

Marijuana Regulation in Vermont

2017 Literature Review Update

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Executive Summary

The “Health Impact Assessment: Marijuana Regulation in Vermont” (HIA) was a comprehensive stakeholder process that included a literature review of research published between 2009 to August 2015. The stakeholders identified 180 articles that addressed the effects of marijuana use across several physical, mental, and social health domains. In an effort to update that review, the Health Department searched peer-reviewed research studies and literature reviews/meta-analyses published between August 2015 and January 2017 and identified an additional 180 articles pertinent to the topic.

This update to the HIA supports the conclusions from the original work: early and persistent use of marijuana can cause long-term adverse effects across several health domains. Of particular concern is the robust relationship between early use and the development of psychotic symptoms especially among those who consume very high potency marijuana. Most of the prospective longitudinal studies cited in this review began 20-30 years ago when marijuana potency (% of THC) was four to five times lower than it is today. The health effects of this significant increase in marijuana potency will not be known for years to come, but it is likely to amplify outcomes already established in current research. In addition, in January 2017 the Institute of Medicine of the National Academy of Sciences issued a report titled “Health Effects of Marijuana: An Evidence Review and Research Agenda.”¹ This report mirrors the conclusions of the original HIA literature review and this update.

¹ <http://nationalacademies.org/hmd/Reports/2017/health-effects-of-cannabis-and-cannabinoids.aspx>

This updated review of the scientific literature on the health effects of marijuana continues to underscore the harms associated with early and persistent marijuana use across several physical, mental, and social health domains. This is particularly evident in prospective longitudinal studies that track individuals over the course of many years, even decades.² These studies demonstrate significant harmful effects for individuals who start using marijuana in adolescence and continue use into young adulthood.

Background

In January, 2016, the Vermont Department of Health published the document “Health Impact Assessment: Marijuana Regulation in Vermont.” This document was the result of a full Health Impact Assessment (HIA) with a broad and expert stakeholder group. In addition to supplying recommendations, the HIA summarized the existing scientific literature on the potential benefits and harms of regulating marijuana in Vermont. The literature review examined over 180 peer reviewed research studies and literature reviews/meta-analyses that were relevant to the topic and were published before August 2015 when the search began. Since that time, the Health Department has identified an additional 180 articles published between August 2015 and December 2016 that relate to the health effects of marijuana.

The rapid increase in literature addressing the health effects of marijuana corresponds to recent changes in state laws allowing for legal adult use. At the time of the original HIA, Alaska, Oregon, Colorado, Washington, and the District of Columbia had passed laws making marijuana legally available for adults age 21 and older. In November 2016, California, Nevada, Maine, and Massachusetts legalized marijuana use by adults. The new research, however, is almost all based on data collected prior to legalization laws going into effect in these various states.

Federally, marijuana remains a Drug Enforcement Administration (DEA) Schedule I drug (substances or chemicals defined as drugs with no currently accepted medical use and a high potential for abuse) under the Controlled Substances Act (CSA). On August 11, 2016, the DEA reaffirmed the Schedule I status of marijuana. However, the Obama Administration did not pursue actions against states that legalized medical marijuana use and has applied this same standard to states that legalized marijuana for adult use.³

Recently the potency of marijuana products has increased, a development not factored into the studies begun many years ago.⁴ For example, in 1995 the proportion of Δ^9 -tetrahydrocannabinol (THC – the main psychoactive ingredient in marijuana) in DEA seized marijuana was 4%. In 2014, this had increased to 12%. In July, 2016, the average THC potency

² The largest United States study of brain development and child health was recently initiated. The Adolescent Brain Cognitive Development (ABCD) study is recruiting 10,000 children 9-10 years old from 21 sites across the country (including the University of Vermont) and will “track their biological and behavioral development through adolescence into young adulthood.” <http://www.abcdstudy.org/about.html>

³ <https://www.justice.gov/sites/default/files/opa/legacy/2009/10/19/medical-marijuana.pdf>

⁴ ElSohly et al. (2016). Changes in Cannabis Potency Over the Last Two Decades (1995-2014): Analysis of Current Data in the United States. *Biological Psychiatry*, 76, 613-619.

for one retailer in the Seattle, Washington area was 21.2%.⁵ The prospective longitudinal studies (studies that are most useful in determining long-term outcomes) began 20 to 40 years ago, meaning that the harmful effects chronicled by these longitudinal reports were a consequence of significantly lower marijuana potency than is currently available. It also means that the effect of higher potency marijuana use will not be known for many years.

Physical Health

There were several new studies published investigating the effects of marijuana on a variety of physical health issues.

Type 2 Diabetes Mellitus: Two studies demonstrated that marijuana use is unrelated to the development of this disorder (Sidney, 2016; Danielson et al., 2016).

Thyroid Function: One study showed no effect of lifetime or recent use of marijuana on thyroid function (Malhotra et al., 2016).

Sleep Disturbances: Three recent studies addressed sleep disturbance. One (Miller et al., 2016) suggested that poor sleep quality and less sleep duration predicted earlier age of onset of use of both marijuana and alcohol. The second (Angarita et al., 2016) suggested that chronic marijuana use, as well as other substances, is a major factor in poor sleep quality. The third (Maple et al., 2016) found “a dose dependent relationship between increased past-year cannabis use and greater past-month self-reported sleep problems” (p. 436). These studies refute anecdotal evidence that has promoted marijuana as a sleep aid (<http://www.leafscience.com/2013/11/25/5-ways-marijuana-affects-sleep/>).

Lung Function/Lung Disease: Three new studies confirm what has already been established. In a structured review, Ribeiro & Ind (2016) found increased forced vital capacity (bronchodilation) in marijuana users, but also an increase in bullous lung disease and emphysema that is confounded by concurrent tobacco use. Their review was inconclusive on the independent relationship between marijuana smoking and the development of lung cancer. Yayan & Rasche (2016) in their review found that marijuana use is linked to a compromised immune system, pneumonia, and bronchitis. They also conclude that the evidence linking marijuana smoking to lung cancer is inconclusive. The third review by Martinasek et al. (2016) suggests “The research indicates that there is a risk of lung cancer from inhalational marijuana as well as an association between inhalational marijuana and spontaneous pneumothorax [collapsed lung], bullous emphysema, or COPD [chronic obstructive pulmonary disease]” (p. 1543).

