptors are also found outside the central nervous system in the myocardium, the vascular endothelium, adipose tissue, the liver, and the reproductive organs. CB<sub>2</sub> receptors are found primarily on immune cells, although some are found in the central nervous system. THC is a partial agonist at both types of cannabinoid receptor.<sup>16</sup> CBD appears to have multiple molecular targets and limited interactions with cannabinoid receptors.<sup>19</sup> Synthetic cannabinoids, not covered here, are full agonists at the CB<sub>1</sub> receptor,<sup>16</sup> which may account for their effects' being broader and more intense than those of THC.

The pharmacokinetics and time course of the effects of THC depend on the route of administration. THC is rapidly absorbed when it is inhaled (smoked or vaporized) — it appears in plasma within seconds, with peak concentration occurring in 5 to 10 minutes.<sup>20</sup> In contrast, oral administration of THC results in slow absorption, with peak plasma concentration occurring in 2 to 6 hours. Persons expecting an immediate effect may take repeated oral doses, sometimes resulting in inadvertent overdosing.

## CANNABIS INTOXICATION

Cannabis use induces a variety of acute psychological and physiological effects that vary in intensity and duration according to the dose (chiefly of THC), the route of administration, and the degree of tolerance in the user.<sup>21,22</sup> Acute psychological effects include euphoria (“high”), relaxation, and sedation (usually desired by persons who use cannabis recreationally), increased appetite (“munchies”) and impaired short-term memory, concentration, and psychomotor coordination. Some people experience increased anxiety, panic attacks, or paranoia, especially at higher doses. Psychotic symptoms, such as perceptual alterations, hallucinations, and delusions, are less common. Acute physical effects include impaired motor coordination, slurred speech, dry mouth, conjunctival injection (“red eye”), tachycardia, orthostatic hypotension, and horizontal nystagmus. Smoked cannabis induces cough, wheezing, and dyspnea; increases sputum production<sup>23</sup>; and exacerbates asthma.<sup>24</sup> Cannabis use, regardless of the route of administration, may be associated with acute transient cardiac arrhythmias, including atrial fibrillation, supraventricular tachycardia, premature ventricular contractions, and nonsustained ventricular tachycardia.<sup>25</sup>

Cannabis use is also associated with acute impairment of driving ability, as assessed by driving simulators and on-road tests. Cross-sectional surveys suggest that recent cannabis use increases the risk of motor vehicle crashes by 30 to 40%.<sup>26</sup> By comparison, a blood alcohol concentration of 0.08% increases the risk of crashes by 250 to 300%.<sup>26</sup>

The time course of cannabis intoxication varies with the route of administration, owing to the pharmacokinetics of absorption and distribution. Intoxication with inhaled (smoked or vaporized) cannabis begins within a few minutes and lasts 3 to 4 hours. Intoxication with oral administration begins 30 minutes to 3 hours after ingestion and lasts 8 to 12 hours. Persons who have not previously used cannabis or use it only occasionally typically become intoxicated when they inhale THC at a dose of 2 to 3 mg or ingest THC orally at a dose of 5 to 10 mg.<sup>27</sup>

Cannabis intoxication is usually mild and self-limited. Most persons with cannabis intoxication never come to medical attention. Persons requiring formal treatment typically have severe anxiety or a panic attack, prominent psychotic symptoms, or severe motor incoordination.<sup>28</sup> Inpatient treatment is warranted if there are severe mood or psychotic symptoms (e.g., suicidality). In children who ingest cannabis, coma, convulsions, or cardiopulmonary instability may develop.<sup>29</sup>

Cannabis intoxication is generally managed without medication. There is no specific antidote; no medication is approved by the Food and Drug Administration (FDA) for the treatment of cannabis intoxication.<sup>30</sup> The patient is placed in a quiet environment and offered supportive reassurance.<sup>21,27</sup> Severe agitation or anxiety is controlled with benzodiazepines. Psychosis usually responds to a second-generation antipsychotic agent, and the dosage can be adjusted to account for the severity of the psychosis.<sup>31</sup>

