Liberalising cannabis legislation in South Africa: Potential public health consequences for adolescents and pregnant women

There is a global trend towards liberalising cannabis legislation amid recognition that previous restrictions caused social harm and impeded medical research on phytocannabinoids.[1,2] Liberal legislation and attitudes toward cannabis may create opportunities to harness the pharmacological benefits of cannabis for epilepsy,[3] chronic pain,[4] nausea and spasticity,[5] among other medical conditions. Nonetheless, laws that potentially increase access to cannabis could have public health consequences with regard to respiratory health, traffic-related injuries, and the mental health of vulnerable populations.[6] Rigorous debate about these public health concerns is needed as South Africa (SA) moves towards ratifying the Cannabis for Private Purposes Bill[7] introduced to Parliament in October 2020. The Bill, which is currently before the Portfolio Committee on Justice and Correctional Services, makes provision for adults to possess, cultivate and process a prescribed quantity of cannabis plants, and to use cannabis, while also explicitly acknowledging the need to protect citizens from potential harms. This prompts questions about who should be protected from cannabis harms. Drawing on recent systematic reviews and expert consensus, we argue that adolescents, pregnant mothers, and fetuses are three groups vulnerable to the harmful effects of cannabis, requiring special consideration as noted in recent Portfolio Committee hearings.

Cannabis exposure and adolescent development

The lack of well-designed longitudinal studies assessing the impact of cannabis on adolescent health makes it impossible to conclude that adolescent cannabis use is safe.[8] If anything, the evidence highlights safety concerns, with regular cannabis use during adolescence associated with persistent functional and structural neurological changes,[9] and cognitive and emotional deficits.[10] Adolescents are more vulnerable than adults to the negative effects of cannabidiol and tetrahydrocannabinol, with regular exposure during adolescence associated with more severe and persistent negative outcomes than use during adulthood.[11,12]

Cannabis use during adolescence causes structural, functional and histological alterations in the frontoparietal, frontolimbic, frontostriatal and cerebellar regions of the brain,[9] and also affects the endocannabinoid system, which is particularly susceptible to the harmful effects of cannabis as it undergoes profound developmental changes during adolescence.[10] Prolonged cannabis use during adolescence also disrupts the neuromaturation processes that occur during this period, with synaptic pruning and white matter development particularly affected.[12] Adolescent cannabis use is also associated with cognitive deficits;[10] adolescents who use cannabis frequently demonstrate more severe executive dysfunction than their adult counterparts.[13] Critically, it is not yet clear whether these effects are reversible,[9] with some evidence suggesting that cannabis-related neurocognitive impairments persist into adulthood, even after prolonged abstinence.[14,15] Furthermore, craving and disinhibition may be greater among adolescents compared with adults, potentially making adolescents more susceptible to substance use disorders.[13]

Although it is unclear how adolescent cannabis use affects the onset of schizophrenia, some studies indicate this as an area of concern and a reason to delay the age at which cannabis use is initiated.[16] Adolescent cannabis use is, however, associated with an increased risk of psychosis in adulthood[17] and other psychopathology,[10] including elevated risk of depression, suicidal ideation and suicidal behaviour.[18] The harmful effects of adolescent cannabis use on mental health appear to be mediated by genetic and environmental factors, although it is unclear how risk factors interact to cause negative outcomes.[19] Nonetheless, most of the clinical and preclinical data point to a correlation between adolescent cannabinoid exposure and persistent adverse neuropsychiatric outcomes in adulthood.[15] It is possible that cannabis is not solely responsible for the observed long-lasting neuropsychiatric effects of adolescent cannabis use; however, cannabis is a significant component of the risk profile.[15]

Consequences of perinatal cannabis exposure

Ethical and methodological problems associated with administering cannabis to pregnant women have resulted in an over-reliance on animal models to make inferences about the harms of *in utero* cannabis exposure. Furthermore, many women who use cannabis during pregnancy also have poor nutrition and inadequate prenatal care, making it difficult to tease out the effects of cannabis on fetal development from these other confounding factors.[20] Nonetheless, evidence suggests that cannabis use during pregnancy increases the risk of adverse outcomes for women and their neonates,[20-22] to the extent that the American College of Obstetricians and Gynaecologists advised physicians to discourage use of cannabis during preconception, pregnancy and lactation.[23]

Prenatal cannabis exposure is associated with an increased risk of fetal growth retardation and childhood behavioural disturbances.[24,25] Infants exposed to cannabis *in utero* tend to have lower birthweights and are more likely to need placement in the neonatal intensive care unit compared with infants without exposure.[21,25] Cannabis use during pregnancy and breastfeeding alters the developmental trajectory of multiple brain regions and may result in lasting functional consequences,[25,26] including impaired higher-order executive functioning (i.e. impulse control, visual memory and attention)[27] and attention deficit hyperactivity disorder during childhood,[28] which affect academic performance and social adjustment. Furthermore, cannabis interferes with the endocannabinoid system (present from approximately day 16 of gestation), believed to be integral to fetal brain development, which in turn could adversely affect fetal brain growth, including structural and functional neurodevelopment.[20] These observed neurocognitive and behavioural changes seem to persist throughout life.[26]

