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LETTERS TO THE EDITOR

Medical Cannabis, Synthetic Marijuana Extracts, and Obstructive Sleep Apnea

Response to Schears et al. Medical cannabis and AASM position statement: the don't ask, don't tell wishing well. *J Clin Sleep Med.* 2018;14(10):1811 and Takakuwa. Stop the attack on Minnesota's courageous stance to allow its residents to sleep safely. *J Clin Sleep Med.* 2018;14(10):1813.

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We stand by our position statement[1] and respectfully disagree with Schears et al.[2] and Takakuwa,[3] who advocate that there is sufficient evidence to support the use of both synthetic dronabinol (an isomeric delta-9 tetrahydrocannabinol [THC] cannabinoid drug), and medical cannabis for the treatment of obstructive sleep apnea (OSA).

The decision by the Minnesota Department of Health to add OSA as a qualifying condition for the state's medical cannabis program was based exclusively on a limited body of research involving dronabinol.[4] More recently, the Minnesota Department of Health posted an online fact sheet that communicates the lack of sufficient research to determine which medical cannabis products—if any—are effective for treating OSA.[5] It also cites the American Academy of Sleep Medicine (AASM) position statement and suggests that other OSA treatments known to be effective should be tried before considering medical cannabis products for OSA.

Similarly, while the National Academies report cited by both letters examined more than 20 studies involving cannabinoids, only one study of dronabinol evaluated treatment efficacy for OSA (ie, reduction in the apnea-hypopnea index [AHI]), and this study was deemed to have a high risk of bias suggesting flaws in the study design that may invalidate results.[6] Other publications that were reviewed include a study of insomnia in fibromyalgia patients and trials that enrolled patients with other conditions (chronic pain or multiple sclerosis), which reported on sleep outcomes. The review does not indicate whether patients in these trials were diagnosed with a sleep disorder. Additionally, most of these trials were judged to have uncertain or high risk of bias, again suggesting flaws in the study design.

To date, only two human studies of dronabinol for the treatment of OSA have been published by one research team: a small proof-of-concept pilot study involving 17 adults and a randomized trial involving 73 adults.[7,8] The study by Prasad et al. was a dose escalation trial involving 17 adults all under the age of 65 years. It found hypothetical treatment effects with no improvement in nocturnal oxygen parameters and treatment-emergent adverse events (ie, reason for ceasing further dose escalation) in 76% of participants receiving 2.5 mg, 57% receiving 5 mg, and 75% receiving 10 mg of dronabinol. The most important adverse event was somnolence, which is especially problematic in patients with OSA, who often experience excessive daytime sleepiness. In the study by Carley et al., the placebo group demonstrated an increase in the AHI of 8.5 events/h at 6 weeks. Therefore, the reduction in baseline AHI was only around 3 events/h, which is not clinically significant, and there was no improvement in nocturnal oxygen parameters. Only 6 patients achieved an AHI of less than 15 events/h with a 50% reduction in AHI, which was the study's response criterion. It is therefore not surprising that the authors of this study concluded that, "Larger scale clinical trials will be necessary to clarify the best potential approach(es) to cannabinoid therapy in OSA." Therefore, based on the limited research currently available, it is far too soon to declare that physicians should prescribe dronabinol for OSA.

A pharmaceutical company that has rights to patents from this dronabinol research has announced plans for a Phase 3 clinical study and submission of a new drug application to the United States Food and Drug Administration (FDA).[9] We will monitor these developments and reevaluate our position statement as necessary.

It is important to emphasize that dronabinol and medical cannabis are not the same. Dronabinol is a synthetic pill comprising only one of the many cannabinoids found in the cannabis plant. In contrast, "The term medical marijuana refers to using the whole, unprocessed marijuana plant or its basic extracts."[10] Both Schears et al. and Takakuwa are premature in stating that there is sufficient evidence supporting the use of medical cannabis to treat OSA, when published research related to OSA has focused exclusively on synthetic extracts rather than medical cannabis.

In addition to comprising numerous cannabinoids, medical marijuana also has multiple delivery methods. The Minnesota Department of Health reports that patients in its program receive medical cannabis as a liquid, pill, or topical application, or the cannabis can be vaporized.[11] Through this program, OSA patients could receive THC, cannabinol, or a combination, but

not the synthetic extracts that are the only cannabinoid forms that have been studied thus far for OSA. The Minnesota Department of Health has assumed that medical cannabis will have the same effect as synthetic cannabis extracts reported in the literature. However, the medical cannabis program could result in patients receiving cannabis or a cannabinoid, and using a delivery method, whose safety and efficacy for OSA have not been assessed.

Furthermore, there are potential adverse effects related to the use of cannabis that are especially concerning for patients with OSA, including increased subjective and objective measures of sleepiness,[12] increased risk of motor vehicle accidents,[13] and increased caloric intake with possible weight gain.[14] Therefore, we strongly defend our statement that medical cannabis should not be used for the treatment of OSA until sufficient supporting evidence is available.

We agree that therapeutic innovations are needed to improve patient-centered care for OSA, and we support their development. However, these treatments need to be validated by sound research before they gain widespread clinical adoption. In this regard, it is instructive to consider the FDA's recent approval of the first drug that contains a purified drug substance derived from marijuana.[15] The approval was based on evidence from three randomized trials involving 516 patients. The FDA emphasized that this level of research is necessary to confirm a drug's medical benefit and ensure that it has uniform strength, consistent delivery and appropriate dosing.[16]

Effective treatment options for OSA include positive airway pressure therapy, oral appliance therapy, positional therapy, weight loss, and surgery. We encourage patients with OSA to discuss their treatment options with a licensed medical provider at an accredited sleep facility.

We also remind readers that the ultimate judgment regarding the propriety of any specific care must be made by the clinician considering the individual circumstances presented by the patient, accessible treatment options, and available resources.

CITATION

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DISCLOSURE STATEMENT

The authors represent the 2018 – 2019 Executive Committee of the AASM. This letter to the editor is intended by the AASM to help physicians and other health care providers make decisions about the appropriate treatment of patients with OSA. It is to be used for educational and informational purposes only.