

Current Topics in MS

Medical Marijuana for MS Symptom Management

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With thanks to Jessica Rice, MD
Recently graduated Portland VA MS fellow



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Disclosures

- ▶ Dr. Cameron has served as an advisor or consultant for: Adamas Pharmaceuticals; Greenwich Biosciences Inc; Helius Medical; Medscape

Outline

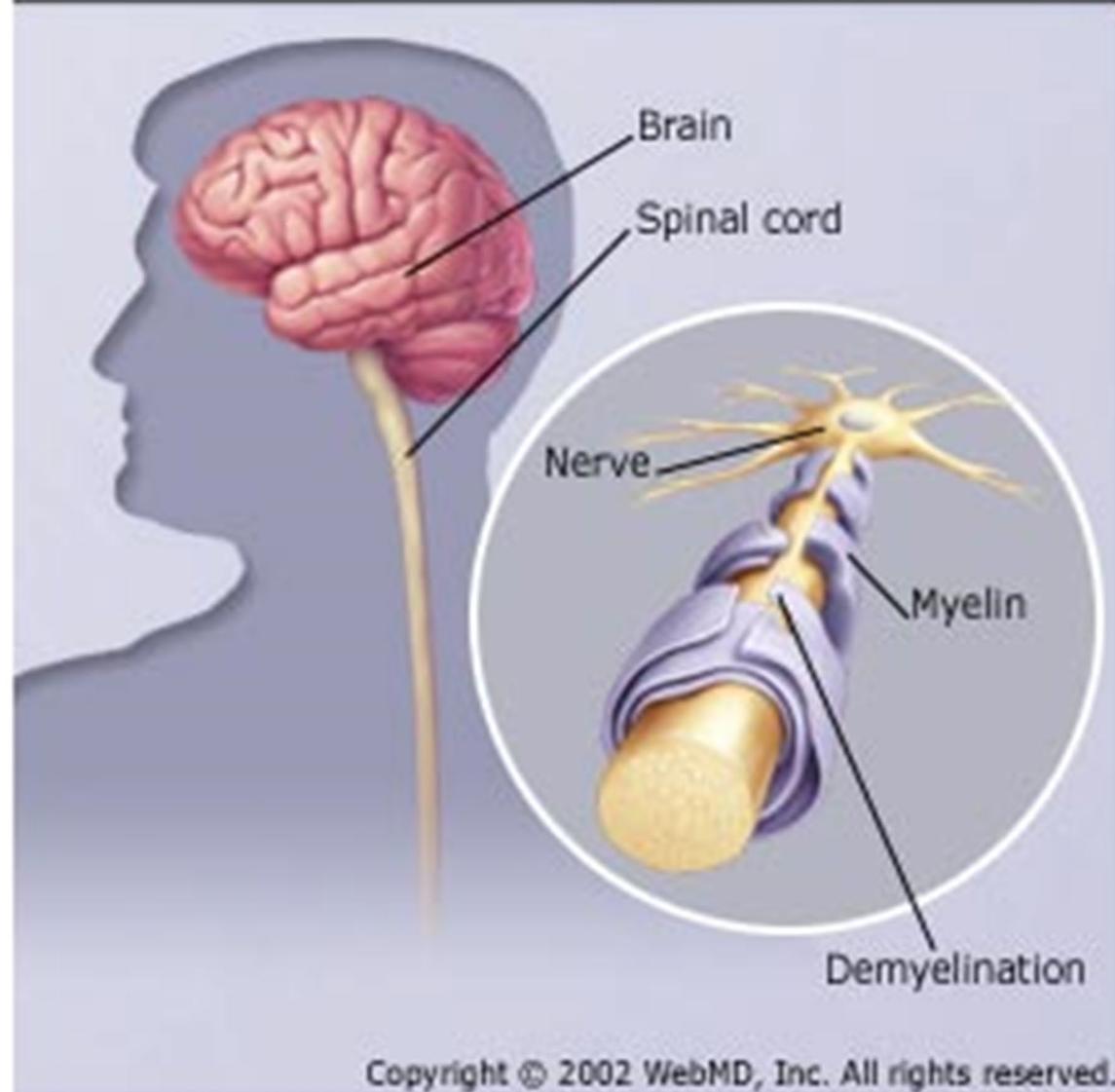
- ▶ Multiple sclerosis (MS) review
- ▶ Introduction to cannabis and cannabinoids
- ▶ Epidemiology of cannabis use in people with MS
- ▶ Evidence for benefit of cannabinoids for MS symptoms
- ▶ Evidence for adverse effects of cannabis/cannabinoids in MS

Learning Objectives

- ▶ After attending this presentation attendees will:
 - ▶ Understand the difference between cannabis and cannabinoids
 - ▶ Know about what proportion of people with MS are using cannabis based products
 - ▶ Be familiar with the evidence for benefits of cannabinoids for MS symptoms
 - ▶ Be familiar with the evidence for harms of cannabinoids in people with MS

Multiple Sclerosis Review

Multiple Sclerosis



- ~1:1,000 (900,000) people in the US have MS
- ~2.5 million world wide
- **Leading cause** of neurologic disability in young adults

MS Symptoms

- ▶ Cognition
- ▶ Vision
- ▶ Headaches
- ▶ Pain - about 2/3 of people with MS experience pain
- ▶ Numbness
- ▶ Weakness
- ▶ Fatigue
- ▶ Reduced mobility
- ▶ Bladder
- ▶ Bowel
- ▶ Sexual dysfunction
- ▶ Spasticity - over 80% of people with MS experience spasticity
- ▶ Depression
- ▶ Social
 - ▶ Work
 - ▶ Home

Rizzo MA, et al. Prevalence and treatment of spasticity reported by multiple sclerosis patients. *Mult Scler.* 2004 Oct;10(5):589-95
Foley PL, et al. Prevalence and natural history of pain in adults with multiple sclerosis: systematic review and meta-analysis. *Pain.* 2013 May;154(5):632-42.