Ischemic Stroke/Subarachnoid Hemorrhage: Six new reports investigated the relationship between marijuana use and stroke particularly in young adult users. Rumalla et al. (2016a) found “among younger adults, recreational marijuana use is independently associated with [a] 17% increased likelihood of AIS [acute ischemic stroke] hospitalization” (p. 191). In a separate study, Rumalla et al. (2016b) found that “recreational marijuana use is independently associated

⁵ Northwest High Intensity Drug Trafficking Area (2016). Washington State Marijuana Impact Report. <http://www.riag.ri.gov/documents/NWHIDTAMarijuanaImpactReportVolume1.pdf>

with an 18% increased likelihood of aSAH [aneurysmal subarachnoid hemorrhage]" (p. 452). In a general population study, Hemachandra et al. (2016) found a 2-fold increased risk for stroke among weekly cannabis users even after adjustments for covariates including tobacco smoking. Wolff et al. (2015) reported a significant increase in stroke among marijuana users under age 45 due to intracranial arterial stenosis compared to their non-using peers. DiNapoli et al. (2016) found that among 725 patients with spontaneous intracerebral hemorrhage there was no difference between marijuana users and non-users; however, marijuana positive patients had milder presentations and fewer problems on discharge.

Cardiovascular Disease: Four new research reports examined the association between marijuana use and cardiovascular disease. Reese et al. (2016) investigated cardiac risk factors, determining that "cannabis is an interactive cardiovascular risk factor (additional to tobacco and opioids), shows a prominent dose-response effect and is robust to adjustment. Cannabis is associated with an acceleration of the cardiovascular age, which is a powerful surrogate for the organismal-biological age" (p. 1). Reese et al. studied 1163 patients (candidates with pre-existing cardiovascular disease were excluded) over a 5-year period and found "patients exposed to cannabis demonstrate an advanced cardiovascular age in a longitudinal time series" (p. 8). In a review article, Franz & Fishman (2016) found a 4-fold increased risk of a myocardial infarction (MI – "heart attack") within 60 minutes after marijuana consumption as well as a 1-4% annual increased risk of an MI among daily marijuana users. Rezkalla et al. (2016) conclude their review by stating "Despite...strong evidence for deleterious effects on the cardiovascular system, marijuana use remains common both for medical treatment and as a recreational substance. Evidence suggests that marijuana use can serve as a trigger for acute coronary syndromes and that marijuana-related vascular complications are associated with elevated mortality" (p. 453). Draz et al. (2016) investigated male patients under 40 years of age with an acute MI. They concluded that "cannabis smoking could be a potential risk factor for the development of cardiac ischemia" (p. 1).

Periodontitis: Shariff et al. (2016) found a significant increase in periodontal disease (serious gum infection) in individuals who reported using marijuana at least once a month. "FRC [frequent marijuana use – defined as using marijuana at least once per month] was associated with deeper probing depths, more clinical attachment loss, and higher odds of having severe periodontitis" (p. 1). Meier et al. (2016) also found that marijuana use was associated with poorer periodontal health in a longitudinal study that followed a birth cohort until age 38.

Emergency Department (ED) Use: Two studies reported an increase in both ED use and hospitalizations in Colorado following legalization. Kim & Monte (2016) reported that "the prevalence of hospitalizations for marijuana exposure in patients aged 9 and older doubled after the legalization of medical marijuana and that ED visits nearly doubled after the legalization of recreational marijuana. In the years after both medical and recreational marijuana legalization, the call volume [to the Colorado poison control center] for marijuana exposure doubled compared with that during the year before legalization" (p. 2). Zhu & Wu (2016) reported "a notable increase in ED visit numbers and rates for both use of cannabis-only and cannabis-polydrug during the study period [2004-2011] particularly among young people" (p. 429).

Cannabinoid Hyperemesis Syndrome (CHS): First reported in 2004, CHS typically presents in the ED as cyclical episodes of vomiting, nausea, and stomach pain and is always predated by at least weekly marijuana use and reliably stops when marijuana use ceases. Pélisser et al. (2016) suggest that CHS is likely to be significantly underdiagnosed because ED staff do not typically delve into drug histories in patients with such an immediate problem. This can result in repeated hospitalizations and potential esophageal distress. Sorensen et al. (2016) provided a review of the literature on CHS; they suggest that “The pathophysiology underlying CHS is unclear. Cannabis cessation appears to be the best treatment” (p. 1).

Asthma: Self et al. (2016) published a review that found no clear evidence of an association between marijuana use and worsening of asthma symptoms.

Pain: There are few articles concerning pain reduction in the context of recreational marijuana use; most address medical uses of marijuana which is not the focus of this HIA.

Disease Burden: Bahorik et al. (2016) examined medical conditions present in patients enrolled in an integrated healthcare system in northern California with substance use disorders including cannabis use disorder (CUD) compared to demographically matched patients without CUD. They found significantly higher rates of diagnosable medical conditions in those patients with CUD compared to non-CUD patients, including acid-peptic disorders, arthritis, asthma, chronic kidney disease, chronic obstructive pulmonary disorder, chronic pain, congestive heart failure, diabetes mellitus, end-stage renal failure, headaches, hepatitis-c, hypertension, injury, poisoning/overdose, ischemic heart disease, pneumonia, obesity, and stroke. Meir et al. (2016) did not find any problems in lung function, systemic inflammation, and metabolic disorders in marijuana using individuals compared to non-using individuals over the course of 38 years.

Metabolic Syndrome: Waterreus et al. (2016) looked at the use of marijuana in individuals with a psychotic illness who also were diagnosed with metabolic syndrome⁶. They found that marijuana “has an apparent cardiometabolic protective effect” and “cannabis may be a proxy for some as yet unidentified factor. Despite the results of our study, it is premature to conclude that people with a psychotic illness should be advised to use cannabis as a mode for offsetting their risk of cardiometabolic disease” (pp. 1659-1660).

