Commentary: Navigating the Complexities of Marijuana

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Abstract

Science needs to drive our thinking as we navigate a new legislative environment in which many Americans have access to marijuana for therapeutic or recreational use. With the responsibility to fund, conduct, and make use of the research on marijuana, and understand the impacts of new policies, comes the obligation of not thinking in simplistic, black-and-white terms about this substance. The drug's unique harms include neurodevelopmental impacts that may be long lasting or permanent, yet some evidence suggests the drug may benefit people with certain medical conditions (e.g., chronic pain). Marijuana use is also entangled with other substance use and should not be considered in isolation. Finally, policy options are not limited to the extremes of prohibition vs. full commercialization; a spectrum of intermediate options can and should be considered *and evaluated* as states create new policies around this drug.

Science needs to drive our thinking as we navigate the new world in which many Americans have access to a third legal drug. Voters in eight states plus the District of Columbia (DC) have chosen to legalize recreational use of marijuana by adults, and 28 states (plus DC) now have passed some kind of medical marijuana law. With the responsibility to fund, conduct, and listen to the science on marijuana and understand the impacts of new policies comes an additional responsibility: that of remaining sufficiently unbiased and nuanced that we do not succumb to the temptations of thinking in simplistic, black-and-white terms about this substance.

Legalization proponents, motivated partly to undo prohibition's disproportionate criminal justice impact on minority/disadvantaged populations, paint a picture of marijuana as a safe drug, less toxic than tobacco or alcohol, impossible to fatally overdose on. Opponents, starting from the assumption that legalization would automatically create a "big marijuana" industry that profits from addiction, skew the sometimes nebulous data in an opposite direction, assuming in advance that vulnerable populations will be greatly harmed. Neither of these perspectives is fully supported by the available science. Marijuana is a complex substance, and optimal public health solutions are unlikely to come from binary thinking, from assuming it is harmful for everyone who uses it, or from thinking about it apart from its

wider context. Fortunately, the options available to states as they implement new laws may be able to address some of this drug's complexities.

We do know that marijuana is addictive, with roughly 30 percent of past-year marijuana users having some degree of marijuana use disorder.[1] The drug acutely affects memory, judgment, sensory experiences, and mood, regardless of whether it is taken for therapeutic purposes or recreationally [the exception being certain strains bred for high cannabidiol content and very low tetrahydrocannabinol (THC)]; and it impairs driving ability, especially when combined with alcohol.[2] Its actual impact on highway safety has proven hard to disentangle from alcohol, but many studies point roughly to a doubling of crash risk after marijuana use.[3] Smoking marijuana likely has some of the same adverse cardiopulmonary effects as cigarette smoking, although we do not yet know if it raises risk for lung cancer.[4]

Marijuana use can raise risk for several substance use disorders,[5] and there is mounting evidence that it can increase risk for psychosis in individuals with an inherited predisposition.[6] Marijuana exposure also likely impacts cognitive functioning and brain development, both prenatally and in adolescence. The endocannabinoid system, with which THC interacts, plays important roles in neurodevelopmental processes such as synapse formation and axonal migration; this provides theoretical justification in support of data suggesting prenatal marijuana exposure may have lasting adverse consequences for the baby.[7, 8] And findings from two large longitudinal studies link heavy, frequent marijuana use, in one case specifically in adolescence, to impairment in cognitive abilities.[9, 10]

We still do not know if these cognitive impacts are reversible. In one of the longitudinal studies, users who met diagnostic criteria for marijuana dependence in their teens lost up to 8 IQ points when it was measured in mid-adulthood, even if they had quit using in the interim; those who initiated marijuana use in adulthood did not show those losses.[10] We do not know if there are safe levels of use; most studies showing adverse cognitive impacts have linked those to heavy or frequent use, and thus it would be premature to assume that all marijuana use is harmful, especially in adults. We also do not know the impact of marijuana use on the aging brain. Current data on this question are mixed, with some preclinical work hinting at possible beneficial effects for Alzheimers.[11] How marijuana may interact with other diseases of the aging body and the medications used to treat them is another unknown.

The shifting ways marijuana is being used in today's world—including therapeutic use, generally increasing THC content (potency), and novel routes of administration (edibles, vaping) — demand consideration. Are people who report daily use on surveys using it once or multiple times a day? Are they combining it with other substances (e.g., tobacco, alcohol)? To what extent is marijuana use a social activity? Some have speculated that shifting patterns of drug use among teens—for instance the overall declines seen in the annual Monitoring the Future survey in most drugs except marijuana[12]—could be related to shifting practices involving social media, mobile devices, and other factors in the lives of adolescents, but at this point there is little evidence from which to draw conclusions. The Adolescent Brain Cognitive Development (ABCD) study, a large 10-year longitudinal study now underway at 21 research centers across the country, will be able to shed some light on these and many other questions.

