



Published in final edited form as:

*Adolesc Psychiatry (Hilversum)*. 2021 ; 11(2): 95–116. doi:10.2174/2210676611666210616163340.

## Marijuana Legalization in Colorado: Increasing Potency, Changing Risk Perceptions, and Emerging Public Health Concerns for Youth

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### Abstract

**Background:** Marijuana legalization occurred gradually in Colorado through political processes.

**Objectives:** This review aimed at describing the history of marijuana legalization and correlated shifts in product availability, use patterns, and risk perceptions and describes associated emerging concerns with this process for adolescents and young adults.

**Methods:** This review focuses on the history of marijuana legalization and correlated shifts in product availability, use patterns, and risk perceptions.

**Results:** Along with the legalization of marijuana, there has been strong commercialization characterized by the widespread development of dispensaries, new products including edibles and concentrates, and an overall lowering of the “price per serving” of marijuana. While the frequency of marijuana use among adolescents does not appear to have shifted substantially, young adult patterns of use have demonstrated an increase in usage. A substantial shift has occurred in the increasing use of concentrates and high potency products. Emerging concerns related to high potency products include increased acute care visits, prevalence and outcomes of comorbid mental health disorders, cannabis-induced psychosis, driving while high, marijuana-related lung injuries, and increased use during pregnancy. Yet, there are also potential medical uses of marijuana.

**Conclusion:** To date, scientific evidence of the mental or physical effects of high potency products is currently very limited. Clinical issues related to the treatment of marijuana use and comorbid psychiatric disorders in youth are discussed with a focus on how low risk perceptions influence treatment considerations.

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### CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

## Keywords

Marijuana; cannabis;  $\Delta$ -9-tetrahydrocannabinol; adolescent; young adult; marijuana legalization; cannabis-induced psychosis; E-cigarette and vaping associated lung injury (EVALI)

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## 1. INTRODUCTION

Marijuana legalization in Colorado occurred through a process of gradual liberalization and relaxation of marijuana policies. In 2000, Colorado legalized medical marijuana and required a physician recommendation (Hopfer, 2014). During 2009, the Department of Justice released the Ogden Memo, deferring enforcement of federal bans on marijuana in legalized states (Ogden, 2009). Over the next two years, the number of individuals with a physician referral for medical marijuana increased 30-fold (Salomonsen-Sautel et al., 2014). In 2012, Colorado legalized recreational marijuana, and recreational sales began in January 2014. Since 2009, the federal government has continued with its policy of “non-interference” and the state’s marijuana industry has continued to expand.

While states continue to expand the liberalization of marijuana policy, policy changes have occurred well ahead of scientific evidence addressing safety and risk or potential medicinal uses (Carnevale, 2018). The paucity of evidentiary guidance likely contributes to many parent’s and provider’s discomfort in talking to adolescents about the consequences and health effects of marijuana use (Brooks et al., 2017; Bull et al., 2017). Consequently, the challenge facing clinicians and researchers is to develop scientifically based responses and provide evidence to guide future policy and regulation.

Recently, a body of literature has started to emerge that explores the impact of marijuana policy liberalization and highlights emerging public health concerns. Herein, we will review the status of marijuana availability in Colorado. Next, we will review the prevalence of marijuana use among adolescents and young adults and changes in modes of use and risk perceptions. We will then explore emerging public health considerations, including acute health care (emergency department) contacts, comorbid mental health disorders including cannabis-induced psychosis, marijuana-related lung injuries, use during pregnancy, and potential medicinal uses. Finally, we will discuss the treatment implications of marijuana legalization for comorbid mental health and other substance use disorders. A review of the evidence will highlight a continuance of changes in availability and behavior regarding marijuana use that outpace research and outline public health concerns that require further study.

## 2. MARIJUANA PRODUCTS AND SALES IN COLORADO

### 2.1. Widespread Availability of Dispensaries

As of April 1<sup>st</sup>, 2020 Colorado lists a total of 1,686 businesses with marijuana licenses that employ 40,257 individuals (Colorado Department of Revenue, 2020a). Of those, 582 cultivators and 587 stores are licensed to produce and sell recreational marijuana. While direct advertising to minors is banned by Colorado law, the majority of dispensaries maintain an online presence with minimal age verification requirements (Bierut et al., 2017).

Of dispensaries surveyed by Bierut *et al.*, only 5% required users to enter their birthdate and 54% required the user to click “yes” to verify age. Several dispensaries also maintain profiles on social media platforms, with young adults aged 20-29 years old being the most common demographic and 15% of followers being younger than 20 years old.

While cannabis use is categorized as medical or recreational, products generally are not exclusive to a category. Recreational use is more frequent, and the vast majority of medical users also report recreational cannabis use (Pacula *et al.*, 2016). Additionally, Salomonsen-Sautel *et al.*, identified substantial diversion of marijuana from registered medical users to 74% of adolescents entering substance use treatment (Salomonsen-Sautel *et al.*, 2012). Adolescents who reported medical marijuana diversion were more likely also to report very easy availability, no friend disapproval of regular cannabis use, and use of cannabis at least 20 times per month in the past year (Thurstone *et al.*, 2011). Thus, classification as medical or recreational is primarily a legal designation authorizing dispensary sales of marijuana.

Implementation of dispensaries, rather than dichotomous indicators of marijuana laws, are positively associated with recreational marijuana use and abuse among adolescents and young adults (Pacula *et al.*, 2015). In the first year of commercialization of marijuana sales, perceived ease of access among high school students increased significantly from 46.5% to 52.1% (Healthy Kids Colorado Survey, HKCS,  $p < 0.0001$ ) (Harpin *et al.*, 2018). Further, commercialization may be a primary contributing factor for decreasing perceived harm from marijuana use (Brooks-Russell *et al.*, 2019), increasing  $\Delta^9$ -tetrahydrocannabinol (THC) potency (Sevigny *et al.*, 2014), and marijuana-involved driving and motor vehicle fatalities (Aydelotte *et al.*, 2019).