## SUBACUTE EFFECTS OF CANNABIS

Cannabis use is associated with four subacute psychiatric syndromes that either persist after the initial 24 hours of acute intoxication or involve symptoms sufficiently severe as to warrant independent clinical attention (Table 1).<sup>3</sup> Their signs and symptoms resemble those of the corresponding nonsubstance-induced disorder. The diagnosis is suggested by the onset of symptoms during (or shortly after) a period of cannabis use or withdrawal (substantial reduction in or cessation of cannabis use) and resolution within 1 month after cannabis abstinence. Treatment is largely supportive and symptom-oriented. There are very few relevant clinical trials, so treatment is determined on the basis of clinical experience.<sup>28</sup>

## CANNABIS-INDUCED ANXIETY DISORDER

Cannabis-induced anxiety disorder may manifest as either general anxiety or panic attacks.<sup>32</sup> Panic attacks that result from cannabis use are similar to those that are not related to cannabis use.<sup>33</sup> Patients with cannabis-induced anxiety disorder comprise 20 to 25% of patients presenting to emergency departments with cannabis-related symptoms.<sup>32</sup> The majority of such patients are

discharged within 24 hours, but we are not aware of any studies involving follow-up of such patients. The overall prevalence of cannabis-induced anxiety disorder is unknown, because many persons with the disorder do not seek medical attention.

#### CANNABIS-INDUCED PSYCHOTIC DISORDER

Transient psychotic symptoms during cannabis intoxication are reported by 5 to 50% of adults, depending on how the symptoms are described in questions.<sup>34</sup> A family or personal history of psychotic symptoms is associated with an increased risk of psychotic symptoms during cannabis intoxication. The annual incidence of adults with cannabis-induced psychosis who come to medical attention is about 3 to 6 per 100,000 (based on national health care registries in Scandinavia).<sup>35</sup> Allelic variations in the gene for catechol O-methyltransferase (an enzyme that metabolizes catecholamines) are associated with an increased risk of cannabis-induced psychosis.<sup>36</sup> Population-based national registry studies show that a long-term psychotic disorder that is indistinguishable from schizophrenia develops in one fifth to one half of patients with cannabis-induced psychotic disorder.<sup>34</sup> This transition is more likely to occur in persons who start using cannabis in adolescence or use cannabis that contains high concentrations of THC (i.e., high potency cannabis).<sup>37</sup>

#### CANNABIS-INDUCED SLEEP DISORDER

Cannabis in general, and THC in particular, decreases sleep latency (the time it takes to fall asleep) and increases sleep duration but has little consistent effect on sleep architecture.<sup>38</sup> These changes tend to diminish with repeated use, presumably owing to tolerance. Conversely, sleep disturbance (insomnia, disturbing dreams) is a common manifestation of cannabis withdrawal and may persist for several weeks after other withdrawal symptoms have subsided.<sup>39</sup> Symptoms of disturbed sleep are reported by about two thirds of persons experiencing cannabis withdrawal,<sup>40</sup> but the prevalence of cannabis-induced sleep disorder is unknown.

There is no proven effective treatment for cannabis-induced sleep disorder.<sup>39</sup> Improvement of sleep hygiene and cognitive behavioral therapy have been suggested but have not been formally

evaluated. Extended-release zolpidem improved sleep duration and quality in a small randomized, controlled clinical trial involving 31 adult inpatients undergoing cannabis withdrawal.<sup>39</sup>

#### CANNABIS-INDUCED DELIRIUM

Cannabis-induced delirium is a poorly understood syndrome. The few published case reports show that hyperactive (hyperadrenergic) delirium, which is characterized by hyperactivity, agitation, autonomic instability, and disorientation, often with hallucinations, is more common than hypoactive delirium.<sup>41</sup> Being treated with tricyclic antidepressants may be a risk factor.<sup>42</sup> Cannabis-induced psychosis with agitation is often misdiagnosed as delirium, so the true prevalence of cannabis-induced delirium is unknown. Treatment with intravenous dexmedetomidine, a selective presynaptic  $\alpha_2$ -adrenergic receptor agonist, was effective in several cases.<sup>41</sup>

#### CANNABIS USE DISORDER

Cannabis use disorder, like other substance use disorders, is a chronic, relapsing condition. The core feature is loss of control over cannabis use, which is reflected in persistent use of cannabis despite adverse consequences. Specific diagnostic criteria are provided in the DSM-5-TR<sup>3</sup> (Table 2).

