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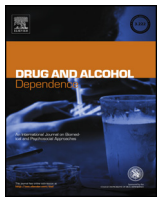

Legalizing marijuana for medical purposes will increase risk of long-term, deleterious consequences for adolescents☆

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1. Introduction

Many Americans view marijuana as a mild drug that is less harmful than alcohol or tobacco (Hart Research Associates/Public Opinion Strategies, 2014). Public opinion regarding marijuana legalization has evolved over the past 45 years, such that more than 50% of Americans surveyed in a recent poll believe marijuana should be legalized for recreational and medical purposes (Saad, 2014). Despite changes in public opinion, a significant body of scientific evidence suggests that repeated use of marijuana during adolescence can produce long-lasting cognitive impairments and increases the risk of serious mental illness (Andreasson et al., 1987; Ehrenreich et al., 1999; Konings et al., 2008; Meier et al., 2012; Solowij et al., 2011). Marijuana use for medical purposes is currently legal in 23 states in the U.S. and Washington, DC. This commentary reviews evidence linking frequent marijuana use in adolescence with risk for mental illness and cognitive impairment, the impact of medical marijuana legalization on increasing rates of adolescent marijuana use, changes in the potency of marijuana over time, and research on marijuana-based medications to make the case that legalizing medical marijuana will increase health-related risks, particularly among adolescents (Johnston et al., 2014; Volkow et al., 2014; Andreasson et al., 1987; Ehrenreich et al., 1999; Konings et al., 2008; Meier et al., 2012; Solowij et al., 2011).

2. Adolescent marijuana use and mental illness

Frequent marijuana use in adolescence has been linked to risk for mental illnesses that include, for example, mood disorders and psychosis. For example, weekly use of marijuana during adolescence doubles the risk of developing anxiety disorders and depression later in life (Patton et al., 2002). This risk was even greater amongst those who reported daily marijuana use.

Perhaps more troubling, however, is the considerable link between marijuana use during adolescence and schizophrenia and other psychotic illness. The link between adolescent marijuana use and psychotic disorders is particularly strong for those with a genetic vulnerability for the disease (Caspi et al., 2005). Perhaps as many as 90% of those suffering from schizophrenia report using marijuana during adolescence (Hambrecht and Häfner, 1996; Stone et al., 2014). Marijuana use very early in adolescence appears to be particularly problematic and may act as an independent risk factor for later psychotic illness (Konings et al., 2008). Additionally, those who report using marijuana frequently during adolescence may be at least twice as likely to develop schizophrenia compared to non-users (Andreasson et al., 1987). There is also evidence that risk of developing psychosis or the severity of symptoms that precede psychosis increases as frequency of use during adolescence increases (Fergusson et al., 2005; Henquet et al., 2005; Miettunen et al., 2008; Tien and Anthony, 1990; van Os et al., 2002; Wiles et al., 2006; Zammit et al., 2002). It is difficult to determine a minimum frequency required to alter risk from these studies because of differences in methodology, but it is worth nothing that daily use was commonly linked with a significant increase in risk. Similarly, heavy marijuana use (i.e., daily use or marijuana dependence) during adolescence is associated with an earlier onset of schizophrenia (De Sousa et al., 2013; Di Forti et al., 2014; Veen et al., 2004).

Similarly, recent meta-analyses of case-controlled and cohort studies indicate that adolescents who use marijuana are at greater risk of developing psychosis than those who began using marijuana in adulthood (Jonsson et al., 2014; Semple et al., 2005). Finally, there is evidence that the first psychotic episode in a subpopulation of schizophrenics may have actually been precipitated by marijuana use (Buhler et al., 2002) and that more than 10% of schizophrenia cases could be prevented if marijuana use were eliminated (Zammit et al., 2002).

Unfortunately, it is not possible to determine the drug dose required to increase risk of schizophrenia because very little is known about the potency of marijuana used in most human studies. Additionally, information about patterns of smoking behavior or smoking topography is generally absent from these sorts of analyses. While efforts are commonly made to control for factors that may affect both drug use and psychiatric illness, the

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possibility of residual confounding or self-selection biases cannot be ignored.

For instance, it is likely that some adolescents use marijuana to self-medicate as symptoms of a developing psychiatric illness appear, but the persistence of the linkage between adolescent marijuana use and schizophrenia and other psychotic illness is sufficient to give us pause. It would be imprudent to ignore the scientific data and proceed with the assumption that adolescent marijuana use plays a negligible role in the etiology of psychiatric disease.