## 2.2. Increased THC Potency

Over the past two decades, THC potency, THC:cannabidiol (CBD) ratio, and products and modes of use have changed significantly (Chandra *et al.*, 2019; Mehmedic *et al.*, 2010; Smart *et al.*, 2017; Wilson *et al.*, 2019). Marijuana preparations confiscated in the United States showed an increasing trend of THC concentration from 3.4% in 1993 to 8.8% in 2008 (Mehmedic *et al.*, 2010) and 17.7% by 2017 (Chandra *et al.*, 2019). Concentrates have also shown a sharp increase in THC concentration, from a mean concentration of 6.7% in 2008 to 55.7% in 2017 (Chandra *et al.*, 2019). Wax or shatter is one form of concentrates that has increased in prevalence. Wax is solidified, highly concentrated THC formulations that are used by dabbing, the flash vaporization of the concentrate by applying it to a hot surface. In states with legalized recreational marijuana use, average THC concentrations are likely higher than these national samples, and commercialization of dispensaries may have the most significant impact on increasing THC potency (Sevigny *et al.*, 2014). In one survey of products in Washington state in 2016, the average THC concentration was 20.6% in flower-based products and 68.7% in extracts (Smart *et al.*, 2017). In Colorado, sampled concentrates as part of the state’s monitoring system routinely have THC concentrations as high as 90-95% (Orens *et al.*, 2015).

Similar to the national trend, concentrates have increased in market share from 11.6% in 2014 to 23.4% by 2017 (Orens *et al.*, 2018). In response to nonlethal overdoses from ingestion of edibles, Colorado implemented guidelines for THC dose equivalent per serving

(10 mg) and packaging. Table 1 presents the average potency and 1-ounce marijuana equivalent for bud or flower, edibles, and concentrates in Colorado in 2015 (Orens et al., 2015).

### 2.3. Increased Sales and Decreased Price Per Serving

Once marijuana became legal for recreational consumption, tracking the number of legal marijuana users became more complicated as individuals were no longer being registered unless they had medical marijuana cards. Tax revenue from marijuana sales has shown a steady increase since 2014. Table 2 below presents the year-by-year increase in Colorado marijuana tax and fee revenue (Colorado Department of Revenue, 2020b).

An analysis of the Colorado marijuana market conducted in 2017 revealed a steady decrease in the “price-per-serving” of marijuana since recreational legalization in 2014 (Orens et al., 2018). The average cost of a 57.1 mg serving of inhaled THC from adult use flower decreased 50.8%, from \$3.68 in 2014 to \$1.81 in 2017. A serving of THC from medical flower decreased 40% from a 2014 average of \$1.79 to \$1.11 in 2017. In both cases, the rate of decline in price-per-serving outpaced the price-per-gram declines due to a combination of falling flower prices and increasing potency from 2014 through 2017. The cost of a serving of THC from concentrated extract products exhibited the largest decrease of all marijuana products in both markets. The average price of a serving of THC from concentrates fell 61.7%, from \$4.70 in 2014 to \$1.80 in 2017, while a serving from medical concentrates fell 57.0%, from \$3.28 in 2014 to \$1.41 in 2017.

### 2.4. Prevalence of Marijuana Use in Adolescents and Young Adults

Analysis of Monitoring the Future, a biennial survey of substance use among 8<sup>th</sup>, 10<sup>th</sup>, and 12<sup>th</sup> grade students, found that states with legalized medical marijuana have a higher prevalence of adolescent marijuana use compared with states where marijuana is not legal (15.87% vs 13.27%, OR 1.27, 95% CI 1.07-1.51, p=0.0057; Hasin, Wall, et al., 2015; Sarvet et al., 2018). Comparing Colorado with neighboring states in the West region using the National Survey on Drug Use and Health ( Substance Abuse and Mental Health Services Administration, 2018), higher rates of past year (Fig. 1) and past 30-day (Fig. 2) marijuana use are observed among Colorado adolescents and young adults. While the prevalence of marijuana use has remained relatively steady among adolescents, a significant increase has been observed in both the past year and past 30-day use among young adults. The prevalence of daily or almost daily users is also higher among Colorado adolescents, compared with the national average (Jones et al., 2018). Of note, 20% of marijuana users may account for up to 80% of consumption by some estimates (Vogel, 2018).

The Colorado Department of Public Health and Environment (CDPHE) conducts the HKCS, a survey of high school students biennially. While the survey has been impacted by lower-than-expected response rates in the past two editions, age of first use has remained steady since 2013, with 82.1% first using cannabis before age 16 years (Ghosh et al., 2017). Since legalization of recreational marijuana, the prevalence of past 30-day use of marijuana has remained essentially steady, whereas past 30-day use of alcohol, tobacco cigarettes, and prescription drugs have continued to decline. The highest rates of past

30-day marijuana use have been reported among young adults (18-25 years, 26.1%) and high school juniors and seniors (26.3% and 27.8%, respectively). Groups with a higher prevalence of past 30-day marijuana use include adolescents who identified as gay, lesbian, or bisexual (30.9% vs 18.2% for heterosexual peers), adolescents of multiple races (27.1%), and Native Hawaiian/Pacific Islander adolescents (23.1%). Other characteristics associated with a higher prevalence of past 30-day use include male gender, older age, lower perceived harmfulness or wrongfulness, earlier age of initiation ( < 13 years old), and current cigarette or alcohol use (Johnson et al., 2016). While legalization of medical or recreational marijuana use has not been associated with further increases in the prevalence of adolescent marijuana use ( Colorado Department of Public Health and Environment, 2018; Cerda et al., 2017; Jones et al., 2018), significantly higher rates of adolescent marijuana abuse/dependence after legalization of medical marijuana have been reported (Schuermeyer et al., 2014).

