Medical Marijuana

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RLS

RESTLESS LEGS SYNDROME FOUNDATION

Agenda

- Introduction
- History
- Components (THC, CBD)
  - Psychotropic
  - Not psychotropic
- Different forms / potency for neurological disorders
- Main short term physical effects
- What conditions are potential treatment option
- Research (why lack of?)
- Federal laws/ guidelines

RLS- Introduction

- Common, under-diagnosed, treatable condition
- Symptoms most consistent with annoying or painful sensory-motor feelings
- Neurological movement disorder associated with sleep disorder
- Prevalence 3 - 15% in the general population
- Incidence increases with age
- More common in adult women 2:1 than in men
  - Pregnancy up to 35% of women
- Diagnosis is based on clinical features

Garcia-Borreguero D, et al. Sleep Med Rev 2006;10:153-167. Allen RP. Am J Med 2007;120:S13-S21.
Trenkwalder C. Nat Clin Pract Neurol 2007;3:474-475.

Description of RLS

- Creeping
- Crawling
- Heebie jeebies
- Burning
- Searing
- Jimmy legs
- The gotta moves
- Electric current inside

- Tugging
- Indescribable
- Pulling
- Drawing
- Aching
- Flowing water
- Elvis legs
- A lot of energy in my muscles that needs to be released

Non-Medical Therapies

- Good sleep hygiene
  - May change sleep time
- Moderate physical activity (e.g. walking, stationary bike riding, kickboxing, etc.)
- Hot or cold packs, baths, massage
- Rubbing or pressure, stretching
- Engage the mind (yoga, meditation)
- Acupuncture
- Eliminate medications that exacerbate
- Treat iron deficiency anemia

Medical Therapy

- Alpha 2- Delta Ligands
  - Gabapentin (*Neurotin®),* Gabapentin-enacarbil (*HORIZANT®*), pregabalin (*LYRICA®*)
- Dopaminergic agonists
- Benzodiazepines
- Opioids
- Iron
- Levodopa/carbidopa
- Other
  - Cannabis/Marijuana
  - Anti-epileptic drugs ETC

History

- 19th Century
  - Marijuana was legally grown and utilized in the U.S.
- 20th Century
  - 1937: The Marijuana Tax Act is passed, prohibiting all use of cannabis on a federal level.
  - 1970: The Controlled Substances Act is passed, prohibiting cannabis federally.
    - Making Marijuana a Schedule I drug.
- 21st Century
  - 2014: The United States House of Representatives passed a bill prohibiting the DEA from using funds to arrest medical cannabis patients in states with medical cannabis laws.
  - **Present**: Many states have either decriminalized, and/or legalized the medical and/or recreational use of marijuana.

Components- Cannabinoids

- Two major types of Marijuana
  - Cannabis sativa: predominantly THC
  - Cannabis indica: contains both THC and CBD
- There are hybrids as well.

Canabinoids

- Cannabidiol- type (CBD)
  - Non- psychotropic
    - Will not experience a “high”
  - MOA: unknown, does not bind to $CB_{1,}$ and may be an antagonist.
- Δ^9-tetrahydrocannabinol (THC)
  - Psychotropic
    - Experience “high”
  - MOA: it is a partial CB_1 agonist

Cannabinoids- Potential Drug Interactions

- Cannabinoids– structurally diverse chemicals
- *Cannabis sativa** has 489 known constituents, 70 of which are cannabinoids, the remainder including potentially neuroactive substances such as ketones, aldehydes etc. that cross the BBB
- Exogenous cannabinoids widely consumed in many forms:
  - Cannabinoid-rich preparations of cannabis in herb (marijuana) or resin form.
  - Cannabinoid containing pharmaceutical products, either containing natural cannabis extracts (Sativex®, GW Rx- Epidiolex)
  - Synthetic cannabinoid (dronabinol, tetrahydrocannabinol (THC) or nabilone)

Maa E et al. Epilepsia, 55(b):783-786, 2014 Stout SM et al. Drug Metab Rev 2014;46(1):86-95.