The mechanisms through which *in utero* cannabis exposure causes neurocognitive and behavioural changes are poorly understood, but it appears that cannabis influences epigenetic regulation, potentially causing persistent fetal genetic changes.[26] Cannabis may be toxic to human chromosomes,[20] with chromosomal changes caused by *in utero* cannabis exposure contributing to the lower fecundity and higher miscarriage rates known to occur among women who use cannabis.[20] The multidimensional chromosomal and genome toxicity of cannabis may also contribute to congenital anomalies and cancer in children.[29] These detrimental consequences are exacerbated by additional environmental and chemical insults, including poor nutrition and exposure to other toxic substances such as alcohol.[26]

Conclusion

With regard to cannabis use during adolescence and pregnancy, scientific research may not have kept pace with the speed at which cannabis laws are being liberalised. This is not to say that cannabis legalisation should be resisted, but rather that the best available evidence suggests that adolescent cannabis use should be actively discouraged and that pregnant women should be advised to avoid cannabis use.[30] It remains to be seen whether the need for caution will be reflected in SA's revised legal frameworks.

Jason Bantjes
Alcohol, Tobacco and Other Drug Research Unit, South African Medical Research Council, Cape Town, South Africa; Institute for Life Course Health Research, Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa
jason.bantjes@mrc.ac.za

Bronwyn Myers
Curtin enAble Institute, Curtin University, Perth, Australia; Alcohol, Tobacco and Other Drug Research Unit, South African Medical Research Council, Cape Town, South Africa

Charles Parry
Alcohol, Tobacco and Other Drug Research Unit, South African Medical Research Council, Cape Town, South Africa; Department of Psychiatry, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

