

Pediatric Concerns Due to Expanded Cannabis Use: Unintended Consequences of Legalization

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Abstract An “unintended consequence” of marijuana legalization is the impact on the pediatric population. From prenatal exposure to unintentional childhood exposures, through concerns of adolescence abuse and marijuana use for medicinal indications in children, marijuana exposure can affect pediatric patients at every stage in childhood. Regardless of the stage or reason of exposure, concerns exist about short-term and long-term consequences in a child’s physical and mental health. The use of cannabidiol (CBD) may have some benefit for the treatment of epilepsy, but emphasis needs to be on rigorous clinical trials to evaluate efficacy and safety. As more states allow both medical and recreational marijuana, availability and prevalence of use will likely increase and more surveillance and research is needed to evaluate the consequences on the pediatric population.

Keywords Marijuana · Cannabis · Cannabidiol · Pediatrics · Adolescents · Breastfeeding · Pregnancy

Introduction

Despite its federal status as a Schedule I substance, marijuana legalization continues to occur at the state level. As of 2016, 23 states and Washington DC have passed legislation allowing medical marijuana, while 4 states (Colorado, Washington, Alaska,

Oregon) have passed laws allowing retail and recreational marijuana [1]. An additional 10 states are predicted to have marijuana legalization on their ballots in the next several years [2].

One “unintended consequence” of marijuana legalization is the impact on the pediatric population. From prenatal exposure to unintentional childhood exposures to concerns of adolescent abuse, marijuana potentially affects pediatric patients at every stage in childhood.

Pregnancy and Breastfeeding

Use of marijuana during pregnancy is not uncommon. The National Survey on Drug Use and Health (NSDUH) found that over 4 % of women surveyed admitted to drug use during pregnancy, with marijuana being the most commonly used substance [3]. Colorado’s largest local health department, Tri-County Health Department, serves more than 26 % of the state’s population. A survey to their Women’s Infants and Children (WIC) Program Clients revealed 7.4 % of mothers aged less than 30 years and 4 % of mothers older than 30 years were current marijuana users [4]. Of all marijuana users (past, ever, current), 35.8 % said that they used at some point during pregnancy, 41 % since the baby was born, and 18 % while breastfeeding. Reasons for use included recreation (39 %), as well as the treatment of symptoms commonly experienced during pregnancy, depression/anxiety/stress (63 %), pain (60 %), and nausea/vomiting (48 %).

Maternal use of marijuana exposes fetuses prenatally to cannabinoids, as tetrahydrocannabinoid (THC) rapidly crosses the human placenta [5]. The metabolites 11-OH-THC and THC-COOH also cross the placenta, although less efficiently [6, 7]. Blackard and Tennes reported that THC in cord blood was three to six times less than that found in maternal blood, with greater transfer of THC to the fetus

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occurring in early pregnancy [8]. Limited research also demonstrates that THC concentrates in breast milk from maternal plasma due to its high lipophilicity [9, 10]. In one woman, the THC concentration in breast milk was 8.4 times higher than in plasma, yielding an estimated daily THC exposure to the infant of 0.01 to 0.1 mg/day. However, the overall body of evidence on prenatal and breastfeeding transmission is limited, and the duration that THC remains in the breast milk after cessation of use has yet to be determined. It is also unclear if the benefits of breastfeeding (nutrition, immune protective factors, sudden infant death syndrome (SIDS), bonding, etc) outweigh the potential risks of THC exposure via breast milk.

Perinatal exposure to marijuana may have negative outcomes in a child's future cognitive development. Some evidence has shown that prenatal exposure leads to decreased IQ scores, cognitive function, and attention [11–14]. Day and colleagues found negative effects on prenatal marijuana exposure (mostly in first and second trimesters) with negative performance demonstrated in 3-year-old children on the Stanford-Binet Intelligence Scores [11]. Goldschmidt and colleagues found increased hyperactivity, impulsivity, and inattention symptoms as measured by the Swanson, Noland, and Pelham (SNAP) checklist at age 10 in children with prenatal marijuana exposures [12]. Two cohort studies (Wilford, Fried) found deficits in visual-motor coordination, processing speed, visual memory, and interhemispheric transfer of information as late as adolescence after prenatal exposure [13, 14]. Some evidence for decreased height has been found in children with prenatal exposure [15, 16]. Minimum evidence exists on a significant association between prenatal and/or breastfeeding marijuana exposure and risk for stillbirth, SIDS, development of depression, delinquent behavior, congenital heart lesions, psychosis, or future marijuana use [17–25]. Limited evidence also exists for preterm and low birth weight [26–36]. More longitudinal studies need to be performed to assess all health effects of perinatal and breastfeeding marijuana exposure.

