the FOUNDATION for PERIPHERAL NEUROPATHY®

# Welcome!

*FPN Webinar:*

# Exploring *the* Use of Medical Marijuana *in* Peripheral Neuropathy Treatment

Thursday, September 5, 2024

***We will begin our presentation shortly.***

the FOUNDATION for PERIPHERAL NEUROPATHY®

***Moderator:***

**Lindsay Colbert**
*Executive Director*
*the* Foundation *for* Peripheral Neuropathy

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# Before We Begin

This presentation is being recorded. The recording link will be emailed to you so you can view it again later.

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If you are having trouble with the audio using your computer, you can dial in by phone (check your email for dial-in instructions).

the FOUNDATION for PERIPHERAL NEUROPATHY®

## *Presenter:*

**Jessica Robinson-Papp, MD, MS, FAAN**
*Icahn School of Medicine at Mount Sinai -*
*Professor of Neuology*

# Medical Marijuana for Peripheral Neuropathy

**Jessica Robinson-Papp, MD, MS, FAAN**
**Professor**
**Vice Chair for Clinical Research**
**Department of Neurology**
**Icahn School of Medicine at Mount Sinai**

Mount Sinai

# Cannabis 101

- Cannabis is one of the oldest cultivated plants.
- Two main varieties with different uses: hemp and marijuana.
- Marijuana is used for recreational and medicinal purposes and has two main active components (both cannabinoids): THC (psychoactive) and CBD.
- Hemp (by definition) is cannabis with <0.3% THC; all other cannabis is marijuana.
- Hemp has many industrial uses: rope, clothes, food items etc.
- Potentially medicinal cannabis-related products include:
  - "Medical marijuana" definition of this varies state by state, sometimes marijuana itself, sometimes a product manufactured from marijuana
  - CBD products made from hemp
  - Pharmaceutically manufactured cannabinoids:
    - Synthetic THC: dronabinol and nabilone
    - Derived from cannabis plant: Epidiolex (CBD only, FDA-approved), nabiximols CBD:THC mix (Sativex) approved outside US

- "Synthetic cannabinoids" or "synthetic marijuana" also refers to unregulated manufactured drugs of abuse that are not necessarily related to cannabinoids, may be highly toxic and have no medicinal use (e.g. Spice and K2)

# A brief history of medical marijuana

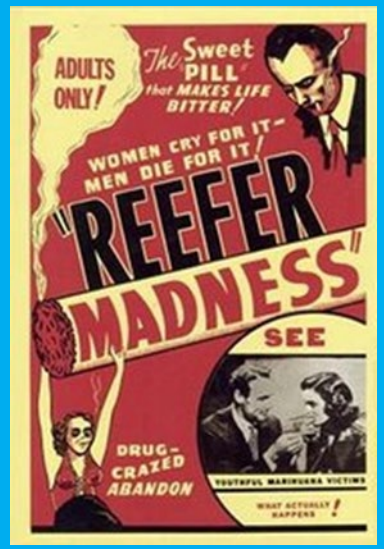
- Use likely originated in ancient Egypt, references date as far back as 2350 BC
- Present in multiple cultures and eras
- 1700 BC: “A treatment for the eyes: celery; hemp; is ground and left in the dew overnight. Both eyes of the patient are to be washed with it early in the morning.”
- 1640 AD: “The same decoction of the rootes, easeth the paines of the goute, the hard tumours, or knots of the joynts, the paines and shrinking of the sinewes, and other the like paines of the hippes: it is good to be used, for any place that hath beene burnt by fire, if the fresh juyce be mixed with a little oyle or butter.”

Fig. 5. *Cannabis in various ancient languages*

EB Russo, 2007

# US Marijuana Timeline: Toward Crimilaization

- 1600-1890s: Hemp production was encouraged for use in making goods like cloth and rope.  Marijuana was an ingredient in many medicinal products
- 1906: Pure Food and Drug Act required labeling of products containing marijuana (first regulations)
- 1930's: Intensification of anti-marijuana propaganda ("Reefer Madness").  First criminalization of marijuana.
- 1970s: Controlled substance act.  Marijuana designated schedule 1 "drug with no currently accepted medical use and a high potential for abuse."
- 1980s: War on drugs.  Three-strikes (life sentences for repeat drug offenders including marijuana).