Mental Health

Mood Disorders: Two recent studies addressed the association between marijuana use and mood disorders. Wilkinson et al. (2016) found that depressive symptomatology preceded marijuana use onset for both males and females in a longitudinal study of adolescence to young adulthood. This suggested a self-medication model of the marijuana-depressive symptoms link. Troup et al. (2016) reported a significant positive association between depressive symptoms and recreational marijuana use in college Colorado undergraduate psychology students following the legalization of recreational marijuana. No relationship was reported for recreational marijuana use and

⁶ Metabolic Syndrome is a cluster of risk factors that can raise the risk of cardiovascular disease and Type 2 diabetes.

anxiety symptoms. Blanco et al. (2016) found no relationship in a large representative US cohort studied over 3 years between marijuana use at time 1 and mood or anxiety disorders at time 2.

PTSD: Johnson et al. (2016) reported on a study they conducted investigating the role of marijuana use and frequency of use in patients with PTSD. In a matched case-control design (marijuana users versus non-users), they found that marijuana use did not reduce PTSD symptoms. In addition, they found that “there was also no association between PTSD scores and frequency of cannabis use” (p. 439). Gentes et al. (2016) investigated marijuana use in a sample of veterans who presented at a specialty outpatient PTSD clinic. After controlling for several potential confounding influences (age, race, service area, and combat exposure) they reported that marijuana use was associated with significantly greater PTSD symptom severity, other drug use, hazardous alcohol use, depressive symptoms, and suicidality.

Psychosis: Since August, 2015, there have been an additional 30 articles (research studies and literature reviews/meta-analyses) published that investigate aspects of the link between marijuana use and the development of psychosis/psychotic symptomatology demonstrating the clinical and experimental interest in this topic. This is an area where high potency marijuana may have a significant adverse effect because typically higher levels of the psychomimetic THC are associated with lower levels of cannabidiol (CBD)⁷ which may have antipsychotic (protective) effects⁸. Of the 30 studies identified, 16 are research studies that directly support the link between early marijuana use and the development of psychosis (Patel et al., 2016; Nesvig et al., 2016; Frascarelli et al., 2016; McHugh et al., 2016; Schoeler et al., 2016; Bergé et al., 2016; Seddon et al., 2016; Bechtold et al., 2016; Giordana et al., 2016; Manrique-Garcia et al., 2016; Arranz et al., 2015; Biancomi et al., 2016; Kelley et al., 2016; Helle et al., 2016; Hodgins et al., 2016; Hickling et al., 2016). Three research studies suggested that marijuana was a moderating or mediating effect through a family history of psychosis (van Winkel et al., 2015; Carey et al., 2016; González-Pinto et al., 2016). One study found no distinct clinical subset of among subjects with diagnosed schizophrenia between individuals with pre-onset cannabis use disorder and those without pre-onset CUD (Sarrazin et al., 2015), and one study indicated that individuals who reported no use and those who reported heavy use of marijuana (daily users) were more likely to report psychotic experiences than those who reported moderate use (monthly to weekly use) (Brañas et al., 2016). This study’s finding describes a quadratic (u-shaped) function.

Finally, on this topic, there were seven review papers published. Gage et al. (2016) reviewed the existing literature including areas that may affect interpretation of results such as confounding, bias, reverse causation, misclassification bias and attrition. They determined that “[t]he longitudinal, case-control, and cross-sectional studies conducted to date have, for the most part, found consistent evidence of an association, even after adjustments for covariates” (p. 553). They also recognize the potential stronger effects that high potency marijuana may have on this association: “However, given that studies conducted before skunk [high potency marijuana] became widely used also showed an association between cannabis and psychosis, it is too early

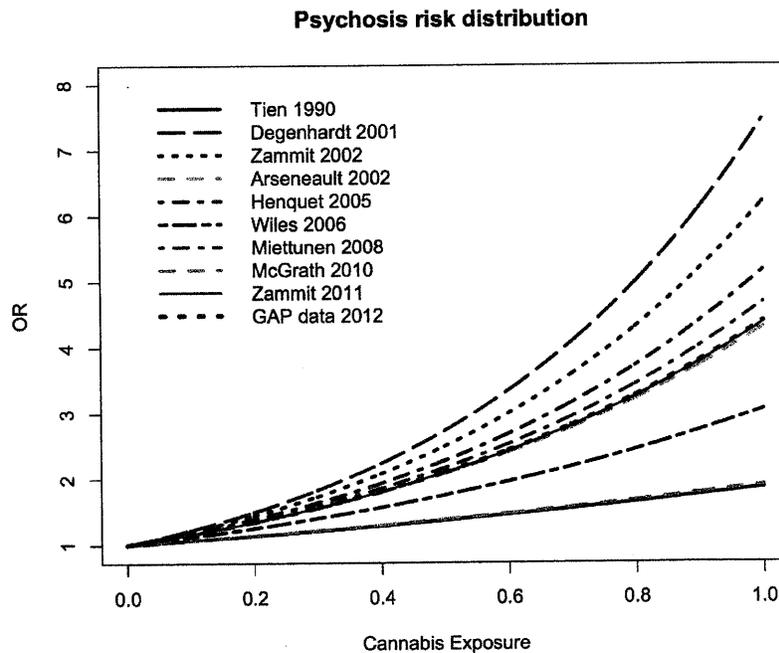
⁷ ElSohly et al. op. cit.