3. Adolescent marijuana use and cognitive impairment

The scientific literature supports a relationship between frequent marijuana use during adolescence and long-term cognitive impairment. Some researchers suggest that the adolescent brain is particularly vulnerable to the effects of frequent marijuana use (Jager and Ramsey, 2008; Schneider, 2008). Data derived from self-reports of marijuana use during adolescence are very valuable, but there are many factors that can contribute to both drug use and impaired cognitive function. To that end, data derived from animal models of adolescence can provide information regarding causality. The following sections review research from studies involving humans and animal models.

3.1. *Evidence from human studies of marijuana use in adolescence*

There is a significant body of evidence that frequent marijuana use early in adolescence is linked to poorer cognitive function in adulthood (Ehrenreich et al., 1999; Fontes et al., 2011; Gruber et al., 2012; Solowij et al., 2011). The long-lasting cognitive impairments that have been linked to adolescent marijuana use include poorer visual scanning capacity, less sustained attention, compromised impulse control and diminished executive function. Working memory also appears to be negatively affected by regular marijuana use during adolescence. Adolescents who report using cannabis regularly display poorer working memory performance than non-users (Harvey et al., 2007) and early onset of marijuana use is associated with sub-optimal performance in brain areas associated with working memory (Becker et al., 2010). These functional alterations may be related to the reduced cerebral blood flow observed in adolescents that use marijuana frequently (Jacobus et al., 2012). More troubling, perhaps, is the evidence of global cognitive impairments and lower IQ scores among those who begin using marijuana during adolescence (Meier et al., 2012; Pope et al., 2003).

However, the purported relationship between adolescent marijuana use and lower IQ scores is complex and troubling enough to warrant further investigation. For instance, the question of whether socioeconomic status, personality differences or pre-existing differences in cognitive performance affect the relationship between adolescent marijuana use and lower IQ scores has not been answered conclusively.

3.2. *Evidence from animal models of marijuana consumption in adolescence*

While studies that examine correlations between human adolescent marijuana use and cognitive function or mental illness cannot establish causality and are prone to residual confounding, animal models can provide more direct evidence of the consequences of frequent marijuana exposure in adolescence. For instance, rats exposed to Δ^9-THC, the primary psychoactive constituent of marijuana, each day during adolescence (i.e., postnatal days 35–45) exhibited neurochemical, cognitive and behavioral alterations in adulthood that bear some resemblance to those observed in schizophrenics (Zamberletti et al., 2014). Other experiments with rats have demonstrated that adolescents and adults are differentially affected by repeated exposure to Δ^9-THC, with adolescents exhibiting memory impairments and hippocampal dysfunction that persist into adulthood (Quinn et al., 2008). Similarly, rats treated with synthetic cannabimimetic drugs during adolescence exhibit memory impairments in adulthood, while drug-exposure in adulthood does not produce long-lasting memory deficits (O'Shea et al., 2004; Renard et al., 2012; Schneider and Koch, 2003). Also, rats exposed to Δ^9-THC each day during adolescence (i.e., postnatal days 35–45) exhibit anatomical alterations in a brain region that is associated with memory and working memory impairments that persist for at least 30 days (Rubino et al., 2009).

Interestingly, daily exposure to a synthetic cannabimimetic drug during late adolescence and early adulthood (postnatal days 45–60) also produced memory impairments that persisted for at least 75 days (Abush and Akirav, 2012). Additionally, very recent evidence from adult mice suggests that the cellular alterations produced by repeated cannabinoid exposure persist for weeks (Dudok et al., 2015). These data suggest the need to determine the duration of memory impairments produced by repeated cannabinoid exposure and whether the adolescent and adults brains are differentially affected in rodents.

While rodent models of adolescence can be informative, experiments with non-human primates may provide better evidence for the cognitive impact of repeated adolescent exposure to marijuana because of the neuroanatomical and cognitive similarities to humans. Research with adolescent rhesus monkeys suggest that repeated exposure to Δ^9-THC produces long-lasting impairments in spatial working memory (Verrico et al., 2014). These results are similar to working memory impairments produced by adolescent marijuana use in humans (Harvey et al., 2007).

4. Trends in adolescent marijuana use

Because frequent marijuana use during adolescence is closely linked with long-term alterations in cognitive function and risk for mental illness, it is important to reduce marijuana use among adolescents. Unfortunately, adolescents in the United States do not appear to be getting this message and there is a trend among adolescents to underestimate the risks posed by marijuana use. The proportion of high school seniors who perceive "great risk" in regular marijuana use has declined consistently since 2006 and is at the lowest point since 1978 (Johnston et al., 2013). In addition, 8th and 10th graders show similar changes in the appraisal of risk associated with regular marijuana use, suggesting a broad change in adolescent attitudes regarding drug abuse (Johnston et al., 2013).