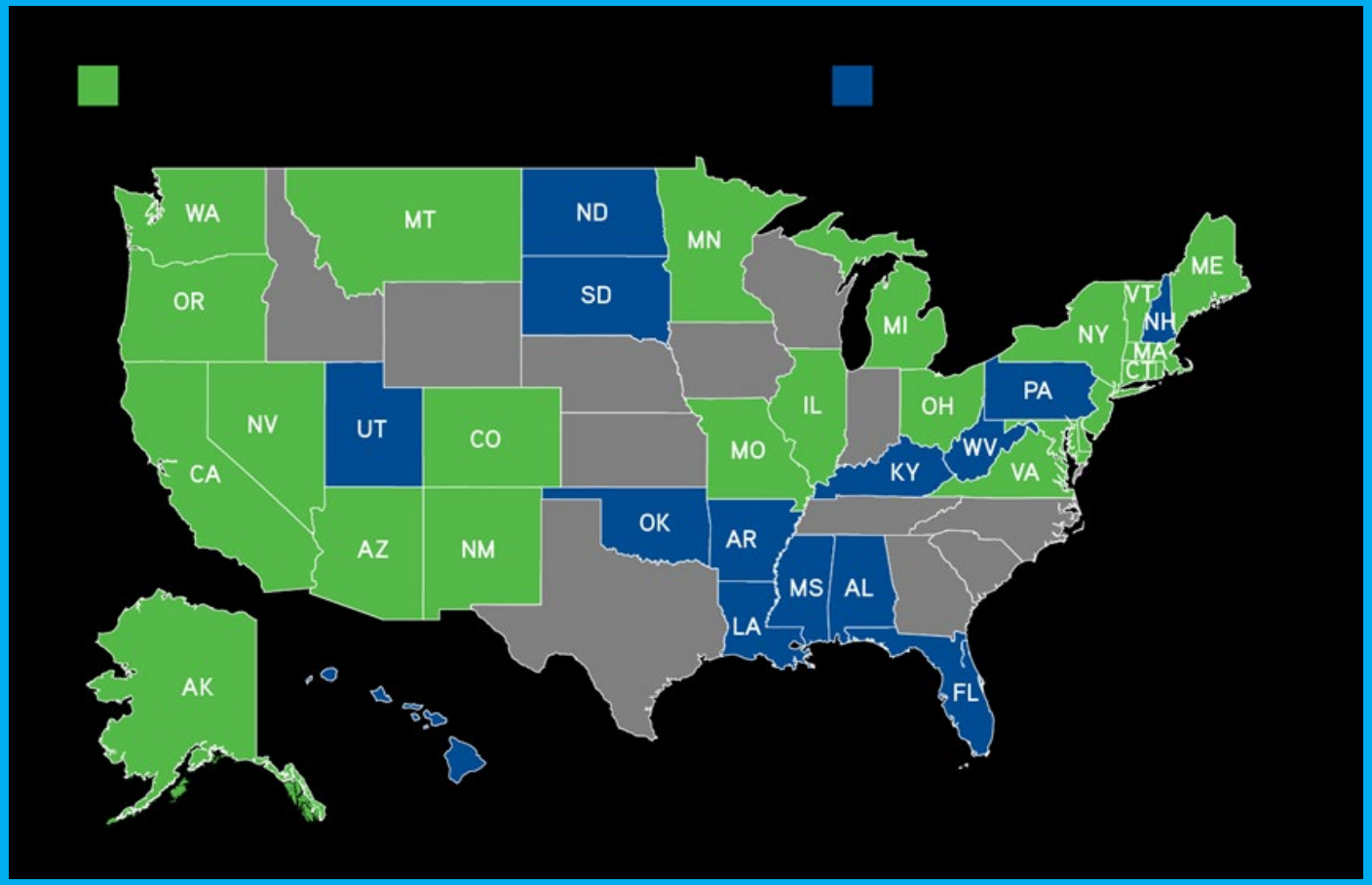

Adapted from:
https://www.pbs.org/wgbh/pages/frontline/shows/dope/etc/cron.html

# US Marijuana Timeline: Toward Legalization

- 1996: First legalization of medical use (California).
- 2012: First legalization of recreational use (Washington and Colorado)
- 2014: Federal law passed barring DOJ from spending funds to interfere with the implementation of state medical cannabis laws
- 2018: Farm bill makes hemp-derived CBD products federally legal → Huge growth in CBD sales