⁸ Rohleder et al. (2016). Cannabidiol as a Potential New Type of an Antipsychotic: A Critical Review of the Evidence. *Frontiers in Pharmacology*, 7, 1-11.

to assume that only skunk cannabis, but not lower potency forms of cannabis, are associated with psychosis risk” (p. 553). Haney & Evins (2016) discussed research that pertains to the marijuana PTSD and the marijuana and psychosis link from their own research perspectives in a debate format. Andrade (2016a, 2016b) summarized the research on the benefits, risks, and psychosis as a long-term adverse risk of marijuana use in a medical context. Volkow⁹ et al. (2016) also reviewed the literature on the effects of marijuana use across several aspects of human behavior including psychosis and reported “...there is strong physiological and epidemiological evidence supporting a mechanistic link between cannabis use and schizophrenia. Tetrahydrocannabinol (particularly at high doses) can cause acute, transient, dose-dependent psychosis (schizophrenia-like positive and negative symptoms). In addition, prospective, longitudinal, epidemiological studies consistently report an association between cannabis use and schizophrenia is which cannabis use precedes psychosis independent of alcohol consumption and even after removing or controlling for those individuals who had used other drugs” (p. 294). Sherif et al. (2016) reviewed human laboratory studies on marijuana and psychosis and concluded “cannabis exposure is highly prevalent in the general population, has been linked to an increased risk of psychosis from epidemiological studies, and may be one of the few modifiable risk factors for the development of psychosis” (p. 534). Marconi et al. (2016) published a formal meta-analysis investigating the association between levels of cannabis use and risk of psychosis. Figure 1 is a graphical representation of their results. “OR” represents the odds ratio. This graph demonstrates a very strong linear relationship between marijuana exposure and the risk of developing a psychosis. The “exposure” measure is a calculated metric based on the data available from each study accounting for both frequency and length of use. “Current evidence shows that high levels of cannabis use increase the risk of psychotic outcomes and confirms a dose-response relationship between the level of use and the risk for psychosis” (p. 1262). These authors also recognize that potency may significantly affect their results: “we could only measure the degree of exposure without taking into account the potency of cannabis or the period of use. There is previous evidence that use of high-potency cannabis as well as early onset of use are stronger risk factors for psychoses” (p. 1267). In this regard, it is important to re-iterate that marijuana available in the regulated retail markets are considerably more potent (i.e., higher THC content) than the illegal marijuana seized in the United States. Seized marijuana in 2014 had an average THC concentration of 12% while marijuana for sale at a retail market in Seattle was as high as 28% (with concentrates as high as 72%). We will discuss the effects of early onset on brain development in the next section.

⁹ Nora Volkow, MD is the director of the National Institute on Drug Abuse (NIDA) one of the National Institutes of Health (NIH).

Figure 1



Brain Development and Neurocognitive Functioning

Twelve new studies were published about the effects of marijuana use on brain development and neurocognitive functioning. Nine of those reports were research studies. Orr et al. (2016) investigated brain morphometry with very high resolution MRI scanning through the Human Connectome Project (HCP)¹⁰. They reported as follows: “Examined from multiple perspectives including white matter integrity, subcortical shape, and brain volume, our parametric analyses suggest that an early onset of marijuana use may be associated with subtle changes in brain regions implicated as being altered in substance abuse. These findings provide for the possibility that marijuana use during adolescence, which is a time of rapid brain development, might, at least in some individuals, have long-lasting effects, independent of the genetic effects suggested by a recent analysis of cortical volume on a somewhat overlapping sample” (p. 55). Filbey et al. (2016) performed MRI scans on 45 regular heavy marijuana users and found that “early MJ [marijuana] use was linked to altered neurodevelopmental patterns in brain regions sub-serving higher-order cognitive processes” (p. 21). Rigucci et al. (2016) scanned 56 first episode psychosis patients (37 marijuana users) and 43 individuals without psychosis (22 marijuana users) and found that “frequent use of high-potency cannabis is associated with disturbed callosal microstructural organization in individuals with and without psychosis. Since high-potency preparations are now replacing traditional herbal drugs in many European countries, raising awareness about the risks of high-potency cannabis is crucial” (p. 841). van de Giessen et al. (2016) performed MRI and PET (positive emission tomography) scans on 11 marijuana dependent individuals and 12 healthy controls matched for age, gender, ethnicity, and parental socioeconomic status. All participants were free of comorbid conditions (other substance dependence and other psychiatric disorders). The active marijuana dependent subjects were

¹⁰ <https://www.humanconnectome.org/documentation/S900/index.html>

admitted to a hospital inpatient unit assuring abstinence for 5-7 days prior to the scans. This was a complex experimental protocol that included measuring dopamine release in specific brain regions after an injected amphetamine challenge. The authors reported “this study demonstrates that severe cannabis dependence, with no other psychiatric or drug comorbidities, is associated with deficits in amphetamine-induced dopamine release [in specific brain structures]. The lower dopamine release...might contribute to the association between heavy cannabis use and psychopathology. These results are important in light of the steady increase in cannabis use in the US, along with continually increasing THC potency and the movement to legalize its use, potentially exposing a wider proportion of the population to the negative impact of cannabis use disorder. In particular, as most of our subjects initiated cannabis use during their adolescent years, our study suggests that adolescent use of cannabis leading to dependence is associated with a compromised dopaminergic system that may have a negative impact on brain function” (p. 10). In another complex protocol study, Amen et al. (2016) found that “this work suggests that marijuana use has potentially deleterious influences in the brain – particularly regions important in memory and learning and known to be affected by AD [Alzheimer’s Disease]” (p. 11). In an MRI study of 74 long-term cannabis users (average of 15.4 years of use) and 37 non-using healthy controls, Yücel et al. (2016) found a relationship between the THC/CBD (cannabidiol) ratio and specific brain structure abnormalities. They also found that these brain deficits may rebound with sustained abstinence. “We confirmed that hippocampal volume is reduced in long-term cannabis users, and found this atrophy can be restored following prolonged abstinence. Moreover, we show for the first time that both hippocampal volume and neurochemistry are reduced to the greatest extent in users exposed to THC without CBD” (p. 5). In a study investigating the independent and combined effects of marijuana use and HIV status (positive or negative), Thames et al. (2016) reported “the current study found main effects for both HIV status and MJ [marijuana] use on neurocognitive functioning. HIV+ moderate-to-heavy users performed significantly worse on learning/memory than other comparison groups, whereas HIV+ light users performed significantly better on verbal fluency than HIV- light users” (p. 630). Koenders et al. (2016) performed gray matter scans on a group of 20 heavy cannabis users and 22 healthy controls and reported “in contrast to our hypothesis, there were no differences between the CB [heavy cannabis users] and the HC [healthy controls] group in GM [gray matter] volume changes [over three years]. Moreover, changes in weekly cannabis use and cannabis use related problems were not significantly related to changes in GM volume. Finally, cross-sectional analyses at baseline and follow-up revealed consistent correlations between GM volumes in the left medial temporal lobe (i.e., hippocampus, amygdala, STG [superior temporal gyrus]) and cannabis related problems and cannabis use (in grams)” (p. 8). The finding of lower GM volumes in specific brain regions among marijuana users is consistent with other study findings (see discussion of reviews of this topic below) but the equity in volume changes between marijuana users and nonusers is not. Finally, Schwitzer et al. (2016) studied 28 regular marijuana users and 24 age and gender matched controls. They found “a delay in transmission of action potentials by the ganglion cells in regular cannabis users, which could support alterations in vision” (p. E1).

