Marijuana Use and Potential Implications of Marijuana Legalization

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Education Gaps

Cannabis availability and access are increasing throughout the United States. Knowledge that marijuana demonstrates health benefits complicates provider-patient conversations, as does the fact that qualifying conditions for medicinal marijuana vary by state. Gaps in longitudinal research to elucidate relationships among early marijuana use, social determinants of health, and psychiatric comorbidities are barriers to safeguarding the health of children and adolescents.

Abstract

Most states in the United States have legalized medical and/or recreational cannabis in response to public demand. Trends in states adopting such legislation demonstrate an increasing prevalence of cannabis use coincident to decreasing perceptions of risk of harm from cannabis products. When providing anticipatory guidance, pediatricians should be prepared to address childhood unintentional ingestion management and prevention, adolescent problem use, and cannabis as an alternative therapy for seizure disorders and other conditions.

Objectives

After completing this article, readers should be able to:

1. Explain clinical presentations of acute exposures/ingestions of marijuana in children.
2. Define cannabis use disorder and symptoms of cannabis withdrawal.
3. List potential outcomes associated with early age of initiation and chronic use of marijuana in adolescents.
4. Identify key policy issues and areas for advocacy in safety and prevention.

AUTHOR DISCLOSURE

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ABBREVIATIONS

AAP American Academy of Pediatrics
CBD cannabidiol
CPS Child Protective Services
CUD cannabis use disorder
DSM-V Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECS endocannabinoid system
RPC regional poison center
SCRA synthetic cannabinoid receptor agonist
SUD substance use disorder
THC tetrahydrocannabinol
THC-COOH 11-nor-9-carboxy-D⁹-tetrahydrocannabinol
The substances tetrahydrocannabinol (THC) and cannabidiol (CBD) are derived from the plant Cannabis sativa. In this review, we use the terms cannabis and marijuana interchangeably. The legal history of cannabis is complex. Cannabis was initially legal and listed in the US Pharmacopoeia in 1851. (1) Federal regulations criminalized cannabis, through the Marihuana Tax Act of 1937 and the Controlled Substances Act of 1970. (2) The criminalization of cannabis arose alongside tensions between ethnic groups, as immigration to the United States from Mexico increased in the early 1900s. (3) Figure 1 depicts the recent trends in many states legalizing cannabis. In 2012, Colorado was the first state to legalize the use of recreational cannabis for people 21 years and older, and most states have legalized cannabis in some form, medically or recreationally. Traditionally, cannabis has been consumed through inhalation, yet a diversity of cannabis products are now available and have become more potent over time. (4)(5) Pediatricians often encounter patients and parents who use cannabis products. In this review, we address the health implications of recreational and medical marijuana legalization in the United States. We describe patterns of its use and the clinical and toxicological effects that pediatric providers should recognize. We present advocacy opportunities to keep patients and their families safe and informed. Given the US trends in recreational and medical marijuana legalization, marijuana use will impact all age groups. This review addresses clinical implications along with opportunities for community engagement to enhance safety and prevention.

EPIDEMIOLOGY

Adolescents

On a population level, as adolescents age, the incidence of cannabis use increases. The rates of initiation of use, frequency of use, and progression to cannabis use disorder (CUD) increase throughout adolescence. The Youth Risk Behavior Surveillance System, the Monitoring the Future survey, the Behavioral Risk Factor Surveillance System, and the National Survey on Drug Use and Health estimate cannabis use by adolescent self-report and demonstrate similar trends of increasing rates in initiation, frequency, and progression of marijuana use. In the 2017 National Survey on Drug Use and Health, 6.5% of 12- to 17-year-olds reported current cannabis use. The prevalence is much higher in older adolescents; 22.1% of 18- to 25-year-olds report cannabis use in the same survey. (6) In high school, 35% to 49% of participants report past and/or current cannabis use. (7)(8) Synthetic cannabinoid use is rising in adolescents and is associated with numerous high-risk behaviors compared with marijuana use. (9)(10)(11)(12)(13)

Children

Most cannabis exposure is unintentional in children younger than 12 years, with the highest number of ingestions between ages 12 and 36 months. (14)(15) The rate of cannabis-related calls to regional poison centers (RPCs) has risen since cannabis legalization. (14)(15)(16)(17) The reports of RPC calls tend to underestimate poisonings because only severe intoxications trigger caregiver calls to poison centers.