## 2.5. Modes of Use: Increase in Rates of Dabbing and Ingesting Edibles

The modes of use of marijuana have also changed over the past decade. Adolescents who consume marijuana by more than one mode tend to combine smoking with other high potency products, including ingesting, vaporizing, and/or dabbing (Schneider et al., 2019). Male high school students are more likely to report vaping, dabbing, and ingesting edibles compared to females (Tormohlen, Brooks-Russell, Ma et al., 2019). Of adolescents who responded to the 2017 HKCS, 35.6% reported ingesting edibles, 34.4% reported dabbing, and 20.3% reported vaping. Over the preceding two years, dabbing (7.6%) and ingesting edibles (9.8%) as the usual method of use increased significantly (from 4.3% and 2.1%, respectively) to their highest level (Colorado Department of Public Health and Environment, 2018). Ingesting edibles was more common among youth who accessed marijuana at a public event or school (Johnson et al., 2016).

The HKCS found the prevalence of vaping remained essentially stable from 2015-2017 (Tormohlen, Schneider, Johnson et al., 2019). The prevalence of vaping increases with age, up to three-fold higher among 12<sup>th</sup> graders compared to 9<sup>th</sup> graders, and it is highest among Asian and White adolescents (Johnson et al., 2016). A higher prevalence of vaping was also associated with the diversion of medical marijuana (OR 3.4, 95% CI 2.0-5.6).

## 2.6. Changing Risk Perceptions

Overall, there has been a significant decrease in adolescent perceptions of harm from marijuana use (Schuermeyer et al., 2014). Colorado adolescents and young adults were less likely to feel adults disapprove of smoking marijuana once or twice a week or to feel smoking marijuana once or twice a week presented a great health risk (Schuermeyer et al., 2014). While the change in perceived risk, and the significance of the change, differ by age and study sample (Cerda et al., 2017; Harpin et al., 2018), some important findings have been reported. First, because marijuana is often described as “natural” and medical uses are often touted, many adolescents and young adults view it as less harmful and less addictive than other drugs and medications, including antidepressants, anxiolytics, and opioid pain medications (Popova et al., 2017). Of licensed retailers surveyed by Bierut *et al.*, the majority made health claims regarding marijuana use (Bierut et al., 2017). Common conditions cited include anxiety, cancer, depression, diabetes, insomnia, pain, post-traumatic

stress disorder, and skin irritation. Conversely, none of the retail stores listed harmful or adverse effects of cannabis use.

Concerning signs and symptoms of cannabis use disorder, individuals often identify emotional or mental dependence on marijuana and habitual urges to use (Popova et al., 2017). In a study of perceived harm, Popova et al. found respondents described physiologic changes due to use, though they generally did not identify tolerance as signs of addiction or report withdrawal symptoms. Of concern, multiple respondents discussed using higher potency products to overcome tolerance to achieve getting high.

Second, there may be changing perceptions regarding the risks of combustible marijuana products compared to higher potency products. In the 2015 HKCS survey, adolescents who reported higher perceived parental disapproval, wrongfulness, or harm from marijuana use were less likely to consume marijuana by modes other than smoking (Tormohlen, Brooks-Russell, Ma et al., 2019). Conversely, in the 2013 HKCS survey, Johnson et al., found that higher perceived harmfulness was associated with an increased likelihood of ingesting edibles or vaping, whereas lower perceived harmfulness is associated with smoking (Johnson et al., 2016). Adolescents who reported high perceived wrongfulness of marijuana use were also less likely to vape. The differences between the 2013 and 2015 surveys may in part highlight changing perceptions regarding the risk of combustible marijuana products. Similarly, a survey of young adults aged 18-26 years old found that combustible products were perceived as more dangerous than vaporizers and edibles (Popova et al., 2017). The risk of unintentional overdose with these higher potency products was also perceived to be lower than the health risks of using a combustible product.

### 3. PUBLIC HEALTH CONSIDERATIONS

#### 3.1. Increase in Unintentional Pediatric Exposures

Legalization of marijuana in Colorado has been associated with increases in marijuana-related regional poison center (RPC) calls, ED or urgent care visits, and hospitalizations for all age groups (Wang et al., 2017). Per the Colorado Hospital Association, ED visits and hospitalizations with marijuana poisoning billing codes have continued to rise since legalization (20.8 per 100,000 hospitalizations and 20.3 per 100,000 ED visits in 2017) (Colorado Department of Public Health and Environment, 2018). The greatest increase in the number of unintentional marijuana exposures was observed in children less than 9 years old (Wang et al., 2017). By 2017, calls to the regional poison control center due to unintentional exposure in children 0-8 years old increased 10-fold, after having remained steady for the preceding decade (Wang et al., 2020; Wang et al., 2014). The majority (60-74%) of these children were subsequently seen by health care professionals, with an overall admission rate of 16% (Wang, 2017; Wang et al., 2014). When compared to non-legal states, exposures in legal states led to more major effects (OR 2.1, 95% CI 1.4-3.1) and critical care admissions (OR 3.4, 95% CI 1.8-6.5; (Wang, 2017). Edible marijuana products accounted for 65.6% of exposures, followed by smokable products at 23.4% (Wang, 2017). The most common sources of THC ingested by minors include cookies, brownies, cake, popcorn, gummies, tootsie rolls, and other edible products (Heizer et al., 2018).



To date, little is known about risks from passive exposure to second-hand smoke, though many carcinogens common to cigarette smoke have been identified (Lee et al., 1976a, 1976b; Moir et al., 2008). Yet, a significant number of children who live in a home where marijuana is smoked daily within the home have detectable levels of THC or its metabolites (Wilson et al., 2018).