Cannabidiol- Potential Drug Interactions

- Cannabidiol Pharmacokinetics:
  - highly lipophilicity
  - high volume of distribution
  - highly protein bound
- Extensively metabolized by liver:
  - hydroxylated to 7-OH-CBD via CYP P450 3A (2/4) and CYP2C (8/9/19)
- $T_{1/2}$ of CBD is ~ 18 to 32 hours

*Devinsky O et al. Epilepsia, 55(6):791-802, 2014.

Cannabidiol- Potential Drug Interactions

- How CBD affects other drugs*
  - CBD potent inhibitor of CYP2C and CYP3A – in vitro and animal models (interactions are generally seen at concentrations much higher than used in human consumption)
  - Chronic administration of CBD may induce CYP2B (1/6) in animal models
    - Valproate (metabolized by CYP2B)
    - Clobazam (metabolized by CYP2B)
- How other drugs may affect CBD/CBN/THC**
  - THC; CYPs 2C9, 3A4
  - Cannabidiol (CBD; CYPs 2C19, 3A4)
  - Cannabinol (CBN; CYPs 2C9, 3A4)

*Devinsky O et al. Epilepsia, 55(6):791-802, 2014. **Stout SM et al. Drug Metab Rev 2014;46(1):86-95

Forms

- Leaf
  - Smoked, eaten (edibles), vaporized
- Plant resin
  - Smoked, eaten
- Oil extracts
  - Nabiximols (Sativex), Cannador
- Single molecule preparations
  - THC: dronabinol, marinol
  - Chemical variant of THC: nabilone (Cesamet)
- Liquid formulation
  - Epidiolex
    - It is a liquid formulation of pure CBD that is used for the treatment of pediatric epilepsy
    - It is in stage III trials.

Forms

Inhaled- “smoke”

- C_{max}: 3-10 min
- F: 10-25%
- Duration: 1-4 hours
- $T_{1/2}$: 19 hours

Oral- “Ingestion”

- C_{max}: 1-3 hours
- F: 5-20%
- Duration: 4-10 hours
- $T_{1/2}$: 7 days

Preparations

Dried Flower Buds

Kief

Hashish

Tincture

Infusion (butter)

