

# Obstructive Sleep Apnea

## ISSUE BRIEF ON OBSTRUCTIVE SLEEP APNEA

### Introduction

Briefings such as this one are prepared in response to petitions to add new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, to members of the Medical Cannabis Review Panel, and to interested members of the public scientific studies of cannabis products as therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) will be included, especially if there are few clinical trials or observational studies. Though interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses, when published in peer-reviewed journals surveys will be included for completeness. When found, published recommendations or opinions of national organizations medical organizations will be included.

Searches for published clinical trials and observational studies are performed using the National Library of Medicine's MEDLINE database using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Finally, the federal government-maintained web site of clinical trials, [clinicaltrials.gov](http://clinicaltrials.gov), was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

### Definition

Obstructive sleep apnea (OSA) is a sleep disorder characterized by repetitive episodes of complete (apnea) or partial (hypopnea) collapse of the upper airway (mainly the oropharyngeal tract) during sleep, with a consequent cessation/reduction of the airflow. The obstructive events cause a progressive asphyxia that increasingly stimulates breathing efforts against the collapsed airway, typically until the person is awakened (Spicuzza 2015). These episodes cause acute physiological disruptions including fragmented sleep, intermittent hypoxia, and exaggerated fluctuations in heart rhythm, blood pressure, and intrathoracic pressure. Over time, the acute disruptions evolve into long-term sequelae such as hypertension and cardiovascular morbidities, reduced cognitive function, decreased mood and quality of life, impaired performance at work and while driving, and premature death (Peppard 2013).

Traditionally, OSA was considered to primarily be a problem of upper airway anatomy, where craniofacial structure or body fat decreased the size of the pharyngeal airway lumen, leading to an increased likelihood of pharyngeal collapse. It is now appreciated that multiple factors contribute to the development of OSA, including small upper airway lumen, low lung volume, respiratory instability, poor upper airway muscle function, and low arousal threshold. One or two of these causal factors might be most important for any given patient with OSA; that is, the disease occurs for different reasons in different patients. Underlying risk factors include obesity, male gender, increased age, nasal congestion, craniofacial structure, and genetics (Jordan 2014).

The International Classification of Sleep Disorders (ICSD) is a diagnostic, epidemiological and coding resource for clinicians and researchers in the field of sleep and sleep medicine. It is produced by the American Academy of Sleep Medicine in association with similar organizations in Europe, Japan, and Latin America. The most recent edition, the third, was published in 2014. It contains a section on diagnostic criteria for OSA with only minor changes from the second edition (2005). A 2014 article in the journal, *Chest*, summarized highlights and modifications in ICSD-3 (Satela 2014). Diagnosis of OSA requires either signs/symptoms (eg. associated sleepiness, fatigue, insomnia, snoring, subjective nocturnal respiratory disturbance, or observed apnea) or associated medical or psychiatric disorder (ie. hypertension, coronary artery disease, atrial fibrillation, congestive heart failure, stroke, diabetes, cognitive dysfunction, or mood disorder) coupled with five or more predominantly obstructive respiratory events (obstructive or mixed apneas, hypopneas, or respiratory effort-related arousals) per hour of sleep during polysomnography - OR - a frequency of obstructive respiratory events  $\geq 15$ /hour even in the absence of associated symptoms or disorders. Data to calculate a respiratory event index, typically called apnea hypopnea index (AHI) expressing number of events per hour, can be collected during an overnight in-center sleep study or during a home sleep study. The data is interpreted and analyzed by a sleep study specialist. Subtle differences in measurement methodologies and interpretations can lead to substantial differences in diagnoses among sleep laboratories (Jordan 2014).

## Prevalence

Approximately one in five adults has at least mild OSA (eg.  $AHI \geq 5$ ) and 1 in 15 has moderate or severe OSA (eg.  $AHI \geq 15$ ). However, >85% of patients with clinically significant and treatable OSA have never been diagnosed. Two population studies indicate the prevalence of OSA has increased over recent decades, likely due at least in part to population increases in obesity (Somers 2008). Though more common in adults, OSA can also occur in children (Sawyer 2011).

## Current Therapies

Lifestyle modifications can reduce the severity of OSA and, especially in mild cases, can be sufficient management (Mayo Clinic 2017). Lifestyle modifications include losing weight, exercise, avoiding alcohol and sedative medications, sleeping on side or abdomen rather than

back, and using saline nasal spray to keep nasal passages open. However, patients with moderate to severe OSA typically need therapy beyond lifestyle modifications. Continuous positive airway pressure (CPAP), generally administered through the nose, is the gold standard of OSA treatment. It decreases the number of nocturnal obstructive events and the number of nocturnal arousals, improving sleep parameters and nocturnal oxygen saturation from the first night of treatment. Daytime and nocturnal symptoms are reversed after a short period of constant use (Spicuzza 2015). Though it is very effective, its effectiveness depends on use every day, with recurrence of symptoms after only a day or two of treatment interruption. A substantial proportion of patients who are started on CPAP find it intolerable for a variety of reasons, with adherence roughly 60-70% (Jordan 2014), or 50-80% (Weaver 2008), depending on population and how adherence is measured. There is growing attention to interventions – especially early in CPAP use – to increase adherence (Sawyer 2011). Several alternative options are available for patients in whom CPAP is unsuccessful (Spicuzza 2015). These include different ways of engineering and delivering the positive pressure, oral devices, upper airway surgery, and electrical stimulation of the hypoglossal nerve – activating the genioglossus muscle to open up the upper airway. And there are other emerging treatment options under development.