Maternal

The American College of Obstetricians and Gynecologists firmly recommends against any cannabis use in the perinatal period. (18) Despite these recommendations, the use of cannabis during pregnancy and lactation continues to rise, with approximately 4% of women reporting cannabis use during the perinatal period. (19)(20)(21) Parents who use cannabis are more likely to use tobacco as well, during and outside the perinatal period. (21)(22)(23)(24)

PHARMACOLOGY

The term cannabinoid refers to a substance that interacts with cannabinoid receptors. Phytocannabinoids are chemicals specifically derived from the cannabis plant. The principal phytocannabinoids are THC, CBD, and cannabidiol. There are also many synthetic cannabinoid receptor agonists (SCRAs). Endocannabinoids are endogenous modulators of cannabinoid receptors. CB1 and CB2 are the 2 main cannabinoid receptors. CB1 receptors are predominantly located throughout the central nervous system, and CB2 receptors are predominantly found in immune cells, the spleen, and other peripheral sites. Agonism of CB1 receptors by THC produces the typical psychoactive effects of marijuana. Inverse agonism of CB2 receptors by CBD causes anti-inflammatory effects. (25)(26) Inverse agonists reduce target receptor activity compared with antagonists, which simply block the effects of agonists.

The pharmacokinetics of cannabis are well understood. (25)(27) When inhaled, THC is detectable in plasma within seconds. Effects after smoking a single marijuana cigarette last approximately 1 to 2 hours. Absorption of orally administered THC differs significantly, with peak plasma THC concentrations reached within 1 to 2 hours and effects lasting up to 6 hours. (28) THC crosses the placenta during pregnancy and enters human milk during lactation.
The pharmacodynamics and pharmacokinetics of THC in lactating women and breastfed infants remain an active area of study because the evidence of health effects on breastfed infants exposed to THC is inconclusive. THC is metabolized primarily in the liver to the active metabolite 11-hydroxy-Δ9-tetrahydrocannabinol and then to inactive 11-nor-9-carboxy-Δ9-tetrahydrocannabinol (THC-COOH). Urine drug screens detect THC-COOH for 3 to 5 days after a single use or for up to several weeks in long-term users. A urine drug screen positive for THC-COOH may be due to acute intoxication or a marker of past use. CBD is not metabolized to THC-COOH, and neither does it cross-react with THC-COOH. Thus, users of products (inhaled or ingested) containing only CBD would not be expected to have THC-positive urine drug screens. Similarly, SCRAs are chemically distinct from THC and are not detected on routine urine drug screens. These factors are important to remember when considering differential diagnoses in patients with altered mental status because a negative urine drug test result does not rule out all forms of cannabis use, and there could be medical-legal implications.

**CLINICAL ASPECTS**

**Acute Intoxications and Effects**

Acute overdose with cannabis generally falls into 3 categories: novice recreational users experiencing unwanted effects, inadvertent excessive recreational use, and unintentional ingestions by children.

THC concentrations in modern cannabis products are now much higher than in the past. A standard marijuana cigarette from the National Institute on Drug Abuse used in Drug Enforcement Administration–approved research contains 5% THC, similar to illegal marijuana from decades past. The cannabis flower now typically contains about 20% THC. Newer production methods can yield extracts with THC concentrations exceeding 70%. Given these trends, novice users are at risk for consuming more cannabis than necessary to achieve their desired effects.

Edible cannabis products (edibles) may cause toxicity in both recreational adolescent users and young children who are unintentionally exposed to cannabis products. Recreational users may consume excessive quantities of edibles because clinical effects are delayed 2 to 4 hours and the listed THC content in the edibles may be underestimated. Edibles are any of the various food items containing THC and/or CBD. Cannabis-infused products include baked goods, gummies, candies, and chocolates and are a common source of exposure in young children. In France, where other forms of cannabis are more common, hashish (a product made by separating and compressing marijuana resin) was responsible for most childhood exposures.

Symptoms of marijuana intoxication are euphoria, giddiness, sedation, pain relief, increased appetite, anxiety, and paranoia. Signs include mild tachycardia, conjunctival injection, and dry mouth. For accidental pediatric ingestions, commonly reported symptoms include sedation, lethargy, ataxia, tachycardia, and vomiting. Central nervous system and respiratory depression requiring intubation are infrequently reported. In these instances, it is not always clear whether intubation was performed for true respiratory depression or whether it was prompted by other circumstances, such as a need for transport, a perceived lack of airway protection, or unclear
Seizures and hypotension have been reported but seem to be rare. No specific end-organ damage is expected from marijuana intoxication. Death related to marijuana use is very rarely reported, and causality is not clear. (48)(49)(50)

CBD is not expected to produce significant symptoms in overdose because it lacks the psychoactive effects of THC, although CBD is more sedating than placebo in clinical trials. (51) Some products marketed as CBD oil have even been discovered to actually contain SCRAs and no CBD. (13)

The diagnosis of marijuana intoxication is largely clinical, but urine drug screens for THC-COOH have utility, especially in cases of children who may have inadvertently been exposed to cannabis. In the appropriate clinical scenario, a positive urine drug screen for cannabinoids may obviate the need for further invasive or expensive evaluation of a patient presenting with altered mental status. Drug testing is not required in adolescents using cannabis unless diagnosis is uncertain or results will inform psychiatric evaluation.