### 3.2. Adolescent and Young Adult Acute Health Care Contacts

Adolescents and young adults have experienced significant increases in intentional exposures resulting in acute medical care (Wang et al., 2017). The annual rate of marijuana-related ED and urgent care visits for adolescents aged 13-20 years old increased from 1.8 per 1,000 visits in 2005 to 4.9 per 1,000 visits in 2015 (Wang et al., 2018). According to Colorado Hospital Association data, in the past year, ED visits were highest among young adults aged 18-25 years old (2,352 per 100,000 ED visits) and hospitalizations with marijuana-related billing codes remain the highest among youth aged 9-17 years old (7,974 per 100,000 hospitalizations; (Colorado Department of Public Health and Environment, 2018). Higher rates of ED visits and hospitalizations have been reported in males and Black patients.

A recent study showed even regular and heavy users inaccurately estimate the amount of cannabis prepared or used (Prince et al., 2018). Not surprisingly, the number of ED visits related to cannabis use by out-of-state visitors rose sharply after commercialization of cannabis sales (Kim et al., 2016). In response to the risk posed by edible cannabis products, Colorado emergently introduced measures to reduce unintentional overdose, including limitations on the maximum THC content per package, demarcated servings, and universal symbols on packaging labels (Ghosh et al., 2017; Vogel, 2018). Over the time period of legalization of recreational cannabis use and commercialization of cannabis sales, a flattening of the curve in the prevalence of Colorado residents presenting to the ED for cannabis-related problems was observed, suggesting a learning curve initially during more widely available cannabis use and change in product potency (Kim et al., 2016).

### 3.3. Comorbid Mental Health Disorders

A review of the Colorado Hospital Association ED discharge data showed a five-fold higher prevalence of mental health diagnoses in marijuana-associated ED visits compared to visits without marijuana between 2012-2014 (Hall et al., 2018). The most prevalent disorders were mood (6.78%) and anxiety (3.82%) disorders, followed by schizophrenia spectrum disorders (2.96%) and suicide or intentional self-inflicted injury (2.79%). Of note, the prevalence ratio of schizophrenia spectrum disorders was 9.18 (95% CI 8.66-9.75) and of suicide or intentional self-inflicted injury was 7.96 (95% CI 7.49-8.46) compared to ED visits without marijuana codes. A review of tertiary care ED and urgent care visits at a Colorado children's hospital system from 2005-2015 found 4,202 episodes of care (Wang et al., 2018). Sixty-two percent of patients were diagnosed with cannabis use, abuse, or misuse. Additionally, 71% received a comorbid psychiatric diagnosis, with the most common being depression (39%) or mood disorder (22%). Twelve percent had co-ingested ethanol, with other substances reported in 4% or fewer visits.

Overall, cross-sectional studies have shown one-third of adolescents with a substance use disorder meet the criteria for a comorbid psychiatric disorder, with up to 80% of adolescents entering substance use treatment having significant psychiatric symptoms (Robinson & Riggs, 2016). Adolescent marijuana use is associated with depression and anxiety disorders, as well as earlier onset of mania or psychosis (reviewed in Levine et al., 2017). Marijuana use is also associated with a higher risk of suicidal ideation (OR 1.50, 95% CI 1.11-2.03) and suicide attempt (OR 3.46, 95% CI 1.53-7.84) (Gobbi et al., 2019).

Comorbid cannabis use disorder and psychiatric disorders also have poorer treatment outcomes, increased treatment dropout, and earlier time to relapse for substance use (Cornelius et al., 2004; Hersh et al., 2013; White et al., 2004). Further, high-potency THC concentrates may also be associated with poorer mental health outcomes and higher use of illicit substances (Chan et al., 2017), though one other study did not find significant differences in mental health outcomes (Prince & Conner, 2019). While multiple associations between marijuana use and mental health have been established, there are notable overlapping factors, including poor parental monitoring, early childhood loss and family disruption, and trauma and multiple shared neurophysiologic changes (Brady & Sinha, 2005; Kendler et al., 2003; Libby et al., 2005; Volkow, 2004).

### 3.4. Cannabis-induced Psychosis

Of particular concern among comorbid psychiatric disorders is the increased risk of early onset schizophrenia and cannabis-induced psychosis. Prior to legalization of medical marijuana, a case series reported a temporal association between marijuana use and psychosis (Clark, 1994), now referred to as cannabis-induced psychosis (Hudak et al., 2015; Rolland et al., 2013). The prevalence of cannabis-induced psychosis is unknown. However, the majority of those who use marijuana do not develop signs or symptoms of psychosis. It seems individuals with the highest vulnerability to cannabis-induced psychosis are those with a familial risk for psychosis or schizophrenia (Hiemstra et al., 2018; Kendler et al., 2019). Primary risk factors may be high THC potency, duration of use, and initiation of marijuana use at a younger age (Di Forti et al., 2015; Di Forti et al., 2009; Di Forti et al., 2014; Keller et al., 2016; Large & Nielsens, 2017; Murray et al., 2016; Pierre, 2017; Pierre et al., 2016; Rabin & George, 2017). Further, adolescent initiation of marijuana use is associated with early onset psychotic disorder in a dose-dependent fashion and associated with poorer course of illness and functional outcomes (reviewed in Bagot et al., 2015). Neuroimaging findings suggest early use of marijuana may alter cortical maturation in susceptible adolescents (French et al., 2015), though the underlying mechanism of cannabis-induced psychosis is unknown.

### 3.5. Increase in Driving While High and Marijuana-related Motor Vehicle Fatalities

Overall, the percent of adolescents riding in a vehicle driven by someone who had been using marijuana or driving when they had been using has remained steady from 2011 (21.7%) to 2017 (19.7%) (Colorado Department of Public Health and Environment, 2018). While studies show individuals drive at slower speeds when high, a counterpoint often cited by the marijuana industry, such driving may also represent a danger on the highway (Vogel, 2018). Marijuana use affects multiple tasks important to driving safety, including attention,



reaction time, and motor skills and has been shown to result in increases in lateral position deviation and slower driving (reviewed in Aydelotte et al., 2019). In adolescents, recent marijuana use, including less-than-weekly use, is associated with increased impairment and risk of motor vehicle collisions (MVC) (Colorado Department of Public Health and Environment, 2018). Driver impairment has been demonstrated at blood THC levels as low as 2-5 ng/mL or after orally ingesting more than 10 mg of THC. The estimated impact of driving impairment is up to 6 hours for smoking and 8 hours for ingesting up to 18 mg of THC.