1. Hudak JJ. Marijuana: A Short History. Washington, DC: Brookings Institution Press, 2016. http://www.jstor.org/stable/10.7864/j.ctt1hfr1qj (accessed 14 March 2022).
2. Schlag AK, Baldwin DS, Barnes M, et al. Medical cannabis in the UK: From principle to practice. J Psychopharmacol 2020;34(9):931-937. https://doi.org/10.1177/0269881120926677
3. Filloux FM. Cannabinoids for pediatric epilepsy? Up in smoke or real science? Transl Pediatr 2015;4(4):271-282. https://doi.org/10.3978/J.ISSN.2224-4336.2015.10.03
4. Banerjee S, McCormack S. Medical Cannabis for the Treatment of Chronic Pain: A Review of Clinical Effectiveness and Guidelines. 2019. Ottawa: Canadian Agency for Drugs and Technologies in Health, 2019. https://www.ncbi.nlm.nih.gov/books/NBK546424/ (accessed 14 March 2022).
5. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: A systematic review and meta-analysis. JAMA 2015;313(24):2456-2473. https://doi.org/10.1001/jama.2015.6358
6. Hall W, Stjepanović D, Caulkins J, et al. Public health implications of legalising the production and sale of cannabis for medicinal and recreational use. Lancet 2019;394(10208):1580-1590. https://doi.org/10.1016/S0140-6736(19)31789-1
7. Parliament of the Republic of South Africa. Cannabis for Private Purposes Bill (B19-2020). https://www.parliament.gov.za/bill/2292553 (accessed 14 March 2022).
8. Fischer AS, Tapert SF, Louie DL, Schatzberg AF, Singh MK. Cannabis and the developing adolescent brain. Curr Treat Options Psychiatry 2020;7(2):144-161. https://doi.org/10.1007/s40501-020-00202-2
9. Lichenstein SD, Manco N, Cope LM, et al. Systematic review of structural and functional neuroimaging studies of cannabis use in adolescence and emerging adulthood: Evidence from 90 studies and 9441 participants. Neuropsychopharmacology 2022;47(5):1000-1028. https://doi.org/10.1038/s41386-021-01226-9
10. Blest-Hopley G, Colizzi M, Giampietro V, Bhattacharyya S. Is the adolescent brain at greater vulnerability to the effects of cannabis? A narrative review of the evidence. Front Psychiatry 2020;11:859. https://doi.org/10.3389/fpsyt.2020.00859
11. Dhein S. Different effects of cannabis abuse on adolescent and adult brain. Pharmacology 2020;105(11-12):609-617. https://doi.org/10.1159/000509377
12. Lubman DI, Cheetham A, Yücel M. Cannabis and adolescent brain development. Pharmacol Ther 2015;148:1-16. https://doi.org/10.1016/j.pharmthera.2014.11.009
13. Gorey C, Kuhns L, Smaragdi E, Kroon E, Cousijn J. Age-related differences in the impact of cannabis use on the brain and cognition: A systematic review. Eur Arch Psychiatry Clin Neurosci 2019;269(1):37-58. https://doi.org/10.1007/s00406-019-00981-7
14. Ganzer F, Bröning S, Kraft S, Sack PM, Thomasius R. Weighing the evidence: A systematic review on long-term neurocognitive effects of cannabis use in abstinent adolescents and adults. Neuropsychol Rev 2016;26(2):186-222. https://doi.org/10.1007/S11065-016-9316-2
15. Levine A, Clemenza K, Rynn M, Lieberman J. Evidence for the risks and consequences of adolescent cannabis exposure. J Am Acad Child Adolesc Psychiatry 2017;56(3):214-225. https://doi.org/10.1016/j.jaac.2016.12.014
16. James A, James C, Thwaites T. The brain effects of cannabis in healthy adolescents and in adolescents with schizophrenia: A systematic review. Psychiatry Res 2013;214(3):181-189. https://doi.org/10.1016/j.pscychresns.2013.07.012
17. Kiburi SK, Molebatsi K, Ntlantsana V, Lynskey MT. Cannabis use in adolescence and risk of psychosis: Are there factors that moderate this relationship? A systematic review and meta-analysis. Subst Abus 2021;42(4):527-542. https://doi.org/10.1080/08897077.2021.1876200
18. Gobbi G, Atkin T, Zytynski T, et al. Association of cannabis use in adolescence and risk of depression, anxiety, and suicidality in young adulthood: A systematic review and meta-analysis. JAMA Psychiatry 2019;76(4):426-434. https://doi.org/10.1001/jamapsychiatry.2018.4500
19. Hurd YL, Manzoni OJ, Pletnikov MV, Lee FS, Bhattacharyya S, Melis M. Cannabis and the developing brain: Insights into its long-lasting effects. J Neurosci 2019;39(42):8250-8258. https://doi.org/10.1523/JNEUROSCI.1165-19.2019
20. Volkow ND, Compton WM, Wargo EM. The risks of marijuana use during pregnancy. JAMA 2017;317(2):129-130. https://doi.org/10.1001/jama.2016.18612
21. Gunn JKL, Rosales CB, Center KE, et al. Prenatal exposure to cannabis and maternal and child health outcomes: A systematic review and meta-analysis. BMJ Open 2016;6(4):e009986. https://doi.org/10.1136/bmjopen-2015-009986
22. Singh S, Filion KB, Abenhaim HA, Eisenberg MJ. Prevalence and outcomes of prenatal recreational cannabis use in high-income countries: A scoping review. BJOG 2020;127(1):8-16. https://doi.org/10.1111/1471-0528.15946
23. American College of Obstetricians and Gynecologists (ACOG). Marijuana use during pregnancy and lactation. Committee Opinion No. 722, October 2017. https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2017/10/marijuana-use-during-pregnancy-and-lactation (accessed 14 March 2022).
24. Tirado-Muñoz J, Lopez-Rodriguez AB, Fonseca F, Farré M, Torrens M, Viveros MP. Effects of cannabis exposure in the prenatal and adolescent periods: Preclinical and clinical studies in both sexes. Front Neuroendocrinol 2020;57:100841. https://doi.org/10.1016/j.yfrne.2020.100841
25. 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. https://doi.org/10.1016/J.biopsych.2015.08.024
26. Scheyer AF, Melis M, Trezza V, Manzoni OJJ. Consequences of perinatal cannabis exposure. Trends Neurosci 2019;42(12):871-884. https://doi.org/10.1016/j.tins.2019.08.010
27. Wu CS, Jew CP, Lu HC. Lasting impacts of prenatal cannabis exposure and the role of endogenous cannabinoids in the developing brain. Future Neurol 2011;6(4):459-480. https://doi.org/10.2217/fnl.11.27
28. Roncero C, Valriberas-Herrero I, Mezzatesta-Gava M, Villegas JL, Aguilar L, Grau-López L. Cannabis use during pregnancy and its relationship with fetal developmental outcomes and psychiatric disorders: A systematic review. Reprod Health 2020;17(1):25. https://doi.org/10.1186/s12978-020-0880-9
29. Reece AS, Hulse GK. Epidemiological overview of multidimensional chromosomal and genome toxicity of cannabis exposure in congenital anomalies and cancer development. Sci Rep 2021;11:13892. https://doi.org/10.1038/s41598-021-93411-5
30. Office of the Surgeon General, US Department of Health and Human Services. U.S. Surgeon General's Advisory: Marijuana use and the developing brain. Last reviewed 29 August 2019. https://www.hhs.gov/surgeongeneral/reports-and-publications/addiction-and-substance-misuse/advisory-on-marijuana-use-and-developing-brain/index.html (accessed 14 March 2022).

S Afr Med J 2022;112(6):393-394. https://doi.org/10.7196/SAMJ.2022.v112i6.16521