Management of adolescents with mild to moderate symptoms of excessive cannabis use is largely supportive, with the option of benzodiazepines to treat anxiety. Symptoms typically abate within hours. Hospital admission is rarely necessary. In one series, two-thirds of patients presenting to hospitals or reported to RPCs were observed and discharged home. The remainder of patients were admitted to hospital wards or ICUs. (14)

Management of young children with marijuana intoxication, although primarily supportive, also warrants Child Protective Services (CPS) notification. If exposure and diagnosis are not in question (eg, found eating a marijuana brownie), the stable child may be observed for 4 to 6 hours and discharged to a safe environment. Gastrointestinal decontamination with activated charcoal may be considered early after ingestion. In the rare instances of more serious effects, treatment and intervention for central nervous system and respiratory depression, seizures, or hypotension may be required.

Although commonly known as “spice” or “K2,” there are dozens of different SCRAs that produce a variety of effects. Intoxication with SCRAs is generally more severe than marijuana, with common effects including agitation, delirium, and seizures. (52) A history of “synthetic marijuana” use, or symptoms inconsistent with traditional THC intoxication, should raise suspicion for intoxication with an SCRA or other novel psychoactive substance.

Cannabis poses other short-term health risks in addition to acute intoxication. Cannabis hyperemesis syndrome, often seen in adolescents, is distinct from acute intoxication and is characterized by intractable vomiting, initiation of

cannabis use early in adolescence, and temporary relief of symptoms with hot showers. The cannabis hyperemesis syndrome incidence has risen with increases in cannabis accessibility. (53) Immunocompromised patients should avoid cannabis due to contaminants. Limited literature suggests an increased risk of Aspergillus infection due to the presence of fungal spores in marijuana leaves and smoke. (54)(55)(56)

Driving
The effect of medical and recreational marijuana legalization on motor vehicle collisions and fatalities is unclear. Investigators found a decline in fatalities after legalization, presumably from a decrease in alcohol use in the driving population, but others found an increased incidence of collisions and fatalities. (57)(58)(59) In controlled studies of cannabis and driving, participants demonstrated impairment in visual tracking, synergistic impairment when combined with alcohol, and impairment lasting up to 6 hours after smoking cannabis. (60)(61)(62)(63)(64) States have not established a standard threshold for biological sample or field sobriety test results to determine impairment. (65) Many variables influence both serum THC concentrations and impairment, such as frequency of use, time of last use, and route of exposure. Urine THC-COOH is an inappropriate marker of acute toxicity because it is detected for days to weeks after use. (66)(67)

Pregnancy, Infants, and Young Children
There is substantial evidence of low birthweight in infants born to mothers smoking cannabis. (68) Evidence is insufficient to determine statistically significant positive or negative associations between maternal cannabis smoking and pregnancy complications or prematurity. (68) Maternal marijuana use did not increase neonatal complications such as jaundice, respiratory distress syndrome, resuscitation, intubation, hypoglycemia, and sepsis, but there is a small but persistent positive association between prenatal cannabis use and NICU admission. (68)(69)(70)(71) Withdrawal syndrome symptoms have not been observed in cases of in utero exposure to cannabis only.

The effects of cannabinoids on the developing endocannabinoid system (ECS) are not clear. In the fetal brain, CB1 receptors are found in areas important for emotional regulation, cognition, and memory. In the early stages of embryonic development, ECS activity influences neuronal connections, paving the way for endocannabinoid modulation of synaptic transmission in the postnatal brain and spinal cord. Repeated exposure to THC disrupts endocannabinoid signaling in the fetus, facilitating rewiring of the
fetal cortical circuitry and possibly altering ECS functionality. (66) Research combining results of animal studies and what is known about neurophysiology and genetic mutations in humans with diagnoses such as schizophrenia, bipolar disorder, and drug addiction supports causality between dysregulated ECS signaling and neuropsychiatric illnesses. (72)

Only approximately half of women disclosing marijuana use received counseling on associated perinatal health risks. (73) Women seeking information about cannabis use during and after pregnancy are looking beyond that provided by traditional health-care providers. Online media sources suggest use of marijuana to relieve nausea and vomiting during pregnancy but do not systematically present the risks and benefits; 69% of dispensaries surveyed in Colorado recommended cannabis for morning sickness. (74)(75)

Rising maternal cannabis use occurs alongside increasing prevalence of preexisting conditions, including hypertension, chronic lung disease, diabetes, and substance use disorder (SUD) in reproductive-aged women. (76) In prenatal visits, providers (and health systems) have competing interests as they address conditions that have well-known, often quantifiable risks to the mother and fetus. Under the umbrella of SUD (which includes CUD), substances such as opioids require complex prenatal and postnatal management and may take precedence over cannabis counseling. (77)

