Medical Cannabis for Obstructive Sleep Apnea: Premature and Potentially Harmful

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In the United States, currently 29 states and the District of Columbia have enacted laws that allow for the medical use of cannabis. The list of conditions that qualify a patient for the use of medical cannabis varies from state to state. Recently, the medical cannabis citizens' review panel at the Minnesota Department of Health (MDH) added obstructive sleep apnea (OSA) to the list of qualifying conditions for medical cannabis, making Minnesota the first state to approve the use of cannabis for OSA. This decision followed a petition that rightly identified OSA as a public health concern associated with sleepiness and substantial cardiovascular consequences.[1] The petition referenced continuous positive airway pressure (CPAP) as the primary treatment option for OSA and proceeded to list alternative therapeutic modalities including medications, acupuncture, upper airway stimulation, and surgeries. The "brief of support" issued by the MDH in November 2017 allows patients certified as having OSA to enroll in the medical cannabis program from July 1, 2018, and obtain medical cannabis beginning August 1, 2018.

The rationale for approving medical cannabis for OSA in the MDH research brief referenced 2 animal studies involving rats, one proof-of-concept study and a recently published randomized controlled phase 2 trial in humans analyzing dronabinol. Dronabinol, a nonselective cannabinoid C1 and C2 receptor agonist, is an isomeric tetrahydrocannabinol (THC) cannabinoid drug. Dronabinol is currently approved by the US Food and Drug Administration (FDA) for the treatment of nausea and vomiting associated with cancer chemotherapy.

Cannabis is considered a drug with high abuse potential and is categorized as a schedule I drug by the US Drug Enforcement Agency (DEA). In contrast, dronabinol, which can result in physiological dependence and has low abuse potential, is categorized as a schedule III drug.

EFFECTS OF CANNABIS ON SLEEP APNEA

The initial study conducted in rats revealed that direct injection of dronabinol into the nodose ganglia, which contain most cell bodies of the vagus nerve, resulted in a reduction in serotonin-induced reflex apnea duration.[2] An increase in phasic, but not tonic, activation of the genioglossus muscle was observed. These findings suggest that dronabinol results in increased upper airway muscle tone and potentially stabilizes respiration in rats when directly injected into the brain. The second study in rats showed that dronabinol decreased the total apnea index, but sleep efficiency and percent of time spent in rapid eye movement sleep also fell.[3] In this study, there was no change in apnea duration after dronabinol administration.

In a proof-of-concept study that recruited adult subjects (n=17) with moderate to severe OSA (apnea-hypopnea index [AHI] of ≥15 events per hour), dronabinol was used at weekly escalating doses starting at 2.5 mg and increasing up to 10 mg.[4] At 3 weeks (10-mg dose), there was a significant overall reduction in the AHI (−14.1±17.5 events per hour; P=.007), with no change in sleep architecture or serious reported side effects. However, 3 of 8 subjects who received dronabinol at a dose of 10 mg demonstrated no change or an increase in the AHI at 3 weeks. The authors made reference to the potential for heterogeneity in the response to cannabinoids for OSA.

A single phase 2 randomized controlled trial, the PACE (Pharmacotherapy of Apnea by Cannabimimetic Enhancement) trial, was performed in 73 adult subjects with moderate to severe OSA (AHI≥15 and ≤50 events per

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hour; mean AHI, 25.9±11.3 events per hour) using highly selective inclusion and exclusion criteria.[5] Subjects were randomized to receive placebo, 2.5 mg of dronabinol, or 10 mg of dronabinol daily, administered 1 hour before bedtime for up to 6 weeks. Dronabinol was generally safe and well tolerated, with adverse event frequency and severity that were no different from placebo. Sleep architecture was also unchanged. In the primary outcome analysis, the authors reported that dronabinol reduced the AHI in a dose-dependent fashion by 10.7±4.4 (P=.02) and 12.9±4.3 (P=.003) events per hour at doses of 2.5 and 10 mg/d, respectively, at 6 weeks. This difference was based on comparison to the placebo group, which demonstrated an unexplained and statistically significant increase in the AHI (increase in AHI of about 8.5/h) (P=.01). The change from baseline AHI after 6 weeks of treatment, however, was only approximately 2-4/h, a reduction unlikely to be of clinical significance. It is notable that only 6 (15.4%) of 39 subjects met the study's response criteria, which were set at a clinically substandard threshold of an AHI of 15 or less per hour along with a reduction in AHI by 50% or more from baseline. Although subjective sleepiness scores improved, there were no changes in nighttime oxygenation parameters or objective measures of sleepiness on maintenance of wakefulness tests.

EFFECTIVE TREATMENTS FOR SLEEP APNEA

There are multiple effective treatment modalities available for OSA.[6] The CPAP is considered first-line therapy for OSA, and there are no known serious side effects. The American Academy of Sleep Medicine (AASM), in published clinical guidelines on the management and long-term care of patients with OSA, outlines interventions that can help improve CPAP adherence in patients who might find it difficult to tolerate CPAP therapy.[6] These guidelines also clearly detail the role and effectiveness of alternative treatments in patients who are unable to use CPAP. Specifically, oral appliances are considered an acceptable treatment modality and have been shown to reduce symptoms and improve outcomes in patients with OSA. In addition, newer treatment options such as upper airway stimulators are now available.

Oral appliances are not mentioned in the petition to the MDH, whereas medications and acupuncture, which are listed as therapeutic options, are not considered evidence-based treatments for OSA. Although the research brief from the MDH cursorily refers to alternative treatments while discussing CPAP nonadherence, it does not make any mention of the efforts that are routinely made by sleep medicine providers to improve tolerability to CPAP and explore effective alternative treatments for OSA. The MDH brief and inclusion of OSA as a qualifying condition could be interpreted to suggest that patients who are unable to tolerate CPAP for OSA can consider obtaining medical cannabis as the next step for treatment of this condition, notwithstanding potential adverse effects related to cannabis use. In a recent position statement, the AASM explicitly recommended against the use of cannabis and/or its synthetic extracts for the treatment of OSA.[7]

POTENTIAL ADVERSE EFFECTS OF CANNABIS USE IN PATIENTS WITH SLEEP APNEA

There are several potential adverse effects of cannabis that raise concerns with its use, especially as first- or second-line therapy, in the treatment of OSA. A study that examined the impact of nighttime administration of THC (the psychoactive component of cannabis), alone and in combination with cannabidiol, demonstrated an increase in both subjective and objective measures of sleepiness the following morning.[8] Somnolence is also a common side effect associated with dronabinol use.[9] In addition, there is evidence suggesting that the use of cannabis is associated with a higher risk of motor vehicle crashes.[10] Although this study examined the effects of smoked cannabis, there is evidence that dronabinol also results in driving impairment.[9,11] In contrast, CPAP has been shown to decrease objective measures of sleepiness and motor vehicle accidents in most studies.[6]

Cannabis use in healthy volunteers has been associated with a greater daily caloric intake and dronabinol has been shown to result in weight gain in studies of subjects with HIV/AIDS and cancer.[10,12] Subjects taking dronabinol in the PACE trial did not demonstrate significant weight gain compared with subjects on placebo (P=.40). However,

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