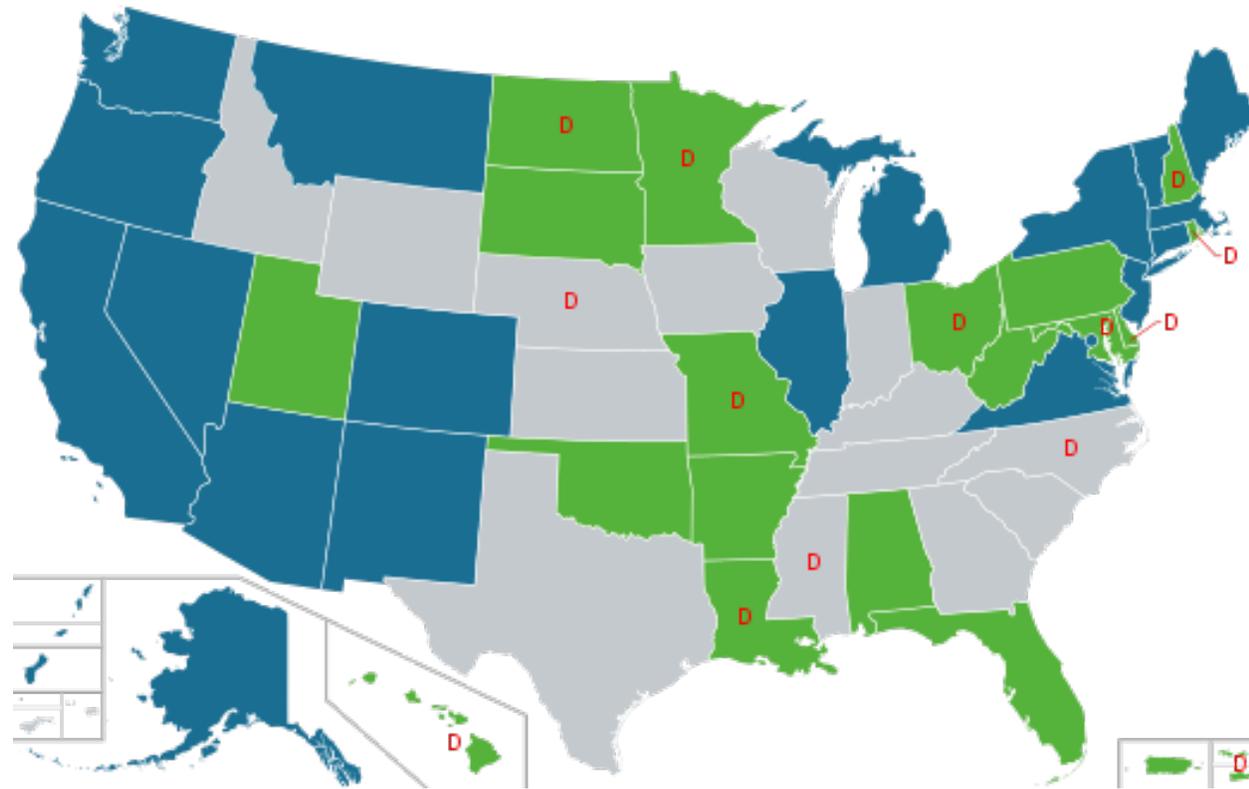
Symptom management vs disease modification in MS

- ▶ This presentation reviews the literature on the effects of cannabinoids on MS symptoms, primarily spasticity and pain, in people with MS
- ▶ I will not review potential disease modifying effects
- ▶ There are data over the last 20+ years regarding effects of cannabinoids (CBD & THC) in experimental autoimmune encephalomyelitis (EAE), a mouse model of MS
- ▶ I know of no controlled trials regarding disease modifying effects in people with MS

Introduction to cannabis and Cannabinoids

Federal Law regarding cannabis

- ▶ **Schedule I Controlled Substance:**
- ▶ “no currently accepted medical use and a high potential for abuse”.
- ▶ Some examples of Schedule I drugs are heroin, lysergic acid diethylamide (LSD), marijuana (cannabis), peyote, and 3,4-methylenedioxymethamphetamine (“Ecstasy”).



Legality of cannabis in the United States

- Legal for recreational use
- Legal for medical use
- Illegal
- D Decriminalized

What is marijuana?