Breastfeeding
Research into the effects of cannabis exposure on breastfed infants and young children is insufficient to determine associations with developmental delays. The American Academy of Pediatrics (AAP) and the Academy of Breastfeeding Medicine recommend weighing risks and benefits when counseling about breastfeeding. Pattern of use and effects on parenting practice should be discussed, and providers should inform women of the potentially harmful effects of cannabis on early childhood brain development. The Academy of Breastfeeding Medicine guidelines note that “although the data are not strong enough to recommend not breastfeeding with any marijuana use, we urge caution.” (78)

Later Childhood Outcomes
The results of 3 large cohort studies—the Ottawa Prenatal Prospective Study, the Maternal Health Practices and Child Development study, and the Generation R Study—serve as a major basis for conclusions regarding later health effects in children exposed to marijuana prenatally. (79)(80)(81) An AAP Clinical Report concludes that marijuana use during pregnancy may not be harmless. (82) Research overall has provided insufficient evidence to support or refute a statistical association between cannabis smoking and asthma development or exacerbations. (83)(84) Studies of perinatal cannabis exposure on long-term child health outcomes are confounded by variations in socioeconomic status, maternal educational achievement, mental illness, and comorbidity with other substance use. (68) Investigators were not able to control for dose and duration of cannabis exposure, recall bias from self-report, and route of exposure. (68)

The Social Context of Cannabis
Adults responsible for supervising children and adolescents should not be under the influence of alcohol, marijuana, or other drugs. (85) State mandatory reporting laws require CPS notification when women test positive for illicit substance use during pregnancy and/or at the time of birth. Parental substance abuse contributes to adverse childhood experiences, which disproportionately affect families living in poverty and historically marginalized populations. (86)(87)(88) Clinicians can inadvertently compound the impact of adverse childhood experiences when they fail to consider the role of implicit bias in their treatment of patients from racially, socioeconomically, and gender-diverse populations. In a study of prenatal alcohol and drug use, white and black women tested positive for these substances at similar rates when universally screened. In the same study population, black women were nearly 4 times as likely to be reported to CPS than white women. (89) Other investigations have demonstrated similar imbalance in the medical-legal system regarding CPS involvement; and persistent racial disproportion in health outcomes and access to care are well-documented throughout adult and pediatric medicine. (75)(90)(91)(92)(93) Practitioners can incorporate equitable standards of care to address child injury prevention (eg, universal mandatory reporting of illicit substance use), screen for perinatal mood disorders (including SUDs), and promote neighborhood safety. Informed care models mitigate health disparities and empower parents, better served by an evidence-based, integrated approach to early learning, comprehensive health services, and family support. The principles of nurturing and stable relationships between children and caregivers can be stepping stones for discussing substance use in an unbiased, non-punitive way. (94)(95)

Risk Behavior in Adolescence
Social learning and risk behavior patterns impact cannabis use and its consequences in adolescents. Parents using cannabis are not routinely discussing cannabis use with their children. (96) After alcohol, cannabinoids were the
second most common substance detected in a study of drug-facilitated sexual assaults. (97) Driving after marijuana use may be perceived as safer than driving after alcohol use, when in fact both cause substantial driver impairment. (98)(99) The 2018 AAP policy statement, The Teen Driver, explores new risks facing adolescent drivers and provides guidance to parents and teens regarding impaired driving caused by the use of alcohol, prescription and nonprescriptions drugs, or combinations thereof. (100) Smoking is the most common method of cannabis consumption. Of note, cannabis smoke contains carcinogens similar to those in tobacco. Discussion of the hazards of smoking, vaping, and inhalation of substances should be countered with efforts to assist teens in cessation. Evidence is insufficient to determine whether cannabis use is associated with heart attacks, stroke, and diabetes. (2)

Adolescent Learning

Volkow et al (101) summarize the myriad of adverse effects of cannabis by duration of use in Table 1. There is moderate evidence of a statistically significant positive association between acute cannabis use (within 24 hours of evaluation) and immediate impairment in the cognitive domains of learning, memory, and attention. (2) Effects were not sustained after a period of cessation, with periods ranging from 12 hours to 1 month. (102)(103)(104)(105) Beale et al (106) reviewed research using functional magnetic resonance imaging during cognitive testing of adult and adolescent cannabis users. Verbal learning, memory, and attention were most consistently impaired by short- and long-term exposure to cannabis. (106) Psychomotor function was most affected during acute intoxication. (102) Cannabis initiation at 14 years or older was associated with larger differences in brain function, suggesting that stages of critical neurodevelopment impart greater vulnerability. (103) Daily users of cannabis who started using before age 17 years were less likely to complete high school and more likely to develop cannabis dependence, use illicit drugs, and attempt suicide. (107)