One key factor associated with increasing rates of marijuana-related driving incidents and fatalities may be the commercialization of recreational marijuana sales (Aydelotte et al., 2017; Aydelotte et al., 2019). Medical marijuana laws have been associated with up to a doubling of the prevalence of driving while under the influence of marijuana by 2013 (Fink et al., 2020). Yet, following the legalization of recreational marijuana use, the proportion of drivers in fatal motor vehicle crashes who were THC-positive in Colorado was decreasing (Salomonsen-Sautel et al., 2014), which may be attributed to increased enforcement efforts (Sevigny, 2018). Following the commercialization of recreational marijuana sales, however, the number of driving under the influence (DUI) citations where marijuana was reported as the impairing substance increased by 16% between 2014 and the first 10 months of 2016 (Ghosh et al., 2017). Simultaneously, there was an increasing trend in proportion of marijuana-positive drivers in fatal MVC and an 80% increase in fatalities that tested positive for marijuana (Salomonsen-Sautel et al., 2014). Analysis of MVC fatalities found an increase of 0.8 fatalities per billion vehicle miles traveled after legalization of recreational marijuana use and an increase of 1.3 fatalities per billion vehicle miles traveled when comparing MVC in the period between legalization and commercialization with MVC after commercialization (Aydelotte et al., 2019).

### 3.6. Marijuana-related Lung Injuries

Recently, there has been increasing concern about marijuana-related pulmonary injuries. The most common marijuana-related pulmonary injuries are bronchospasms, pneumothorax, and aspergillus infection (McGraw et al., 2018). Acute and chronic pulmonary injuries in adolescents and young adults have been associated with contaminated marijuana products, including talcum (Scheel et al., 2012), formaldehyde and phencyclidine (Gilbert et al., 2013), and other chemicals (Moatemri et al., 2016). Three cases of an adolescent male with eosinophilic pneumonia with silica-induced pneumoconiosis and acute hypersensitivity pneumonitis associated with recent cannabis inhalation were reported in Colorado in 2018 (McGraw et al., 2018). In 2019, a multistate outbreak of electronic cigarette or vaping product-use associated lung injury (EVALI) cases was reported, with 805 cases and 12 deaths reported to the Centers for Disease Control (CDC) through September 2019 (Perrine et al., 2019; Schier et al., 2019). Seventy-seven percent of patients reported using THC-containing products in the 30 days preceding the onset of symptoms. Over half of patients were younger than 25 years old (54.2%), and 23.9% of patients were 25-34 years old. EVALI cases were reported in previously healthy individuals and resulted in acute lung injuries, often necessitating intubation or intensive care admissions (Civiletto et al., 2020; Perrine et al., 2019; Schier et al., 2019). Subsequent analyses of recovered cartridges

implicated vitamin E acetate, a diluent used in some cannabis oil products (Duffy et al., 2020). Other cases of marijuana-related lung injury have been reported, including exogenous lipoid pneumonia or chemical pneumonitis (Gay et al., 2020), acute lung injury mimicking atypical pneumonia (Stephens et al., 2020), and diffuse alveolar hemorrhage (Alqahtani et al., 2019).

### 3.7. Increased Use During Pregnancy

Marijuana use before pregnancy (15.2%), during pregnancy (7.8%), and while breastfeeding (4.4%) trended upward from 2014-2018 (Colorado Department of Public Health and Environment, 2018). The American College of Obstetricians and Gynecologists strongly recommend against the use of marijuana during pregnancy or lactation (Committee on Obstetric Practice, 2017). Yet, of Colorado dispensaries surveyed by Dickson et al., 69% recommended marijuana products for the treatment of morning sickness (Dickson et al., 2018). Marijuana use during pregnancy is highest among younger moms aged 15-19 years (13.3%) and 20-24 years (12.3%) compared with moms that are 25-34 years or older than 34 years (5.3% and 3.4%, respectively). Marijuana use is also higher among women with unintended pregnancies compared to women with intended pregnancies (10.4% vs 4.1%). THC rapidly crosses the placenta, with cord blood THC levels measured three to six times lower than that found in maternal blood (Blackard & Tennes, 1984). There is a greater transfer of THC early in pregnancy, at a time when the fetus may be most vulnerable to the neurodevelopmental consequences of exposure and some women may not know they are pregnant. THC also concentrates in breast milk (Atkinson et al., 1988; Perez-Reyes & Wall, 1982), though the degree to which and how long after cessation of use has yet to be determined.

The endocannabinoid system, through which THC exerts its effects, is present in the fetus as early as 16-22 days gestation and is fundamental to neurodevelopment (Campolongo et al., 2011; American College of Obstetrics and Gynecology, 2017; Szutorisz et al., 2014; Volkow et al., 2017). The effects of exogenous cannabinoids on neurodevelopment have not been well-characterized, yet it is of great concern. Human studies of prenatal marijuana exposure have also raised concerns for lower birth weight, smaller head circumference, and higher stillbirth rate (Campolongo et al., 2011; American College of Obstetrics and Gynecology, 2017; Volkow et al., 2017). Children exposed *in utero* also exhibit cognitive and behavioral deficits, impairments in executive functioning, lower processing speed and visual problem solving, and increased impulsivity and externalizing behaviors (Goldschmidt et al., 2012; Szutorisz et al., 2014). It is important to note there are multiple confounders in studying prenatal marijuana exposure, including comorbid use of alcohol or tobacco and demographic, social, and psychological factors among participants most likely to participate in these studies.