Clarifying what the greatest risks and harms from marijuana use are and what populations are most at risk will provide guidance on what kinds of prevention interventions and policies are likely to be of greatest benefit. Among other things, prevention research should investigate whether selective interventions, perhaps aimed at preventing use by pregnant women and drivers and escalation from experimentation to heavy use among at-risk youth would be better investment of limited prevention resources than universal interventions painting a blanket dire picture of marijuana. The science does not fully support the latter picture, and it is unlikely to be believed by a public increasingly persuaded of the opposite (also not accurate) view, that marijuana is basically harmless.

Nuanced thinking around marijuana additionally means not taking considering it in isolation but in its relationship to other substances. For example, it will be valuable to learn whether marijuana substitutes for, complements, or impedes cessation of tobacco use.[13] The effects of marijuana policies on alcohol consumption also need clarification. Some data currently support a possible substitution effect—more liberal marijuana laws associated with reduced alcohol consumption—and some evidence supports a complementary effect in which more liberal marijuana policies increase both marijuana and alcohol use.[14]

Greatly complicating the marijuana policy picture, of course—as well as further distinguishing this substance from alcohol and tobacco—is the likelihood that marijuana (or its constituents) may provide therapeutic benefits for some users. Most indications for medical marijuana are based on little or no scientific evidence, but there are a few notable exceptions. THC-based drugs are already FDA-approved for chemotherapy-induced nausea and wasting, and they are approved in other countries for pain. Some research supports the possible efficacy of cannabinoids for chronic neuropathic or cancer pain.[15]

This is highly relevant given the current opioid crisis. Two studies have now linked medical marijuana availability to a reduced rate of increase in opioid overdose deaths.[16, 17] Another study found that medical marijuana laws were associated with lower rates of 21- to 40-year-old fatally injured drivers testing positive for opioids.[18] And a study using Medicare records has shown fewer opioid prescriptions for diseases that marijuana may be used to treat (especially pain) in states with medical marijuana laws.[19] If further research bears out a substitution effect, this could have important public health implications.

Caution is necessary, however.[20] The effects of marijuana use for pain, especially long-term, are unknown, and some small studies have already hinted that it could pose some of the same problems lately being identified for opioids, such as hyperalgesia.[21] And at this point, potential users and doctors in a position to recommend marijuana face great uncertainties and a lack of authoritative guidance. Little is known about the necessary constituents, proper dosing, alternative routes of administration, interactions with other drugs, or risks for different patient populations. Medical marijuana is being dispensed in forms that are not standardized, in haphazard ways, according to widely variable state laws, and with few exceptions is indistinguishable from marijuana sold and used for recreational purposes.

There is no reason that some of these issues cannot be addressed. The laws are rapidly changing, but not so fast that existing science cannot be used to guide how they are

implemented. As policymakers consider how to minimize negative impacts of marijuana legalization and leverage any potential benefits from it, they need to consider a wide spectrum of regulatory options. Fortunately the choices are not limited to continued prohibition versus a free marijuana market. As revealed in a recent RAND report prepared for the state of Vermont, a range of intermediate regulatory approaches could remove criminal sanctions (decriminalization) yet not facilitate full commercialization or the creation of an industry that has powerful lobbying potential and profits most from the heaviest users, as is the case with tobacco.[22]

Only by thinking about the whole landscape of marijuana and its use and effects, in an unbiased way, will states be able to develop a strong, and honest, public health framework for their approach to marijuana. Crafting smart, realistic policies requires confronting the reality that marijuana has its own unique harms and possible benefits and that it cannot be shoehorned into the molds of other legal drugs or thought of in isolation. As researchers, we must continue to study this substance intensively, from all angles and in the context of other substances, and we must also take full advantage of the natural experiments created by changed policies in specific states as well as other countries to learn all we can. With that knowledge we can foster the rational and informed public discourse needed to make wise decisions and implement new policies in the best possible way.

References

1. Hasin DS, Saha TD, Kerridge BT, et al. Prevalence of Marijuana Use Disorders in the United States Between 2001–2002 and 2012–2013. JAMA Psychiatry. 2015; 72(12):1235–1242. DOI: 10.1001/jamapsychiatry.2015.1858 [PubMed: 26502112]

2. Hartman RL, Huestis MA. Cannabis effects on driving skills. Clin Chem. 2013; 59(3):478–492. DOI: 10.1373/clinchem.2012.194381 [PubMed: 23220273]

3. Asbridge M, Hayden JA, Cartwright JL. Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. BMJ. 2012; 344:e536.doi: 10.1136/bmj.e536 [PubMed: 22323502]

4. Tashkin DP. Effects of marijuana smoking on the lung. Ann Am Thorac Soc. 2013; 10(3):239–247. DOI: 10.1513/AnnalsATS.201212-127FR [PubMed: 23802821]

5. Blanco C, Hasin DS, Wall MM, Flórez-Salamanca L, Hoertel N, Wang S, Kerridge BT, Olfson M. Cannabis Use and Risk of Psychiatric Disorders: Prospective Evidence From a US National Longitudinal Study. JAMA Psychiatry. 2016; 73(4):388–395. DOI: 10.1001/jamapsychiatry.2015.3229 [PubMed: 26886046]