Adolescent Mental Health

In 2014, a national survey from the Substance Abuse and Mental Health Services Administration identified 20.2 million adults with SUD, and among these, 7.9 million had both a mental health disorder and SUD. (108) Research suggests that predisposing risk factors (genetics, environment) contribute to the development of comorbidity. There is substantial evidence for an association between cannabis use and psychotic outcomes, with the most frequent and earliest cannabis users at highest risk. (109)(110) Heavy cannabis users have a higher incidence of suicide attempts and suicide completion. (111)(112) Except for social anxiety disorder, cannabis use does not seem to have a statistically significant association with anxiety disorders. (113)(114) Although data do not suggest an increased likelihood of bipolar disorder or posttraumatic stress disorder, cannabis use was strongly associated with alcohol use disorder, other SUDs, and nicotine dependence. (115)

Adolescent Problem Use

CUD is classified as a SUD in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), and approximately 20% of lifetime users met the DSM-V criteria for CUD. (116)(117) Of the 23% of individuals with severe CUD, 48% were unemployed and undereducated. (118) Individuals with CUD are vulnerable to other substance abuse and mental health illness and are more likely to experience significant disability. (116) Clinical diagnosis of cannabis withdrawal requires 3 of 7 symptoms developing within 1 week of cessation or reduction of prolonged cannabis use: 1) irritability, anger, or aggression; 2) nervousness or anxiety; 3) sleep difficulty; 4) decreased appetite or weight loss; 5) restlessness; 6) depressed mood; and 7) somatic symptoms causing significant discomfort. (117) The 15-item Marijuana Withdrawal Checklist lists additional withdrawal symptoms less frequently reported. (119) No standardized withdrawal scales are yet available. (120)(121)

In a large national study of adults, the lifetime cumulative probability of transition from use to dependence was 67.5% in nicotine users, 22.7% in alcohol users, 20.9% in cocaine users, and 8.9% in cannabis users. (122) Individuals from certain ethnic minority groups and those with psychiatric and substance dependence comorbidities showed an increased risk of transitioning from use to dependence. There is substantial evidence that being male and smoking cigarettes, and earlier age of initiation, are risk factors for problem cannabis use. (2)

Characteristics of frequent users who develop dependence include cannabis use as a coping strategy, inability to control desire or cut down use, and number of negative life events. (123) In a review of longitudinal studies, Courtney et al (124) opined that the adolescent peer environment, past substance use, and pre/comorbid psychopathology (ie, conduct disorder, mood disorders) significantly influence the risk of transition to CUD. In research combining functional brain magnetic resonance imaging, behavioral studies relating peer factors with adolescent cannabis use, and neuroscience models of regulatory and motivational systems, Caouette and Feldstein Ewing (125) opined that the rewarding value of cannabis use and the propensity to avoid negative peer evaluation were essential to decision-making in

66 Pediatrics in Review

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adolescents (Fig 2). The authors suggest 4 mechanistic models to explain teen behavior: 1) high social approach, lower reward sensitivity—using cannabis to fit in, not primarily to get “high”; 2) high social approach, higher reward sensitivity—using cannabis mainly to explore the “high,” less influenced by peers; 3) high social avoidance, high reward sensitivity—using cannabis to ease anxiety and “escape” negative perceptions by peers; and 4) high social avoidance, low reward sensitivity—using cannabis to reduce anxiety and depression and to cope with psychological consequences of negative experiences (eg, bullying, victimization). These early models begin to deconstruct the complicated psychosocial and neurodevelopmental factors that influence adolescent cannabis use. (125) Similar emerging research underlines the pediatrician’s obligation to consider the social environment in which adolescents undertake substance exploration. Effective screening is contingent on the availability of appropriate and accessible substance abuse treatment programs. In the state of Washington, marijuana misuse and abuse are state priorities. Using the Substance Abuse and Mental Health Services Administration Strategic Prevention Framework, state and community prevention stakeholders assessed, planned, and implemented a 5-year strategic plan using a data-driven process (Fig 3). (126) Ongoing program evaluation and cultural competency help make this a sustainable statewide system of substance abuse prevention and mental health promotion.

