Focusing on the evidence: Cannabis and Cannabinoids as Medicines

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Definitions (NIDA)

- *Cannabinoids*
  - Chemicals derived from the Cannabis plant (or manufactured)
  - Dronabinol (pill and liquid) and Nabilone – synthetic FDA-approved Δ-9 THC/ Δ-9 THC-like products
- *Medical cannabis (medical marijuana; MMJ)*
  - Whole, unprocessed cannabis plant or its basic extracts to treat symptoms of illness and other conditions
  - FDA has not recognized or approved the cannabis plant as medicine

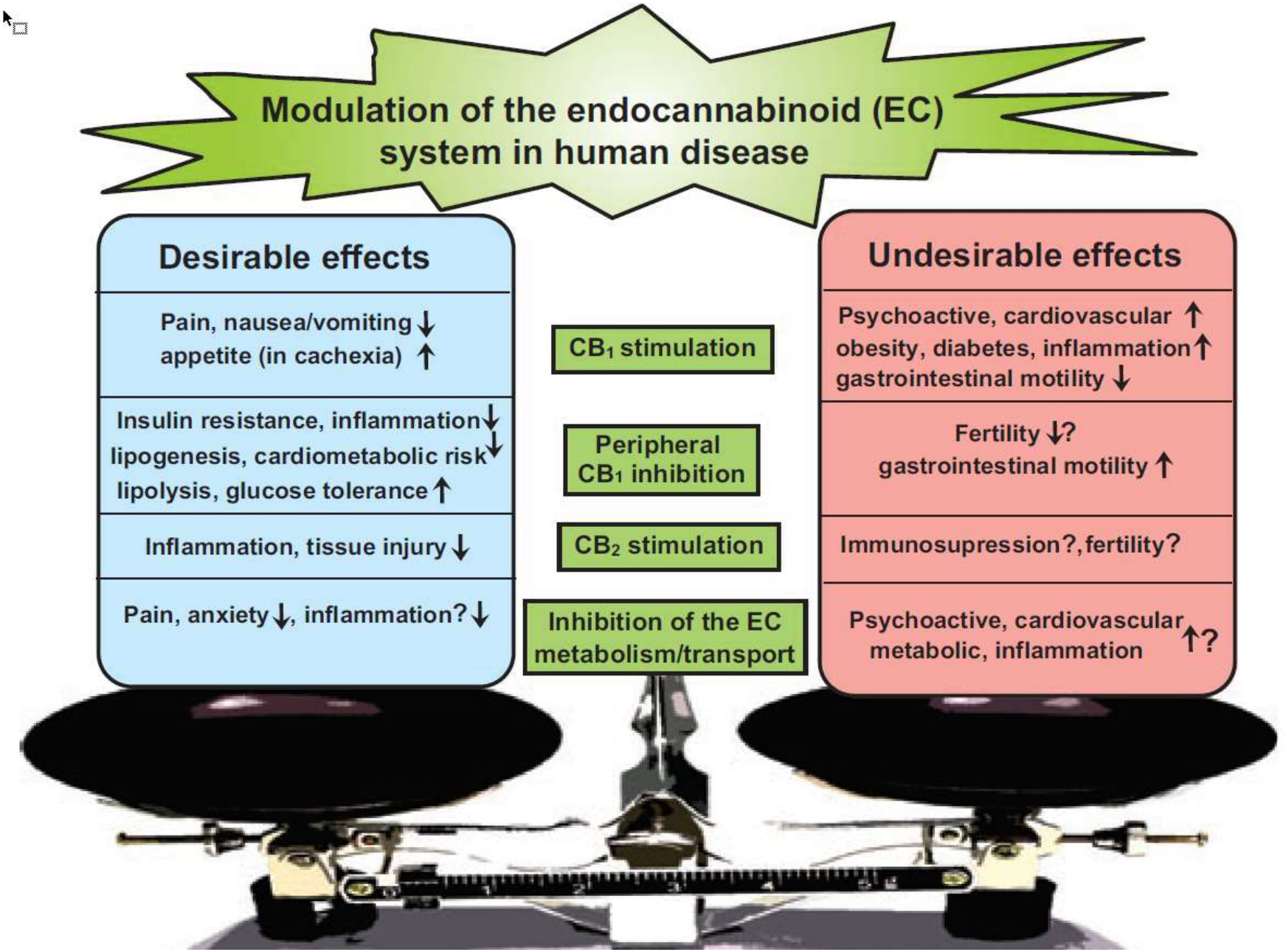
- "Because the [cannabis] plant contains chemicals that *may* help treat a range of illnesses and symptoms, many people argue that it *should* be legal for *medicinal* purposes…"

