AMERICAN ACADEMY OF NEUROLOGY®

201 Chicago Avenue
Minneapolis, Minnesota 55415

Tel: (612) 928-6100
Fax: (612) 454-2744

AAN.com

July 1, 2024

Anne Milgram
Administrator
Drug Enforcement Administration
8701 Morrissette Drive
Springfield, VA 22152

RE: Schedules of Controlled Substances: Rescheduling of Marijuana [DEA-1362]

Dear Administrator Milgram,

The American Academy of Neurology (AAN) is the world's largest association of neurologists and neuroscience professionals, with over 40,000 members. The AAN's mission is to enhance member career fulfillment and promote brain health for all. A neurologist is a doctor with specialized training in diagnosing, treating and managing disorders of the brain and nervous system. These neurological conditions affect over one in three people worldwide and include Alzheimer's disease, stroke, concussion, epilepsy, Parkinson's disease, multiple sclerosis, headache, migraine, and more.

The Department of Justice (DOJ) and the Drug Enforcement Administration (DEA) are proposing to "transfer marijuana from schedule I of the Controlled Substances Act (CSA) to schedule III of the CSA, consistent with the view of the Department of Health and Human Services (HHS) that marijuana has a currently accepted medical use as well as HHS's views about marijuana's abuse potential and level of physical or psychological dependence."[1] HHS has recommended that marijuana be transferred from schedule I to schedule III rather than from schedule I to schedule II based on the agency's determination that "the drug has a relatively lower level of abuse compared to drugs currently scheduled in schedules I and II and its evaluation that marijuana may lead to moderate or low physical dependence and has a low likelihood of psychic dependence."[2]

The AAN appreciates the opportunity to respond to this proposal and submits comments in alignment with our organization's position statement on the "Use of Medical Cannabis for Neurologic Disorders."[3]

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[1] 89 Fed. Reg. at 44597.
[2] 89 Fed. Reg. at 44620.
[3] Fee, Dominic, Dan Freedman, et al. AAN Position: Use of Medical Cannabis for Neurologic Disorders, American Academy of Neurology (9 Sept. 2020), www.aan.com/advocacy/medical-cannabis-position-statement.

AAN Position on Rescheduling

The AAN recognizes that the DOJ and DEA must treat HHS's scientific and medical determinations as binding, but believes it is critical that the agency understand the current body of evidence concerning cannabis use for the treatment of neurologic disorders prior to finalizing this rulemaking.

Currently, the AAN does not support the use of, nor any assertion of therapeutic benefits of, cannabis products as medicines for neurologic disorders in the absence of sufficient scientific peer-reviewed research to determine their safety and specific efficacy. The AAN supports all efforts to allow for rigorous research to evaluate the long-term safety and efficacy of cannabis and compounds derived from the plant. This includes proposals that increase access for the study of cannabis under Institutional Review Board (IRB) approved research protocols and the reclassification of cannabis used for medical purposes from its current Schedule I status to Schedule II to allow for and encourage medical research. Efforts to conduct rigorous medical research and reclassify marijuana in the DEA schedule will increase the potential for additional scientific data to inform clinicians and medical professionals. The AAN recognizes that the endocannabinoid system offers potentially highly valuable drug targets, and that cannabis may thereby contain agents with important future therapeutic applications for neurologic disorders.

The AAN does not have a position on the legalization and regulation of public sale of cannabis products. The AAN acknowledges additional cannabis policy issues that require more research, including criminalization, which disproportionally penalizes people of color.

Evaluation of Available Body of Research in Neurology

In HHS's findings with regards to whether marijuana has a currently accepted medical use, the agency "identified mixed findings of effectiveness across indications, ranging from data showing inconclusive findings to considerable evidence in favor of effectiveness, depending on the source."[4] Of the seven indications the agency examined, the analysis included two indications that are highly relevant for neurology: epilepsy and pain. The analysis indicated that of the seven indications, the "largest evidence base for effectiveness exists for marijuana use within the pain indication (in particular, neuropathic pain)."[5]

Existing limited medical research does not support the promotion of cannabis-based products as treatment options for the majority of neurologic disorders.[6] Most studies are small and inadequately designed. There are concerns regarding the composition of cannabis purportedly for medical use as well as the consistency of quality control and assurance measures used in production. There are also concerns regarding the safety of using cannabis in medical settings, especially for pediatric patients[7] and people with disorders of the nervous

[4] 89 Fed. Reg. at 44618.
[5] Id.
[6] Koppel, Barbara S., et al. "Systematic Review: Efficacy and Safety of Medical Marijuana in Selected Neurologic Disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology." *Neurology* vol. 82,17 (2014): 1556-63. doi:10.1212/WNL.0000000000000363.
[7] Patel, Anup D. "Medical Marijuana in Pediatric Neurological Disorders." *Journal of Child Neurology* vol. 31,3 (2016): 388-91. doi:10.1177/0883073815589761.

system who use cannabis to treat neurologic diseases.[8] Psychiatric and neurocognitive adverse effects have been described in studies of recreational and medical use,[9] which may be particularly problematic in a population with compromised neurologic function. The interaction of these compounds with prescription medications is uncertain and may introduce unnecessary and unknown risk for patients living with chronic, complex neurologic diseases that require one or more prescription drugs.[10] In addition, inconsistency and inaccurate labeling exists for the products that are outside the purview of the Food & Drug Administration (FDA).