Potential Medical Uses in Minors
The AAP currently opposes the decriminalization of marijuana, as well as the dispensing of medical marijuana to children and adolescents when dispensed outside Food and Drug Administration (FDA) regulation committee policies. (82)(127) The AAP has acknowledged that cannabis and cannabinoid preparations may benefit children and youth with life-threatening and severely debilitating conditions refractory to current therapies. (82)(128) Using cannabis products as alternative and complimentary therapies for challenging conditions raises ethical concerns for families and pediatricians. (128)

TABLE 1. Adverse Effects of Short-Term Use and Long-Term or Heavy Use of Marijuana (101)

<table>
<thead>
<tr>
<th>Effects of short-term use</th>
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<tbody>
<tr>
<td>Impaired short-term memory, making it difficult to learn and to retain information</td>
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<tr>
<td>Impaired motor coordination, interfering with driving skills and increasing the risk of injuries</td>
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<tr>
<td>Altered judgment, increasing the risk of sexual behaviors that facilitate the transmission of sexually transmitted diseases</td>
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<tr>
<td>In high doses, paranoia and psychosis</td>
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<table>
<thead>
<tr>
<th>Effects of long-term or heavy use</th>
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<tbody>
<tr>
<td>Addiction (in ~9% of users overall, 17% of those who begin use in adolescence, and 25% to 50% of those who are daily users)</td>
</tr>
<tr>
<td>Altered brain development</td>
</tr>
<tr>
<td>Poor educational outcome, with increased likelihood of dropping out of school</td>
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<tr>
<td>Cognitive impairment, with lower IQ among those who were frequent users during adolescence</td>
</tr>
<tr>
<td>Diminished life satisfaction and achievement (determined on the basis of subjective and objective measures compared with such ratings in the general population)</td>
</tr>
<tr>
<td>Symptoms of chronic bronchitis</td>
</tr>
<tr>
<td>Increased risk of chronic psychosis disorders (including schizophrenia) in persons with a predisposition to such disorders</td>
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</tbody>
</table>

*The effect is strongly associated with initial marijuana use early in adolescence.*
Double-blinded randomized controlled trials have demonstrated the safety and efficacy of cannabidiol (CBD), an oral solution, now an FDA-approved option for treatment-resistant epilepsy, including convulsive seizures in Dravet syndrome and drop seizures in Lennox-Gastaut syndrome. (51) CBD therapy does not work well for all patients with treatment-refractory seizures, and there is insufficient evidence to support CBD for the treatment of childhood anxiety and posttraumatic stress disorder. (2)(129)

Whiting et al (130) performed a systematic review and meta-analysis of the quality of evidence available to determine the effectiveness of cannabinoids in various conditions. They noted moderate-quality evidence that cannabinoids are effective for chronic neuropathic or cancer pain and for spasticity due to multiple sclerosis. (130) In many conditions, findings were inconclusive due to the lack of high-quality evidence. Similarly, evidence for nausea and vomiting in patients receiving chemotherapy, weight gain in patients with human immunodeficiency virus, sleep disorder, and Tourette syndrome was lower-quality and, thus, inconclusive regarding cannabinoid effectiveness. Short-term adverse effects were balance problems, confusion, dizziness, diarrhea, euphoria, drowsiness, dry mouth, hallucination, nausea, somnolence, and vomiting. No studies evaluated long-term adverse effects of cannabis prescribed for indicated conditions.

Medical marijuana is legal in most states and the District of Columbia. States have autonomy to implement marijuana laws and define qualifying conditions. Some states have limited legalization to nonpsychoactive CBD, whereas others authorize all portions of the cannabis plant for medicinal use. Medical marijuana in legalized states is available to minors with physician authorization and consent of a legal guardian, despite known disrupting effects on neuropsychological development and limited evidence of efficacy in pediatric populations. Legal protection for physicians prescribing medical marijuana varies by state. (131) Pediatricians should be ready to discuss undesirable health effects and discourage exposures while acknowledging the emerging science of health benefits.
SUGGESTED ANTICIPATORY GUIDANCE

- Pediatricians can organize initiatives to distribute lockboxes for safe storage of cannabis in homes and provide information about local RPCs at health supervision visits. (14)
- When it is necessary to perform urine toxicology screens, providers should obtain informed consent and remind parents that federal law categorizes cannabis as an illicit substance, mandating reports to local CPS of pediatric exposures to marijuana.
- Early and long-term marijuana use are risk factors for SUD with adverse mental health outcomes. Three of 10 casual cannabis users will develop CUD.
- Children and adolescents with a family history of psychosis should be educated about the risks of cannabis use and be advised not to use cannabis.
- Immunocompromised patients should be educated about the risk of serious infection from handling, consuming, vaporizing, and inhaling dispensary-sourced cannabis.