- ▶ Cannabis - a genus of flowering plants indigenous to Asia
- ▶ Three main components
 1. Terpenoids
 - **Aromatic chemicals** also found in pine trees, citrus flora, and other odoriferous plants
 - Produce the unique aroma and flavor of cannabis
 2. Flavonoids
 - Chemicals common to most plant life
 - Many considered to have anti-inflammatory and antioxidant properties
 3. [Phyto]cannabinoids
 - Highest concentration found in female flowers
 - Bind to cannabinoid receptors and alter neurotransmitter release



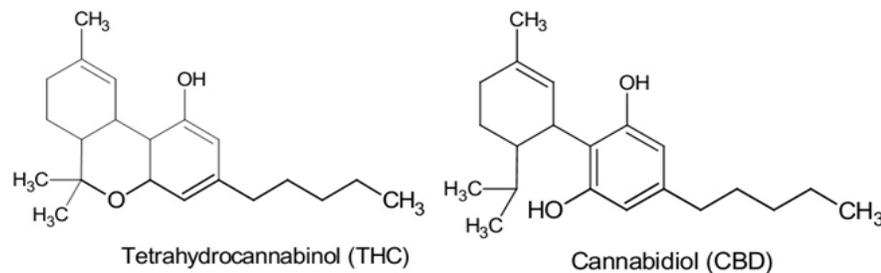
Phytocannabinoids

Delta-9-tetrahydrocannabinol (THC)

- Major psychoactive component in cannabis
- Naturally occurs in concentrations anywhere from 0.5 - 20% depending on cannabis strain

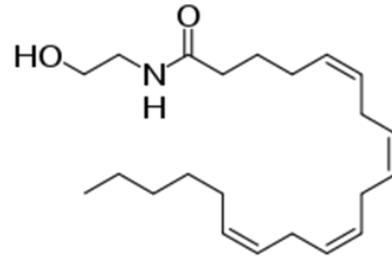
Cannabidiol (CBD)

- Lacks any noticeable psychoactive effects
- Has low affinity for endogenous cannabinoid receptors
- Increases the action of/exposure to THC

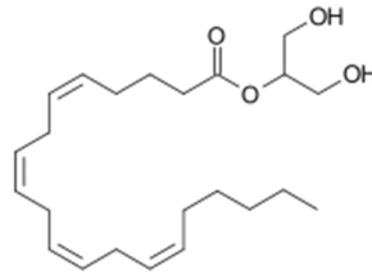


Endocannabinoids

Anandamide



2-arachidonoylglycerol (2-AG)



Cannabinoid receptors

CB₁ - identified in 1988

- Located in central nervous system and peripheral nerves
- Activation produces classic marijuana high

CB₂ - identified in 1993

- ▶ Located on B lymphocytes and natural killer cells
- ▶ Possible role in immunity

Pharmaceutical cannabinoids

Dronabinol (Marinol[®], Syndros[®])

- Synthetic Δ 9-THC in sesame oil
- Capsules or liquid

Nabilone (Cesamet[®])

- Mimics THC; **synthetic** cannabinoid receptor agonist
- 7 times more potent than Δ 9-THC
- Capsules

Nabiximols (Sativex[®])

Not currently available or FDA approved in the USA

- **Plant derived** ~1:1 THC and CBD mixture
- Oromucosal spray.

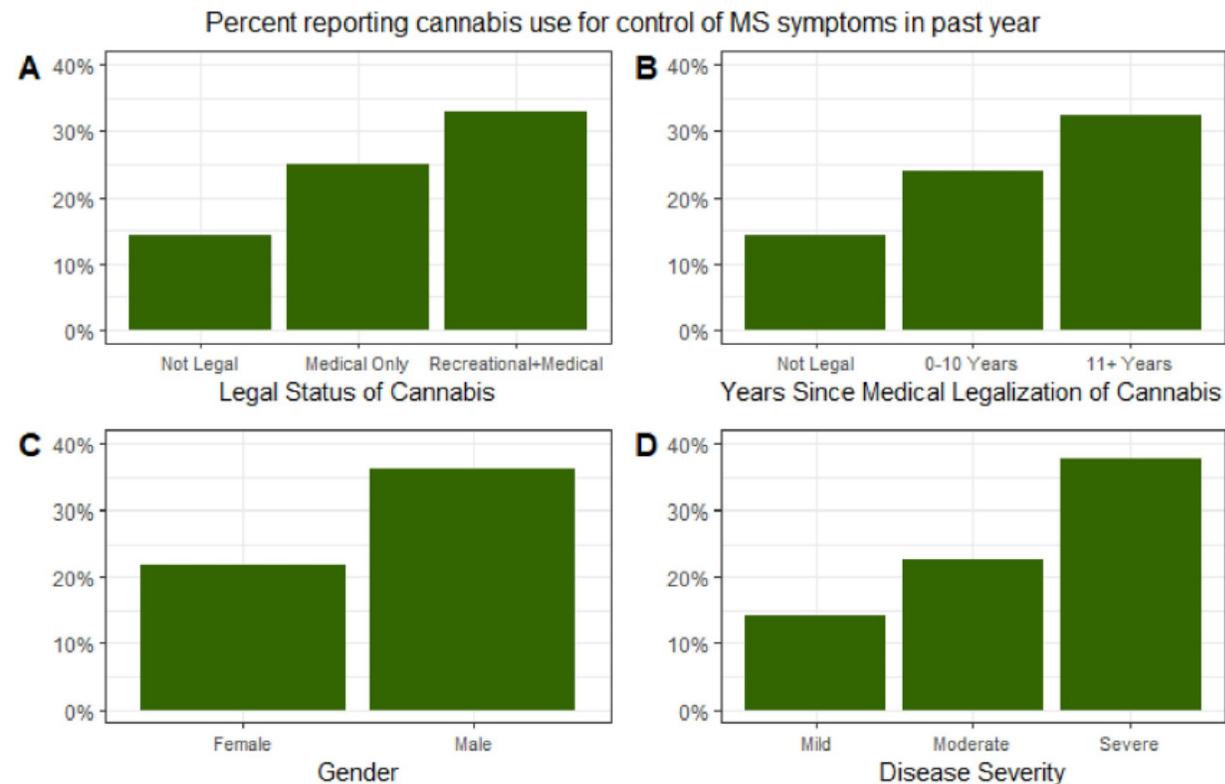
Cannabidiol (Epidiolex[®])