## 4. POTENTIAL MEDICAL USES OF CANNABIS

In addition to the recreational market, a growing number of Americans use marijuana for medicinal purposes (Hasin, Saha, et al., 2015; Substance Abuse and Mental Health Services Administration, 2017). In Colorado, the most common medical condition cited for

medical marijuana referrals is severe pain, with the exception of children younger than 11 (seizures). As of March 2020, there were 21,400 registered adolescents and young adults with medical marijuana referrals (Table 3). A medical evaluation and registration with the state is mandatory for a medical marijuana referral, though no ongoing monitoring or counseling is required.

A recent National Academy of Sciences, Engineering, and Medicine review reported marijuana affects a wide range of organ systems, including the central nervous system, gastrointestinal system, and immune system, among others (Maccarrone et al., 2015; National Academies of Science, 2017). Marijuana has been implicated in chronic illnesses, including bronchitis, cardiovascular disease, some cancers, metabolic syndrome, and psychiatric illness (National Academies of Science, 2017; Volkow et al., 2014). However, there is also preliminary evidence it may be efficacious for other medical conditions. Relatively small controlled trials of marijuana or cannabinoid derivatives in patients have shown potential efficacy for appetite regulation, muscle spasticity, nausea, pain, and seizures (Ben Amar, 2006; Watson et al., 2000). Animal studies investigating anti-inflammatory properties of cannabinoids suggest they may also be efficacious for some inflammatory diseases, including the gastrointestinal tract (Esposito et al., 2013; Nagarkatti et al., 2009). To date, the FDA has approved two pharmaceutical-grade forms of CBD (Epidiolex) for seizures associated with Lennox-Gastaut or Dravet syndromes and THC (Marinol and Syndros) for anorexia associated with AIDS (Food and Drug Administration, 2020). The use of marijuana or plant-derived products has not been federally approved.

Proponents of medical marijuana legalization often suggest a substitution effect with opioids that might result in fewer opioid related deaths in medical marijuana states. However, a recent review identified a non-significant reduction compared with states where marijuana is not legal, including a modest reduction of 7% in opioid overdose mortality and 6% reduction in opioid prescriptions among Colorado Medicaid and managed care enrollees (Chihuri & Li, 2019).

## 5. TREATMENT IMPLICATIONS OF MARIJUANA LEGALIZATION

The adolescent and young adult treatment implications of marijuana legalization for psychiatry can be divided into a number of areas: 1) the treatment of cannabis use disorder, 2) the treatment of other substance use or psychiatric conditions where marijuana use may be worsening or exacerbating the condition but the patient does not wish to discontinue use, and 3) the situations where the patient reports that marijuana use has beneficial/medicinal effects and requests a medical marijuana referral or the provider's approval for continued use.

The greatest area of scientific consensus for marijuana use is that it is harmful for adolescents, particularly in domains of cognitive functioning, the development of psychosis, and effects on long-term social adjustment (Volkow et al., 2016). For young adults, there is a broad literature that associates marijuana use with a range of negative psychosocial outcomes; however, whether marijuana is a cause of these psychosocial outcomes or a marker for other associated conditions remains unclear. However, the "medical" legal status

for marijuana is unusual and creates unique perception and status issues for marijuana compared to other substances. Despite tobacco use being associated with weight loss (Audrain-McGovern & Benowitz, 2011) and alcohol having some anxiolytic properties (Gilman et al., 2008), neither have a general sense of medical approval nor legal status as medicinal.

Similar to the treatment of alcohol use disorder in adults, the treatment of cannabis use disorder under the conditions of legalization remains fairly straightforward, with marijuana identified as the “problem substance.” Cannabis use disorder is primarily addressed with psychosocial treatments such as motivational interviewing, contingency management, and cognitive behavioral therapy. For cannabis use disorder, the primary decision to be made is whether a “harm reduction” or “abstinence” model is the primary treatment goal (Potter et al., 2019; Stockings et al., 2016). As abstinence models typically apply to the use of any substance, marijuana use is incompatible with this treatment model. Harm reduction treatment plans may focus on reduction in the amount or frequency of use and identifying how the substance is influencing the patient’s functioning.

In adolescents with comorbid psychiatric disorders, cannabis use disorder should be treated in an integrated fashion due to the interaction between disorders (Hinckley & Riggs, 2019). Recently, Arias *et al.*, demonstrated a relationship between decreasing cannabis use and decreasing depression symptoms in adolescents receiving psychosocial intervention for cannabis use disorder (Arias et al., 2020). When considering pharmacotherapy, it is typically indicated only for comorbid conditions, such as depression or anxiety. Analysis of treatment outcomes of adolescents receiving outpatient motivational interviewing and cognitive behavioral therapy indicates overall treatment remains effective in a state with legalized cannabis (LeNoue et al., 2017). Few studies have investigated the efficacy and safety of psychopharmacologic agents in adolescents with cannabis use disorder (Cornelius et al., 2010; Hinckley & Riggs, 2019; Riggs et al., 2007; Winhusen et al., 2011).

There has been particular concern regarding comorbid ADHD and marijuana use. ADHD has been associated with increased use of marijuana and other substances through young adulthood, as well as more impairing symptoms of ADHD (Bidwell et al., 2014; Molina et al., 2018). Marijuana has been shown to cause neuropsychological impairment, including inattention. However, the interaction between marijuana use and ADHD remains unclear. Research suggests the relationship between childhood ADHD and later marijuana use may be due to shared familial environment and genetics rather than a causal relationship (Elkins et al., 2018). To date, few studies of medications for ADHD have included patients with comorbid substance use. One study of osmotic-release methylphenidate found it is generally well-tolerated in adolescents with substance use disorders (Riggs et al., 2011; Wilens & Upadhyaya, 2007), though its efficacy for ADHD is unclear. It is also unclear if medical stimulant use in comorbid ADHD may reduce the risk of substance use (Hammerness et al., 2017; Riggs et al., 2011). Inconsistent findings may be due to a tendency to underdose stimulants in those with substance use disorders (Skoglund et al., 2017). Further, pharmacologic treatment of ADHD does not appear to increase the risk for SUD (Wilens & Upadhyaya, 2007). While there is much we do not know, clinicians should decide they would consider prescribing controlled substances for ADHD with comorbid marijuana use

and if prescribing would be conditional upon concurrent substance use monitoring and/or treatment.