TABLE 2. Lessons in Advocacy

<table>
<thead>
<tr>
<th>CURRENT STATE</th>
<th>RECOMMENDED ACTIONS</th>
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<tbody>
<tr>
<td>1. Medical and recreational cannabis users are diverse populations with varying motives, patterns of use, and risks of developing cannabis use disorder, polysubstance abuse, and mental illness. Public health messages need to appeal to many audiences.</td>
<td>Understand population demographics and customize public health messages.</td>
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<tr>
<td>2. Cannabis nonusers seek more information about marijuana laws and adverse effects after state legalization than do current users. (132) Despite no state prohibitions to block public messages at retail sites, Dilley et al (133) found no cities or counties in Washington State that required restrictions on marijuana advertising or directives for messaging aimed to counter pro-marijuana marketing.</td>
<td>Pass local ordinances to promote abstinence in nonusers and warn users at retail sites of health hazards.</td>
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<tr>
<td>3. Pregnant women use marijuana to relieve nausea, vomiting, and anxiety. In Vermont, stakeholders recommended expansion of screening for marijuana use and education of health-care providers, opting for a public health and medical approach to substance use during pregnancy. (134)</td>
<td>Implement statewide provider educational training and expanded screening for substance use.</td>
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<td>4. Medical and recreational legislation needs to be logical. Lack of alignment of recreational and medical marijuana legalization regulations in Colorado led to discrepancies in taxation, allowable amounts for possession, testing requirements, and labeling/packaging. (135) Lessons from alcohol and tobacco control suggest that preventing use among youth and minimizing harms to adults is better accomplished by policies germane to communities. (133)</td>
<td>Target logical, coherent regulations of medical and recreational marijuana. Mirror marijuana policies to reflect effective policies limiting youth access and media exposure to alcohol and nicotine.</td>
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<td>5. Policy surveillance at the community (versus the state) level is required to better understand its implementation and identify communities successfully mitigating negative impacts of legal marijuana. (131)</td>
<td>Direct policy surveillance to highlight what measures are keeping the public safe.</td>
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<tr>
<td>6. Cannabis smoke and edibles are appearing in homes, threatening poisonings, worsening asthma control, and calling attention to caregiver behavior and relaxed attitudes assuming marijuana is safe.</td>
<td>Guide local measures to reduce harm, eg, ban home delivery; limit hours of retail operation; require dispensaries to publicize addiction hotlines; enforce buffer zones.a</td>
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<tr>
<td>7. Federal restrictions on marijuana necessitate that all product testing be performed within each state. Accurate testing for THC/CBD concentrations, pesticide and microbial contaminants, and residual solvents is imperative to public health and trust. States should establish laboratories and amend regulations based on analysis of reliable data and scientific discovery. (136)</td>
<td>State-controlled reference laboratories could verify concentration and potency of THC/CBD and screen for product contaminants to inform and protect the public.</td>
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CBD=cannabidiol, THC=tetrahydrocannabinol.
aBuffer zones are zonal areas that segregate regions and serve various purposes. Regarding marijuana legislation, buffer zones serve to shield and protect residential areas, schools, places of worship, rehabilitation facilities, and commercial businesses from exposure to marijuana growers and dispensaries.
Providers in academic and community settings can standardize screening for cannabis using evidence-based tools such as CRAFFT (Car, Relax, Alone, Forget, Friends, Trouble) and SBIRT (Screening, Brief Intervention, and Referral to Treatment) per AAP Bright Futures guidelines.

Pediatricians can empower parents to advocate for prevention through statewide investments in mental health resources in schools and libraries, using evidence-based protocols in neighborhood programs to tackle youth marijuana use, and local ordinances for educating the public and restricting exposure to marijuana in their communities (Table 2).

SUGGESTED READINGS AND WEB RESOURCES


The University of Washington Alcohol & Drug Abuse Institute’s Learn About Marijuana webpage (http://learnaboutmarijuanawa.org/index.htm) is a hub for research, policy and law updates, factsheets, videos, and e-learning modules for consumers, teens, parents, and providers.

The National Conference of State Legislatures’ State Medical Marijuana Laws website (http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx) displays state and federal perspectives and resources. They update a “deep dive page” with the newest policy trends and analyses.

Summary

Based on many observational cohort investigations, the incidence of cannabis use is increasing in adolescent and adult populations, as well as in children due to unintentional ingestion. Pediatricians can track trends in marijuana use, attitudes, and health effects by accessing state health department impact reports and publicly available national survey data sets.

Numerous toxicological investigations and reliable observational studies provide strong evidence showing that cannabidiol and tetrahydrocannabinol act on distinctive receptors throughout the body and use different metabolic pathways. Clinical and legal conclusions drawn from these results should be interpreted prudently based on knowledge of these diverse systems.

Based on a comprehensive literature review of perinatal outcomes, there is a statistically significant association between prenatal cannabis use and low birthweight. High-quality evidence is not available from which to draw strong conclusions about the positive or negative associations between perinatal outcomes and cannabis use.

The clinical presentation of cannabis exposure varies widely, and data are based on observational investigations and case reports. Clinicians should consider cannabis exposure in any patient with altered mental status, with or without vital sign instability.