- **Plant derived** purified cannabidiol
- Oral solution

Epidemiology of Cannabis use in MS

Epidemiology of cannabis use in people with MS

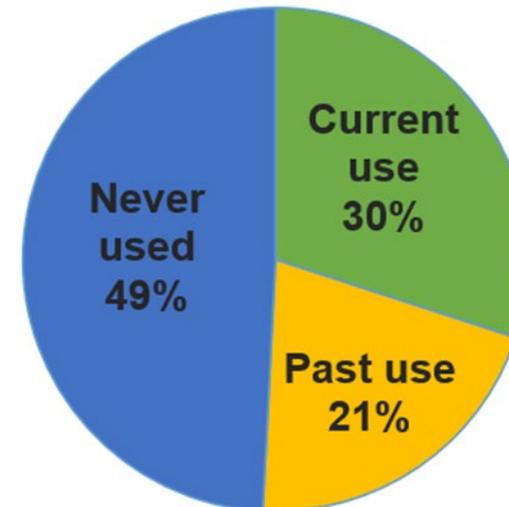
- ▶ Depends on legality, how you ask, current vs past use
- ▶ Estimates range from 9.4% in upper New York state prior to any legalization, to 66% in the US in a NMSS web-based survey (Gupta et al. 2019; Kindred et al. 2017)
- ▶ Our recent national study found 24% of 600 people with MS across the US reported using cannabis for MS symptoms in the past year (Hildebrand et al. 2020)



Cannabis use in people with MS - OR and SW WA

- ▶ Our recent survey of CAM use in Oregon and SW Washington found 30% of 1000 people with MS reported current cannabis use for their MS
- ▶ The odds of current cannabis use were higher in people with MS who:
 - ▶ Were younger
 - ▶ Had lower household income
 - ▶ Had secondary progressive MS
 - ▶ Had greater MS disability

HISTORY OF CANNABIS USE

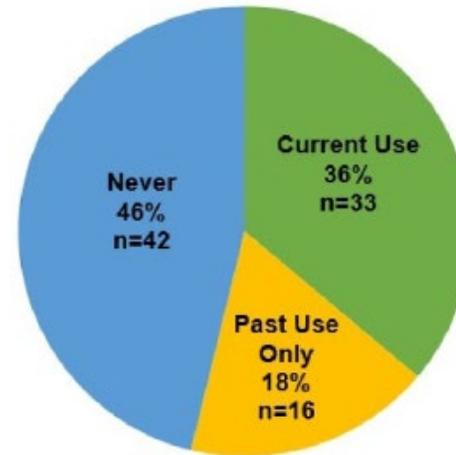


Rice J, et al. A Cross-Sectional Survey of Cannabis Use by People with MS in Oregon and Southwest Washington. *Mult Scler Relat Disord*. Under Review.

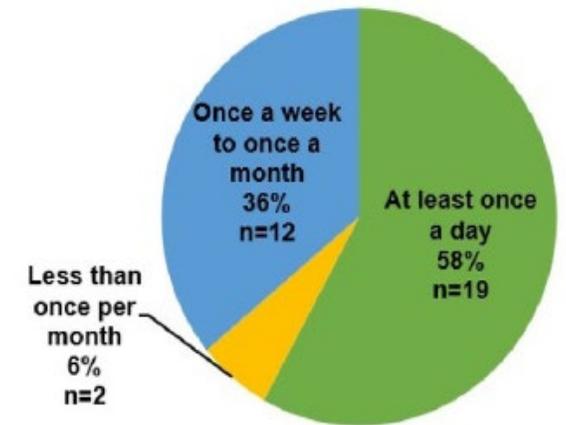
Cannabis use in people with MS and spasticity

- ▶ Cross-sectional analysis of self-reported cannabis use for MS symptoms in people with MS enrolling in a randomized controlled rehabilitation trial for MS-related spasticity in Oregon (Rice et al. 2020)
- ▶ 36% of 91 respondents reported currently using cannabis for their MS symptoms
- ▶ Of current users, 58% (n=19) used at least once a day

HISTORY OF CANNABIS USE



FREQUENCY OF CURRENT CANNABIS USE



Evidence for Benefit for MD Spasticity

There is level I (high quality) evidence that cannabinoids can reduce which of the following in people with multiple sclerosis?

- A. Self-reported spasticity
- B. Clinician-measured spasticity
- C. Disease progression
- D. Cognitive dysfunction

Systematic Reviews and Evidence-based Guidelines

1. Complementary and alternative medicine (CAM) in MS

- ▶ Nabiximols (Sativex oral spray 1:1 THC:CBD), oral cannabis extract (OCE, 2:1 THC:CBD) and synthetic THC (dronabinol) are **probably effective at reducing patient-reported symptoms of spasticity** (LEVEL 1). Nabiximols, oral cannabis extract (OCE) and synthetic THC are **probably effective at reducing MS-related pain** (LEVEL 1)
 - ▶ However, OCE and synthetic THC were **not found to be effective for spasticity when spasticity was measured on tests administered by a physician (i.e. Ashworth scale)**

Yadav V, et al. Summary of evidence-based guideline: complementary and alternative medicine in multiple sclerosis: report of the guideline development subcommittee of the American Academy of Neurology. *Neurology*. 2014 Mar 25;82(12):1083-92.

2. Medical marijuana in MS, epilepsy, and movement disorders

- ▶ The only **strong evidence was in MS, for reducing patient-reported spasticity and for reducing central pain**

Koppel BS, et al. Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2014 Apr 29;82(17):1556-63.