Adapted from: http://www.nytimes.com/interactive/2013/10/27/us/marijuana-legalization-timeline.html#/#time283_8137

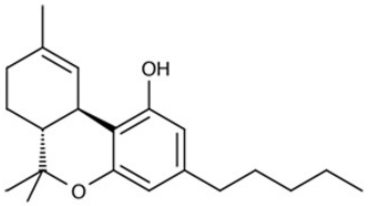
# Cannabis laws by state



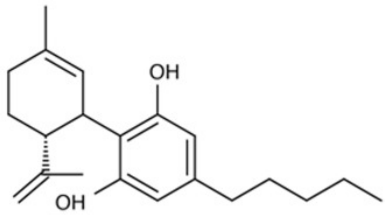

From: Rockefeller Institute of Government: https://rockinst.org/intheweeds/

# Active Ingredients

- Marijuana contains >400 chemical entities with >60 cannabinoid compounds
- 4 major cannabinoid compounds: **d-9-THC, CBD**, d-8-THC, cannabinol
- THC has the major psychoactive effects: hypoactivity, hypothermia, spatial and verbal short-term memory impairment
- CBD does not have psychoactive effects on it's own but can potentiate the effects of THC
- Also "entourage" compounds: terpenes and flavonoids



Delta-9-tetrahydrocannabinol (THC)

