MDH Minnesota Department of Health
OFFICE OF MEDICAL CANNABIS

Insomnia

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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, 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

Insomnia is a persistent condition in which a person has difficulty falling asleep, staying asleep, or both, in spite of the opportunity for adequate sleep (Mayo Clinic). In some cases, insomnia is an independent disorder; however insomnia can often result from another coexisting condition and can also persist even with successful management of the coexisting condition (Bonnet). The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) describes major diagnostic criteria for insomnia (American Psychiatric Association 2013):

- Dissatisfaction with sleep quantity or quality, with one or more of the following symptoms: difficulty initiating sleep, difficulty maintaining sleep, early-morning awakening
- The sleep disturbance causes significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning
- The sleep difficulty occurs at least 3 nights per week, is present for at least 3 months, and despite adequate opportunity for sleep
- The insomnia does not co-occur with another sleep disorder
- The insomnia is not explained by coexisting mental disorders or medical conditions

While the DSM-V requires persistence of symptoms for 3 months to constitute a diagnosis, many clinicians consider symptom persistence for one month or longer to constitute chronic insomnia. Additionally, the DSM-V criteria excludes insomnia related to other medical or mental conditions, but many epidemiologic studies include all patients with a defined set of insomnia symptoms, regardless of underlying cause.

According to the Mayo Clinic, symptoms of insomnia may include not feeling well rested after sleep, tiredness, irritability, depression, anxiety, attention deficits as a result during waking hours, as well as tension headaches and gastrointestinal distress (Mayo Clinic).

Insomnia can result from a variety of causes, including stress, anxiety, depression, comorbid conditions including cancer, chronic pain, arthritis, conditions causing respiratory difficulties including heart failure and lung disease, and many others, poor sleep hygiene, environment or schedule changes, medications, intake or caffeine, nicotine or alcohol, eating patterns, and aging (Mayo Clinic).

Diagnosis

Diagnosis of insomnia will require physical examination and interview by a health care practitioner to determine the patient's medical history, to ascertain potential causes of insomnia, and sleep history, to understand the scope of the sleep disturbance and identify potential causes. Health care providers will also perform a physical examination and blood testing to rule out possible causes of sleep disturbance, and in some cases a sleep study, involving overnight polysomnogram (PSG) recording of brain activity, eye movements, heart rate, and blood pressure, to identify or rule out possible underlying sleep disorders.

Complications and Consequences

Serious complications can arise from chronic insomnia. Among patients with chronic illness (a common cause of insomnia), those who also suffered from insomnia reported a lower quality of life compared to chronic illness patients without insomnia (Katz 2002). Ongoing complications related to insomnia include reduced job or academic performance, reduced reaction time, increased psychiatric problems (depression, anxiety), weight gain, irritability, and increased risk of substance abuse and chronic illness related to short-term symptoms including hypertension, heart disease or diabetes (Mayo Clinic).

Prevalence

Estimating prevalence of insomnia in the general population is challenging because of the variations in defining this condition- some estimates use a broad definition without criteria relating to severity or duration. A clinical review from the Stanford School of Medicine Sleep Disorders Center provides some recent estimates for the various criteria used in the literature. A number of studies estimate the prevalence of insomnia symptoms which occur at least 3 nights a week, "often" or "always" (no duration specified) to be from 16%-21% in the general population (Ohayon 2002). Few studies estimate the prevalence of insomnia diagnoses but a review by Ohayon et al reported that population estimates of the prevalence of insomnia diagnoses including those related to other medical conditions or mental disorders, ranged from 4.4% to 6.4% (Ohayon 2002).