Which of the following is TRUE?

- A. The Ashworth scale measures self-reported spasticity
- B. The Ashworth scale is designed to measure pain in multiple sclerosis
- C. The numeric rating scale (NRS) is used to capture clinician-rated spasticity severity
- D. The numeric rating scale (NRS) is used to capture patient-rated spasticity severity

Ashworth Scale/ Modified Ashworth Scale

Applied to each muscle group e.g. quadriceps,

- ▶ 0 = no increase in tone
- ▶ 1 = a slight increase in tone with a 'catch'
- ▶ 1+ = slight increase in tone with a catch followed by minimal resistance throughout the remaining ROM
- ▶ 2 = marked increase in tone but still easily moved
- ▶ 3 = considerable increase in tone making movement difficult
- ▶ 4 = the limb is rigid

NRS-S

On a scale of 0 to 10, please indicate your level of spasticity over the last 24 hours

Please check (☒) one box only.

No spasticity

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 Worst possible spasticity

0 1 2 3 4 5 6 7 8 9 10

Spasticity 0-10 numeric rating scale.

Cannabinoids for medical use - Systematic Review

- ▶ Use of cannabinoids for multiple indications
- ▶ Included 11 studies, with a total of 2138 patients, comparing the effect cannabinoids with placebo on spasticity related to MS.
- ▶ Although the specific details of the studies vary, **most studies suggest that cannabinoids are associated with improvements in self-reported spasticity in people with MS.**
- ▶ The improvements in objectively measured spasticity generally do not reach statistical significance

Whiting PF, et al. Cannabinoids for medical use: A systematic review and meta-analysis. JAMA. 2015 Jun 23-30;313(24):2456-73.

Systematic review with meta-analysis: Efficacy and Tolerability of Cannabinoids in MS

- ▶ 17 trials with 3,161 patients
- ▶ Standard mean differences (SMD) for cannabis vs placebo were in **favor of benefits for subjective spasticity** (-0.25 SD; 95% CI, -0.38 - -0.13), **pain** (-0.17 SD; 95% CI, -0.31 - -0.03) and, **bladder dysfunction** (-0.11 SD; 95% CI, -0.22 - -0.0008) (SMD - size of effect relative to variability)
- ▶ Tolerability: RR 1.72 patient-years for AEs and 2.92 patient-years for withdrawals due to AEs (RR - probability in exposed versus placebo), no difference in serious AEs
- ▶ CONCLUSIONS: The results suggest a **limited efficacy of cannabinoids for the treatment of spasticity, pain, and bladder dysfunction in patients with MS. Therapy using these drugs can be considered as safe.**

Torres-Moreno MC, Papaseit E, Torrens M, Farré M. Assessment of efficacy and tolerability of medicinal cannabinoids in patients with multiple sclerosis: A systematic review and meta-analysis. *JAMA Netw Open*. 2018;1(6):e183485.

Reviews of Reviews

1. “there is **substantial evidence that oral cannabinoids are effective for improving patient-reported multiple sclerosis spasticity symptoms.**”

National Academies of Sciences, Engineering and Medicine. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Washington, DC: National Academies Press; 2017

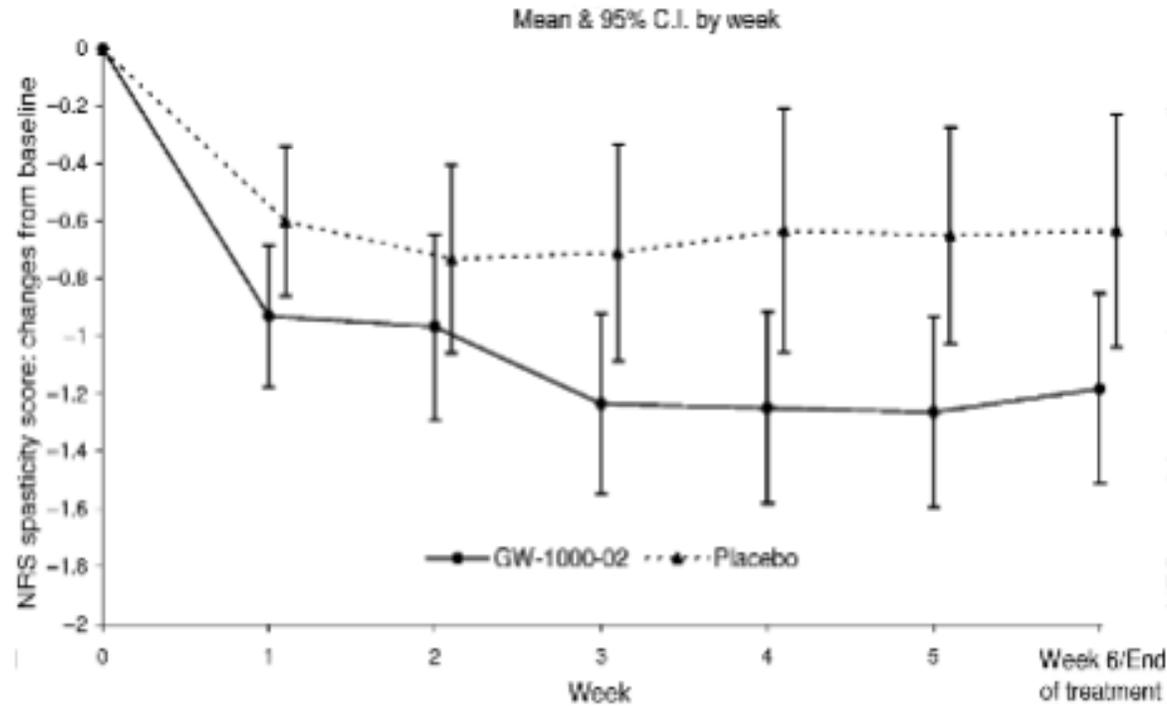
2. **Cannabinoids might improve spasticity** (primarily in multiple sclerosis)... “**Adverse effects are very common,** meaning benefits would need to be considerable to warrant trials of therapy.”