Unintentional Pediatric Exposures

Commercialization of medical and recreational marijuana has led to the development of a marijuana industry that has generated over \$900 million in sales in 2015, in Colorado alone [37]. Marijuana-infused food products, or marijuana edibles, account for a significant portion of the revenue. These products often look, smell, and taste like their equivalent non-infused food product and pose a unique challenge in unintentional pediatric exposures. There is no other drug or substance found in a palatable attractive vehicle innately sought out by young children. With THC concentrations anywhere from 5 to over 100 mg in a single gummy candy, cookie, or brownie, the potential ingested dose can be large and lead to significant symptoms and hospitalizations.

In Colorado, a regional tertiary-care children's hospital saw a significant change in emergency room visits for marijuana exposures in children after commercialization of medical marijuana. Between 2005 and 2009, there were no emergency department (ED) visits for children <12 years of age for marijuana exposures; after 2009, there were 14 ED visits [38]. The majority of patients had central nervous system (CNS) effects (such as lethargy or somnolence) with respiratory insufficiency as the most serious symptom. Most patients received an extensive work-up, including blood work, radiographs, and lumbar punctures. A high percentage of these patients were admitted to the hospital; eight (57 %) were admitted with two (14 %) admitted to the intensive care unit due to respiratory insufficiency and CNS depression. Eight of the 14 (57 %) marijuana exposures were from ingestions of marijuana edibles.

Although regional poison center calls for pediatric marijuana exposures were low overall in comparison to the total human exposure calls annually reported, states that have passed medical marijuana legislation have had significant rises in pediatric marijuana exposure calls. From 2005 to 2011, there were 985 unintentional marijuana exposures in children less than 9 years of age, with a median age of exposure of 1.7 years [39]. A high percentage of these children (60–74 %) were seen in a health care facility. Non-legal states had a non-significant increase of 1.5 % per year (95 % CI –3.5 %, 6.7 %) in calls to poison centers ($p=0.52$) [39]. In comparison, decriminalized states had a significant increase of 30.3 % (95 % CI 22.5 %, 38.5 %) in calls to poison centers from 2005 to 2011 ($p<0.001$) [39]. There was a significant difference in rates between non-legal states and decriminalized states (28.3 %, 95 % CI 19.0 %, 38.4 %) [39]. Exposures in legal states had more major and moderate effects (OR 2.1, 1.4, 3.1) and admissions to critical care units (OR 3.4, 1.8, 6.5) [39]. Overall admission rate to hospitals was 16 %. The higher rates of calls may be due to increased availability or increased comfort by caregivers in contacting or presenting to a health care facility for evaluation due to legal status in their state. Concern exists that more severe effects and hospital admissions may be due to availability of higher concentration products where commercialization of marijuana has occurred. A similar study evaluating marijuana exposures in children less than 6 years of age from 2000 to 2013 found that the rate of marijuana exposure was significantly (2.82 times) higher in states where its use was legalized prior to 2000 compared with states where its use is not legal [40]. From 2000 to 2006, there was no significant change (0.6 % per year; 95 % CI –2.0 to 3.3 %) in the annual rate of marijuana exposure per 1 million <6-year-old children [40]. However, the rate increased significantly by 147.5 % (15.0 % per year; 95 % CI = 12.2 to 17.8 %) from 2006 (4.21) to 2013 (10.42) [40]. The impact recreational/retail marijuana legalization has on unintentional exposures has yet to be evaluated.

Child-resistant packaging is a proven intervention in poison prevention [41–43]. Child-resistant packaging has been in

existence since the 1950s and mandated by the Poison Prevention Packaging Act of 1970 for scheduled pharmaceuticals and potentially harmful household products [44]. Colorado has adopted regulations requiring use of Consumer Product Safety Commission-approved child-resistant packaging for marijuana products, similar to what is required for household chemicals and pharmaceutical products. Other regulations have included dose limitations (10 mg THC per serving size and 100 mg THC in total package), not allowing mass marketing campaigns or marketing toward children, opaque packaging, and mandated label warnings to “keep out of reach of children” [45]. Rules on marking marijuana products with a recognizable symbol have recently been passed in Colorado and Oregon. Washington has also passed similar packaging and labeling laws [46, 47]. Oregon lawmakers have proposed even lower dose limits, at 5 mg serving size and 50 mg THC limitations in retail products. Going forward, further surveillance is needed to evaluate if packaging is making an impact on unintentional exposures and if other methods, such as educational campaigns or dose limitations, are effective.