## 6. CONCLUSION

When patients seek a medical marijuana referral or provider approval to use marijuana, clinicians should have an established policy. While many youth report using marijuana to self-treat depression, anxiety, insomnia, or other mental health conditions, a recent meta-analysis found scarce evidence that pharmaceutical-grade cannabinoid products improve mental health disorders (Black et al., 2019). The American Psychiatric Association (APA) issued a position statement in opposition to the use of marijuana as medicine, citing the lack of scientific evidence supporting marijuana as medicine, that no medications are currently smoked, that dosages consumed are unclear, and that ballot initiatives should not form the basis for medical decision making (American Psychiatric Association, 2019). While the American Academy of Child and Adolescent Psychiatry (AACAP) has encouraged more scientific evaluation to determine whether there is a medical indication for marijuana in children and adolescents (American Academy of Child and Adolescent Psychiatry, 2012), the organization has issued statements opposing medical marijuana dispensing to adolescents and more recently opposing the use of marijuana in autism spectrum disorder (American Academy of Child and Adolescent Psychiatry 2019). Further, the American Academy of Pediatrics opposes medical marijuana outside of the regulatory process of the US Food and Drug Administration (American Academy of Pediatrics, 2015). Thus, institutions and providers should consider the risks and benefits of recommending marijuana for medicinal use to determine *a priori* guidelines.

## 7. FUTURE DIRECTIONS

In summary, while marijuana legalization has outpaced scientific research, recent studies highlight changing trends in the availability, potency, and modes of use, and risk perceptions and raise emerging public health concerns that warrant further investigation. Commercialization of marijuana in Colorado created an environment of increasing availability and increasing THC potency and decreasing price per serving. The acute and chronic effects of high potency THC exposure are unknown, as are differences in route of consumption. Yet, clinically, increased acute care encounters, cannabis-induced psychosis, EVALI and recent EVALI-related deaths, and the incidence of comorbid mental health conditions are of great public health concern. As potency increases and price decreases, higher doses of THC are more readily available to adolescents. Demand for marijuana, as with other intoxicating substances, is responsive to monetary price and legal risk (Aston et al., 2017; Hunt & Pacula, 2017; Pacula & Lundberg, 2014; Smart et al., 2017).

While it does not appear the prevalence of use has changed among adolescents, there is a paucity of baseline data prior to marijuana legalization, complicating pre- and post-legalization analyses (Ghosh et al., 2017). Further, studies differ in findings of use prevalence based on analysis and dataset (Dilley et al., 2019). It might also be that no post-legalization increase in prevalence was observed because public opinion and perceived acceptance and risk may have already shifted (Palamar et al., 2014), resulting in an

environment where legalization is feasible. Insufficient data provides a challenge to further elucidating the relationship between the evolution of social acceptance, legalization, and prevalence of use.

Further, it remains to be seen how changes in risk perception will affect prevalence and frequency of use, and it is unknown if changes in risk perception contribute to the increasing use of high-potency products among adolescents. However, individual and societal perceptions and beliefs do influence marijuana consumption patterns. As demonstrated by Popova *et al.*, combustible products and manufactured or chemically manipulated products are viewed as more harmful (Popova et al., 2017). It is likely that concerns about combustible and chemically manipulated products are driven by years of public health campaigns and knowledge about the risks of tobacco smoking. Thus, informed, evidence-based public health campaigns regarding marijuana use may be an effective tool for influencing marijuana use.

The impact of marijuana on mental health and other substance use disorders remains largely unknown. While associations between cannabis and psychosis have been demonstrated, a causal relationship is difficult to establish due to limitations of methodology and the prevalence of marijuana use in adolescents. Yet, marijuana use, as with other substance use, also leads to lower treatment compliance and more adverse outcomes in adolescents with mental health disorders. Further studies are also needed to understand the impact of marijuana legalization on the use of other substances, including alcohol, tobacco, and opioids.

In this first decade of marijuana legalization, policy and public opinion have outpaced, and even superseded science and public health. Emerging studies raise the concern that such an approach may have negatively impacted youth and the public. As outlined in this qualitative review, marijuana research, particularly with products consumed by the public, is in its nascency. As such, quantitative investigations are not yet feasible. Other reports that may be of interest and expand on the scope of data in this review include the NIDA National Advisory Council on Drug Abuse cannabis policy research recommendations (Carnevale, 2018), the National Academy of Sciences report (Maccarrone et al., 2015; National Academies of Science, 2017), and the Rocky Mountain High Intensity Drug Trafficking Area impact report (Rocky Mountain High Intensity Drug Trafficking Area, 2020). It is vital for the research and medical community to respond with evidence supported by research to address public health concerns and guide future policies and regulations. The outcomes of these studies are fundamental to evidence-based, public health awareness campaigns that will inform universal prevention strategies and selective interventions, as well as youth and parent education.

## ACKNOWLEDGEMENTS

Drs. Hinckley and Hopfer receive research funding from the National Institute on Drug Abuse, the Colorado Clinical Sciences and Translational Institute, and the University of Colorado Department of Psychiatry.