Current Therapies

Patients suffering from insomnia should receive treatment for any underlying or exacerbating conditions including chronic illness, psychiatric problems, substance abuse or other sleep disorder. A generalized approach includes counseling on sleep hygiene and stimulus control (minimizing other uses of bed or sleeping area such as reading, watching television, etc.) If insomnia symptoms persist in spite of treatment of any underlying conditions, or in the case of isolated insomnia not attributable to any other condition, a patient may receive behavioral therapies beyond basic counseling, medications to treat insomnia, or a combination of behavioral therapy and medication. Bonnet et al compiled a thorough review of current therapies for insomnia and their efficacy and adverse effects in "Treatment of insomnia," published on Uptodate.com (Bonnet). The following is a summary of Bonnet's review.

Behavioral Therapy

A number of behavioral therapy strategies have been found to be effective in treating insomnia. Relaxation therapy is a common strategy that is implemented before each sleep period; two approaches of relaxation therapy are a progressive relaxing of muscles throughout the body until the entire body is relaxed, and a relaxation response approach involving developing a relaxed abdominal breathing rhythm while maintaining a restful position. A few small randomized studies have reported relaxation therapy to be associated with modest benefits in sleep quality when compared to placebo, but not necessarily associated with improved daytime functioning (Means 2000, Edinger 2001). Another common behavioral therapy is sleep restriction therapy, which limits the amount of time the patient spends in bed to counteract the negative effects produced by insomnia patients' frequent tendency to stay in bed longer and delay sleep onset for the following night. The regimen begins with the patient spending as much time in bed as they report sleeping; this amount is only increased in increments of 15-30 minutes when sleep efficiency (time asleep divided by time in bed) is greater than 85% (Bonnet). A review of four randomized trials of sleep restriction therapy found that sleep restriction therapy was associated with improvements in subjective sleep

variables with an effect comparable to cognitive behavioral therapy (Miller 2014, Montgomery 2003).

Cognitive behavioral therapy (CBT) refers to a therapist-guided short term course consisting of a combination of the behavioral treatments described above, often administered over 6-8 weeks. This may include several therapy sessions, each focusing on a particular behavioral strategy for insomnia treatment. There is a base of strong evidence supporting CBT as an effective therapy; a 2015 meta-analysis combining results from 20 trials, CBT was found to significantly improve sleep onset latency, decrease wake time after sleep onset and improve sleep efficiency when compared with no intervention (Trauer 2015).

While CBT has been shown to be effective for treating some cases of insomnia, one important drawback is the reliance of the therapy on a highly trained clinician; there is evidence that outcomes depend on the amount of experience held by the administering clinician (Espie 2007). Another drawback is the need for a high degree of patient compliance, which is difficult especially in challenging therapies such as sleep restriction.

Medication Therapy

There are several options for pharmacotherapy. Choosing medication requires balancing the potential therapeutic benefit against risks including respiratory suppression, mental incapacitation (decision-making) and addiction. Common medications for insomnia are benzodiazepines, nonbenzodiazepines (drugs molecularly dissimilar from benziodiazepines but producing similar benefits and side effects), melatonin agonists, orexin receptor antagonists, and occasionally other sedatives including antidepressants, diphenhydramine, antipsychotics, and barbiturates. There are few studies directly comparing various medications' efficacy of treating sleep disorders. Selection of a medication, therefore, is often made on the basis of the type of symptoms experienced by the patient. For patients who have difficulty falling asleep, short-acting medications (such as zolpidem or lorazepam) are preferred whereas patients who have trouble maintaining sleep are often prescribed longer-acting medications (such as extended-release zolpidem or eszopliclone).

Adverse effects of insomnia medications can be serious. Benzodiazepines andnonbenzodiazepines can cause residual sedation, drowsiness, dizziness, cognitive impairment, and dependence; they are also respiratory suppressants (Bonnet). Nonbenzodiazepines tend to have less severe adverse effects, as they have shorter half-lives. Melatonin agonists and orexin antagonists are associated with risks including somnolence and headache; melatonin agonists also are associated with risk of dizziness, nausea and fatigue but do not carry great risk of abuse.