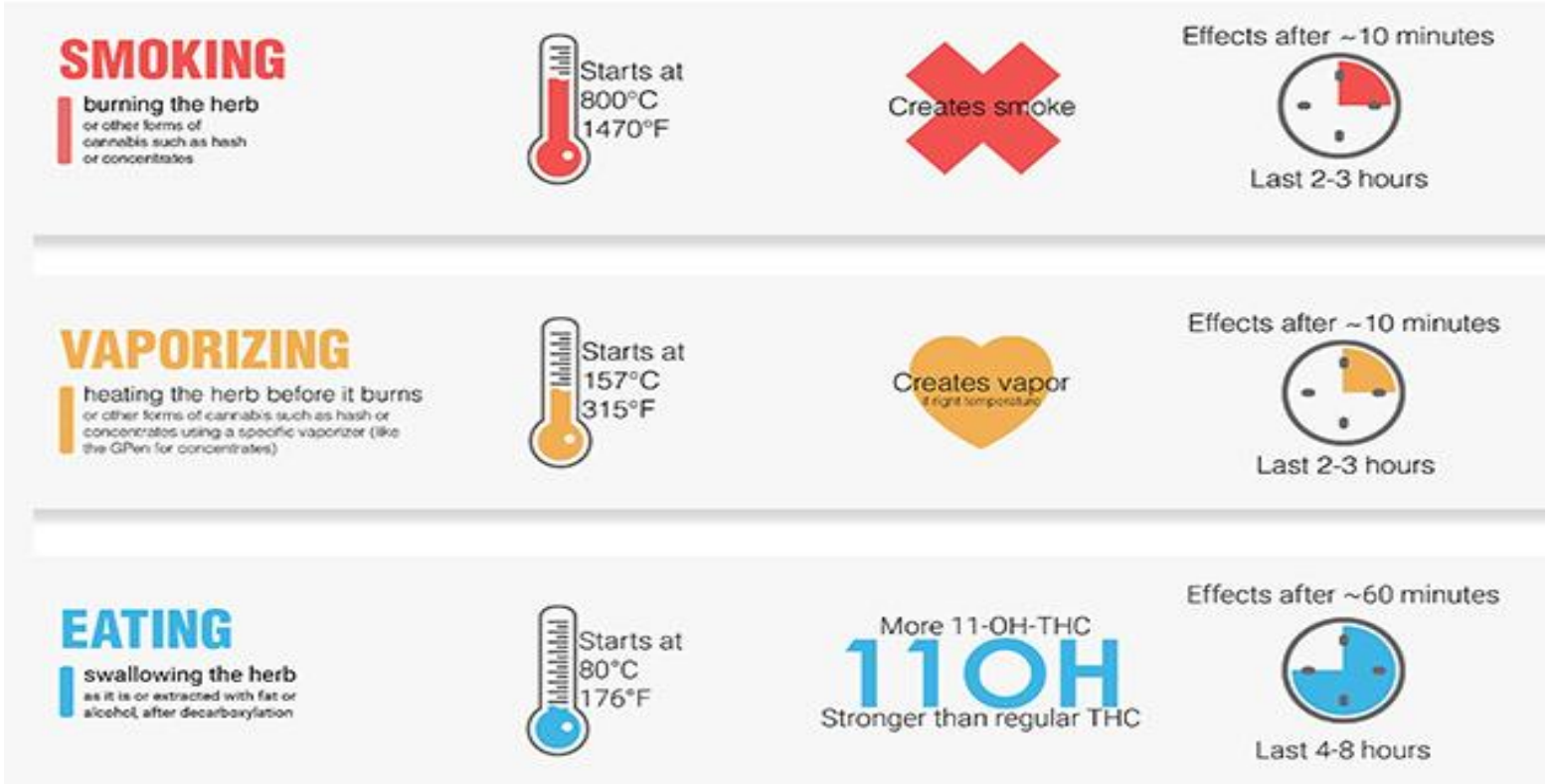
Hash Oil

Vaporizer: the detachable balloon fills with vapors.

Pipe Resin

https://en.wikipedia.org/wiki/Cannabis_%28drug%29

MARIJUANA CONSUMPTION



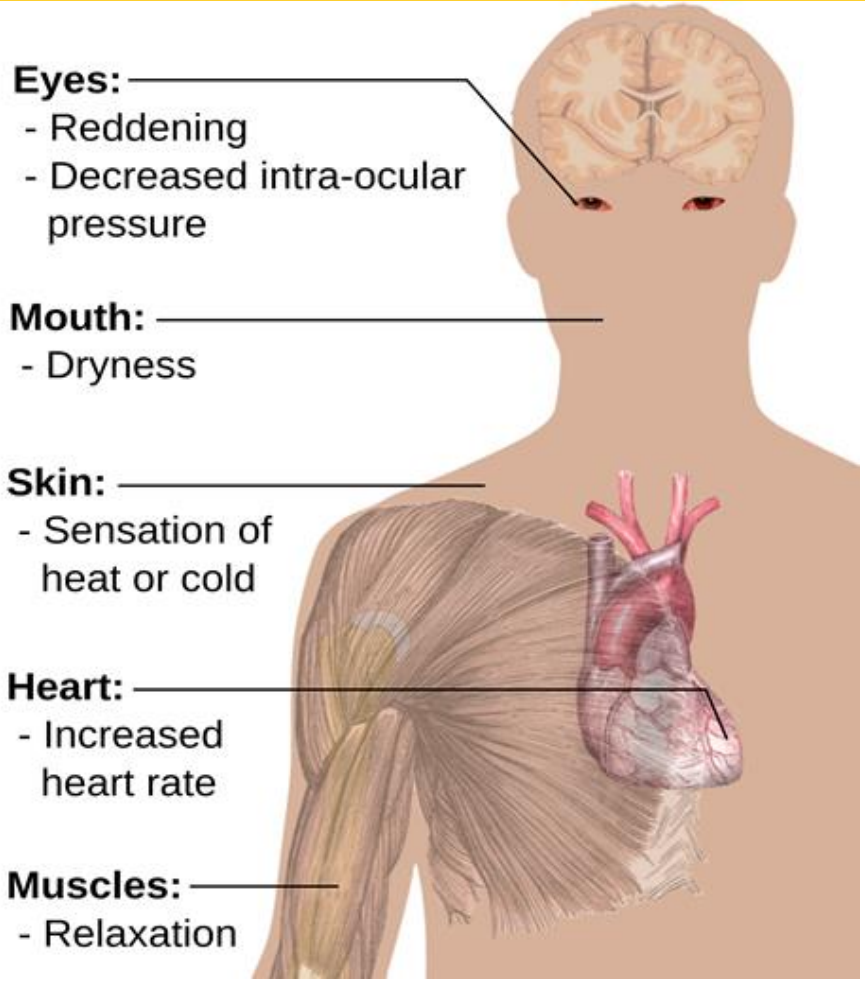
http://azmarijuana.com/dans-stash/marijuana-consumption-styles/