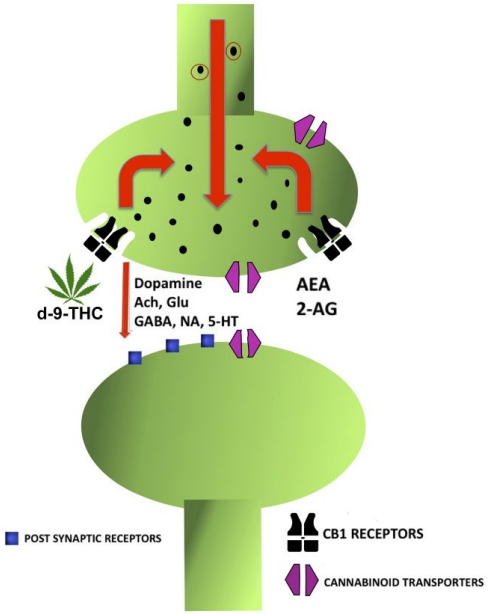


Cannabidiol

Atakan, 2012

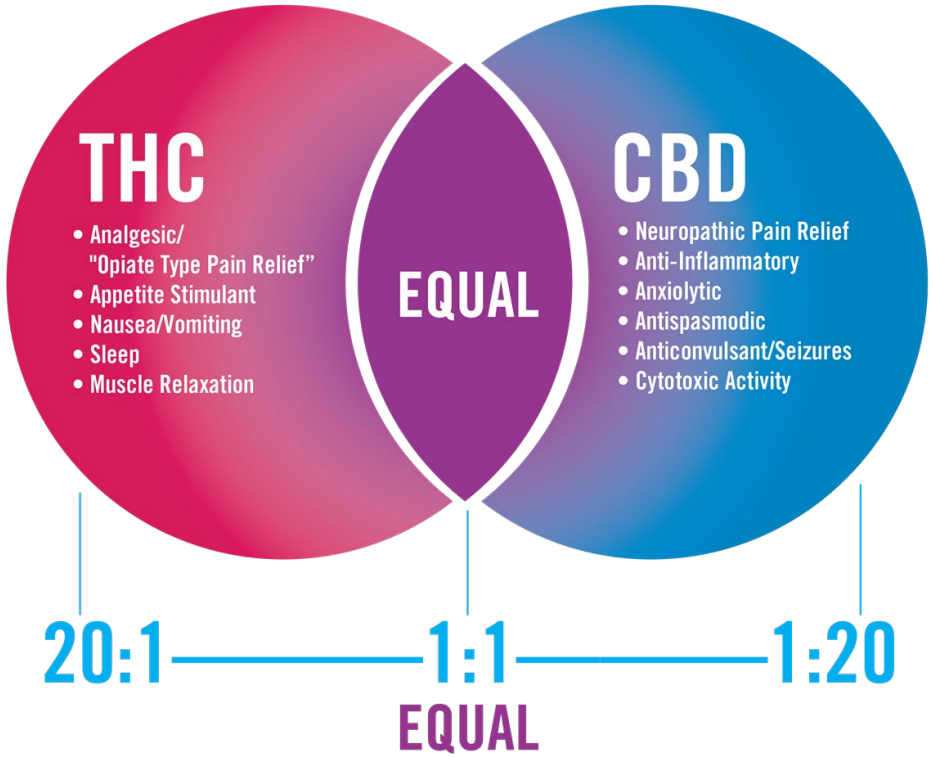
# Cannabinoid receptor system

- Receptors activated by cannabinoids were discovered in the late 1980s-early 1990s
- Cannabinoid 1 and 2 receptors (CB1R and CB2R) are designed to bind cannabinoids produced naturally by our bodies (endocannabinoids)
- The effect of a cannabinoid depends on whether it binds CB1R, CB2R or both
- CB1R mostly in the brain
- CB2R more in the immune system




Atakan, 2012

# Effects of THC vs CBD




| Effect | THC | CBD |
|---|---|---|
| Anticonvulsant | + | ++ |
| Muscle relaxant | ++ | + |
| Anxiolytic | ± | ++ |
| Antiemetic | ++ | ++ |
| Sedation | + | – |
| Appetite | + | – |
| GI motility (slowed) | ++ | + |

Graphic from Columbia Care

Atakan, 2012

# Entourage effect

- Idea that other compounds in cannabis (e.g., terpenes and flavonoids) are important in therapeutic effect of cannabis.
- Has wide lay-popularity (rationale behind why natural cannabis products are superior to synthetics), but little scientific evidence

SCIENTIFIC AMERICAN

CHEMISTRY

**Some of the Parts: Is Marijuana's "Entourage Effect" Scientifically Valid?**

Industry players swear pot's many chemicals work in concert, but most scientists hear a THC solo

By Angus Chen on April 20, 2017

Medical grade marijuana display at dispensary in Denver, Colorado. *Credit: Jon Paciaroni Getty Images*

# Clinical Trials

RESEARCH

## Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: a systematic review and meta-analysis of randomised clinical trials

Li Wang,[1,2,3] Patrick J Hong,[4] Curtis May,[5] Yasir Rehman,[2,3] Yvgeniy Oparin,[1] Chris J Hong,[6] Brian Y Hong,[7] Mahmood AminiLari,[2,3] Lucas Gallo,[8] Alka Kaushal,[9] Samantha Craigie,[2] Rachel J Couban,[2] Elena Kum,[3] Harsha Shanthanna,[1] Ira Price,[10] Suneel Upadhye,[3,11] Mark A Ware,[12] Fiona Campbell,[13] Rachelle Buchbinder,[14] Thomas Agoritsas,[3,15] Jason W Busse[1,2,3,16,17]

Moderate to high certainty evidence shows that, compared with placebo, non-inhaled medical cannabis or cannabinoids results in a small to very small increase in the proportion of people living with chronic pain who experience an important improvement in pain relief, physical functioning, and sleep quality.

High certainty evidence shows that, compared with placebo, non-inhaled medical cannabis or cannabinoids does not improve emotional, role, or social functioning.

Moderate to high certainty evidence shows that, compared with placebo, non-inhaled medical cannabis or cannabinoids results in a small increase in the proportion of patients experiencing cognitive impairment, vomiting, drowsiness, dizziness (and large increase at longer follow-up), impaired attention, and nausea, but not diarrhoea.

