America's Cannabis Experiment

David Goldman, MD

Cannabis is widely used, psychoactive, and addictive. Given the choice, people in several US states and the District of Columbia have voted to legalize it. In the nation's capital, it is now legal to possess as many as 3 *Cannabis sativa* plants. Meanwhile, it remains illegal to have cannabis on federal land, which is problematic in a mosaic of federal and local jurisdictions. Further, a federal worker stands to be fired if discovered to be using cannabis. In the cannabis debate, does the science of consequences and addictive liability matter? Studies of humans and animals strongly indicate that cannabis changes the structure and function of the brain,[1] and the propensity to cannabis addiction is heritable,[2] which means that some are more vulnerable. On the other hand, it has been advocated that cannabis should be legalized or at least delisted as a schedule I drug. Nicotine and alcohol are regulated, taxed, and routinely enjoyed, providing a blueprint for the deregulation of other drugs that are supposedly less noxious.[3] However, these licit addictive drugs lead to serious social and medical consequences. For example, alcohol accounts for 5.1% of the global burden of disease and injury as measured by disability-adjusted life-years. We should be careful in extrapolating long-term consequences of cannabis legalization.

Related articles pages 994 and 1002

Cannabis users differ from nonusers, as many do not recognize but as has been shown by systematic studies. However, users differ from nonusers for many reasons, including inheritance and early life exposures, as well as drug use. The heritability of cannabis addiction is moderate,[2] although previous studies, including the one by Pagliaccio and colleagues[4] in this issue of *JAMA Psychiatry*, find that cannabis addiction may be as heritable as other addictions. Preexisting interindividual differences in genotype or early exposures can confound well-conceived studies, including longitudinal studies, because people who choose to use a drug differ from others who do not.

Inverse causality in which the effects of cannabis on subcortical brain structure were shown to be due to preexisting differences was neatly demonstrated by Pagliaccio et al.[4] They studied young adult sibling pairs discordant or concordant for cannabis use, thus separating the effects of cannabis exposure from genes and early environment. The cannabis-exposed individuals were worse off. They tended to be poorer, less agreeable, more likely to use other drugs, and more likely to discount larger future rewards for the immediacy of smaller ones. Cannabis predicted reductions in brain volumes within the range of normal variation. Any effect on brain structure is a serious concern. Tellingly, if one sibling was exposed to cannabis, both siblings tended to have lower brain volumes. However, sex-matched siblings discordant for cannabis use did not differ in brain volumes. Even with partial control of genotype (ie, the 50% coefficient of relationship of siblings), cannabis exposure did not influence brain volume.

The Vulnerable Brain

Genotype and environment can be better controlled in animal models, leading to more consistency of effects, especially on physiology. Humans are messier. Because of diversity in genotype and environment, one person's sugar may be another's poison. Also in this issue, French and colleagues[5] took a very different approach to investigate the role of genotype in the effects of cannabis on brain structure. In 3 longitudinally studied populations comprising more than 1500 adolescents, they found that a polygenic risk score for schizophrenia, a disease that may be triggered by cannabis, can worsen the effects of cannabis.[5] The risk score was based on 108 schizophrenia loci identified by the Psychiatric Genetics Consortium. Intriguingly, the polygenic risk score predicted a reduction of cortical thickness in cannabis-exposed men but not women. More needs to be learned about the risk score and the genes that could be driving the effects on cortical development. Presuming the validity of the 108 schizophrenia genes, not all would moderate cortical thickness because schizophrenia is not just a disease of cortical thickness. Also, genes not implicated in schizophrenia might alter cortical thickness. If replicated, these genotype-mediated effects of cannabis use are of special concern in young men made vulnerable by genetic background.

Cannabis Caveat

Although siblings discordant for cannabis use were similar in brain structure, it would be wrong to conclude that it is safe to use cannabis or, as could be wrongly inferred from the French et al study,[5] to conclude that it would be safe for people with the right genetic makeup or women, in particular, to use cannabis. Both siblings in a pair were likely to have smaller brain volumes if either one or both used cannabis. Drug effects, including neurotoxicity, are dose dependent and dependent on the mode of delivery. Easy access to high tetrahydrocannabinol content cannabis may change the equation. Several consequences of cannabis exposure were not measured in either the Pagliaccio et al[4] or French et al[5] studies, and neither included people with psychopathologies that are often comorbid and that may be consequent to cannabis use. When cannabis changes the brain, whether for good or more usually for bad, we need to learn whether the effects are pharmacologic in nature or due to shifts in socialization, study, work, exercise, or use of other psychoactive agents.

Conclusions

In weighing the costs and benefits of cannabis and other psychoactive drugs, we need to attend to the negative consequences of exposure, which are diverse and not necessarily measured sensitively or specifically with available tools. People using cannabis often and in potent forms are more likely to experience negative consequences. Yet, data on the effects of heavy exposures are lacking, even as access to potent cannabis is be-

coming easier. The burden of cannabis' effects may fall more heavily on people who, because of genetic makeup or early life exposures, are at greatest risk for brain structural changes, psychosis, or addiction. It is safer not to expose people to psychoactive drugs. However, in evaluating safety, it is important to dissociate correlation from causation, even in longitudinal studies. People predisposed to use cannabis differ from nonusers, regardless of whether they choose to use the drug.

ARTICLE INFORMATION

Author Affiliation: Laboratory of Neurogenetics, Office of the Clinical Director, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Rockville, Maryland.

Corresponding Author: David Goldman, MD, Laboratory of Neurogenetics, Office of the Clinical Director, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, 5625 Fishers Ln, Room 3S32, Rockville, MD 20852 (davidgoldman@mail.nih.gov).

Published Online: August 26, 2015. doi:10.1001/jamapsychiatry.2015.1332.

Conflict of Interest Disclosures: None reported.

Disclaimer: The views expressed in this article are those of the author and do not reflect the official position of the National Institutes of Health.

REFERENCES

1. Volkow ND, Baler RD, Compton WM, Weiss SRB. Adverse health effects of marijuana use. *N Engl J Med*. 2014;370(23):2219-2227.

2. Goldman D, Oroszi G, Ducci F. The genetics of addictions: uncovering the genes. *Nat Rev Genet*. 2005;6(7):521-532.

3. van Amsterdam J, Nutt D, Phillips L, van den Brink W. European rating of drug harms. *J Psychopharmacol*. 2015;29(6):655-660.

4. Pagliaccio D, Barch DM, Bogdan R, et al. Shared predisposition in the relationship between cannabis use and subcortical brain structure [published online August 26, 2015]. *JAMA Psychiatry*. doi:10.1001/jamapsychiatry.2015.1054.

5. French L, Gray C, Leonard G, et al. Early cannabis use, polygenic risk score for schizophrenia, and brain maturation in adolescence [published online August 26, 2015]. *JAMA Psychiatry*. doi:10.1001/jamapsychiatry.2015.1131.