AMERICAN ACADEMY OF OPHTHALMOLOGY®
In partnership with the AMERICAN GLAUCOMA SOCIETY
Special Commentary

American Glaucoma Society Position Statement on Cannabinoid Use in Pediatric Glaucoma Patients

Adriana L. Grossman, MHA, MPH - *Miami, Florida*
Matthew J. Javitt, BS - *Miami, Florida*
Steven J. Moster, MD - *Philadelphia, Pennsylvania*
Alana L. Grajewski, MD - *Miami, Florida*
on behalf of the Pediatric Glaucoma Subcommittee of the American Glaucoma Society (2017–2018)

Pediatric glaucoma refers to a group of conditions in which elevated intraocular pressure (IOP) leads to damage of the developing eye in infancy and early childhood. In addition to anatomic effects specific to children, particularly ocular enlargement, elevated eye pressure at any age can damage the optic nerve, resulting in vision loss. Ophthalmologists face challenges choosing appropriate treatment methods to prevent childhood blindness. Standard treatment for most childhood glaucoma types includes surgical intervention. Medical management is a primary treatment and is used in conjunction with surgical intervention in all pediatric glaucoma types, but surgery, examinations under anesthesia, or both are an integral part of the treatment for infants and children with glaucoma. As cannabinoids become progressively more accessible through legislation reform, parents and patients may begin turning to ophthalmologists to discuss their usefulness in children in place of medications and surgery.

There is no evidence that medical cannabinoids currently are an effective treatment for improving IOP or preserving ganglion cell function in patients with glaucoma.

Cannabinoid receptors play a role in appetite, pain, mood, and memory in the body. Type 1 receptors are located in the central nervous system, lungs, and kidneys. Animal studies have shown both neuroprotective effects[1,2] and neurotoxicity[2] when cannabinoids are administered after experimental nerve injury. There is limited evidence in rat models suggesting that subjects receiving tetrahydrocannabinol analogs showed better preservation of retinal structures compared with controls.[3] These findings present an interesting avenue for continued research into methods of preserving optic nerve function alongside IOP-lowering therapies but are far removed from clinical relevance. A systematic review of randomized controlled trials[4] identified one very small trial that showed a short-term ocular hypotensive effect of 1 of 3 tested cannabinoids when administered as an oromucosal spray.[5] To date, other studies showing positive effects also have found that pressure reduction lasts only a few hours, which would require dosing schedules that would limit clinical usefulness. A recent study showed that cannabidiol, the cannabinoid that has shown effectiveness as an antiepileptic, increased IOP in mouse models by inhibiting type 1 receptor activation. Moreover, the transient hypotensive effects shown in previous studies were attributed to the more psychoactive cannabinoid, tetrahydrocannabinol.[6] It is important to note that the concentrations of tetrahydrocannabinol used in the above studies are much lower than those found in common strains of cannabis sold in dispensaries.[7] Achieving therapeutic hypotensive effects of cannabis therefore may require use of the most hallucinogenic ingredients in high doses.[8] In summary, there is no evidence that medical cannabinoids currently are an effective treatment for improving IOP or preserving ganglion cell function in patients with glaucoma.

Many studies suggest that early cannabinoid use during adolescence, usually defined as use before 16 years of age, is associated with subsequent impaired neurocognitive development.[6] A birth cohort of 1037 individuals, who underwent neurophysiologic testing before cannabis use and at intervals up to 38 years of age, compared those cohort members who became regular cannabis users with nonusers or irregular users. The persistent cannabis users showed neuropsychological decline broadly across several domains of functioning with trends toward lower intelligence quotient scores even after controlling for years of education.[9] Radiographic studies of regular cannabis users and nonusers found changes in white matter development in early-onset users compared with later-onset users and nonusers. Early-onset users also demonstrated cognitive deficits in executive functioning and increased impulsivity.[10] Early use of cannabinoids during adolescence is associated with a disproportionate prevalence of users having psychiatric disorders, such as schizophrenia,[11] psychotic symptoms,[12] future substance abuse,[13] and depression in adulthood.[14] At this point, the clinical and preclinical literature on early exposure to cannabis does not prove causality, but early use is correlated with neurocognitive developmental changes and affective outcomes in adulthood.