## LIST OF ABBREVIATIONS

<b>ADHD</b>	Attention deficit/hyperactivity disorder
<b>CBD</b>	Cannabidiol
<b>ED</b>	Emergency department
<b>EVALI</b>	e-cigarette and vaping related lung injury
<b>HKCS</b>	Healthy Kids Colorado Survey
<b>MVC</b>	Motor vehicle collision
<b>OR</b>	Odds ratio
<b>RPC</b>	Regional poison control center
<b>THC</b>	-9-tetrahydrocannabinol

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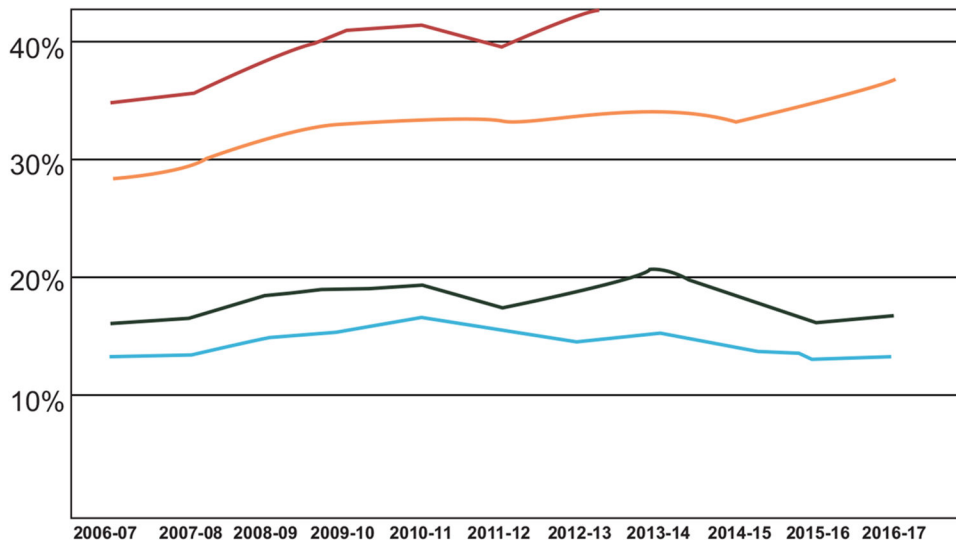
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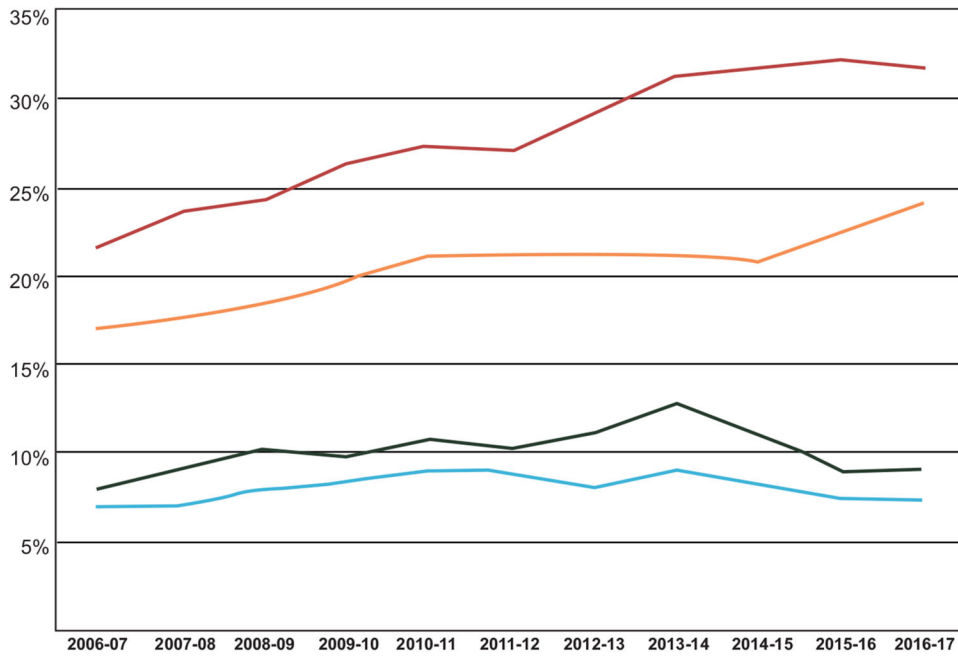
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**Fig. (1). Past year marijuana use in Colorado compared to the West region.** Prevalence of past year use of marijuana is presented by year from 2006-2017 by age group and state or region: 1) Colorado residents aged 18-25 years (red), 2) residents of other West region states aged 18-25 years (yellow), 3) Colorado residents aged 11-17 years (green), and 4) residents of other West region states aged 11-17 years (blue). (*A higher resolution / colour version of this figure is available in the electronic copy of the article.*)



**Fig. (2). Past 30-day marijuana use in Colorado compared to the West region.** Prevalence of past 30-day use of marijuana is presented by year from 2006-2017 by age group and state or region: 1) Colorado residents aged 18-25 years (red), 2) residents of other West region states aged 18-25 years (yellow), 3) Colorado residents aged 11-17 years (green), and 4) residents of other West region states aged 11-17 years (blue). (A higher resolution / colour version of this figure is available in the electronic copy of the article).

**Table 1.**

Marijuana products and dose equivalency.

Product	Average THC Potency	1-ounce Equivalent <sup>1</sup>	Mode of Use
Bud/flower	17.1%	1 ounce	Smoke
Edibles	Variable	83 10 mg servings	Ingest
Concentrates	62.1%	7.72 grams	Vaporize, dab

<sup>1</sup> Amount of product with THC equivalency of 1 ounce of bud/flower



**Table 2.**

Colorado revenue from marijuana taxes, licenses, and fees.

Calendar Year	Annual Revenue
2015	\$130,411,173
2016	\$193,604,810
2017	\$247,368,473
2018	\$266,529,637
2019	\$302,458,426

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**Table 3.**

Colorado medical marijuana referrals by age.

Age Group	Number (% of Total Registry)	Most Common Condition
11-17	168 (0.21%)	Severe pain
18-20	3,598 (4.40%)	Severe pain
21-30	17,634 (21.58%)	Severe pain