BMJ, 2021

# Clinical Trials

| Neuropathic pain (n=10) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NCT00710424 [4] | 2006 | Parallel trial | 297 | Diabetic neuropathy | ≥6 | 59.5±10.5 | 114 (38.4) | 2 | Spray | THC/CBD | Placebo | 98 | 98 |
| Nurmikko [5] | 2007 | Parallel trial | 125 | Peripheral neuropathic pain | 75.6±72.6 | 53.3±15.5 | 74 (59.2) | 2 | Spray | THC/CBD | Placebo | 35 | 35 |
| Frank [6] | 2008 | Cross-over trial | 192 [b] | Chronic neuropathic pain | 76.4±69.1 | 50.2±13.6 | 25 (26) | 2 | Oral | THC | Dihydro-codeine | 42 | 42 |
| Selvarajah [7] | 2010 | Parallel trial | 30 | Diabetic neuropathy | NR | 56.3±10.2 | 11 (36.7) | 2 | Spray | THC/CBD | Placebo | 84 | 84 |
| Toth [8] | 2012 | Parallel trial | 26 | Diabetic neuropathy | 85.8±98.4 | 61.2±14.9 | 12 (46.2) | 2 | Oral | THC | Placebo | 35 | 35 |
| Langford [9] [c] | 2013 | Parallel trial | 339 | Central neuropathic pain in multiple sclerosis | 65.5±65.5 | 49±10.5 | 230 (67.8) | 2 | Spray | THC/CBD | Placebo | 98 | 98 |
| Serpell [10] | 2014 | Parallel trial | 246 | Peripheral Neuropathy | 75.6±78.6 | 57.3±14.3 | 150 (61) | 2 | Spray | THC/CBD | Placebo | 98 | 98 |
| Andresen [11] | 2016 | Parallel trial | 73 | Spinal cord injury-related neuropathic pain | ≥3 | 56.3±11.5 | 19 (26) | 2 | Sublingual | PEA | Placebo | 84 | 84 |
| Schimrigk [12] [c] | 2017 | Parallel trial | 240 | Central neuropathic pain in multiple sclerosis | NR | 47.7±9.6 | 175 (72.9) | 2 | Oral | THC | Placebo | 112 | 112 |
| Xu [13] | 2020 | Parallel trial | 29 | Peripheral Neuropathy | ≥3 | 68.1±8.4 | 11 (37.9) | 2 | Trans-dermal | CBD | Placebo | 28 | 28 |
| Eibach [14] | 2020 | Cross-over trial | 68[b] | HIV-Associated Neuropathic Pain | 157.2 ±106.44 | 50.31±8.96 | 1(6.3) | 2 | Oral | Cannabidivari (CBDV) | Placebo | 28 | 28 |

# A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment

M. Serpell, S. Ratcliffe, J. Hovorka, M. Schofield, L. Taylor, H. Lauder, E. Ehler

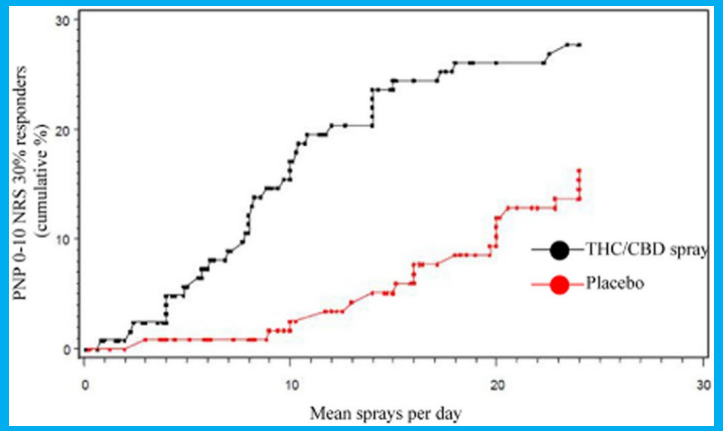
First published: 13 January 2014 | https://doi.org/10.1002/j.1532-2149.2013.00445.x | Citations: 126