The major risk factors for development of cannabis use disorder are the frequency and duration of cannabis use. The amount and the potency of the cannabis that is used are also likely risk factors, but they have not been well studied because of the difficulty in reliably quantifying the amount and the potency of the THC content of products that are illicit at the federal level and loosely regulated at the state level. The potency of cannabis has doubled over the past 2 decades, according to analyses of samples seized by U.S. law enforcement,<sup>43</sup> which may contribute to the increased risk of cannabis use disorder and cannabis-induced psychosis.<sup>44</sup> The risk of cannabis use disorder is significantly positively associated with the frequency of cannabis use: 3.5% prevalence of cannabis use disorder is seen with yearly use (<12 days per year), 8.0% with monthly use (<4 days per month), 16.8% with weekly use (<5 days per week), and 36% with daily or near daily use (>4 days per



week).<sup>45</sup> The prevalence of past-year cannabis use disorder among adolescents (12 to 17 years old) is positively associated with their overall duration of cannabis use: 11% among those who have been using cannabis for 1 year or less, 15% among those who have been using cannabis for 1 to 2 years, 18% among those who have been using cannabis for 2 to 3 years, and 21% among those who have been using cannabis for more than 3 years.<sup>46</sup>

Several clinical and sociodemographic factors are associated with an increased risk of cannabis use disorder, including the use of other psychoactive substances such as alcohol and tobacco; having had adverse childhood experiences (such as physical, emotional, or sexual abuse); having a history of a psychiatric disorder or conduct problems as a child or adolescent; depressed mood, anxiety, or abnormal regulation of negative mood; stressful life events (such as job loss, financial difficulties, and divorce); and parental cannabis use.<sup>47-49</sup> These significant associations do not necessarily indicate a direct causal influence on cannabis use disorder, because many of these factors are also highly associated with both cannabis use and frequent cannabis use.

Genetic factors account for about half the variability in the development of cannabis use disorder in persons who use cannabis, according to family, twin, and genomewide association studies.<sup>50,51</sup> A substantial proportion of this genetic influence is shared with other substance use disorders. No gene or single nucleotide polymorphism is consistently associated with these traits, which suggests that the genetic influence arises from many different genes, each exerting a very small influence. There is also evidence of genetic influence on the subjective effects of cannabis, such as craving and euphoria.<sup>52,53</sup>

Cross-sectional surveys of adolescents and young adults have shown that several sociodemographic factors are associated with a risk of cannabis use disorder that is lower than that in persons without those sociodemographic factors. Protective factors include personal attendance at religious services<sup>54</sup> and close parental monitoring of adolescent behavior.<sup>55</sup> Longitudinal studies are needed to evaluate the persistence of these associations.

**Table 2. DSM-5-TR Diagnostic Criteria for Cannabis Use Disorder.\***

<b>Impaired control over cannabis use</b>
1. Using cannabis for longer periods of time than intended or using larger amounts than intended
2. Unsuccessful in reducing or controlling cannabis use, despite wanting to do so
3. Spending a great deal of time getting or using cannabis or recovering from its use
4. Strong desire or craving to use cannabis
<b>Social impairment due to cannabis use</b>
5. Failure to fulfill major role obligations at work, school, or with family due to cannabis use
6. Continued cannabis use despite having persistent cannabis-related interpersonal or social problems
7. Giving up or reducing time spent on important activities because of cannabis use
<b>Risky use of cannabis</b>
8. Repeated use of cannabis in physically dangerous situations
9. Continued use of cannabis even though the person is aware that use is likely to be causing or worsening a cannabis-related physical or psychological problem
<b>Pharmacologic indicators</b>
10. Tolerance. With chronic cannabis use, the effects of cannabis decrease when it is repeatedly used in the same amount, or the amount of cannabis needed to achieve the same effects must be increased
11. Withdrawal. Either a typical cannabis withdrawal syndrome or use of cannabis to avoid experiencing a withdrawal syndrome

\* Cannabis use disorder requires meeting 2 or more criteria within a 12-month period. Mild cannabis use disorder requires meeting 2 to 3 criteria, moderate cannabis use disorder requires meeting 4 to 5 criteria, and severe cannabis use disorder requires meeting 6 or more criteria. Partial remission is defined as no longer meeting any criteria for cannabis use disorder for 3 months. Full remission is defined as no longer meeting any criteria for 12 months.