Besides unintentional ingestion, passive (or secondhand) marijuana smoke exposure is also a significant source of concern with limited available data. Marijuana smoke has similar components to those found in nicotine/cigarette smoke, including several carcinogens [48–50]. There have been no studies evaluating systemic absorption of passive marijuana smoke by children. Children may be a vulnerable population due to their increased minute ventilation and potential exposure to newer marijuana preparations containing higher concentrations of THC. It is unclear if passive marijuana smoke increases risk for upper respiratory infections, asthma exacerbations, otitis media, and/or SIDS, which have all been described in passive nicotine cigarette exposure [51–54]. Furthermore, concerns exist over chronic passive marijuana smoke exposure and potential long-term cognitive and behavioral effects in children.

The responsibility of health care providers and social services in cases of unintentional marijuana exposures remains controversial. In Colorado, there is no consensus statement from health care providers, social services, or counties on reporting marijuana exposures in children. Arguments have been made that marijuana is a state “legal” substance and should not be treated uniquely; these cases should be managed similar to cases of unintentional exposure to alcohol or pharmaceutical products, where mandated reporting does not occur. Despite state laws, marijuana remains a Schedule I substance under the Federal Controlled Substances Act, and some experts support mandated reporting after childhood exposures. Whether the exposure is from marijuana, or other potentially dangerous substance, a report and/or investigation should be paid if there are any concerns regarding the ability for the caregiver to supervise the child, child abuse, and/or neglect.

Adolescent Use

Since 1975, the Monitoring the Future (MTF) survey has measured drug, alcohol, and cigarette use, and related attitudes among 12th graders, nationwide in both public and private schools. Overall, 41,675 students from 389 public and private schools in the 8th, 10th, and 12th grades participated in the 2013 survey. According to the MTF, marijuana use by adolescents declined from the late 1990s to the mid-to-late 2000s but has since been on the increase. In 2013, 7 % of 8th graders, 18 % of 10th graders, and 23 % of 12th graders used marijuana in the past month, up from 6, 14, and 19 % in 2008 [55]. Daily use has also increased; 7 % of 12th graders now use marijuana every day, compared to 5 % in the mid-2000s. The Substance Abuse and Mental Health Services Administration (SAMSHA) also noted recent trends in adolescent perception of “great risk” from smoking marijuana (once or twice a week) has declined over 5 years, from 54.6 % in 2007 to 44.8 % in 2011 [56].

In Colorado, the Healthy Kids Colorado Survey collects health information biennially, every odd year, from Colorado public school students. In 2013, 40.7 % (37.9, 43.5) of US high school students reported ever using marijuana while 36.9 % (35.4, 38.3) of Colorado high school students reported “ever use” of marijuana [57]. Similarly, 23.4 % (21.3, 25.7) of US high school students had used marijuana in the past 30 days compared to 19.7 % (18.7, 20.6) of Colorado high school students [57]. In a trend analysis of historical data, there was no significant trend (increase or decrease) or change between 2009 and 2011 for the three marijuana use indicators. The impact of Colorado’s legalization of recreational marijuana on adolescent use may be demonstrated after the 2015 survey is complete.

Adolescents are also finding novel methods for marijuana use. In 2014, 3847 Connecticut HS students completed an anonymous survey assessing e-cigarette and marijuana use.

Vaporizing cannabis using e-cigarettes was common among lifetime e-cigarette users, lifetime cannabis users, and lifetime dual users (e-cigarette 18.0 %, cannabis 18.4 %, dual users 26.5 %). Students reported using e-cigarettes to vaporize hash oil and wax infused with THC and using portable electronic vaporizers to vaporize dried cannabis leaves [58]. There is significant concern for the use of “alternative” methods of marijuana (including edibles and vaporizers) in adolescents, as there may be misperceptions that these modalities are “safe” ways to use marijuana. Also, there are concerns regarding the use of concentrated products, such as oils and wax, especially at a young age. Both the short- and long-term health effects from non-traditional modes of marijuana use, or highly concentrated products, have yet to be determined.

The concern for adolescent marijuana use is the potential effects on cognitive outcome and ability and risk for behavioral health disorders. In several cohort studies, adolescents who reported marijuana use were more likely to have impaired cognitive and academic abilities despite 28 days of abstinence [59–62].

In longer-term studies, they are less likely to graduate high school and attain a college degree [63, 64]. Other studies have shown that adolescent marijuana users are more likely to be addicted to other drugs after adolescence, including tobacco, alcohol, and opioid analgesics [65–70]. There also appears a positive association with psychotic symptoms or disorders like schizophrenia and marijuana use [71–75]. This association could greatly impact a mental health system already stressed for more resources.

Medical Use in Pediatrics

Marijuana has been used to treat various ailments including seizures, chronic pain, cachexia from HIV/AIDS, muscle spasm, migraines, PTSDH, and glaucoma [76]. The prevalence of use and medical indications of marijuana in the pediatric population continue to grow. In December of 2015, there were 107,534 active patients in the Colorado Medical Marijuana Registry Program; 231 were patients aged less than 10 years and 132 between 11 and 17 years of age [77]. The most common condition reported in the pediatric age group is seizures, but other reported conditions include chronic pain and muscle spasm. Other reported uses are for treatment of inflammatory bowel disease and neuro-oncologic disorders.