Potency for Neuro Disorders

- Each individual's metabolism and tolerance of marijuana is different which can make it difficult to use correctly and safely.
- Dosing changes of marijuana will be based on the patient's therapeutic response.

Borgelt, Laura M., et al. "The pharmacologic and clinical effects of medical cannabis." *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy* 33.2 (2013): 195-209.

Main Short Term Physical Effects



https://en.wikipedia.org/wiki/File:Bodily_effects_of_cannabis.svg

Conditions

- Sleep issues
  - Potentially RLS
- Pain treatment
- Anxiety
- Used in cancer patients for chemo induced nausea/vomiting
- Increasing appetite
- Glaucoma- decreasing ocular pressure-
- Relieves spasticity of muscles
- Epilepsy, multiple sclerosis

Research

- There is a lack of marijuana research in the U.S. because it is still federally illegal and hard to get funding.
- We currently use patient anecdotes and research conducted in Europe to make medical decisions regarding marijuana.
- Private entities in the U.S. are beginning to conduct marijuana based research to gain a better understanding of its medicinal properties.
- One major problem with current studies is that they use standardized preparations which are not usually available in the U.S.

Research

- In regards to RLS
  - Can refer to studies with marijuana on sleep and pain
    - Sleep
    - Pain
  - There are currently no studies that have been directly done on marijuana and RLS.

Research- Pain

- “Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials”
  - 18 controlled trials. Formulations consisting of smoked, extract, THC, Nabilone, and Unique molecule.
    - 15/18 reported improvement in pain
    - 4/18 reported improvement in sleep
    - A limitation to the study is that the duration of the studies were short.
  - It can be assumed that from these studies cannabis decreased the pain therefore allowing some patients to better quality sleep. However, the review did not discuss the duration of which that patient’s pain was not present or by how much the pain improved.

Lynch, Mary E., and Fiona Campbell. "Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials." *British journal of clinical pharmacology* 72.5 (2011): 735-744.

Research- Pain

- "Systematic review and meta-analysis of cannabis treatment for chronic pain."
  - 18 trials.
  - Systematic review and meta analysis of double-blind randomized controlled trial that compared cannabis preparation to placebo amongst patients with chronic pain
  - The study showed cannabis does yield moderate effects for the treatment of chronic pain. They also recommend that a study be done clarifying benefits to harms.

Martín-Sánchez, Eva, et al. "Systematic review and meta-analysis of cannabis treatment for chronic pain." *Pain medicine* 10.8 (2009): 1353-1368.

