Cannabinoids and Sleep - Update for 2021

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No conflicts
Patients Queries

• “I am having problems sleeping especially when I am feeling anxious or have had a hard day at work. The only thing that helps me is smoking some weed”
• “I have sleep apnea and cannot sleep with CPAP. I heard on an online forum that marijuana can help with my sleep apnea”
• “Smoking marijuana helps me with my anxiety”
• “Marijuana helps my restless legs at night”
• “After a night shift, I smoke some weed and I am able to sleep”.
• “My pain is controlled with marijuana and I have heard it is safer than using opioids and I sleep better when my pain is controlled”
**Sativa**
- light green
- tall and lean
- long and narrow fan leaves

**Indica**
- dark green
- short and dense
- short and wide fan leaves

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**Forms of Medical Marijuana**
- Pills
- Spray
- Cookie
- Tincture
- Vaporizer
- Bong
- Patches
The Main Components of the Cannabis Plant

- Tetrahydrocannabinol (THC)
- Cannabidiol (CBD): non-psychoactive
- Cannabinol: similar to THC but less potent
- Cannabigerol: non-psychoactive substance, potential treatment for glaucoma
- Other endocannabinoids
- β-Caryophyllene: anti-inflammatory
- Dronabinol (synthetic THC)
- Sativex (synthetic THC)
- Nabilone (synthetic THC & CBD)
Classification of Cannabinoids

**Class**
- Endocannabinoids
- Phytocannabinoids
- Synthetic Cannabinoids

**Characteristics**
- Endocannabinoids: Endogenously synthesized lipid-based neurotransmitters in the central and peripheral nervous systems
- Phytocannabinoids: Compounds naturally present in the cannabis plant that bind to and interact with human endocannabinoid receptors
- Synthetic Cannabinoids: Synthetic molecules analogous to endocannabinoids or phytocannabinoids

**Examples**
- Endocannabinoids: Anandamide, 2-arachidonoylglycerol
- Phytocannabinoids: Delta-9-tetrahydrocannabinol, Cannabidiol, Cannabinol
- Synthetic Cannabinoids: Dronabinol, Nabilone, Rimonabant
Location of CB1 and CB2 cannabinoid receptors

* Hypothalamus: master control center of sleep and circadian rhythm
** Cortex: cortical neurons are excited by neurons originating from thalamus and hypothalamus, creating wakefulness
*** Medulla (part of brain stem): contains ascending reticular activating system responsible for wakefulness/consciousness
Endocannabinoid System

- The purpose of the endocannabinoid system is not precisely clear due to the widespread nature of the receptors and the modulating nature of their stimulation.
- Possible involvement with appetite, learning, memory, anxiety, pain, and inflammation,
- Mediator in diseases such as depression, schizophrenia, stroke, multiple sclerosis, epilepsy, addiction, glaucoma, and cancer
- THC appears to have its effect on CB1 receptors
- CBD on CB2 receptors.

FDA approved Cannabis compounds

<table>
<thead>
<tr>
<th>Name</th>
<th>US brand name</th>
<th>Year approved</th>
<th>Characteristics</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabidiol</td>
<td>Epidiolex</td>
<td>2018</td>
<td>Purified cannabidiol from cannabis plant</td>
<td>Seizures associated with Lennox-Gastaut or Dravet syndrome</td>
</tr>
<tr>
<td>Dronabinol</td>
<td>Marinol, Syndros</td>
<td>1985, 1992</td>
<td>Synthetic delta-9-THC</td>
<td>Chemotherapy-induced nausea and vomiting refractory to conventional therapy</td>
</tr>
<tr>
<td>Nabilone</td>
<td>Casamet</td>
<td>1985–1989*, 2006</td>
<td>Synthetic analog of delta-9-THC</td>
<td>Chemotherapy-induced nausea and vomiting refractory to conventional therapy</td>
</tr>
</tbody>
</table>

*FDA approval withdrawn for commercial reasons prior to re-approval*
Pharmacokinetics

- Marijuana products chiefly consist of varying concentrations of 3 lipophilic components: THC, CBD, and other cannabinoids (100 identified compounds).
- THC and CBD are the most abundant components in the native cannabis plant, and their relative ratios and concentration vary by plant strain, growing conditions, and handling.
- Highly lipid-soluble and readily absorbed through dermal and mucosal surfaces.
- Most widely used form is direct combustion of the flower buds or leaves and inhalation of the produced smoke.
- Oral ingestion of concentrates are growing in popularity.
- Formulations are rapidly being developed as the commercial industry expands, and include topical salves, candies, drinks, and foods.
Pharmacokinetics