There were four reviews of this literature published since August, 2015. Brumback et al. (2016) concluded their extensive review by stating “mounting evidence suggests marijuana use

negatively impacts brain structure and function. While there is potential for recovery from some of the negative effects of prolonged use, long-term deleterious effects are present and more likely with early age of onset and protracted use” (p. 56). Similarly, Weinstein et al. (2016) concluded “regular use of cannabis results in structural changes indicated by volumetric, and gray matter changes in the human brain” and “regular use of cannabis affects cognitive processes such as attention, memory, inhibitory control, decision-making, emotional processing, and social cognition and their concomitant brain areas” (p. 10). A review of the effects of marijuana on human cognition by van Hell et al. (2016) found “Further significant evidence has emerged supporting the finding that acute and chronic exposure to cannabinoids impairs cognition, especially in the domain of verbal learning, memory, and attention” and “...it is clear from the literature reviewed that cognitive impairment on a range of domains can persist beyond the period of acute intoxication and potentially affect daily functioning in cannabis users and hence the range of adverse educational and other psychological outcomes identified as associated with frequent use, in particular for adolescent users” (p. 563). Ganzer et al. (2016) reviewed 38 MRI and fMRI studies of abstinent marijuana users published between 2004 and 2015 and found “functional imaging demonstrates clear differences in activation patterns between CU [cannabis users] and controls especially in hippocampal, prefrontal, and cerebellar areas. Structural differences are found in cortical areas, especially the orbitofrontal region and the hippocampus” (p. 186).

Summary of Brain Development and Neurocognitive Effects: Since these studies tend to be rife with technological jargon and anatomical terms that may not be accessible to the casual reader, they can sometimes be hard to fully comprehend. So, to be clear, almost all studies and reviews of the literature in this area conclude that early and persistent use of marijuana can adversely affect brain structure and function. It is also clear that higher THC potency levels and more frequent use have greater negative impacts in a shorter period of time. What is unclear is whether any, some, or all of these adverse consequences are reversible with prolonged abstinence of use.

Marijuana and Driving

Six papers have been published since August, 2015 that address aspects of driving under the influence of marijuana. Three of these reports have been research studies and three have been reviews (and responses to the reviews). Declues et al. (2016) investigated the efficacy of the Field Sobriety Test (FST – developed originally to detect driving impairment caused by alcohol intoxication). They found that the FST was equally sensitive the effects of driving under the influence of marijuana. Lio et al. (2016) investigated the influence of marijuana and other drugs on risky driving behaviors that led to a driver fatality. They found that drivers fatally injured who tested positive for marijuana only were significantly more likely to be unrestrained (unbelted) than drivers who were unimpaired. Since unbelted drivers are three to four times more likely to die this is noteworthy. They also reported significantly higher counts of speed related violations for those using marijuana only and even greater risk for those testing positive for both alcohol and marijuana. Huang et al. (2016) looked at the use of child restraints in

passengers aged 0 to 14 in fatally injured drivers that tested positive for alcohol and drugs. They found that “of screened drivers involved in a fatal collision while transporting a child passenger, approximately one-fourth were positive for drugs, alcohol, or both. In addition to their previously reported riskier driving patterns, such drivers contribute to child endangerment because their child passengers are less likely to be restrained or appropriately seated. More than one-fourth of child passengers transported by drivers who screened positive for cannabis were unrestrained. This finding is concerning, “particularly with the growing legalization of cannabis for medical and recreational use” (p. 10).

Rogeberg & Elvik (2016a) reanalyzed two previously published meta-analyses on the effects of marijuana intoxication on motor vehicle collisions¹¹. Ashbridge et al. originally concluded that there was approximately a two-fold increase of a motor vehicle collision while driving under the influence of marijuana. Li et al. (2012) reported that “Epidemiologic studies published in the past 2 decades demonstrate that marijuana use by drivers is associated with a significantly increased crash risk. The crash risk appears to increase progressively with the dose and frequency of marijuana use” (p. 70). Rogeberg & Elvik (2016a) determined that errors were made in both meta-analyses that led to an inflated risk ratio for the influence of marijuana on motor vehicle crashes. Their revised estimate was substantially lower than Ashbridge et al. (2012) and Li et al. (2012). A letter to the journal Gjerde & Mørland (2016) suggested that Rogeberg & Elvik (2016a) themselves made errors and “in fact, the cited studies that represented the period of acute cannabis intoxication demonstrated rather high risks for RTC [Road Traffic Crash] involvement” (p. 1494). In their response, Rogeberg & Elvik (2016b) stated “...we would summarize as follows: driving while intoxicated by cannabis is a traffic hazard that raises the risk of a road traffic crash, but past studies – including ours – have been flawed. The average risk increase associated with cannabis intoxication and recent use based on a random-effects meta-analysis is 1.35 (1.12 – 1.61), implying an upper bound OR [odds ratio] associated with high THC driving of approximately 2” (p. 1498).

Marijuana and Pregnancy

Prevalence: Brown et al. (2017) reported that “among pregnant women, the prevalence of past-month marijuana use increased 62% from 2002 to 2014. Prevalence was highest among women aged 18-25 years, indicating that young women are at greater risk for prenatal marijuana use” (p. 208). Volkow et al. (2017) commented in an accompanying editorial on a growing number of concerning internet posts promoting marijuana to treat pregnancy-related nausea; Volkow et al. stated “pregnant women and those considering becoming pregnant should be advised to avoid using marijuana or other cannabinoids either recreationally or to treat their nausea” (p.130).