The U.S. Preventive Services Task Force recommends screening all adolescents and adults in primary care settings for substance use disorders, including cannabis use disorder, as long as “services for accurate diagnosis, effective treatment, and appropriate care can be offered or referred.”<sup>56</sup> Screening is best done with a validated, brief instrument, to be completed by the patient, either used as a stand-alone questionnaire or embedded in a larger health questionnaire. Testing for cannabis (THC in body fluids such as urine, saliva, or blood) is not an appropriate screening method for cannabis use disorder, because a positive test result indicates only that the person used cannabis recently, not that the person has cannabis use disorder.

A person's own report of cannabis use or cannabis use disorder is fairly reliable if the context in which the person is asked about it poses no potential adverse consequences (e.g., criminal charges or job loss).<sup>57</sup> In such contexts, 1-to-4-item screening instruments have a sensitivity of 79 to 82% and a specificity of 95% for identifying heavy cannabis use and a sensitivity of 71 to 83% and a specificity of 75 to 95% for identifying cannabis use disorder.<sup>58</sup>

An evaluation for cannabis use disorder should be triggered by a positive screening response or by signs or symptoms suggestive of cannabis use disorder.<sup>3</sup> These include otherwise unexplained impairment in social, educational, or vocational functioning; exacerbation of conditions known to be worsened by cannabis (e.g., depression and anxiety); chronic conjunctival injection; yellowing of the fingertips; cannabis odor on clothing; and increased appetite. The evaluation for cannabis use disorder should be conducted in a private setting, with a nonjudgmental approach.

The Screening, Brief Intervention, and Referral to Treatment model should be used.<sup>59</sup> Patients who are identified as having mild cannabis use disorder are offered brief intervention. Those who have moderate or severe cannabis use disorder or who did not respond to brief intervention are referred for specialty treatment.

Brief intervention typically consists of one or two sessions, lasting 15 to 30 minutes each, of patient-centered, nonjudgmental counseling using motivational enhancement techniques. Brief intervention has short-term efficacy in reducing cannabis use and manifestations of cannabis use disorder, primarily in persons who are identified by screening and in adolescents.<sup>60,61</sup> More intensive treatment for cannabis use disorder uses psychosocial methods. Medication plays little or no role in the treatment of cannabis use disorder.

Psychosocial treatments have significant short-term (2 to 4 months) efficacy in helping patients reduce or stop their cannabis use.<sup>58,62</sup> Few studies of longer-term treatment outcomes have been conducted, but cannabis abstinence is usually sustained over the long term by less than 50% of patients. The most robust evidence of efficacy is for cognitive behavioral therapy (CBT) and motivational enhancement therapy (MET).<sup>58,62</sup>

CBT emphasizes identification and management of the patient's thoughts, behaviors, and external triggers that promote cannabis use. MET is a directive, patient-centered form of psychotherapy that aims to enhance the patient's motivation to reduce or stop cannabis use by using personalized feedback and education regarding the patient's maladaptive patterns of cannabis use. Adolescent patients gain additional benefit from family-based treatment.<sup>63</sup> Patients who do not have an adequate response to CBT or MET may benefit from combining the two or from augmentation with contingency management. Contingency management uses behavioral reinforcement techniques to encourage specific beneficial behaviors. Typically, patients are rewarded with a voucher (redeemable for a low-value prize) each time they attend a treatment session or provide a urine sample that is negative for cannabis. There is little evidence that generic counseling for substance use disorder or attendance at mutual self-help groups such as Marijuana Anonymous (analogous to Alcoholics Anonymous) is effective in the treatment of cannabis use disorder.

Patients can use a computer, tablet, or smartphone to engage in CBT, MET, and similar psychosocial treatments.<sup>64</sup> Such treatments reduce cannabis use in patients with mild cannabis use disorder.

No medication is approved by the FDA for the treatment of cannabis use disorder. Several medications that are FDA-approved for other indications significantly reduced cannabis use in small, controlled clinical trials, but none produced extended abstinence or reduced the severity of cannabis use disorder.<sup>65,66</sup> These medications include N-acetylcysteine, topiramate, gabapentin, and varenicline. Two experimental cannabinoid medications, nabiximols<sup>65</sup> and CBD,<sup>67</sup> have shown promise in small randomized, controlled trials.