## Pre-Clinical Research

A review by Carley and Radulovacki (Carley 2008) discusses evidence that stimulation of vagus nerve afferent (carries nerve impulses from sensory receptors or sense organs toward the central nervous system) pathways plays a role in sleep related breathing disorders and the presence of cannabinoid receptors in the vagus nerve's nodose ganglion. Calik and collaborators found dronabinol (synthetic THC) reduced serotonin-induced apnea and increased upper airway muscle tone (genioglossus muscle) in rats when injected into the vagus nerve's nodose ganglion (Calik 2014), but not when the injection was into the brain's right ventricle (Calik 2016). This suggests that the effects of dronabinol on apneas (at least those induced by serotonin in rats) are peripherally mediated via suppression of vagal nerve activity (Calik 2016).

## Clinical Trials

Two clinical trials of a cannabinoid to treat OSA have been published. No additional trials were found on clinicaltrials.gov.

**Prasad B, Radulovacki MG, Carley DW. Proof of concept trial of dronabinol in obstructive sleep apnea. *Front Psychiatry* 2013. Jan 22;4:1. doi: 10.3389/fpsy.2013.00001.**

This was a proof of concept, single-center dose-escalation study of dronabinol (synthetic THC). Seventeen adults with a baseline Apnea Hypopnea Index (AHI)  $\geq 15$ /hour were enrolled. Polysomnography (PSG) was performed after a 7-day washout of continuous positive airway pressure treatment. Dronabinol was administered after baseline PSG, starting at 2.5 mg once daily. The dose was increased weekly, as tolerated, to 5 mg and finally 10 mg once daily. Repeat PSG assessments were performed on nights 7, 14, and 21 of dronabinol treatment. Change in AHI was significant from baseline to night 21 ( $-14.1 \pm 17.5$ );  $p=0.007$ ). Dose was held constant if minor adverse events or new symptoms potentially related to study were reported. Two

participants remained at 2.5 mg and five remained at 5 mg dronabinol at day 21. Two participants were withdrawn due to adverse events: one due to palpitations and one due to oxygen saturation falling below 75% for >5% of the total sleep time on day 7 PSG (a participant with severe OSA at baseline, AHI=93/h). Treatment-emergent adverse events were reported in 76% of participants receiving 2.5 mg, 57% receiving 5 mg, and 75% receiving 10 mg of dronabinol. The most frequent adverse event was somnolence.

**Carley DW, Prasad B, Reid KJ, Malkani R, Attarian H, Abbott S, Vern B, Xie H, Yuan C, Zee PC. Dronabinol reduces AHI and daytime sleepiness in patients with moderate to severe obstructive sleep apnea syndrome. *Sleep* 2017;40:Abstract Supplement:A207-A208(Abstract #0558).**

Results of this trial were recently published as an abstract for the SLEEP 2017 (June, 2017) conference (Carley 2017). It was a clinical trial of dronabinol (synthetic THC) versus placebo in 56 adults with BMI<45, Epworth Sleepiness Scale (ESS)>7, and polysomnography (PSG)-documented Apnea-Hypopnea Index (AHI) between 15 and 50. Participants were randomized to 2.5 mg dronabinol by mouth (n=19), 10.0 mg dronabinol (n=20) or placebo (n=17) daily, one hour before bedtime for 6 weeks. Repeat in-laboratory PSG followed by maintenance of wakefulness (MWT) testing was completed every 2 weeks during the treatment period. At each visit, the ESS and Treatment Satisfaction Questionnaire for Medications also were completed. Baseline AHI was  $26.0 \pm 6$  (SD), MWT latency was  $19.9 \pm 12$  min, BMI was  $33.8 \pm 5.4$  kg/m<sup>2</sup> and these were equivalent among all treatment groups. ESS and age differed slightly among placebo, 2.5 mg, and 10 mg treatment groups: ESS= $11.5 \pm 3.8$ ,  $10.1 \pm 3.7$ ,  $13.7 \pm 3.7$  (p=0.01); Age= $58.6 \pm 6.1$ ,  $52.7 \pm 7.7$ ,  $54.7 \pm 7.0$  (p=0.04). In comparison to placebo, the end of treatment changes in AHI were  $-13.2 \pm 4.0$  (p=0.001) and  $-9.7 \pm 4.1$  (p=0.02) for the 10 and 2.5 mg dronabinol groups, respectively. ESS did not change significantly with treatment in the placebo or 2.5 mg groups, but decreased by  $4.0 \pm 0.8$  (p=0.0001) units for subjects receiving 10 mg dronabinol. There were no significant changes in MWT latency or BMI with treatment in any group. The above conclusions were not altered after controlling for baseline ESS and age. Subjects receiving 10 mg dronabinol also expressed the greatest overall satisfaction with treatment (p=0.02).

## Observational Studies

No observational studies for use of cannabis or cannabinoids as therapy for OSA were found.

## National Medical Organization Recommendations

No national medical organization recommendations were found.

The 2017 National Academy of Sciences, Engineering, and Medicine report, *The Health Effects of Cannabis and Cannabinoids*, in the “Sleep Disorders” section, describes the Prasad 2013 study and makes this statement, “Conclusion 4-19: There is moderate evidence that cannabinoids, primarily nabiximols, are an effective treatment to improve short-term sleep

outcomes in individuals associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis.”

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