Older adults are generally more susceptible to adverse effects of hypnotic medications (including benzodiazepines, nonbenzodiazepines, melatonin, and other insomnia medications); use of these drugs in elderly patients is also associated with increased risk of falls (Gray 2006, Cummings 2003, Kudoh 2004, Tom 2016). Finally, there is observational data showing an increased risk of all-cause mortality and/or cancer with the use of hypnotic medications (Kripke 2012, Hausken 2007, Belleville 2010, Kripke 1998, Weich 2014).

Pre-Clinical Research

The endocannabinoid system, which includes the endogenous cannabinoids (endocannabinoids) as well as the cannabinoid receptors to which cannabinoids bind, is still a relatively new field of scientific inquiry. Translational research has shown that the endocannabinoid system may play a role in sleep: Murillo-Rodriguez et al found that anandamide, an endocannabinoid, increases slow wave sleep in rats (Murillo-Rodriguez 2006); Herrera-Solis et al found that anandamide administration in rats increases rapid eye movement (REM) sleep (Herrera-Solis 2010).

Clinical Trials

A study sponsored by the University Health Network in Toronto (principal investigator: Colin Shapiro) is registered on the NIH Clinical Trials website to study the effect of nabilone, a cannabinoid approved for use in Canada, on sleep disturbance and insomnia in patients with pain. This is a double-blind crossover design that will enroll patients 18-65 years old and use change in sleep efficiency, verified by PSG, as the primary endpoint. The status of recruitment is unclear, as the study details were most recently verified in 2005. Use of the Cannabinoid Nabilone for the Promotion of Sleep in Chronic, Non-Malignant Pain Patients. https://clinicaltrials.gov/ct2/show/NCT00384410?term=cannabis+insomnia&rank=3

Ware MA, Fitzcharles M, Joseph L, Shir Y. The Effects of Nabilone on Sleep in Fibromyalgia: Results of a Randomized Controlled Trial. *Pain Medicine*. 2010 Feb; 100(2):604-310.

This is a randomized, double-blind, active-control trial to assess non-inferiority of nabilone, a synthetic cannabinoid, compared to amitriptyline, a tricyclic antidepressant, in improving sleep quality in fibromyalgia patients. The authors note that prevalence estimates of insomnia in fibromyalgia patients exceed 75%. Each drug was administered for a two-week period, with a two-week washout period between the two phases. Patients were recruited from a pain clinic and were adults with self-reported chronic insomnia (defined as disturbed sleep every other night or every night over the past 6 months). Subjects received either 0.5 mg nabilone or 10 mg amitriptyline at the start of each phase; after 7 days, their dosage either was maintained or doubled, depending on evaluation by a physician. The primary study outcome was sleep quality, assessed with two validated subjective tools: the Insomnia Severity Index (ISI) and the Leeds Sleep Evaluation Questionnaire (LSEQ). This study included 29 patients who were randomized and completed the study; in this group, nabilone was found to have a greater positive impact on sleep quality than amitriptyline based on ISI scores. The LSEQ scores comparison showed no difference between the two drugs, though subjects reported more restful sleep while taking nabilone. No other differences were noted in secondary outcomes of pain, mood, or quality of life. Dose adjustment (doubling the dose after 7 days) occurred more frequently when patients took amitriptyline compared to when taking nabilone. While no serious adverse events (AE) occurred during the trial, 91 AEs (most commonly dizziness, nausea, dry mouth and drowsiness) were attributed to nabilone while only 53 were attributed to amitriptyline. The main limitation of this study is the short duration of treatment for each drug;

long-term safety and efficacy remain unknown. Furthermore, any effects of nabilone or other cannabinoids on sleep architecture, versus subjective assessment as is measured in this study, remain unknown.

Russo EB, Guy GW, Robson PJ. Cannabis, Pain and Sleep: Lessons from Therapeutic Clinical Trials of *Sativex*®, a Cannabis-Based Medicine. *Chemistry & Biodiversity*. 2007; 4:1729-1743.