## Methods

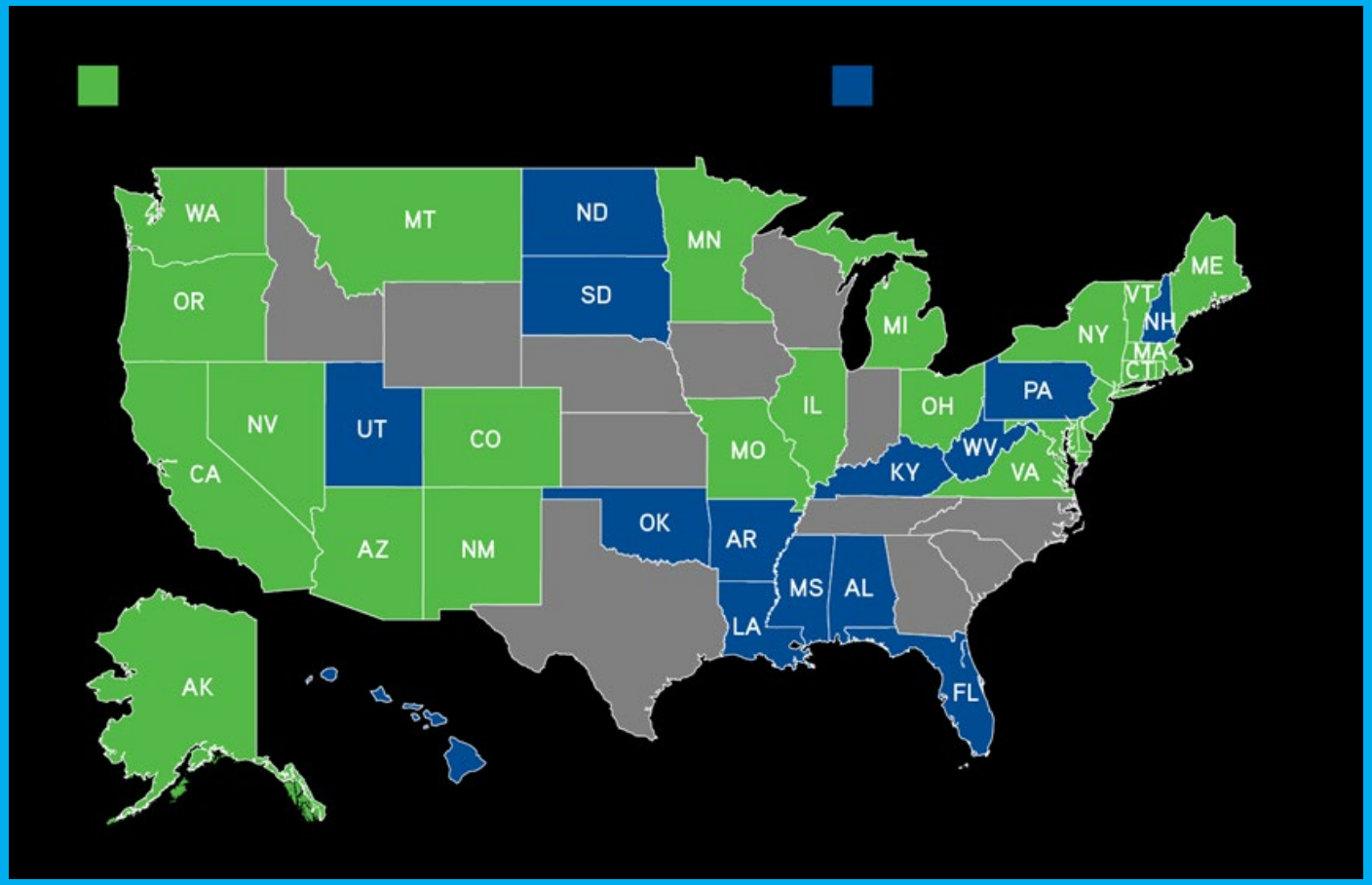
In total, 303 patients with PNP associated with allodynia were screened; 128 were randomized to THC/CBD spray and 118 to placebo, in addition to their current analgesic therapy. The co-primary efficacy endpoints were the 30% responder rate in PNP 0–10 numerical rating scale (NRS) score and the mean change from baseline to the end of treatment in this score. Various key secondary measures of pain and functioning were also investigated.