Research- Pain & Sleep

- "Smoked cannabis for chronic neuropathic pain: a randomized controlled trial.“
  - Adults with neuropathic pain were randomly assigned to receive cannabis at 4 potencies (0%, 2.5%, 6%, and 9.4% tetrahydrocannabinol) for 14 days in a crossover trial. Daily average pain was measured using an 11 point scale.
  - The study indicated that a single inhalation of 25 mg of .4% tetrahydrocannabinol cannabis three times a day for 5 days significantly reduced the intensity of pain improved as well as the quality of sleep. The other lower effects had minimal to no effect on pain and sleep.

Ware, Mark A., et al. "Smoked cannabis for chronic neuropathic pain: a randomized controlled trial." *Canadian Medical Association Journal* 182.14 (2010): E694-E701.

Research- Sleep

- "The effects of cannabinoid administration on sleep: a systematic review of human studies.“
  - 39 clinical trials. Formulations consisting of smoked, THC/Nabilone, Cannador/Nabiximols, and other oral forms.
    - The information provided does not allow for strong clinical decisions to be made because the studies featured many different conditions and formulations.
    - The results of the studies are mixed, but nonetheless show that cannabis does effect sleep. Some studies had strong biases, indicating the need for a study to be conducted on the specific effects of cannabinoids in regards to sleep.
  - A noted observation is that the use of cannabis with a condition that disrupts sleep may result in a decrease in night time interruptions and the improvement in the quality of sleep.

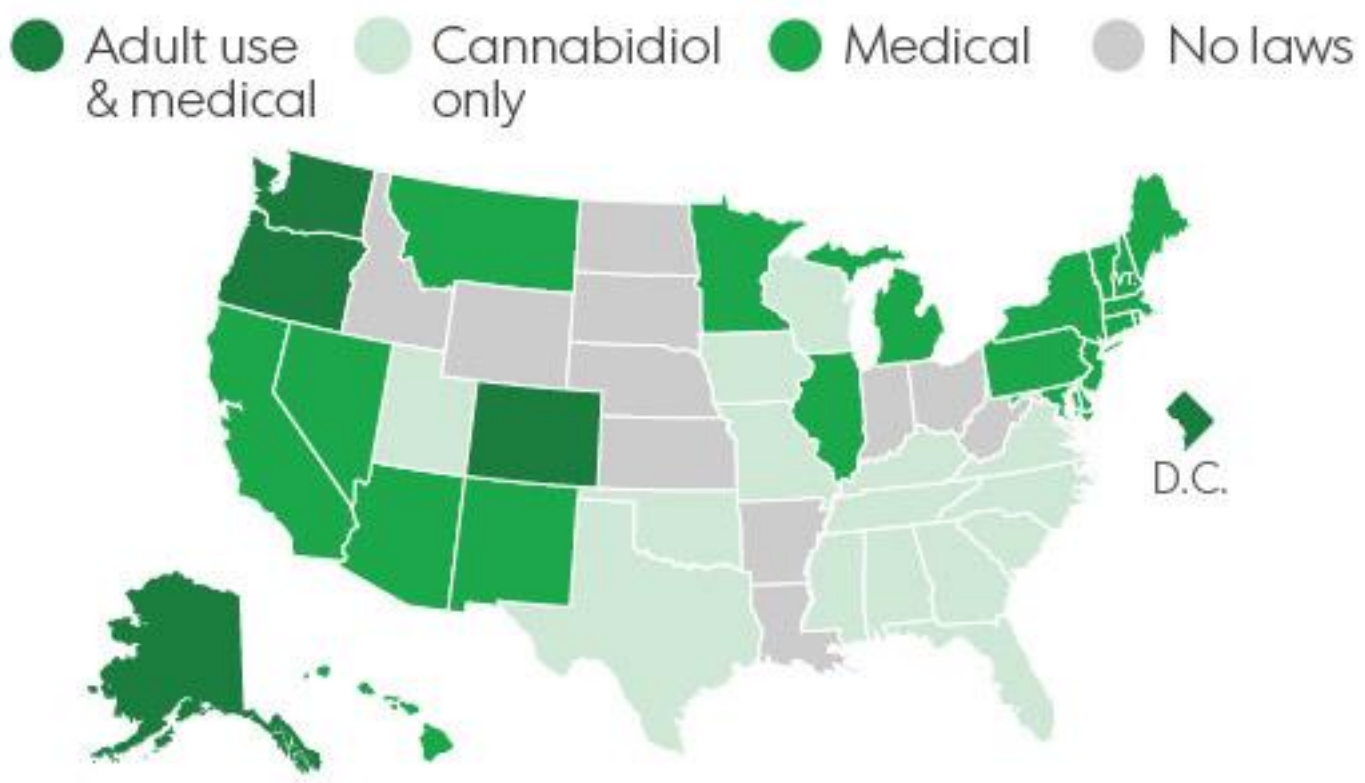
Gates, Peter J., Lucy Albertella, and Jan Copeland. "The effects of cannabinoid administration on sleep: a systematic review of human studies." *Sleep medicine reviews* 18.6 (2014): 477-487.