Not surprisingly, marijuana use among adolescents has increased as appraisal of risk has declined. The most recent data indicate that rates of daily use amongst high school seniors are higher than they have been in more than 30 years (Johnston et al., 2013) and the proportion of high school seniors who use marijuana daily has nearly tripled since 1993 (Johnston et al., 2014).

There is also evidence that marijuana use patterns that develop in adolescence (i.e., ~15 years old) are relatively stable and tend to persist into early adulthood (i.e., ~24 years old) (Swift et al., 2008). Further, even individuals who report using marijuana only occasionally in adolescence have an elevated risk of marijuana dependence in early adulthood compared to those who did not report marijuana use in adolescence (Swift et al., 2009). In addition, more than 50% of individuals who reported using marijuana at least once a week in adolescence were

marijuana-dependent as early adults (Swift et al., 2009). These data suggest that in addition to increased risk of psychotic illness, increased marijuana use by adolescents will likely persist into adulthood and result in greater future risk for marijuana dependence.

To some, these findings beg the question of whether there has been a corresponding increase in schizophrenia in the general population as marijuana use increases amongst adolescents. The trends in the incidence of schizophrenia are mixed and variable (Boydell et al., 2003; Bray et al., 2006; Frisher et al., 2009; Hardoon et al., 2013; Kirkbride et al., 2009; Sankaranarayanan and Puumala, 2007; Toh et al., 2013; National Institute of Mental Health, 2009; Regier et al., 1993; McGrath et al., 2004). Reasons for this variability likely include methodological differences (e.g., sampling, age range). While there is substantial variation in estimates of schizophrenia incidence, there is no convincing evidence that schizophrenia is generally becoming more or less common over time. However, given recent increases in marijuana use among youth, understanding the relationship between the well-documented mental health risks associated with marijuana use during adolescence and the incidence of schizophrenia represents an important pathway for future research.

5. Medical marijuana laws and adolescent marijuana use

It appears that marijuana use and state medical marijuana laws are related. For instance, marijuana use and dependence is more common in states with legalized medical marijuana (Cerda et al., 2012). There is also evidence that legalizing marijuana for medical purposes is associated with a 10–20% increase in illegal marijuana use (Chu, 2014). More to the point, legalizing medical marijuana has been linked to an increase in adolescent marijuana use of up to 30% (Friese and Grube, 2013; Harper et al., 2012; Pacula et al., 2013; Wall et al., 2011). These changes in use rates are consistent with data regarding the intention by adolescents to initiate marijuana use if it were legalized for medical purposes (Schwartz et al., 2003) and appraisal of risk associated with marijuana use by adolescents (Harper et al., 2012; Wall et al., 2011). Other evidence suggests that legalizing marijuana across the board would likely result in increased use even among adolescents considered at low-risk for marijuana use (Palamar et al., 2014). The linkage between adolescent marijuana use and the legal status of medical marijuana persists even though state laws legalizing medical marijuana typically restrict use by those under the age of 18.

While the nature of the linkage between marijuana use and the legal status of medical marijuana is unclear, these data are completely consistent with what is known about age-restricted access to drugs. Despite the fact that the national minimum drinking age in the United States is 21, a quarter of 18–20 year olds report consuming alcohol on 5 or more occasions within the previous 30-day period (Office of Juvenile Justice and Delinquency Prevention, 2005). Similarly, nearly 20% of those in grades 9–12 report smoking cigarettes at least once in the previous 30-day period and nearly 90% of those that smoke currently report buying cigarettes directly from a retail seller (Centers for Disease Control and Prevention, 2010). While there are long-standing regulations that restrict access to alcohol and tobacco products, experience with those products in the United States clearly demonstrates that legal age restrictions do not prevent underage consumption.

The same facts are true regarding marijuana. Adolescents are able to get marijuana even in states where marijuana is currently illegal and there is no reason to believe that legal age restrictions will be effective means of preventing the increase in adolescent marijuana use that accompanies legalization for medical purposes. In short, there is very little evidence that we can reduce access to recreational marijuana for adolescents while simultaneously increasing the availability medical marijuana for adults.