• Once exposed to mucosal or dermal surfaces, cannabinoids are rapidly absorbed into the bloodstream and widely distributed to vascularized tissues.
• With inhalation, peak concentrations occur in minutes and last around 30 min.
• With oral ingestion, there is extensive hepatic cytochrome P450 first-pass metabolism, and peak levels occur in one or more hours and last 5 to 6 h or more.
• The cannabinoids distribute to adipose tissue and linger for days, with 90% elimination at 5 days.
• Not clear if one should use oral vs inhaled form.

Use of Cannabis to Relieve Pain and Promote Sleep by Customers at an Adult Use Dispensary

Journal of Psychoactive Drugs, 51:5, 400-404,

• 1000 customers at 2 retail stores in Colorado

• 65% reported taking Cannabis to relieve pain
  • 80% reported it was helpful and reduced/stopped OTC analgesics or opioids

• 74% reported taking Cannabis to improve sleep
  • 84% reported to it be helpful and either stopped or reducing OTC sleep aids and Rx sleep medicines
Studies on Cannabis and effect on sleep and sleep architecture

- Mixed results
- some studies showed a decrease in sleep onset latency and wake after sleep onset
- Some studies showed increase in slow wave sleep and a decrease in REM
- Method of delivery varied from smoked form to oral use and with different concentrations of CBD and THC
- Observational studies in chronic marijuana users and naïve users.
- Different effect on sleep architecture in chronic vs acute use.

Cannabis withdrawal and sleep

- Sleep disturbance and vivid dreams is one of the most common symptoms reported on withdrawal from cannabis

- Can be a significant factor in relapsing to use of marijuana

- Effect can last up to 45 days post cessation of marijuana use.
Polysomnogram changes in marijuana users who report sleep disturbances during prior abstinence-  Sleep Medicine 11(9) 2010

- 18 heavy marijuana users
- PSG was recorded on nights 1, 2, 7, 8 and 13 after abrupt discontinuation
- TST, sleep efficiency and amount of REM sleep declined
- Wake after sleep onset and PLMs increased
- Quantity of joints smoked and duration of use was positively associated with PLMS
- Poor sleep can be responsible for relapse in patients attempting to stop using marijuana.
Insomnia
Insomnia Studies

• Consistent - subjective improvements in sleep quality, reduction in sleep latency.
• Less consistent - decreased subjective sleep disturbances, increased subjective total sleep time, and decreased daytime sleepiness.
• Insomnia outcome is secondary, often examining pain, spasticity, anxiety, nightmares, or PTSD symptoms as the primary outcomes, with often favorable results for those domains, but the studies did not consistently use validated scales for insomnia severity, or use subjective reports.
• Objective measures of insomnia with polysomnography show inconsistent changes
• Less REM sleep, less slow wave sleep, more N2 sleep, and more sleep fragmentation with dosed oral THC products
• Some studies show increased EEG delta power and slow wave sleep.

### Chronic Pain disorders

<table>
<thead>
<tr>
<th>Reference Paper</th>
<th>Form of Marijuana</th>
<th>Treatments Effect on Sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic pain</td>
<td>Nabilone</td>
<td>Flexible-dose nabilone 1–4 mg/d improved overall quality of sleep as defined by an 11-point NRS, for patients with diabetic peripheral neuropathic pain</td>
</tr>
<tr>
<td>Narang et al. 51</td>
<td>Dronabinol</td>
<td>Two phase study on patients suffering from chronic noncancer-related pain. Patients receiving dronabinol reported less sleep-interfering pain, as measured by the Brief Pain Inventory</td>
</tr>
<tr>
<td>Blake et al. 52</td>
<td>Sativex</td>
<td>Increased sleep quality (dose effect was unclear) in patients suffering from pain caused by rheumatoid arthritis</td>
</tr>
<tr>
<td>Porteroy et al. 53</td>
<td>Sativex</td>
<td>Decreased sleep disruption on low dose (1–4 sprays per day) and medium dose (6–10 sprays per day). No effect seen with high dose (11–16 sprays per day). Patients had cancer and were on opioid treatment and suffered from chronic pain</td>
</tr>
<tr>
<td>Notcutt et al. 54</td>
<td>Oral spray dose of THC or CBD alone, or THC combined with CBD</td>
<td>Percentage of “good” nights favored THC with CBD (55.4%), over THC (42.9%), CBD (36.9%), and placebo (17%). THC-CBD, THC, and CBD were all significantly more than placebo</td>
</tr>
<tr>
<td>Ware et al. 18</td>
<td>THC joints</td>
<td>Improved subjective sleep latency and sleep restoration on high-dose (9.4%) THC joints only; no effect on number of night time awakenings and sleep quality. Patients were suffering from chronic neuropathic pain</td>
</tr>
</tbody>
</table>
The Effects of Nabilone on Sleep in Fibromyalgia: Results of a Randomized Controlled Trial- Analgesia Vol. 110, No. 2, February 2010

