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Cannabinoid May Be First Drug for Sleep Apnea

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Dronabinol, a synthetic form of the cannabis compound tetrahydrocannabinol (THC), shows efficacy in the treatment of obstructive sleep apnea, possibly representing a first pharmacologic approach to the tough-to-treat, but potentially serious, condition.

"These findings support the therapeutic potential of cannabinoids in patients with obstructive sleep apnea," the authors, led by Phyllis Zee, MD, the Benjamin and Virginia T. Boshes Professor of Neurology at Northwestern University Feinberg School of Medicine and director of the Northwestern Medicine Sleep Disorders Center, Chicago, Illinois, write.

"In comparison to placebo, dronabinol was associated with lower AHI [apnea/hypopnea index], improved subjective sleepiness and greater overall treatment satisfaction," they add.

The study was published in the January issue of *Sleep*.

No Medications

With no approved pharmacotherapies available for sleep apnea, current first-line treatment is a continuous positive airway pressure (CPAP) device that applies continuous air pressure to keep the airways open during sleep. Though effective, the device can be cumbersome to wear, and long-term adherence is low.

Dronabinol, specifically a synthetic formulation of the molecule delta-9 THC and a nonselective cannabinoid type 1 and typ2 receptor agonist, was first approved in 1985 by the US Food and Drug Administration (FDA) for the treatment of nausea and vomiting associated with chemotherapy and is also indicated for appetite stimulation in AIDS-related wasting syndrome.

In previous studies involving rodents and a small pilot study of 17 humans, however, the authors of the current study noted that dronabinol also showed some signs of reducing spontaneous sleep apneas.

To expand on this research in the multisite, phase 2 Pharmacotherapy of Apnea by Cannabimimetic Enhancement (PACE) study, the authors enrolled 73 adult patients with moderate or severe sleep apnea.

Patients were randomly assigned to treatment with 2.5 mg of dronabinol (n = 21), 10 mg dronabinol (n = 27), or placebo (n = 25) 1 hour before bedtime for up to 6 weeks. They had a mean baseline body mass index (BMI) of 33.4 kg/m^2 and a mean age of 53.6 years. The mean baseline AHI was 25.9 and mean Epworth Sleepiness Scale score was 11.5.

The primary endpoint was change from baseline in AHI after 6 weeks of treatment. The study showed significant improvements in the 2.5-mg group, with a reduction of 10.5 events per hour (P = .02), and in the 10-mg group, with a reduction of 12.9 events per hour (P = .004), in rapid eye movement (REM) as well as non-REM sleep, after adjustment for factors including age, race, ethnicity, and baseline AHI.

No significant changes were observed in the placebo group after adjustment, and the differences in improvement between the 2.5- and 10-mg groups were not statistically significant.

The 10-mg group also showed a significant reduction in the secondary primary endpoint of subjective daytime sleepiness, assessed by the ESS, with a reduction of 3.8 points from baseline (P < .0001), and a reduction of 2.3

points compared with placebo (*P* = .05), while the reductions in the ESS score in the 2.5-mg and placebo groups from baseline were not statistically significant.

Patients receiving the 10-mg dose also expressed that highest overall satisfaction with their treatment, as assessed on the Treatment Satisfaction Questionnaire for Medication (*P* = .04).

There were no changes in objective measures of the maintenance of wakefulness test (MWT), including sleep latencies, gross sleep architecture, and overnight oxygenation measures, in any of the groups.

During the study, 7 patients discontinued participation because of adverse events, and an additional 10 elected to discontinue for other reasons. However, there were no significant differences in rates of dropout according to randomization group, BMI, baseline AHI, or other factors, and rates of adverse events were similar between those who did and did not complete the study. There was a trend of men more likely to discontinue than women (*P* = .07).

Impact on REM, Non-REM Sleep

Whereas most patients (88%) experienced one or more adverse events during the study, most events were mild, and there were no significant differences between the groups in terms of the number or severity of events.

There was one serious adverse event — diarrhea and vomiting during treatment, for which the patients was admitted to the hospital for hydration and monitoring. The patient was released after 24 hours and completed the study; the adverse event was determined to be possibly related to the study medication.

The groups did not significantly differ for treatment adherence, with nearly two thirds of patients taking all scheduled doses.

With dronabinol's indication for appetite stimulation in HIV-infected patients, weight gain was a concern. However, weight change did not differ between groups.

The fact that improvement was seen in non-REM as well as REM sleep was a notable finding, the authors said.

"Most patients with OSA [obstructive sleep apnea] experience a significant number of disordered breathing events during both NREM [non-REM] and REM sleep. Thus, for any therapeutic intervention to be generally effective, it should be able to control disordered breathing throughout all stages of sleep. Here, we observed significant dronabinol-related decreases of disordered breathing events during both NREM and REM sleep," they write.