¹¹ The two previously reported studies were:

Ashbridge et al. (2012). Acute Cannabis Consumption and Motor Vehicle Collision Risk: Systematic Review of Observational Studies and Meta-analysis. *British Medical Journal*, 344, e536.

Li et al. (2012). Marijuana Use and Motor Vehicle Crashes. *Epidemiological Review*, 34, 65-72.

Placental Abnormalities: Carter et al. (2016) reported that “alcohol, methamphetamines, and cannabis [use during pregnancy] were associated with distinct patterns of [placental] pathology” (p. 753).

Maternal and Neonatal Effects: Chabarria et al. (2016) reported that “after controlling for potential confounders, while marijuana exposure alone was not associated with significant perinatal adverse outcomes, co-use with cigarette smoking rendered increased risk over either alone” (p. 506.e1).

Long-Term Offspring Outcomes: Six studies published since August, 2015 examined the effects of maternal marijuana use on longer term offspring outcomes. Richardson et al. (2016) provided a theoretical review of the “Double Hit Hypothesis” of prenatal cannabis exposure (PCE). They argue that PCE not only adversely perturbs fetal neurodevelopment (the first “hit”) which compromises the endogenous cannabinoid signaling system to allow for a specific phenotype that will be more vulnerable to postnatal stressor (the second “hit”) thereby “predisposing the offspring to abnormalities in cognition and altered emotionality” (p. 1). McLemore & Richardson (2016) offer long-term data from three longitudinal studies to support the double hit hypothesis. El Marroun et al. (2016) conducted an MRI study of 6 to 8-year-olds who were prenatally exposed to marijuana and/or tobacco compared to those who were not exposed. They concluded “overall, we detected significant associations between prenatal cannabis exposure and brain morphology in young children, particularly in the frontal brain” (p. 977). Four reports from a prospective longitudinal study investigating the long-term effects of prenatal marijuana exposure (PME) – the Maternal Health Practices and Child Development Study - were published since August, 2015. Day et al. (2016) found that controlling for covariates such as other prenatal substance exposure, race, gender and offspring substance use at 22 years, PME was significantly associated with early age of onset of marijuana use compared to their non-PME peers. In addition, they reported an indirect effect of PME on the development of psychotic symptoms at age 22. Sonan et al. (2015) reported that PME was linked to offspring marijuana use at age 22 controlling for significant covariates. Prenatal alcohol exposure, race, and gender were also significant predictors of young adult use. Sonon et al. (2016) found two indirect pathways from PME to cannabis use disorder (CUD) at age 22. The first is from PME through depressive symptoms at age 10 and the second is from PME through early age of initiation of marijuana use. The last study from this group, Goldschmidt et al. (2016), reported significant indirect pathways from PME to “negative adult roles including increased risk of being arrested, lower educational attainment, having a child without being married, and unemployment” (p. 1). The pathways identified were PME → early age of marijuana initiation → negative adult roles, and PME → behavior problems at age 3 → early age of marijuana initiation → negative adult roles. Smith et al. (2016) reported data from another prospective longitudinal study – Ottawa Prenatal Prospective Study (OPPS). Functional MRI (fMRI) scans were performed on 16 offspring prenatally exposed to marijuana and 15 offspring who were not prenatally exposed to marijuana (mean age = 21) to assess four executive functioning tasks. There were no differences across a number of demographic, personality, IQ, and level of education between the two groups. “Capitalizing on the ability of fMRI to act as a window into the working brain and the wealth of information obtained from these young adults throughout their lives, the results endorse the findings that there are in fact long term neurophysiological consequences of prenatal marijuana exposure” (p. 4).

There have been two new systematic/meta-analyses published in 2016 on the effects of prenatal marijuana use and neonatal outcomes. Interestingly both looked at roughly the same literature but arrived at different conclusions. Conner et al. (2016) reported that “maternal marijuana use during pregnancy is not an independent risk factor for adverse neonatal outcomes after adjusting for confounding factors [e.g., tobacco use, other drug use, selected socioeconomic and demographic factors]” p. 713. Gunn et al. (2016) found that infants exposed to prenatal marijuana were significantly more likely to weigh less (LBW – low birth weight) than those nonexposed. LBW is associated with many adverse outcomes including neurosensory deficits, decreased IQ, and educational attainment, and increased psychopathology. They also suggested that rates of use may have been suppressed because of social desirability factors (i.e., not wanting to report drug use because people might disapprove). It is unclear how to reconcile the two disparate findings from these meta-analyses¹². We note again that potency of marijuana was likely significantly lower in all these studies than the potencies available today.

Summary of Marijuana and Pregnancy: All but one new study and systematic review found negative neonatal effects and/or long term adverse effects specifically linked to maternal use of marijuana during pregnancy. The American College of Obstetricians and Gynecologists has weighed in on the issue in 2015: “Because of concerns regarding impaired neurodevelopment, as well as maternal and fetal exposure to the adverse effects of smoking, women who are pregnant or contemplating pregnancy should be encouraged to discontinue marijuana use.”

Additional Longitudinal Studies on Cognitive and Social Outcomes:

Jackson et al. (2016) published a report on two longitudinal twin studies that contradicted the Meier (2012) report demonstrating a decline in IQ among early and persistent marijuana users. Jackson et al. (2016) found no such decline in IQ. However, the subjects in the Meier et al. (2012) study were age 38 at the time of the latest IQ test while the subjects in the Jackson et al. (2016) report were 17-20. Meier herself responded to the findings:

“Our 2012 study (Meier et al. PNAS 2012) reported cognitive decline among individuals with a far more serious and far more long-term level of cannabis use. That is, we found cognitive decline in individuals followed up to age 38 who started cannabis use as a teen and who thereafter remained dependent on cannabis for many years as an adult. This new study is different; the two papers report about completely different doses of cannabis, and about participants 2 decades apart in age. The new study reports cognitive test scores for individuals followed up to only age 17-20, fewer than half of whom had used cannabis more than 30 times, and only a fifth of whom used cannabis daily for > 6 months. This new study and our prior study agree and both report the same finding: no cognitive decline in short-term low-level cannabis users. The message from both studies is that short-term, low-level cannabis use is probably safer than very long-term heavy cannabis use.

