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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

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