It should be noted that the link between legalizing marijuana for medical purposes and increased marijuana use by adolescents is controversial. Some evidence suggests that legalizing marijuana for medical purposes is unrelated to rates of adolescent marijuana use (Lynne-Landsman et al., 2013). The fact that some studies failed to confirm a significant relationship between legalizing medical marijuana and adolescent marijuana use does not invalidate other studies that do confirm a link. These discrepancies simply highlight how little we know about what drives the association between legalizing marijuana for medical purposes and increased marijuana use by adolescents.

6. Changes in the chemical composition of marijuana

There is also some data that suggest current strains of marijuana may pose a greater cognitive risk than strains that were available a few years ago. Marijuana contains more than 60 different cannabinoids comprising a dozen distinct cannabinoid-types (El Sohly and Slade, 2005). While Δ^9-THC is the primary psychoactive constituent, marijuana also contains a structurally-related compound called cannabidiol (CBD). Interestingly, there is evidence that CBD opposes the cognitive impairment produced by acute exposure to Δ^9-THC (Englund et al., 2013; Fadda et al., 2004; Morgan et al., 2010; Wright et al., 2013). Over the last 15–20 years, however, there has been a consistent reduction in CBD content in many strains of marijuana while Δ^9-THC content has risen (Burgdorf et al., 2011; Potter et al., 2008; Zamengo et al., 2014). There is no evidence that this trend is moderating. To the contrary, there is evidence that Δ^9-THC content of marijuana increases after legalization for medical purposes (Sevigny et al., 2014).

There is very little current information regarding the cognitive impact and mental health consequences of long-term exposure to marijuana strains high in Δ^9-THC and low in CBD. There is some very recent evidence that daily use of marijuana strains high in Δ^9-THC and low in CBD during adolescence reduces the age at which psychosis appears (Di Forti et al., 2014). Also, those dependent on high Δ^9-THC/low in CBD marijuana strains display cognitive disturbances that are similar to those suffering the prodromal symptoms of schizophrenia (Morgan et al., 2012). These observations strongly suggest that the cognitive impact of chronic exposure to varying doses and dose combinations of Δ^9-THC and CBD should be determined in pre-clinical animal models.

7. Marijuana-based medications

Humans have used marijuana therapeutically for millennia. The ancient Assyrians used two words to refer to marijuana (Mechoulam et al., 2014). One of those words referred to the therapeutic benefits of marijuana, while the other referred to the intoxicating and subjective effects. Modern research suggests that the abuse liability of marijuana is produced by the combined effect of individual chemical components of the drug (Klein et al., 2011; Vann et al., 2008). Unfortunately, it is difficult to predict the subjective effects produced by any individual plant because different marijuana strains have variations in cannabinoid content and concentration (Burgdorf et al., 2011; Potter et al., 2008; Zamengo et al., 2014). Individually, Δ^9-THC and CBD have differing pharmacological profiles that are subjectively distinct from marijuana (Long et al., 2010; Parker et al., 2004). Using unprocessed plant material for medical purposes is complicated by this inconsistent drug content. If there are medical benefits unique to marijuana, they almost certainly lie in the constituent chemical components, not the unprocessed plant material.

7.1. Potential for therapeutic benefit

While legalizing medical marijuana is linked to increased marijuana use by adolescents in some studies (Friese and Grube, 2013; Harper et al., 2012; Pacula et al., 2013; Wall et al., 2011), the potential clinical applications of the constituent components of marijuana should not be ignored (Joy et al., 1999). There is evidence that several of these cannabinoids have biological activity that could, in theory, be exploited for therapeutic benefit. For instance, CBD may have anticonvulsant properties (Carlini and Cunha, 1981; Cunha et al., 1980) and cannabigerol (CBG) may be an effective treatment for glaucoma and inflammatory bowel disease (Borrelli et al., 2013; Colasanti, 1990; Colasanti et al., 1984). A variety of other cannabinoids may also have therapeutic properties (Kaplan et al., 2003; Nahas et al., 1977; Turner and El Sohly, 1981). While there are bits of information that suggest potential clinical applications for several cannabinoids, the vast majority of research has focused on Δ^9-THC and CBD with very little information being available on the other chemical constituents of marijuana.