THC is the principal component of cannabis linked to the psychotropic effects associated with its use. However, no such psychoactive effects were observed in the study. "In our study, [the treatment] did not seem to have this effect," Dr Zee told *Medscape Medical News*.

The mechanisms of dronabinol that are speculated to play a role in treatment of obstructive sleep apnea include signals to regions of the brain involved in respiratory regulation.

"Based on a series of animal investigations, we proposed that drugs which dampen afferent vagal feedback to the medulla may be effective in stabilizing respiratory pattern generation and increasing activation of upper airway dilating muscles during sleep," the authors note.

Dr Zee added that larger studies will be necessary to shed more light on dronabinol's specific clinical applications in sleep apnea.

"Due to the phase 2 study, it would be premature to comment on how the compound will be used in clinical settings. Larger studies that can be generalized to the obstructive sleep apnea population are needed. It could conceivably be used in patients who fail CPAP, [and] other approved therapies, such as oral appliances or as adjunctive therapy," she said.

Phase 3 Trial Needed

While the current study focuses on dronabinol, the University of Illinois at Chicago is in an intellectual property licensing agreement with the pharmaceutical company RespireRx that also covers other cannabinoid drugs for the treatment of sleep-related breathing disorders, according to the study's co-lead author David W. Carley, PhD, the Katherine M. Minnich Endowed Professor Emeritus of Biobehavioral Health Sciences, Medicine and Bioengineering at the university.

"For example, other formulations may target specific cannabinoid receptors or selectively target receptors in the peripheral vs central nervous system," Dr Carley told *Medscape Medical News.*

Dr Carley holds patents on some of the drugs for sleep apnea indications.

He noted that the next steps in terms of dronabinol will likely be to determine parameters necessary from the FDA on possibly moving ahead with a pivotal phase 3 trial.

"Broadly speaking, we need more tools in the apnea treatment toolbox. No current treatment is sufficient for all patients. There are at least 1 million individuals in the US with diagnosed obstructive sleep apnea who have refused, failed or abandoned all available treatments, [and for this] reason, new drug treatments would have a great clinical impact," he said.

While agreeing further research is needed, sleep specialist James A. Rowley, MD, who was not involved in the research, said the study sheds light on a potentially beneficial therapy.

"There really is no pharmacological therapy for obstructive sleep apnea," Dr Rowley, who is interim chief of the Division of Pulmonary, Critical Care & Sleep Medicine and medical director of the Detroit Receiving Hospital Sleep Disorders Center at Wayne State University, Detroit, Michigan, told *Medscape Medical News.*

"Most studies that have looked at various agents, often serotonergic agents, have been small studies that do not show any significant improvements in the severity of obstructive sleep apnea, as measured by the AHI."

"Hence, this study marks an advancement in the pharmacologic therapy of obstructive sleep apnea. However, it is only a phase 2 study, so will need replication in a larger, phase 3 study, before dronabinol can be considered for obstructive sleep apnea therapy."

While improvement seen in the endpoint of the AHI with dronabinol is not as significant as is reported with CPAP, the improvement in sleepiness observed in the study is more impressive, Dr Rowley said.

"The change in AHI is less than what would be expected with CPAP, which generally gets the AHI to less than 5 events per hour, and the number of responders would also be less than with CPAP. However, the change in Epworth score is similar to many studies of CPAP," he noted.

Dr Rowley added that the lack of improvement seen in the objective MWT measures with dronabinol was not necessarily surprising.

"It does not concern me that there was no significant change in the MWT as other studies of CPAP using the MWT have also been negative," he said.

On the other hand, dronabinol's role as a synthetic form of THC is more of a concern, he said.

"Until we have a phase 3 study, it would concern me that the drug is a synthetic THC. [We] clearly would need to find out more about its side effects (and) whether it effects driving ability, et cetera."

Dr Rowley added that a likely reason for the lack of research on pharmacologic approaches to sleep apnea is that a multitude of brain centers and neurotransmitters are involved in the control of breathing and control of upper airway muscles.

"Thus, finding a single pharmacologic agent can be difficult. Also, most patients present for diagnosis of obstructive sleep apnea after years of actually having it; hence, it is unclear if there have been long-term changes in brain neurochemistry that are not easily fixed by one medication," he said.

The research was supported by grant from the National Institutes of Health. University of Illinois at Chicago has licensed intellectual property related to dronabinol to the pharmaceutical company RespireRx. Dr Carley is the inventor of intellectual property assigned to the University of Illinois at Chicago, including US patent 7,705,039; US patent 8,207; US patent application 20130281523; and US patent application 20120231083. He holds shares of common stock in RespireRx Pharmaceuticals. He has not been paid by, nor does he advise, RespireRx Pharmaceuticals. Dr Zee and Dr Rowley have disclosed no relevant financial relationships.

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