## Results

At the 30% responder level, there were statistically significant treatment differences in favour of THC/CBD spray in the full analysis (intention-to-treat) dataset [$p = 0.034$; 95% confidence interval (CI): 1.05–3.70]. There was also a reduction in mean PNP 0–10 NRS scores in both treatment groups that was numerically higher in the THC/CBD spray group, but which failed to reach statistical significance. Secondary measures of sleep quality 0–10 NRS score ($p = 0.0072$) and Subject Global Impression of Change (SGIC) ($p = 0.023$) also demonstrated statistically significant treatment differences in favour of THC/CBD spray treatment.



# Cannabis laws by state




From: Rockefeller Institute of Government: https://rockinst.org/intheweeds/

# Nationally legal: Hemp-derived CBD products

CBD present in industrial hemp, legal to make products from it, but requires large amounts of hemp

Potential for contamination with pesticides, microbiological contaminants (mold, bacteria), heavy metals, residual solvents



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**Spiked vapes and emergency room visits reveal dark side of CBD craze**

***CN: Cannabinoid Profile & Potency [WI-10-17 & WI-10-17-01]*** *Ana*

The client sample was analyzed for plant-based cannabinoids by Liquid Chromatography (LC) for certified reference standards at known concentrations.

*51994-CN*

| ID | Weight % | Concentration |
|---|---|---|
| D9-THC | ND | ND |
| THCV | ND | ND |
| CBD | 99.40 wt % | 994.00 mg/g |
| CBDV | 0.31 wt % | 3.11 mg/g |
| CBG | ND | ND |
| CBC | 0.01 wt % | 0.13 mg/g |
| CBN | ND | ND |
| THCA | ND | ND |
| CBDA | ND | ND |
| CBGA | ND | ND |
| D8-THC | ND | ND |
| exo-THC | ND | ND |
| Total | 99.72 wt% | 997.23 mg/g |
| Max THC | - | - |
| Max CBD | 99.40 wt% | 994.00 mg/g |

***HM: Heavy Metal Analysis [WI-10-13]***

This test method was performed in accordance with the requirements of ISO/IEC 17025. report. Reports may not be reproduced except in their entirety.

*51994-HM*

| Symbol | Metal | Conc.[1] | Units | MDL |
|---|---|---|---|---|
| As | Arsenic | ND | µg/kg | 4 |
| Cd | Cadmium | ND | µg/kg | 1 |
| Hg | Mercury | ND | µg/kg | 2 |
| Pb | Lead | ND | µg/kg | 2 |

***MB1: Microbiological Contaminants [WI-10-09]***

This test method was performed in accordance with the requirements of ISO/IEC 17025. report. Reports may not be reproduced except in their entirety.

*51994-MB1*

| Symbol | Analysis | Results |
|---|---|---|
| AC | Total Aerobic Bacterial Count | <100 |
| CC | Total Coliform Bacterial Count | <100 |
| EB | Total Bile Tolerant Gram Negative Count | <100 |
| YM | Total Yeast & Mold | <100 |

Products that post recent certificates of analysis or that are “US Hemp Authority Certified” are more trustworthy

## Products legalized by states; Example: NY State

- NYS has medical and "adult use" programs
- Both are tightly regulated and inspected by the state so products should be trustworthy
- All legal dispensaries listed on NYS cannabis website; most sell online
- Medical program is stricter and requires registration by a medical professional
- Medical may be better for people who want very precise and consistent dosing

## Routes of administration

| Route | Onset | Duration | Notes |
|---|---|---|---|
| Vapor/Inhaled/ Smoked | 30s-2m | 1-2h | Smoking/vaping may have health hazards. Safer vaporization requires special device |
| Transmucosal | 2-15m | 4-6h | Patients must be counseled not to swallow the liquid, or onset will be much slower (up to 2 hours) |
| Oral | 1-2h | 8-10h | First pass hepatic metabolism |

# Examples of products available through NYS Medical Program

Sativa

**Amnesia [AMN] Whole Flower**

Columbia Care

Whole Flower (3.5G)