¹² It does, however, point out that meta-analyses are subject to several biases and therefore may not be the final word on a topic. For more on the problems of meta-analysis see Coyne et al. (2010). *Ain't Necessarily So: Review and Critique of Recent Meta-Analyses of Behavioral Medicine Interventions in Health Psychology. Health Psychology, 29, 107-116.*

The big problem remains that for some teens, short-term low-level teenaged cannabis use leads onward to long-term dependence on cannabis when they become adults. That is what is cause for concern.

Imagine if a study reported that teenagers drinking alcohol didn't harm cognitive function by age 17-20, would you reasonably conclude from that study that persistent alcoholism for years cannot damage the cognitive function of adults in their late thirties? Hardly."¹³Six other recently published prospective longitudinal studies addressed effects of marijuana use across several cognitive and social domains. McKetin et al. (2016) recruited a sample of midlife Australians (age 40-46) and followed up 4 and 8 years later. They found that marijuana users had poorer verbal recall than non-users but this was not related to current levels of marijuana use.

Zhang et al. (2016) followed a group of pre-adolescents to age 43 to determine the effect of marijuana use on unemployment status. They found five different latent trajectories of marijuana use over time: chronic users/decreasers, quitters, increasing users, chronic occasional users, and nonusers/experimenters. They found that compared to nonusers/experimenters, chronic users/decreasers were 3.5 times more likely to be unemployed at age 43 even after controlling for gender, age, marital status, being a professional, low education level, depressive mood, physical health problems, and cigarette smoking.

Green et al. (2016) followed a group of 608 urban (Baltimore) children from age 6 to age 25. They identified four latent classes of alcohol/marijuana use: non-use, moderate alcohol use, moderate alcohol/increasing marijuana use, and high dual use. They found "consistent with research on the negative consequences of adolescent substance use, non-users of alcohol and marijuana in high school were the least likely to have a substance use disorder or an arrest record, and they were the most likely to have completed high school" (pp. 158-159).

Pardini et al. (2016) also studied urban (Pittsburgh Youth Study) youth prospectively from mid-adolescence through the mid-20s. They identified four latent trajectories of marijuana use: chronic high, adolescence-limited, late increasing, and low/nonusers. They found "young men who engage in chronic marijuana use from adolescence into their 20s are at increased risk for exhibiting psychopathic features, dealing drugs, and enduring drug-related legal problems in their mid-30s relative to men who remain abstinent or use infrequently" (p. 797).

Auer et al. (2016) followed a large cohort of young adults (18-30 at baseline) for 25 years and found "past exposure to marijuana to be significantly associated with worse verbal memory in middle age" (p. 360).

Silins et al. (2016) investigated the effects of early alcohol and marijuana use on educational attainment in three integrated prospective longitudinal cohorts from Australia and New Zealand. They found "after covariate adjustment... adolescent cannabis use (weekly+) was associated with 1 ½ to two-fold increase in the odds of high school non-completion, university non-enrollment, and degree non-attainment. In contrast, adjusted associations for all measures of alcohol use were inconsistent and weaker. Attributable risk estimates indicated adolescent cannabis use

¹³ <https://learnaboutsam.org/madeline-meier-responds-to-latest-iq-study/>

accounted for a greater proportion of the overall rate of non-progression with formal education than adolescent alcohol use” (p. 90).

Other Research on the Potential Health/Social Effects of Marijuana Use/Regulation

Wang et al. (2016) reported on unintentional pediatric exposure to marijuana before and after legalization in Colorado. They found that the rate of marijuana-related visits to children’s hospitals doubled after legalization. Calls to the Regional Poison Center increased by a factor of 5 after legalization. Both rates were significantly higher than the national rates. “Furthermore, compared with most unintentional pediatric exposures, symptoms after marijuana exposure can be severe: 35% of patients presenting to a hospital required admission, increasing the hospital burden and using more health financial resources” (p. 4).

Schuster et al. (2016) reported that early-onset marijuana use among young adults (18-25) was associated with increased learning deficits. Dahlgren et al. (2016) investigated cognitive performance in a group of heavy, chronic marijuana users and non-using controls. They found “marijuana smokers had poorer executive function relative to control participants...primarily driven by individuals with early onset of marijuana use (before age 16)” (p. 298).

Han et al. (2016) reported on trends in marijuana use among older adults (50-64 and 65+) in the US. They found that prevalence of marijuana use among those individuals 65+ had increased from 0.4% in 2006 to 1.4% in 2013 – a 250% increase. Bradford & Bradford (2016) investigated Medicare Part D prescription claims and found that in states where medical marijuana was legal (between 2010-2013), the number of prescriptions filled was significantly reduced for treatment of anxiety, depression, nausea, pain, psychosis, seizures, sleep disorders, and spasticity. This counter-intuitive finding was challenged by Caputi & Humphreys (2016) who analyzed individual-level data from the 2013 and 2014 National Survey on drug Use and Health (NSDUH). They found that “fewer than 3% of Medicare recipients in states with medical marijuana laws use marijuana for medical purposes. If Bradford & Bradford’s conclusions were correct, this small percentage of Medicare recipients would have to be responsible for an extremely large reduction in the use of multiple prescription drug classes in states with medical marijuana laws. Furthermore...we found that Medicare recipients who used marijuana for medical purposes were at significantly higher risk for nonmedical use of prescription pain relievers compared to other recipients” (p. 436).

Four new studies investigated the role of marijuana use in violent behavior. Alniak et al. (2016) found that current substance use was associated with a three-fold increase in risk of violence in male patients with bipolar disorder. The most common current substances used were alcohol, marijuana, and synthetic marijuana. Dharmawardene & Menkes (2016) reported that in a sample of inpatients with a diagnosis of bipolar disorder, schizoaffective disorder, or schizophrenia, that “cannabis use was found to significantly predict lifetime history of violence; other independent variables (gender, age, ethnicity, alcohol use, psychiatric diagnosis) did not” (p. 1). Few et al. (2016) studied twins discordant for nonsuicidal self-injury (NSSI). They found “lifetime cannabis use and early use were associated with increased odds of NSSI and this association remained when accounting for covariates: (p. 873). Shorey et al. (2016) reported on a daily diary

study of female dating violence victimization and found “marijuana use also preceded and increased the odds of sexual victimization” (p. 509)¹⁴.