The real question, however, is whether any therapeutic benefit conferred by any constituent components of marijuana is unique. While most of the purported uses for medical marijuana can be better treated with other medications that produce fewer adverse effects (Joy et al., 1999), it is possible that some constituent component of marijuana could offer unique therapeutic benefits. For instance, there is a body of evidence suggesting that CBD offers relief for the unremitting and catastrophic seizures that are characteristic of Dravet syndrome (Maa and Figi, 2014), but these data are drawn from case studies and small studies with limited methodologies (Devinsky et al., 2014). Very little is known about the long-term effects of chronic exposure to CBD in humans. Research with rodents, however, suggests that repeated exposure to CBD produces a variety of behavioral changes (Long et al., 2010). Currently, there is no convincing evidence for a unique therapeutic benefit conferred by any constituent component of marijuana.

7.2. Impediments to developing marijuana-based medications

Research into therapeutic benefits of the constituent components of marijuana is restricted by Federal law. In the United States, the entire marijuana plant, including all constituent components, is classified as Schedule I by the Controlled Substances Act (US Department of Justice, 2012). Drugs classified as Schedule I are deemed to have a high potential for abuse and lack both an accepted medical use and a standard for safe use under medical supervision. Conducting research with Schedule I drugs requires considerable institutional, state and federal oversight as well as licensure, including DEA registration. Purchasing, transporting and disposing of Schedule I drugs also require compliance with additional regulations. Extensive record keeping is also required and labs that work with Schedule I drugs are subject to additional inspection protocols. Each of these restrictions places a strain on already scarce resources and serves to constrain research into marijuana-based medications.

Most problematic, however, are inconsistencies in which compounds are classified as Schedule I. Though all constituent components of marijuana are classified as Schedule I, there is virtually no scientific evidence of a high potential for abuse for some of those compounds. For instance, CBD prevents drugs like Δ^9-THC from binding at the relevant receptor, does not produce subjective experiences consistent with intoxication in humans, blocks the rate-decreasing effects of Δ^9-THC in monkeys, does not substitute for Δ^9-THC in rats trained in drug discrimination, does not produce conditioned place-preference in rats and is generally inactive in the battery of tests used to detect cannabinoid activity in mice (Brady and Balster, 1980; Karniol et al., 1975; Long et al., 2010; Perez-Reyes et al., 1974; Thomas et al., 2007; Vann et al., 2008). Despite these data, none of which are suggestive of a high potential for abuse, CBD is classified as a Schedule I drug.

In contrast, synthetic Δ^9-THC is classified as a Schedule III drug and is available by prescription from retail pharmacies in United States. Perhaps even more confusing is the fact that the other synthetic cannabimimetic drugs are not classified as controlled substances at all despite the fact they act at the same receptor as Δ^9-THC and have a pharmacological profile that indicates potential for abuse (Braida et al., 2001a,b; Lefever et al., 2014). The evidence suggests that classification of the constituent components of marijuana as Schedule I drugs is more related to a history of being abused than any scientific evidence suggesting great potential for abuse. The current myriad of regulations, elevated costs and confusing legal standards almost certainly serve to reduce the amount of research conducted on potential marijuana-based drugs.

Worldwide, a few other governments have been somewhat more progressive in permitting the development of marijuana-based drugs. In 1998, for instance, the British government licensed GW Pharmaceuticals to grow marijuana for research purposes (Kroll, 2014). In 2005, GW Pharmaceuticals received approval from the Canadian government to market Sativex®, a 1:1 blend of D9-THC and CBD as a treatment for neuropathic pain produced by multiple sclerosis. Since then, Sativex® has been approved for use in 11 other countries. Notably, the drug has not been approved by the U.S. Food and Drug Administration. However, an oral preparation of CBD (i.e., Epidiolex®) produced by GW Pharmaceuticals is undergoing clinical trials in the United States as a treatment for severe and debilitating forms of pediatric epilepsy (U.S. Food and Drug Administration, 2013).

8. Conclusions

Public opinion has evolved in the United States regarding the legal status of marijuana for medical purposes, but this change has not been guided by advances in scientific knowledge. A growing body of evidence suggests that repeated use of marijuana during adolescence can produce long-term cognitive impairment and increase the risk of serious mental illness. Unfortunately, adolescent marijuana use continues to increase as more states legalize marijuana for medical purposes. The relationship between legal status and marijuana use rates is intuitive and consistent with the inadequacies of current minimum age requirements for alcohol and tobacco products. Too many adolescents have access to marijuana currently and there is very little evidence that adolescent access to recreational marijuana can be reduced while simultaneously increasing the availability of medical marijuana for adults. Public health interests would be better served by streamlining the bureaucracy that impedes research on marijuana-based medications and focusing our efforts on identifying compounds in marijuana that confer unique therapeutic benefit.

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