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#### CANNABIS WITHDRAWAL

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A substantial reduction or a cessation of cannabis use after heavy or long-term use results in a withdrawal syndrome that is usually mild and self-limiting.<sup>39</sup> Cannabis withdrawal is clinically significant as a negative reinforcer for the resumption of cannabis use. Common psychological

symptoms of cannabis withdrawal include depressed mood, anxiety, restlessness, irritability, decreased appetite, and sleep disturbance. Physical signs and symptoms are less common and include abdominal cramps, muscle aches, tremor, headache, sweating, chills, and weight loss. These signs and symptoms typically begin within 1 to 2 days, peak within 2 to 6 days, and last for several weeks. The symptoms of cannabis withdrawal substantially overlap with those of tobacco (nicotine) withdrawal, which makes the differential diagnosis difficult in persons who use both substances. The probability and severity of cannabis withdrawal are positively correlated with the frequency and duration of cannabis use but not with age, gender, or co-occurrence of other substance use disorders.<sup>68</sup> The prevalence of any withdrawal symptoms is almost 50% in persons who were using cannabis daily. Cannabis withdrawal can be monitored systematically with the 14-item modified Marijuana Withdrawal Checklist, a standardized self-report instrument.<sup>39</sup>

Cannabis withdrawal typically requires formal treatment only if sleep or mood disturbances interfere with daily life.<sup>39</sup> Inpatient treatment is warranted only with suicidality or exacerbation of a coexisting psychiatric disorder. The mainstay of treatment is psychosocial — supportive counseling or CBT.<sup>39</sup> No medication is FDA-approved for this indication. Substitution treatment with CBD (dronabinol, nabilone, or nabiximols) to suppress withdrawal has shown promise in several small randomized, controlled trials.<sup>39</sup> Medication can be used to target specific symptoms, such as zolpidem for insomnia and benzodiazepines for anxiety.<sup>39</sup>

impairment in cognitive function and an increased risk of substance use and delinquent behavior during childhood and adolescence.<sup>71</sup> THC appears in breast milk at concentrations several times higher than concentrations in plasma and may persist for up to 2 days after the most recent cannabis use.<sup>72</sup> Cannabis use changes the composition of breast milk; it increases the concentration of lactose and decreases the concentration of secretory immunoglobulin A (the major antibody in breast milk).<sup>73</sup> Long-term effects on infants fed with breast milk are unclear; the majority of persons using cannabis while breast-feeding an infant also used cannabis during pregnancy. The American College of Obstetricians and Gynecologists recommends against cannabis use during pregnancy and nursing.<sup>74</sup>

Cannabinoid hyperemesis syndrome, a form of cyclic vomiting syndrome that is often accompanied by abdominal pain, occurs during or within 48 hours after frequent and heavy cannabis use.<sup>75</sup> Cannabinoid hyperemesis syndrome is a major reason for cannabis-related visits to emergency departments, and it accounts for about 10% of patients with cyclic vomiting syndrome.<sup>76</sup> Cannabinoid hyperemesis syndrome is distinguished from cyclic vomiting syndrome by its temporal association with cannabis use, relief with hot baths or showers, and resolution with extended abstinence from cannabis. Patients often have difficulty accepting the diagnosis and continue using cannabis to self-medicate. The symptoms of cannabinoid hyperemesis syndrome are treated with benzodiazepines, haloperidol, and topical capsaicin. Traditional antiemetic agents are usually ineffective.

#### ADVERSE EFFECTS OF LONG-TERM CANNABIS USE

Pregnant persons who use cannabis expose their neonates to cannabis. Such in utero exposure is associated with increased risk among newborns of having low birth weight, being small for gestational age, and being admitted to the neonatal intensive care unit, but cannabis use is not associated with adverse maternal outcomes.<sup>69</sup> The association of in utero exposure with long-term neurodevelopmental outcomes remains unclear.<sup>70</sup> There is low-quality evidence of subtle

#### CONCLUSIONS

Cannabis use disorder and heavy or long-term cannabis use have adverse effects on physical and psychological health. Research on the endocannabinoid system is needed to better elucidate the pathophysiology of these effects and to develop better treatments. Psychosocial methods are the mainstay of treatment for cannabis use disorder. No medication is shown to be broadly effective.

Disclosure forms provided by the author are available with the full text of this article at [NEJM.org](https://www.nejm.org).

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