Research

- More! More! More!
  - More studies need to be done to assist in the proper use of cannabis for RLS.

Federal Laws

- **Marijuana is a Schedule I drug under the federal Controlled Substances Act**
  - Makes possession, usage, purchase, sale, and/or cultivation of marijuana illegal
  - Crude marijuana may not be **prescribed, administered, or dispensed**
  - Other Schedule I drugs include:
    - Lysergic acid diethylamide (LSD)
    - Diacetylmorphine (Heroin)
    - Gamma Hydroxybutyric Acid (GHB)
    - MDMA (“ecstasy”)
    - Mescaline



http://www.usatoday.com/story/news/2016/05/21/dea-could-reschedule-marijuana-allowing-doctors-conduct-more-research/84670716/

Guidelines

- American Academy of Neurology
  - The AAN endorses the use of Cannabis for the treatment of the following diseases:
    - Symptoms of multiple sclerosis
    - Uncontrolled movements of Parkinson's Disease
    - Motor Symptoms in Huntington's Disease
    - Tics in Tourette syndrome
    - Cervical dystonia (abnormal neck movements)
    - Seizures in epilepsy
  - It had the strongest evidence for the use of oral cannabis extract pills from pure CBD to lessen patient's spasticity and moderate evidence for THC pills and oral spray to lessen spasticity and painful spasms.

https://www.aan.com/guidelines/home/getguidelinecontent/650

Frequently asked Questions

- How can I get medical marijuana - in my state or what Dr. prescribes it?
  - Refer to the laws of your state. In the case that medical marijuana is legal your doctor would have to give you a medical marijuana card that can be used at dispensaries. If you are in a state in which recreational marijuana is legal but your intentions are to use marijuana for medial purposes, still consult with your provider.

Frequently asked Questions

- Does cannabis based oil/oils do anything?
  - According to the following studies yes (maybe)!
    - "A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment."
      - There were clinical improvements in pain and sleep quality with the THC/CBD spray, but the study did not show statistical significance.
    - Each patient should be dealt with case by case

Serpell, M., et al. "A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment." *European Journal of Pain* 18.7 (2014): 999-1012.

Frequently asked Questions

- Is marijuana effective in treating RLS?
  - We are unsure due to the lack of evidence.
  - As addressed in the preceding slides studies that focused on sleep and pain can be used to assist in making clinical decisions.
  - It may be effective in treating RLS but more efficacy studies are needed.

- How can I be involved in studies for its use?
  - ClinicalTrials.gov

Frequently asked Questions

- Is there research being done?
  - No. There are no studies utilizing marijuana for the treatment of RLS.

Conflict of Interest & Disclaimer

- Jacquelyn Bainbridge has no conflict of interests

- RLSF Disclaimer

No studies have documented the benefits of medical marijuana for treating RLS and its use remains illegal under federal law.

It's important to speak with your healthcare provider before making any changes to your treatment regimen, and to take into consideration the legal status of marijuana in your jurisdiction.

Q & A

www.rls.org

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