This 2007 review from GW Pharma, the producer of the cannabis-based medicine Sativex, summarized the results of 13 trials of cannabis-based medicine (6 pain studies; 3 multiple sclerosis studies; 4 other condition studies) with sleep as a secondary outcome. The authors interpret the study results by stating that while there may be no objective sleep effect observed in these trials, there is a consistent subjective benefit perceived by patients with neuropathic pain as well as multiple sclerosis. The review by Gates et al (2014) in the "Observational Studies" section summarizes a number of these studies and their findings, though the most obvious limitation is that they did not examine sleep as a primary outcome in a population with inclusion criteria of sleep disturbances or disorders. These studies are useful in projecting how cannabis therapy may affect sleep disorders within selected populations (multiple sclerosis patients, chronic pain patients, etc.) but they do not address whether cannabis has a therapeutic benefit in patients with insomnia in the absence of an underlying condition precipitating the insomnia.

Observational Studies

Data on the impact of cannabis on sleep in humans is limited. As with the process of diagnosing insomnia, interpreting the literature surrounding cannabis and its impact on sleep is a challenge because of different measures of impact. Many studies report results from patient self-reported impact of cannabis on sleep quality, which is inherently subjective. However, a smaller number of studies report impacts on objectively-defined measures of sleep, including length of sleep phases and time to sleep onset; these measures can be assessed through a polysomnogram (PSG). A number of these are described in this section.

Gates PJ, Albertella L, Copeland J. The effects of cannabinoid administration on sleep: a systematic review of human studies. *Sleep Medicine Reviews*. 2014; 18:447-487.

The authors completed a comprehensive review of clinical and observational studies of both medical and recreational cannabis use and its effects on sleep. The authors note that while many recreational cannabis users report sleep as a major motive in cannabis use, there is little data to support or refute its usefulness in treating sleep disorders, specifically insomnia. Limited data that exists is difficult to interpret due to methodological variation (objective versus subjective measures of sleep, lack of control for confounding variables) and small sample sizes. The authors reviewed all findings through the end of 2012; articles describing the prevalence of sleep problems among cannabis users or described the effects of cannabis withdrawal on sleep were excluded. Each paper was assessed for quality and scored accordingly.

Eleven studies were identified which examined recreational cannabis use and its impact on sleep. The authors note that the quality of these studies was poor and subject to a high risk of bias as they did not account for known confounders including age or gender. Of these, six examined objective measures of sleep and five examined subjective measures of sleep. The six studies using objective sleep outcomes yielded inconsistent results- three studies reported a decrease in slow wave sleep while one study reported an increase. One study reported an increase, and another a decrease, in REM sleep while the remaining four found no effect attributed to cannabis use. Of four studies measuring sleep onset latency, one reported an increase in sleep latency and one reported a decrease on a high THC dose. Of the remaining five studies using subjective sleep outcomes, three reported a decrease in sleep latency, but none of the studies reported an effect on night time sleep awakenings. Effects on overall sleep time varied as well. Among recreational use studies, three studied different dosages and found no dose-dependent effects on sleep.

The authors reported on 28 studies on medicinal cannabis as a treatment for other conditions beside insomnia which include measures of sleep-related outcomes; this includes 12 studies with pain patients, 9 studies with multiple sclerosis patients, as well as patients with anorexia, cancer and immune deficiency (7 studies). Included in this group were 14 papers studying synthetic cannabinoids (Marinol, dronabinol or nabilone). The authors rated the quality of this evidence as poor, often due to the use of non-validated sleep measures and lack of adequate blinding to cannabis dose. Of the total 28 studies on medicinal cannabis, 20 report some type of positive impact on sleep. Of the 20 reporting sleep improvements, two reported that improvements dropped off by the end of the experiment and one reported a lessening of bad dreams rather than improved sleep quality or quantity. Five studies compared medicinal cannabis to other medications for sleep outcomes; each compared a different medication. These reports found cannabis to be more effective than diazepam (for patients with anorexia) and amitriptyline (for patients with fibromyalgia and resulting insomnia), and less effective than ketoprofen (among pain and nausea patients), gabapentin (treating neuropathy) and dihydrocodeine (treating neuropathy).