The American Medical Association recognizes the potential usefulness of marijuana in certain conditions. They include treatment for adults with chemotherapy-associated nausea and vomiting, cachexia, and certain neurologic conditions such as spasticity associated with multiple sclerosis. Data on its effectiveness in pediatric populations are limited to its role in decreasing seizures in recalcitrant

https://doi.org/10.1016/j.ogla.2019.07.007
ISSN 2589-4196/19

epilepsy.[15] Currently, the American Academy of Pediatrics does not support the use of marijuana in patients younger than 21 years, given the possibilities of adverse health and brain development.[16] However, it does recognize that it may be used as an option for children with life-limiting or severely debilitating conditions that are unresponsive to current therapies.

There are currently no studies on the effects of cannabinoids on IOP in the pediatric population. There are unclear but potentially negative neurocognitive developmental implications in pediatric patients using cannabinoids. Current medical and surgical management to stop the progression of glaucoma is effective. The American Glaucoma Society does not support the use of cannabinoids for treatment of pediatric glaucoma.

Acknowledgment. Members of the Pediatric Glaucoma Subcommittee of the American Glaucoma Society: Allen D. Beck, MD, Lauren S. Blieden, MD, Elena Bitrian, MD, Ta C. Chang, MD, Sharon F. Freedman, MD, Elizabeth Hodapp, MD, Keren M. Joos, MD, Bibiana J. Reiser, MD, and Angelo P. Tanna, MD.

References

1. Yoles E, Belkin M, Schwartz M. HU-211, a nonpsychotropic cannabinoid, produces short- and long-term neuroprotection after optic nerve axotomy. *J Neurotrauma*. 1996;13(1):49–57.
2. Sarne Y, Mechoulam R. Cannabinoids: between neuroprotection and neurotoxicity. *Curr Drug Targets CNS Neurol Disord*. 2005;4(6):677–684.
3. Lax P, Esquiva G, Altavilla C, Cuenca N. Neuroprotective effects of the cannabinoid agonist HU210 on retinal degeneration. *Exp Eye Res*. 2014;120:175–185.
4. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA*. 2015;313(24):2456–2473.
5. Tomida I, Azuara-Blanco A, House H, et al. Effect of sublingual application of cannabinoids on intraocular pressure: a pilot study. *J Glaucoma*. 2006;15(5):349–353.
6. Miller S, Daily L, Leishman E, et al. Δ9-Tetrahydrocannabinol and cannabidiol differentially regulate intraocular pressure. *Invest Ophthalmol Vis Sci*. 2018;59(15):5904–5911.
7. Pujari R. Treating glaucoma with medical marijuana: peering through the smoke. *Ophthalmol Glaucoma*. 2019;2:201–203.
8. 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.
9. 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.
10. Gruber SA, Dahlgren MK, Sagar KA, et al. Worth the wait: effects of age of onset of marijuana use on white matter and impulsivity. *Psychopharmacology (Berl)*. 2014;231(8):1455–1465.
11. Galvez-Buccollini JA, Proal AC, Tomaselli V, et al. Association between age at onset of psychosis and age at onset of cannabis use in non-affective psychosis. *Schizophr Res*. 2012;139(1–3):157–160.
12. Moore THM, Zammit S, Lingford-Hughes A, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet*. 2007;370(9584):319–328.
13. Mayet A, Legleye S, Falissard B, Chau N. Cannabis use stages as predictors of subsequent initiation with other illicit drugs among French adolescents: use of a multi-state model. *Addict Behav*. 2012;37(2):160–166.
14. Womack SR, Shaw DS, Weaver CM, Forbes EE. Bidirectional associations between cannabis use and depressive symptoms from adolescence through early adulthood among at-risk young men. *J Stud Alcohol Drugs*. 2016;77(2):287–297.
15. Stockings E, Zagic D, Campbell G, et al. Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence. *J Neurol Neurosurg Psychiatry*. 2018;89(7):741–753.
16. Ammerman S, Ryan S, Adelman WP, et al. The impact of marijuana policies on youth: clinical, research, and legal update. *Pediatrics*. 2015;135(3):e769–e785.

Footnotes and Financial Disclosures

Financial Disclosure(s): The author(s) have no proprietary or commercial interest in any materials discussed in this article.

Correspondence:
Alana L. Grajewski, MD, 900 NW 17th Street, 465A, Miami, FL 33136.
E-mail: agrajewski@med.miami.edu.