- randomized, double-blind, active-control, equivalency crossover trial to compare nabilone-synthetic THC (0.5-1.0 mg before bedtime) to amitriptyline (10-20 mg before bedtime) in 31 patients with FM with chronic insomnia.
- Subjects received each drug for 2 wk with a 2-wk washout period.
- The primary outcome was sleep quality, measured by the Insomnia Severity Index and the Leeds Sleep Evaluation Questionnaire.
- Secondary outcomes included pain, mood, quality of life, and adverse
Effects of nabilone and amitriptyline on the Insomnia Severity Index (ISI).

Treatment effects of nabilone compared with amitriptyline on sleep items in the Leeds Sleep Evaluation Questionnaire (LSEQ).

Note that treatment effects shifted to the right favor nabilone, whereas effects shifted to the left favor amitriptyline. The x axis is the magnitude of the effect on a scale from 0 to 10. Shifts to the right represent improvements on the sleep subscales (shown on the y axis).

Cannabidiol in Anxiety and Sleep: A Large Case Series
Perm J 2019;23:18-041

- CBD less psychoactive effects
- Aim- assess if CBD improved sleep or anxiety in a clinic population
- Retrospective study in Colorado in a psychiatric clinic
- 72 patient with documented anxiety and sleep problems
- 47 had primary compliant of anxiety and 25 had a primary compliant of poor sleep
- Sleep concerns were tracked at monthly visits using the Pittsburg Sleep Quality Index.
- Anxiety levels were monitored at monthly visits using the Hamilton Anxiety Rating Scale
Cannabidiol in Anxiety and Sleep: A Large Case Series
Perm J 2019;23:18-041

- Anxiety and sleep improved for most patients, and these improvements were sustained over time.
- At the first monthly assessment 79.2% (57/72) reported improvement in anxiety and 66.7% (48/72) an improvement in sleep.
- Results were more sustained for anxiety than sleep over 3 month period.

Table 1. Descriptive statistics for anxiety and sleep scores among adults using cannabidiol treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HAM-A, mean (SD)</th>
<th>PSQI, mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety (n = 47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>23.87 (9.87)</td>
<td>10.98 (3.43)</td>
</tr>
<tr>
<td>1-month follow-up</td>
<td>18.02 (7.56)</td>
<td>8.88 (3.68)</td>
</tr>
<tr>
<td>2-month follow-up</td>
<td>16.35 (8.80)</td>
<td>8.59 (2.91)</td>
</tr>
<tr>
<td>3-month follow-up</td>
<td>16.36 (9.80)</td>
<td>9.25 (2.46)</td>
</tr>
<tr>
<td>Sleep disorder (n = 25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>22.18 (7.55)</td>
<td>13.08 (3.03)</td>
</tr>
<tr>
<td>1-month follow-up</td>
<td>17.82 (9.72)</td>
<td>10.64 (3.89)</td>
</tr>
<tr>
<td>2-month follow-up</td>
<td>17.36 (10.91)</td>
<td>9.39 (3.81)</td>
</tr>
<tr>
<td>3-month follow-up</td>
<td>13.78 (7.86)</td>
<td>9.33 (4.63)</td>
</tr>
</tbody>
</table>

HAM-A = Hamilton Anxiety Rating Scale; PSQI = Pittsburg Sleep Quality Index; SD = standard deviation.
PTSD and sleep

- Following a traumatic event patient can develop recurrent nightmares, intrusive thoughts, avoidant behavior
- Sleep disturbances present in 90% of patients
- Prazosin only medicine that Level A evidence for treatment of PTSD associated nightmares
- The endocannabinoid system may be involved in the pathophysiology of PTSD. One imaging study showed a lower endocannabinoid tone in PTSD (Neumeister Psychiatry 2013)
- Nabilone, a synthetic THC cannabinoid with CB1 receptor agonist, available in Canada since 1985
The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: A preliminary randomized, double-blind, placebo-controlled cross-over design study
PTSD