Allan GM, Finley CR, Ton J, et al. Systematic review of systematic reviews for medical cannabinoids: Pain, nausea and vomiting, spasticity, and harms. Can Fam Physician. 2018;64(2):e78-e94.

3. **Cannabinoids may be effective for symptoms of pain and/or spasticity in MS... Cannabinoids may have *modest* effects in MS for pain or spasticity.** Future research should include studies with non-cannabinoid comparators.

Nielsen S, Germanos R, Weier R, et al. The use of cannabis and cannabinoids in treating symptoms of multiple sclerosis: As systematic review of reviews. Current Neur & Neurosci Rep. 2018;18(2):8.

Change from Baseline in Spasticity NRS with Nabiximols vs Placebo

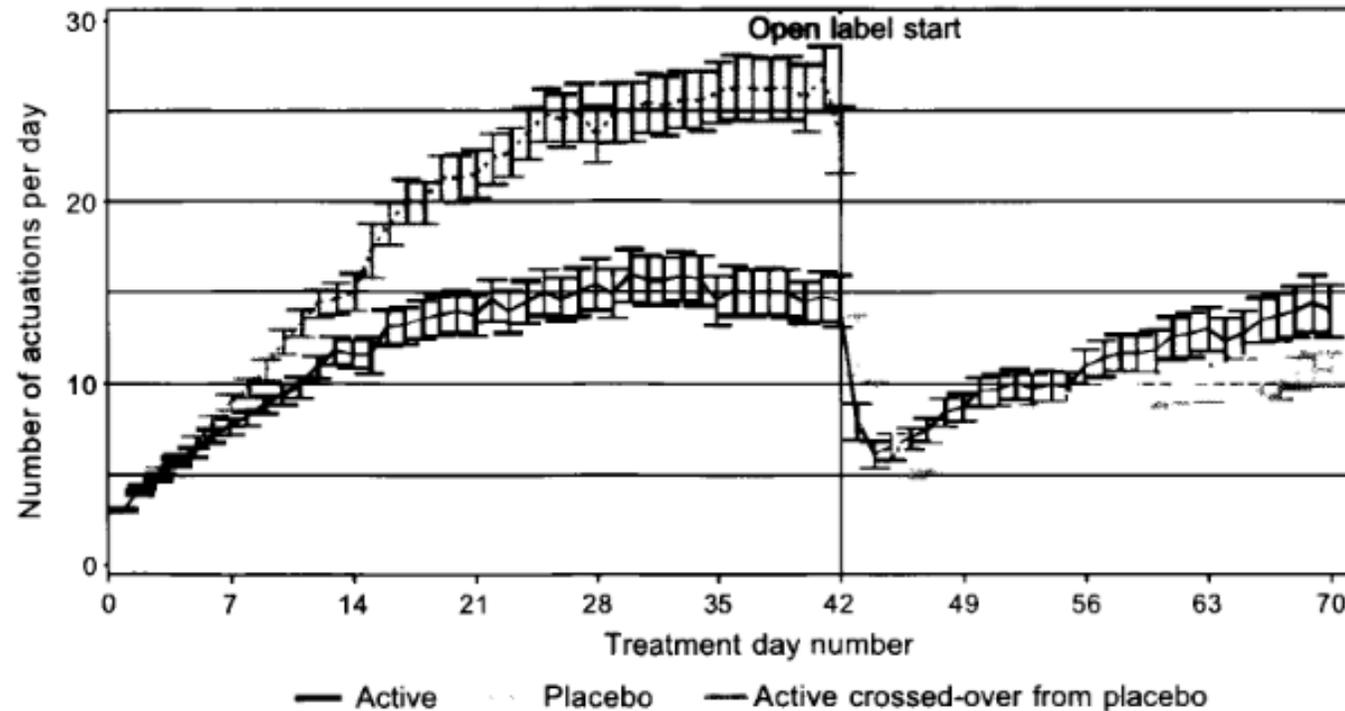


Collin C, et al. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. *Eur J Neurol.* 2007 Mar;14(3):290-6.

In clinical trials, when people with MS-related spasticity use cannabinoids, which of the following is TRUE?

- A. They increase their dose gradually over weeks until they reach a balance between benefit and adverse effects and then stabilize
- B. They increase their dose gradually throughout the study without ever reaching a stable dose, likely due to progressive tolerance
- C. They increase their dose and reach a balance between benefit and adverse effects in a few days and then stabilize
- D. Most trials used fixed dose titration regimens

Actuations/day (1 actuation = 2.7mg THC/2.5mg CBD)



Wade DT, et al. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. *Mult Scler.* 2004 Aug;10(4):434-41.