Seven of 28 medicinal cannabis studies reported on validated but subjective measures of sleep (Medical Outcomes Study sleep scale and LSEQ were the most common tools). Here, the results are also varied: four studies which report on sleep disturbance found a reduction in sleep problems; of three studies looking at sleep quality, two found improvements while the third found no effect. Only two studies reported on sleep onset latency, of which one found an improvement (reduction in sleep onset time). Two studies reported on an overall sleep score and one found improvements in sleep while the other found no change associated with cannabis use. Finally, two papers studied night time awakenings and neither found any association in either direction. Of three studies examining dosing effects, two found that higher doses of THC improved sleep more than lower doses.

The authors conclude that current evidence regarding the effect of cannabis or its synthetic analogs on sleep is of poor quality and mixed findings, but they note that among populations with conditions which cause sleep disturbance, cannabis appears to improve sleep quality though not affecting total sleep time. They propose a plausible interpretation of their

findings to be that cannabis may be effective in improving sleep quality among patients with sleep-interrupting symptoms, but may not be beneficial for populations without sleep-disrupting medical conditions. The authors state that the effects of cannabis on various aspects of sleep are yet unclear and due to the risk of bias in the reviewed studies, more longitudinal and well-controlled studies are needed to fully understand these effects.

Schierenbeck T, Riemann D, Berger M, Hornyak M. Clinical Review. Effect of illicit recreational drugs upon sleep: Cocaine, ecstasy and marijuana. *Sleep Medicine Reviews*. 2008; 12:381-389.

This review included 16 PSG-validated studies with small sample sizes (between 1 and 32); six included chronic marijuana users. The authors point out that many limitations to interpreting their results- the studies are small and heterogeneous in subject selection (cannabis-naïve subjects versus habitual cannabis users) and type of cannabis product administered (varying doses, routes of administration and ratios of THC: CBD); additionally, the studies which compare cannabis use to a baseline of no cannabis use within current cannabis users did not account for any cannabis withdrawal effects that could confound results. The authors found that the few reports on cannabis effects on sleep produced conflicting conclusions- in some cases THC was found to decrease the time needed to fall asleep (sleep onset latency) whereas in a few studies, including those using higher doses of THC or marijuana-naïve subjects, sleep onset latency increased. In two studies, slow wave sleep was reduced by cannabis use but there was also a report of increased slow wave sleep. In a few studies, cannabis use was associated with increased sleepiness the next morning. The authors of this review state that the most consistent finding across these studies is that cannabis use decreases total REM sleep and REM density.

Webb CW, Webb SM. Therapeutic Benefits of Cannabis: A Patient Survey. Hawai'i Journal of Medicine & Public Health. 2014 Apr; 73(4): 109-111.

This article describes the results of a survey distributed to 100 patients re-enrolling in the Hawaii medical cannabis program which asked patients to describe any pain symptoms they experienced before and after medical cannabis treatment (using a universal pain scale), as well as to report any benefits and/or adverse effects. The response rate was 94%; average age was 49.3 years and 97% of respondents reported using cannabis primarily for the treatment of chronic pain. Patients responded to the open-ended question about benefit by reporting relief from stress or anxiety (50%), insomnia (45%) and also reported improved appetite (12%), decreased nausea (10%), increased concentration (9%) and relief from depression (7%). This study has major limitations, in that it relies entirely on self-reported information without any adjudication of diagnosis, symptoms, or relief perceived from cannabis treatment, as well as the selection bias inherent in querying patients who have elected to continue in the medical cannabis program. However, it reflects the consistent impression of patients receiving cannabis treatment that their sleep is improved.

National Medical Organization Recommendations

No guidance documents or recommendations from national medical organizations for the therapeutic use of cannabis or cannabinoids in the treatment of insomnia were found.

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