Treatment of PTSD-associated nightmares

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Change from baseline for both periods.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nabilone ( n = 10 )</td>
</tr>
<tr>
<td>CAPS(^b)</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>(-3.6 \pm 2.4)</td>
</tr>
<tr>
<td>CGI-C(^c)</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>(1.9 \pm 1.1)</td>
</tr>
<tr>
<td>WBQ(^d)</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>(20.8 \pm 22.1)</td>
</tr>
</tbody>
</table>

\(^a\) Wilcoxon Rank-Sum test.
\(^b\) Clinician-Administered PTSD Scale (DSM-IV). Recurring and Distressing Dream Item, Frequency + Intensity.
\(^c\) Clinical Global Impression of Change.
\(^d\) General Well Being Questionnaire.
Sleep Disordered Breathing
Obstructive Sleep apnea

- Animal studies in a rat model showed that endocannabinoids play a role in regulating respiration during sleep mainly through serotonergic effects on upper motor neurons.
- Endocannabinoids (oleamide) and exogenous cannabinoids-THC reduced apneic events in this rat model.
- Study on rats with dronabinol (synthetic THC) pretreated with CB1 And CB2 receptor antagonist showed that this effect is mediated through these receptors and mainly through CB2 receptors suggesting it is a peripheral effect rather than a central effect.

Pharmacotherapy of Apnea by Cannabimimetic Enhancement, the PACE Clinical Trial: Effects of Dronabinol in Obstructive Sleep Apnea
- Should not be used for treatment of OSA based on small pilot studies
  - Somnolence was reported in most patients
  - Long term effects on other sleep measures and side effects were not known
  - Medical Cannabis and related compounds are not FDA approved for treatment of OSA
  - Unreliable delivery methods
- Strongly recommended that OSA should not be listed as one of the chronic medical conditions on State Medical cannabis programs
Shift work disorder
• examined the effect of smoked cannabis on performance, mood and sleep
• 10 experienced marijuana smokers completed 23 day residential study
• 3 consecutive days of either night shift or day shift
• Shifts alternated 3 times during the study with one day off between shifts
• Smoked 1 marijuana cigarette (varying concentrations of THC) or placebo after waking up.
• Underwent psychomotor performance testing and mood rating.
• Sleep was measured objectively using Night Cap sleep system (measured TST, Sleep efficiency)
• Participants received a higher dose of THC
  • felt less tired on their night shifts
    Improved objective and subjective measures of sleep when recovery sleep was permitted
    Performed better on vigilance tasks
    Reported being less miserable and tired

• When participants smoked placebo cigarettes,
  • psychomotor performance was reduced during the night shift compared to the day shift
  • Felt less confident and more tired
Restless Leg Syndrome

- Limited evidence
- Anecdotal reports from patients to their providers
- 20 case reports of complete eradication of RLS Sx and improved sleep with the addition or substitution of regular RLS medicines with smoked marijuana
- Proposed mechanisms
  - Direct dopaminergic properties of THC
  - Activation of similar nervous tissue as opioids, as CB1 and Mu receptors have extensive overlap in CNS
  - Direct effect of CB2 receptors in the peripheral nervous system. Analgesic effect
  - Indirect sedative ad anxiolytic effect

Sleep Med 2017; 36:182-3
Sleep Breath 2020; 24(1): 277-9
Potential therapeutic benefit of Cannabis

- Insomnia associated with anxiety.
- Sleep disturbances associated with PTSD
- Sleep disturbances related to chronic pain
- Sleep apnea
- Sleep disturbances associated with a variety of neurological disorders like Multiple Sclerosis where it has been shown to reduce spasticity
- Case reports of reducing dream enactment behavior in patients with PD
- Sleep disturbances in HIV related symptoms
Summary

- Cannabis/Marijuana is here to stay and limited research and history has shown that it has an important role to play in providing treatment for some sleep related and other medical conditions.
- Patient will access cannabis if they perceive some benefit
- Research on cannabis and sleep is in its infancy and has yielded mixed results
- Federal and state laws are confusing and make research difficult
- Clear cut distinctions labelling THC psychoactive and CBD as medically therapeutic are probably not correct and we may need a combination of both
- Pharmacokinetics of different delivery systems need to be worked out
- More basic science research on the endocannabinoid system