Cannabidiol (CBD) is one of the more popular forms of marijuana being used in the pediatric population for medical indications. Specifically, CBD oil (high in CBD and low in THC) has been used to treat pediatric epilepsy. CBD is a cannabinoid found in marijuana that has been shown to have anticonvulsant properties in several animal models [78–86]. Human evidence for CBD and treatment of seizures is limited at this time. A parental survey of 19 parents using CBD for their child's epilepsy condition showed that 84 % of patients reported reduction in seizure frequency, with 2 reporting complete seizure freedom [87]. Another survey of CBD oil users revealed that 100 % of 13 patients reported reduction in weekly frequency of motor-type seizures and 5 of 11 are seizure free [88]. Rigorous randomized control trials have not been performed to evaluate the efficacy and safety of CBD for prevention of seizures in humans. A Cochrane Review of cannabidiol for treatment of seizures examined four randomized reports [89]. A total of 48 patients used cannabidiol as the treatment agent. One report was an abstract, and another was a letter to the editor. The overall study designs were poor; anti-epileptic drugs were continued in all, no details of randomization were included, and there was no analysis of control and treatment groups. All the reports were low quality. The four reports only answered the secondary outcome about adverse effects. The review concluded that no reliable conclusions could be drawn regarding the efficacy of cannabinoids as a treatment for epilepsy.

Recently, a pharmaceutical grade cannabidiol is being trialed for treatment of pediatric epilepsy. The FDA has granted the investigational drug orphan drug designation for treatment in Dravet and Lennox-Gastaut syndromes and granted it

intermediate expanded access (EA) as an Investigational New Drug [90]. Recent results of observation trials have been presented at the 2015 American Epilepsy Society annual meeting [91]. Twenty-three patients with treatment-resistant epilepsies (average age of 10 years) demonstrated that 39 % of patients had a greater than 50 % reduction in seizures, with a median reduction of 32 % after 3 months of therapy. Seizure freedom occurred in 3 of 9 Dravet patients and 1 of 14 patients with other forms of epilepsy. Adverse effects were mostly mild or moderate and included somnolence, fatigue, AED level increases, decreased appetite, weight gain, diarrhea, increased appetite, and weight loss. The investigators also found that a subset of patients experienced an increase in clobazam concentrations that was thought to be causing sedation and required a dose adjustment.

The use of CBD may have some benefits for treatment of epilepsy, but emphasis needs to be on rigorous RCT clinical trials to evaluate efficacy, along with safety and harm. Federal changes in scheduled classification and/or research regulations surrounding use of medical marijuana would improve ability to study marijuana and cannabinoids, not just CBD in epilepsy. Federal restrictions create barriers and hurdles for investigators' ability to perform well-designed research, especially at academic institutions, regardless of state legal status. Caution should be used with CBD oils for treatment of pediatric epilepsy. Many manufacturers make false claims on treatment and indications. The long-term impact of cannabinoids on a young child's brain has not been addressed. None of the products have been FDA approved and have not undergone rigorous testing for content and purification. Specific contents may be inaccurate, including cases where CBD was not found in products at all [92]. Proper dosing has not been adequately established for efficacy, and the side effects of use have not been determined. Although it has been praised as a natural remedy, lack of oversight and regulation may lead to contamination with pesticides and heavy metals [93]. There are also concerns for known and unknown drug interactions with current anticonvulsant medications which may lead to dangerous adverse drug events or poor control of epilepsy [94]. Furthermore, caregivers may adjust or change their own medication regimen without recommendations from a neurologist, which can have dangerous consequences for a patient's seizure control. The potential health benefits of cannabidiol, specifically in epilepsy, need to be explored. However, similar to any FDA-approved drug, it should be carefully studied evaluating all the potential benefits and risks and should not be treated as a panacea for epilepsy.

Conclusions

Marijuana can potentially affect pediatric patients from in utero to adolescence, and medicinal use has been increasing. Regardless of the stage or reason of exposure, concerns exist about both short-term and long-term consequences on a child's

physical and mental health. As more states legalize both medical and recreational marijuana, availability and prevalence of use will likely increase. More research needs to be performed to evaluate the health impact on the pediatric population. Existing studies may not have generalizable conclusions due to changes in marijuana potency and use patterns. Discrepancies between federal and state regulations create barriers to performing well-designed research on health outcomes. Going forward, the medical community must continue to monitor the potential health effects of marijuana and the potential unintended consequences and impact on the pediatric population.

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Compliance with Ethical Standards

Conflicts of Interest None

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