6. Radhakrishnan R, Wilkinson ST, D'Souza DC. Gone to Pot - A Review of the Association between Cannabis and Psychosis. Front Psychiatry. 2014; 5:54.doi: 10.3389/fpsyt.2014.00054 [PubMed: 24904437]

7. Wu C-S, Jew CP, Lu H-C. Lasting impacts of prenatal cannabis exposure and the role of endogenous cannabinoids in the developing brain. Future Neurol. 2011; 6(4):459–480. [PubMed: 22229018]

8. El Marroun H, Tiemeier H, Franken IHA, et al. Prenatal cannabis and tobacco exposure in relation to brain morphology: a prospective neuroimaging study in young children. Biol Psychiatry. 2016; 79(12):971–979. [PubMed: 26422004]

9. Auer R, Vittinghoff E, Yaffe K, Künzi A, Kertesz SG, Levine DA, Albanese E, Whitmer RA, Jacobs DR, Sidney S, Glymour MM, Pletcher MJ. Association Between Lifetime Marijuana Use and Cognitive Function in Middle Age: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. JAMA Intern Med. 2016; 176(3):352–361. DOI: 10.1001/jamainternmed.2015.7841 [PubMed: 26831916]

10. Meier MH, Caspi A, Ambler A, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. Proc Natl Acad Sci U S A. 2012; 109(40):E2657–E2664. DOI: 10.1073/pnas.1206820109 [PubMed: 22927402]

11. Cao C, Li Y, Liu H, Bai G, Mayl J, Lin X, Sutherland K, Nabar N, Cai J. The potential therapeutic effects of THC on Alzheimer's disease. J Alzheimers Dis. 2014; 42(3):973–84. DOI: 10.3233/JAD-140093 [PubMed: 25024327]

12. Johnston, LD., O'Malley, PM., Miech, RA., Bachman, JG., Schulenberg, JE. Overview, key findings on adolescent drug use. Ann Arbor: Institute for Social Research, The University of Michigan; 2016. Monitoring the Future national survey results on drug use, 1975–2015.

13. Rabin RA, Ashare RL, Schnoll RA, Cinciripini PM, Hawk LW, Lerman C, Tyndale RF, George TP. Does cannabis use moderate smoking cessation outcomes in treatment-seeking tobacco smokers? Analysis from a large multi-center trial. Am J Addict. 2016; 25:291–296. DOI: 10.1111/ajad.12382 [PubMed: 27187893]

14. Guttmannova K, Lee CM, Kilmer JR, Fleming CB, Rhew IC, Kosterman R, Larimer ME. Impacts of Changing Marijuana Policies on Alcohol Use in the United States. Alcohol Clin Exp Res. 2016; 40:33–46. DOI: 10.1111/acer.12942 [PubMed: 26727520]

15. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, Keurentjes JC, Lang S, Misso K, Ryder S, Schmidlkofer S, Westwood M, Kleijnen J. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. JAMA. 2015; 313(24):2456–2473. DOI: 10.1001/jama.2015.6358 [PubMed: 26103030]

16. Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999–2010. JAMA Intern Med. 2014; 174(10):1668–1673. DOI: 10.1001/jamainternmed.2014.4005 [PubMed: 25154332]

17. National Bureau of Economic Research. Do Medical Marijuana Laws Reduce Addictions and Deaths Related to Pain Killers?. Cambridge, MA: National Bureau of Economic Research; 2015. Working Paper No 21345

18. Kim, June H., Santaella-Tenorio, Julian, Mauro, Christine, Wrobel, Julia, Cerdà, Magdalena, Keyes, Katherine M., Hasin, Deborah, Martins, Silvia S., Li, Guohua. State Medical Marijuana Laws and the Prevalence of Opioids Detected Among Fatally Injured Drivers. American Journal of Public Health. Nov; 2016 106(11):2032–2037. DOI: 10.2105/AJPH.2016.303426 [PubMed: 27631755]

19. Bradford AC, Bradford WD. Medical Marijuana Laws Reduce Prescription Medication Use In Medicare Part D. Health Aff. Jul; 2016 35(7):1230–1236.

20. Choo EK, Feldstein Ewing SW, Lovejoy TI. Opioids Out, Cannabis InNegotiating the Unknowns in Patient Care for Chronic Pain. JAMA. 2016; 316(17):1763–1764. DOI: 10.1001/jama.2016.13677 [PubMed: 27802551]

21. Walter C, Oertel B, Lötsch J. THC may reproducibly induce electrical hyperalgesia in healthy volunteers. Eur J Pain. 2015; 19(4):516–8. [PubMed: 25070926]

22. Caulkins, J., Kilmer, B., Kleiman, M., et al. Considering marijuana legalization: Insights for Vermont and Other Jurisdictions. Santa Monica, CA: RAND Corporation; 2015. Available at: http://www.rand.org/pubs/research_reports/RR864.html