THC 4.40% CBD 6.40%

~~$35.00~~ **$21.00/3.5g**


Sativa

**Super Lemon Cookie Haze [SCK] 1g Pre Roll...**

B-Noble

Pre R... (2g / 2g per pack)

THC 15.90%

**$30.00**


Indica

**[Seed & Strain] 20:1 Royal Gorilla [RGR]...**

Columbia Care

Cartridge (.5G)

THC 4.00% CBD 0.20%

**$65.00/.5g**


Hybrid

**Cherry Soft Chews [12ct]**

Columbia Care

69

Soft Chew (EACH)

120mg 12pk

**$40.00**

Hybrid

**ClaraCeed 1:20 Oral Tablets [30ct]**

Columbia Care

14

Tablets (EACH)

30pk

**$100.00**



Hybrid

**ClaraCeed Sublingual Liquid Tincture [15ml]**

Columbia Care

Tinctures & Spr... (EACH)

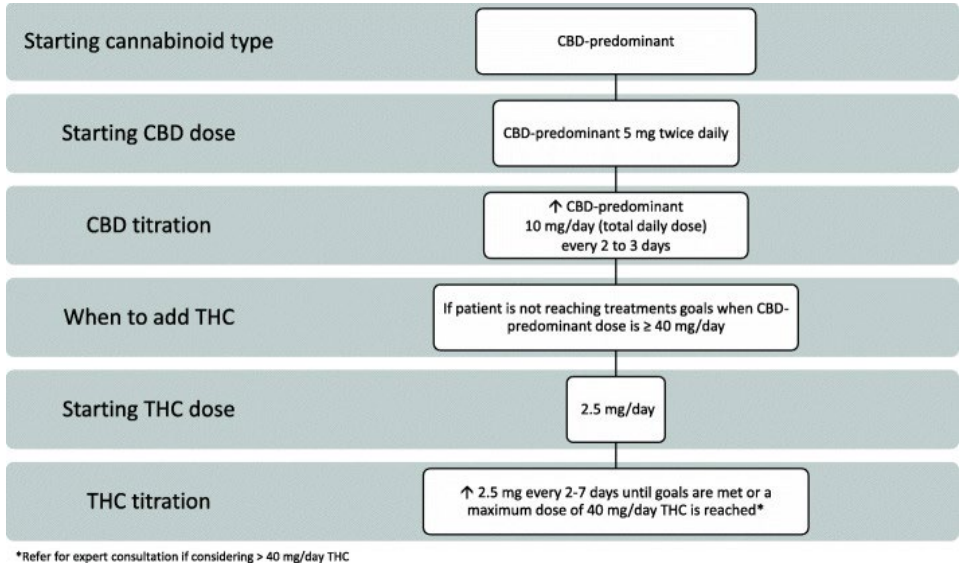
15ml

~~$100.00~~ **$50.00**




# Dosing

- Varies based on route of administration (oral doses are higher)
- Not very well established, but there are some consensus guidelines
- Start low, go slow




Consensus recommendation for oral
Bhaskar et al 2021

Recommended titration for Sativex oral mucosal spray
1 spray = 2.7mg THC and 2.5mg CBD
Australian Packaging
Day 14 dose:
-AM: 13.5/12.5mg THC/CBD
-PM: 18.9/17.5mg THC/CBD

| Day | Number of sprays in the morning | Number of sprays in the evening | (Total number of sprays per day) |
|---|---|---|---|
| 1 | 0 | 1 | 1 |
| 2 | 0 | 1 | 1 |
| 3 | 0 | 2 | 2 |
| 4 | 0 | 2 | 2 |
| 5 | 1 | 2 | 3 |
| 6 | 1 | 3 | 4 |
| 7 | 1 | 4 | 5 |
| 8 | 2 | 4 | 6 |
| 9 | 2 | 5 | 7 |
| 10 | 3 | 5 | 8 |
| 11 | 3 | 6 | 9 |
| 12 | 4 | 6 | 10 |
| 13 | 4 | 7 | 11 |
| 14 | 5 | 7 | 12 |

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# Questions?

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