Based on randomized controlled trials, cannabidiol oral solution is currently Food and Drug Administration (FDA)–approved for the treatment of refractory seizures and specific seizure disorders. There are currently no other FDA-approved cannabis-derived preparations for medicinal use in pediatric patients.

Experimental studies demonstrate obvious motor vehicle driver impairment when under the influence of THC. Population-level evidence does not support an association between cannabis use and increased incidence of motor vehicle collisions; however, epidemiologic studies are more confounded than laboratory studies.

Based on expert opinion, teens and young adults should avoid consumption of marijuana. The adolescent brain is uniquely vulnerable to cannabis exposure with short- and long-term health effects. Cannabis use is strongly associated with alcohol use disorder and nicotine dependence, and there is substantial evidence for a positive association between cannabis use, suicidality, and psychosis.

Based on the lack of evidence of the safety of cannabis use in pregnant and lactating women, adolescents, and children, pediatricians should follow the precautionary principle, ie, advising their patients to avoid exposure to a potentially harmful material until safety has been established.

Marijuana Use and Potential Implications of Marijuana Legalization

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1. A 20-month-old infant was found by his mother eating a brownie known to contain marijuana. In the first half hour after ingestion the infant seemed to be his usual and normal self. In the ensuing hour he became increasingly irritable and ataxic. Which of the following is the best explanation for the delay in manifestation of this infant’s irritability and ataxia?
   A. Initial and early manifestations of euphoria due to marijuana ingestion is difficult to recognize in infants.
   B. Plasma concentration of ingested tetrahydrocannabinol peaks within 1 to 2 hours after ingestion.
   C. Reduced sensitivity and paucity of CB1 receptors present in the brains of infants.
   D. Slow release of cannabidiol (CBD) in edibles.
   E. The infant was likely chronically exposed to inhaled and ingested marijuana.

2. A 17-year-old boy is brought to the clinic for evaluation of recurrent episodes of nausea, abdominal pain, and vomiting with a 22-lb (10-kg) weight loss during the past 3 months. He reports that long hot showers provide him with some relief of symptoms. He began using marijuana at age 13 years. During the past 2 years, the frequency of his marijuana use has increased to almost daily and includes smoking and consumption of edibles. He also has a history of binge alcohol use and tobacco use. Which of the following diagnoses is consistent with this patient’s presentation?
   A. CBD use toxicity.
   B. Cannabis hyperemesis syndrome.
   C. Cannabis withdrawal.
   D. Phencyclidine-contaminated cannabis use.
   E. Synthetic cannabinoid use.

3. A 16-year-old girl is brought to the clinic to establish care. She is accompanied today by her grandmother who recently obtained custody of her. They have lived together for the past 2 weeks. The grandmother is concerned because her initially pleasant granddaughter has become easily angered and has a decreased appetite. It has also been a struggle to get her granddaughter to school on time. The girl has a known history of smoking marijuana that began in middle school. For this patient, which of the following additional findings will substantiate a clinical diagnosis of cannabis withdrawal?
   A. Bilateral hand tremors.
   B. Hallucinations.
   C. Hypertension.
   D. Sleep difficulties.
   E. Tachycardia.
4. A 13-year-old girl who has a diagnosis of juvenile myoclonic epilepsy that requires long-term treatment is followed in the clinic. She responded well to the initial treatment with sodium valproate and has been seizure free for 1 year. The mother is concerned about teratogenic risks of valproate and asks the clinician about the option of treating her daughter with marijuana. The clinician’s discussion with the mother acknowledges the emerging science of possible health benefits of marijuana. The clinician reviews the availability of a wide array of marijuana products and the variability of tetrahydrocannabinol and CBD content. However, the clinician expresses concerns about the vulnerability of adolescent brain function to marijuana and adverse effects associated with short- and long-term use. The clinician shares with the mother that randomized controlled clinical trials have demonstrated the safety and efficacy of CBD oil solution, and consequently Food and Drug Administration (FDA) approval for the treatment of which of the following clinical conditions?
   A. Certain treatment-resistant seizures.
   B. Menstrual cramps.
   C. Morning sickness of pregnancy.
   E. Spasticity due to cerebral palsy.

5. A 16-year-old boy has been smoking marijuana almost daily for the past month. When available he also consumes edibles. He has a long history of school truancy and first smoked marijuana at age 12 years with an older brother. He tells you that marijuana helps him cope with stress and he often smokes it alone. You are concerned that this adolescent is at risk for short- and long-term health consequences of his cannabis use. There is substantial evidence that his cannabis use increases his risk for which of the following conditions?
   A. Bipolar disorder.
   B. Cardiovascular disease.
   C. Liver toxicity.
   E. Suicidality.
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