The AAN supports the appropriate treatment of pain, noting that pain disorders have a significant impact on a large number of neurology patients. Opioids are often used to treat pain but are associated with increased risk of dependency and adverse effects, including death. Moreover, there is insufficient evidence that opioids are effective for the treatment of neuropathic pain, and definitive evidence that they often worsen migraine, a headache disorder.[11] At this time there is a clear need for further research to promote the development of and access to non-opioid therapies for pain. The AAN believes the proposed rescheduling of cannabis is a critical step to developing appropriate pain therapies, improving treatment of chronic pain, and ultimately reducing opioid misuse, abuse, and overdose.

The AAN appreciates the DEA's clarification that hemp and many products containing predominantly cannabidiol (CBD) are excluded from the definition of marijuana in relation to the proposed rescheduling. The AAN notes that studies do support the use of the FDA-approved plant-based mostly purified pharmaceutical grade CBD product that can be legally prescribed in all 50 states without need for a special DEA license to treat seizures associated with Lennox-Gastaut syndrome (LGS)[12] and Dravet syndrome[13] for patients one year and older, and tuberous sclerosis complex (TSC) for patients one year and older.

More quality and thorough research in areas outside of epilepsy is urgently needed to determine the safety and potential medical benefit of various forms of cannabis for neurologic disorders, especially those for which anecdotal evidence is available but where strong scientific data is lacking. Anecdotal evidence may engender public support for the use of cannabis to treat neurologic diseases, but such information must be supported and substantiated by rigorous research, which can then inform government policy.

Finally, safety is of critical importance when cannabis is used in patients with underlying neurologic disorders, or in children whose developing brains may be more vulnerable to its

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[8] Wong, Shane Shucheng, & Timothy E Wilens. "Medical Cannabinoids in Children and Adolescents: A Systematic Review." *Pediatrics* vol. 140,5 (2017): e20171818. doi:10.1542/peds.2017-1818.
[9] Whiting, Penny F., et al. "Cannabinoids for Medical Use: A Systematic Review and Meta-analysis." *JAMA* vol. 313,24 (2015): 2456-73. doi:10.1001/jama.2015.6358.
[10] Gaston, Tyler E., et al. "Interactions between Cannabidiol and Commonly Used Antiepileptic Drugs." *Epilepsia* vol. 58,9 (2017): 1586-1592. doi:10.1111/epi.13852.
[11] Bigal, Marcelo E. & Richard B. Lipton. "What Predicts the Change from Episodic to Chronic Migraine?" *Current Opinion in Neurology* vol. 22,3 (2009): 269-76. doi:10.1097/WCO.0b013e32832b2387.
[12] Devinsky, Orrin, et al. "Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome." *The New England Journal of Medicine* vol. 378,20 (2018): 1888-1897. doi:10.1056/NEJMoa1714631.
[13] Devinsky, Orrin, et al. "Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome." *The New England Journal of Medicine* vol. 376,21 (2017): 2011-2020. doi:10.1056/NEJMoa1611618.

potentially toxic effects from certain compounds found in the plant, such as THC.[14] Research is necessary to develop cannabis-based compounds that have minimal psychoactive properties while retaining any therapeutic pharmacologic effects. Just as it is important to know the potential therapeutic benefit of these compounds, neurology providers and patients also need to know the side effects and drug interactions that can occur. Many medications have shown potential benefits in Phase I and II studies, only to fail in Phase III trials because of side effect profiles.

Conclusion

The AAN appreciates the opportunity to provide comments in response to this historic proposal. The AAN lauds both the DEA and HHS for the thoughtful consideration that underpins this rescheduling recommendation. The AAN has a deep and abiding interest in assuring the best possible care of patients with all types of neurologic disorders and believes it is critical that the agency move forward with rescheduling to support the development of scientific data to support optimal neurologic care. The AAN supports rescheduling marijuana from Schedule I to Schedule II to encourage further scientific research into its safety and benefits. Please contact Matt Kerschner, the AAN's Director, Regulatory Affairs and Policy, at mkerschner@aan.com or Cale Coppage, the AAN's Senior Government Relations Manager, at ccoppage@aan.com with any questions or requests for additional information.

Sincerely,

Carlayne E. Jackson, MD, FAAN
President, American Academy of Neurology

[14] Koppel, Barbara S, et al. "Systematic Review: Efficacy and Safety of Medical Marijuana in Selected Neurologic Disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology." *Neurology* vol. 82,17 (2014): 1556-63. doi:10.1212/WNL.0000000000000363.