Post-approval phase 4 studies

Post-approval studies

- ▶ 20 patients taking nabiximols
- ▶ 3-D gait analysis demonstrated increased speed, cadence and stride length after treatment and changed dynamics at the pelvis, hip and knee
Coghe G, Paul M, Corona F, et al. Walking improvements with nabiximols in patients with multiple sclerosis. J Neurol 2015;262(11):2472-7.
- ▶ All patients (165) starting nabiximols Jan 2014 - Feb 2015 from 30 MS centers in Italy
- ▶ After 1 month of treatment, 70.5% had $\geq 20\%$ improvement, 28.2% had $\geq 30\%$ improvement, mean NRS reduction from 7.5 to 5.8
- ▶ Greatest response in progressive MS, baseline NRS > 8
- ▶ At 6 months, 39.5% discontinued treatment, mostly for lack of effectiveness (26.2%) and/or adverse events (18.7%)

Patti F, Messina S, Solaro C, Amato MP, Bergamaschi R, Bonavita S, et al. Efficacy and safety of cannabinoid oromucosal spray for multiple sclerosis spasticity. J Neurol Neurosurg Psychiatry. 2016;87(9):944-51.

Post-approval observational studies: MOVE-2 (MObility ImproVEment)

- ▶ Prospective *observational* study of real life clinical outcomes in >1,000 patients treated with nabiximols in Europe, with up to 300/country, planned to complete in 2017 but no recent publications
- ▶ Comparing effect of nabixomols on clinical outcomes in patients with treatment-resistant spasticity
- ▶ Trial of therapy approach - given Rx, f/u @ 1 month, those with $\geq 20\%$ response continue and f/u in 2 more months
- ▶ Web-based real-time data collection and diaries
 - ▶ Patient based numerical rating scale (0-10)
- ▶ Physician rated Ashworth scale

Trojano M. THC:CBD Observational Study Data: Evolution of Resistant MS Spasticity and Associated Symptoms. Eur Neurol. 2016;75 Suppl 1:4-8.

Flachenecker P, Henze T, Settl UK. Nabiximols (THC/CBD oromucosal spray, Sativex) in clinical practice - results of a multicenter, non-interventional study (MOVE2) in patients with multiple sclerosis spasticity. Eur Neurol. 2014;71:271-279.

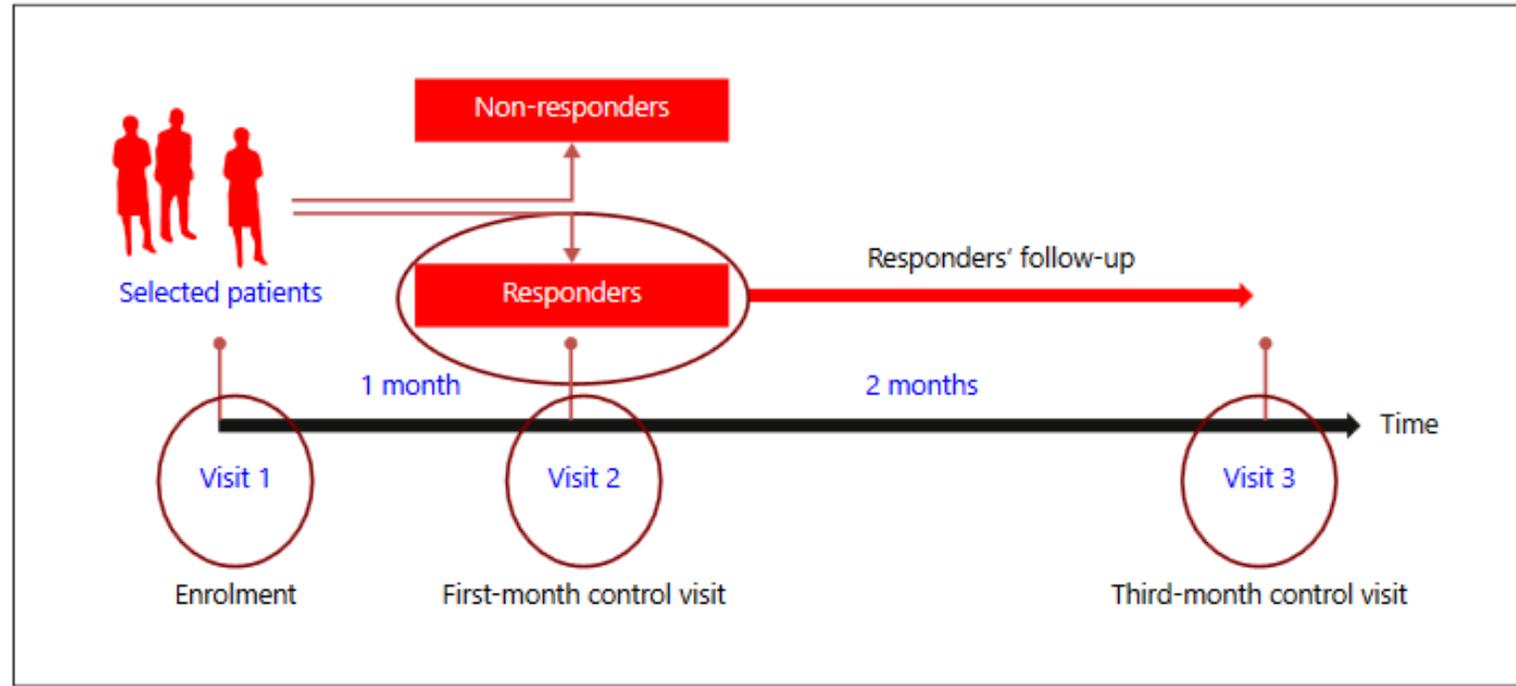


Fig. 1. MOVE 2 study design.