Another study (Lagerberg, 2016) found that cannabis use disorder was associated with a more severe illness course in bipolar disorder (BD) patients who also used tobacco. Tobacco using bipolar patients who fulfilled DSK-IV criteria for cannabis use disorder were significantly associated with an earlier age of onset of BD, higher frequency of hospital stays, and higher rates of manic episodes.

Agrawal et al. (2016) investigated unsafe sexual activity and marijuana use in a cohort of female twins. They determined that early-onset marijuana use was associated with repeated voluntary unprotected sex.

Compton et al. (2016) used data from the National Survey on Drug Use and Health from 2002-2014 to track trends in the prevalence of marijuana use and perception of harm. They found “prevalence and frequency of marijuana use increased in adults in the USA starting in approximately 2007 and showing significantly higher results in multivariable models during 2011-2014 (compared with 2002). The association between increases in marijuana use and decreases in perceiving great risk of harm from smoking marijuana suggest the need for education regarding the risk of smoking marijuana and prevention messages” (p. 954).

Marijuana Use and Other Substance Use

Four new studies investigate the role of marijuana use in initiation, persistence, or exacerbation of use/misuse of other substances. Weinberger et al. (2016) investigated the association between marijuana use at baseline (Time 1) among individuals with no history of alcohol use disorder (AUD) and AUD three years later (Time 2). They found a five-fold increase in the incidence of AUD at Time 2 among marijuana users with no AUD at time 1 compared to nonusers of marijuana. They also found that individuals who did have an AUD at Time 1 and used marijuana had an increased use of a persistent AUD at Time 2 compared to individuals who had an AUD at time 1 but did not use marijuana.

Arteberry et al. (2016) studied the initiation, reinitiation, and persistence of non-medical prescription drug use (NMPDU) among non-users, prior users, and current users of opioids, tranquilizers and the association with marijuana, alcohol, and tobacco use. They report “notably, cannabis use was a consistent risk factor more than any other substance that increased the likelihood of NMPDU initiation as well as higher risk stages such as reinitiation and persistence, where cannabis (early onset and frequency) was the only substance that increased the likelihood of sedative/tranquilizer persistence. These findings suggest that cannabis use may play a role in the progression of opioid and sedative/tranquilizer use” (p. 91).

¹⁴ They also stressed that “It should be clearly stated that the sole responsibility for stopping the perpetration of violence is always with the perpetrator and that the victim is never to blame for violence, regardless of whether substance use occurred before their victimization.” (p. 515)

Subbaraman et al. (2017) examined the influence of current marijuana use on individuals in treatment for AUD. They reported “among participants in a large, randomized controlled trial of treatment for AUD, any cannabis use was associated with fewer abstinent days at treatment end when compared to no cannabis use; each additional day of cannabis use was related to approximately 4 fewer days of alcohol abstinence” (p. 9). Similarly, Hayaki et al. (2016) found that “the concurrent presence of both DSM-5 AUD and CUD [cannabis use disorder] is associated with heavier drinking patterns and greater marijuana problems than disordered use of either substance alone, thus affirming the magnified severity of alcohol and marijuana use that accompanies dual DSM-5 alcohol and marijuana use disorders” (p. 579).

Indirect Health Effects:

There is one other issue that indirectly contributes to adverse health effects of marijuana and that is the unfavorable impact of commercial-size marijuana cultivation on the environment. Carah et al. (2015) present a discussion on the adverse environmental impact of marijuana cultivation on water resources, fish and wildlife die-offs due to pesticide use, and lack of specific state and local regulatory policies and staff to enforce existing land use laws that pertain to marijuana farming. They point out that significant portions of tax revenue from recreational marijuana sales are dedicated to public health and education, but little if anything is set aside for mitigation of adverse environmental impact of large scale marijuana cultivation.

Summary and Conclusions

Since August 2016, there have been over 180 peer reviewed papers published on the health effects of marijuana. Nearly all of these studies found adverse health effects in a dose-dependent manner at varying levels of marijuana use (infrequent to daily use). It is important to note that potency of marijuana was almost never taken into account in these reports. Particularly in the longitudinal studies spanning decades, potency was likely low compared to what is currently available in retail stores in states where marijuana has been legalized for recreational use. This is a major public health concern given that 80% of marijuana products currently available in Colorado legal markets exceed 16% THC, and attempts to limit THC content have been vigorously opposed by the marijuana industry¹⁵.

Another major concern is the frequency of use of marijuana products. The 2015 Vermont Youth Risk Behavior Survey indicated that of those 9th through 12th graders who report marijuana use in the previous 30 days, 45% report using it on ten or more days. The 2016 Vermont Young Adult Survey reported that of those 18-25 year-olds who report past month marijuana use, 51% report using on 20 or more days.¹⁶ Contemporary adolescents and young adults are using more potent marijuana more frequently than their peers from the 1950s, 60s, 70s, 80s, and 90s, and even the early 2000s. Even if the number of adolescent marijuana users did not increase (which is unlikely in an expanding market),

¹⁵ <http://www.thecannabist.co/2016/07/08/amendment-139-thc-limits/57930/> The Colorado Health Research Council was formed by the Colorado marijuana industry on June 30, 2016 specifically to oppose Amendment 139 which would have limited THC potency to 16%.

¹⁶ The Vermont Young Adult Survey is conducted by the Pacific Institute for Research and Evaluation under an evaluation contract with Vermont Department of Health. Results have not yet been publicly released.

the effects of more potent marijuana may pose a serious long-term public health issue that could have considerable adverse health effects and burden both the physical and mental health systems of care in the United States in years to come. While tax revenues will increase and the cost associated with state criminal prosecution will decrease, it is unclear whether this will offset increased health care costs associated with marijuana dependence, drugged driving, negative environmental impact, and the adverse health effects delineated in the original HIA and this update.