MOVE2 published results

Germany - completed

- ▶ 335 patients entered, 79% of those evaluated at 1 month continued i.e. were responders, continuation to visit 3 was 55%.
- ▶ ~50% discontinued for lack of efficacy, 25% for lack of tolerability, 25% for other reasons
- ▶ Dose: mean 19mg THC
- ▶ Effect: Spasticity NRS decreased from 6.3 to 4.7 (25% reduction), with 40% achieving clinically relevant $\geq 30\%$ reduction in NRS.

Italy - interim analysis

- ▶ 322 patients recruited, 82.9% responders at 1 month, 49% (158) still continued at 3-month
- ▶ Dose: mean 13 - 16mg THC/day
- ▶ Effect (data available for 119): Mean NRS decreased from 6.8 to 5.5, 25% recorded a clinically meaningful improvement

Evidence for Benefit for Pain in MS

Cannabinoids for pain in MS

- ▶ Pain affects around 2/3 of people with MS
- ▶ Many different types of pain:
- ▶ Pain from MS is most commonly central neuropathic pain or pain from spasms
- ▶ Data from other trials for neuropathic pain may apply, and these trial often include people with MS

Foley PL, et al. Prevalence and natural history of pain in adults with multiple sclerosis: systematic review and meta-analysis. *Pain*. 2013 May;154(5):632-42.

Cannabinoids for pain in MS - RCT

- ▶ A 2005 randomized, double-blind, placebo-controlled parallel group study focused on the effect of cannabinoids for pain in patients with MS (Rog et al. Neurology 2005.)
- ▶ N = 66 people with MS and central pain
- ▶ Randomized to placebo or nabiximols for 4 weeks.
 - ▶ The active group was allowed to titrate up to a maximum of 130 mg THC per day, reaching an average of 26 mg THC per day.
- ▶ This study found a **41% decrease in mean pain intensity in the group taking nabiximols compared to a 22% decrease in pain in the group taking the placebo** (p = 0.005)

Systematic Reviews: pain

- ▶ AAN systemic review and guideline: **Cannabis is probably effective at reducing MS-related pain** (Yadav et al 2014):
 - ▶ Nabiximols (oral spray containing 1:1 CBD:THC) (Level B)
 - ▶ Oral cannabis extract (Level A)
 - ▶ Synthetic THC (Level B)
- ▶ A 2011 systematic review of RCTs evaluated the effects of cannabinoids of any type (smoked cannabis, oral extracts, Nabilone, synthetic THC, nabiximols) on chronic non-cancer pain (including but not limited to pain from MS). (Lynch et al. 2015)
 - ▶ In 15 of the 18 studies, **cannabinoids provided at least modest pain relief**.
- ▶ A 2015 update by the same authors that evaluated 11 additional studies found that 7 of these 11 studies also found **cannabinoids to be more effective than placebo** (Lynch et al. 2015)

Evidence for Adverse Effects in MS

Adverse Events

From therapeutic RCTs

Table 4 Summary of treatment-related adverse events with greater than 4% incidence

<i>Adverse event</i>	<i>Active - n (%)</i>	<i>Placebo - n (%)</i>
<i>n</i>	80	80
Dizziness	26 (32.5)	10 (12.5)
Disturbance in attention	7 (8.8)	0 (0)
Headache	7 (8.8)	13 (16.3)
Fatigue	12 (15)	3 (3.8)
Somnolence	7 (8.8)	1 (1.3)
Disorientation	6 (7.5)	0 (0)
Feeling drunk	4 (5)	0 (0)
Vertigo	5 (6.3)	0 (0)
Application site discomfort	21 (26)	18 (22.5)
Nausea	7 (8.8)	5 (6.3)
Diarrhoea	6 (7.5)	2 (2.5)
Mouth ulceration	4 (5)	1 (1.3)

From Phase 4 studies

AEs in MOVE from Germany & Italy

- ▶ Dizziness
- ▶ Confusion
- ▶ Somnolence/drowsiness
- ▶ Fatigue
- ▶ Nausea
- ▶ Dry mouth

Adverse Effects

May worsen cognitive dysfunction in MS

- ▶ One study comparing 25 regular cannabis users with 25 non-users, and another comparing 20 users with 19 non-users, overall users had:
 - ▶ Slower information processing speed (PASAT)
 - ▶ Worse working memory (2-back)
 - ▶ Worse executive function
 - ▶ And, were twice as likely to be cognitively impaired

Honarmand K, et al. Effects of cannabis on cognitive function in patients with multiple sclerosis. *Neurology*. 2011; (76) 13:1153-1160.

Pavisian B, et al. Effects of cannabis on cognition in patients with MS: A psychometric and MRI study. *Neurology*. 2014 May 27;82(21):1879-87.

Discussion & Conclusions: Cannabinoids for Symptoms in *MS*

Conclusions

- ▶ Cannabis legalization is growing
- ▶ Many people, ~ 30%, with MS use cannabis for their MS symptoms
- ▶ Cannabinoids reduce self-reported spasticity and pain in MS
 - ▶ BUT
- ▶ All RCT data is from pharmaceutically prepared oral or oromucosal spray preparations, not other forms or sources of cannabinoids
- ▶ The mean effect is small to moderate
- ▶ Tolerability is fair but there are AEs
 - ▶ ~50% seem to keep using, ~ 50% stop due to lack of efficacy or AEs

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- ▶ Patti F, et al. Efficacy and safety of cannabinoid oromucosal spray for multiple sclerosis spasticity. *J Neurol Neurosurg Psychiatry*. 2016;87(9):944-51.
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