Anthony et al., 2017 Curr Pharm Des; Mead 2017 EB

Pacher and Kunos, FEBS Journal 2013

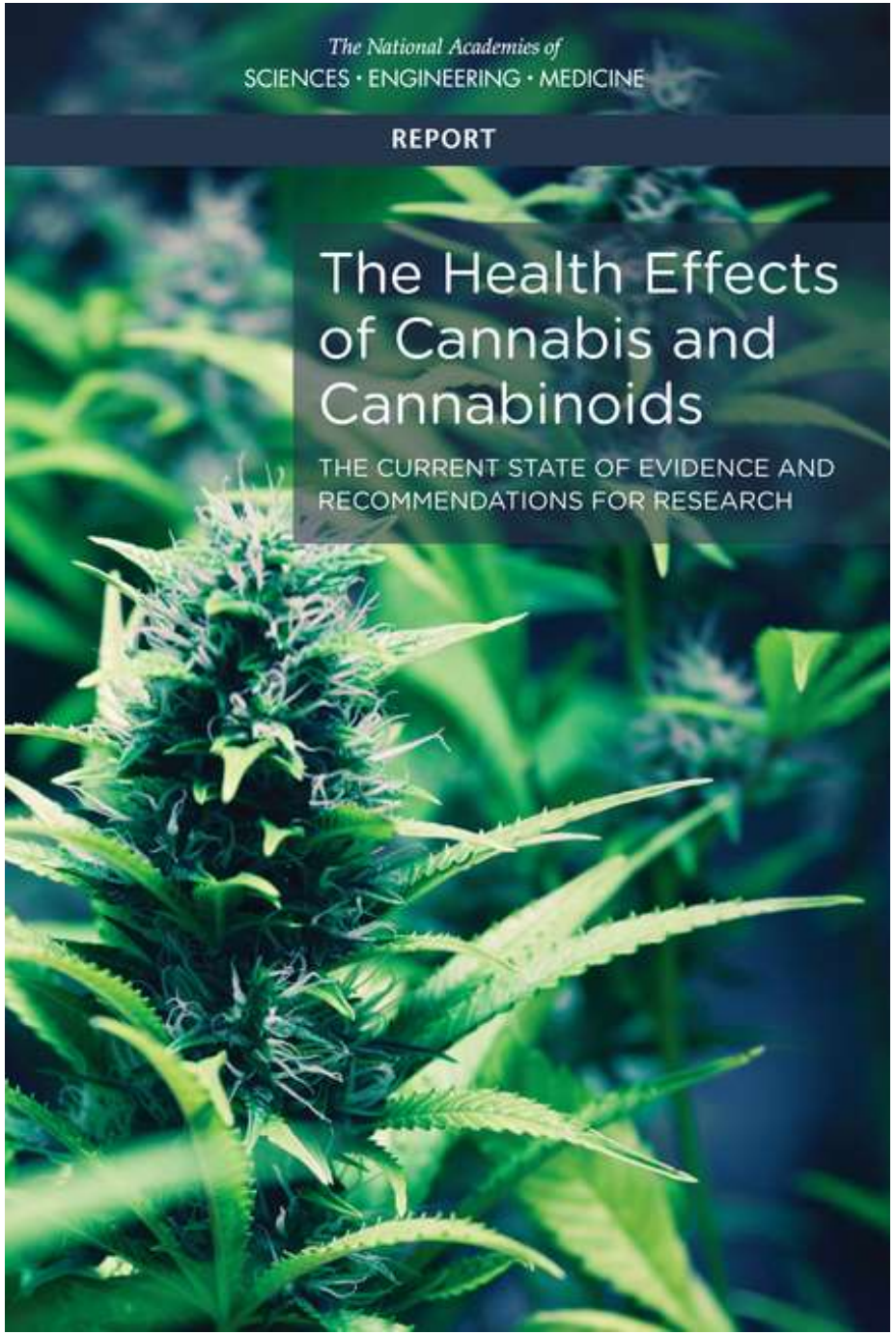
"…Modulating the endocannabinoid system (ECS) holds therapeutic potential in a broad range of diseases affecting humans…"

"… modulating endocannabinoid activity may have therapeutic potential in almost all disease affecting humans including obesity/metabolic syndrome, diabetes and diabetic complications, neurodegenerative, inflammatory, cardiovascular, liver, gastrointestinal, skin diseases, pain, psychiatric disorders, cachexia, cancer, chemotherapy-induced nausea and vomiting, among many others… (p. 1918)



Modified after Ethan Russo, MD

- **Releases by National Academies of Sciences, Engineering, and Medicine in 2017 under the guidance and support from:**
- CDC Foundation
- Centers for Disease Control and Prevention
- National Highway Traffic Safety Administration
- NIH (several Institutes including NIDA)
- **US FDA**
- Several others



Chronic Pain

- **Conclusion 1**: There is substantial evidence that cannabis is an effective treatment for chronic pain
- Műcke et al., (Cochrane Database; 2018) – numerous RCTs were registered as completed with clinicaltrials.gov indicating advantage of cannabis over placebo for the treatment of chronic pain (at least 10 with plant-derived Δ^9-THC:CBD combinations and at least 2 that used synthetic Δ^9-THC)
- Stockings et al., (Pain, 2018) – Meta-analysis of available data:
  - Cannabis outperforms placebo but the effects are limited (long-term data very limited)
  - AE: no impact on physical or emotional functioning; modest improvement in sleep and global impression of change

Cancer-related pain (Johnson et al., 2010)

- 177 patients with cancer pain, who experienced inadequate analgesia despite chronic opioid dosing
- 2-week parallel group multi-center, double-blind RCT: Δ^9-THC:CBD extract (n = 60), THC extract (n = 58), or placebo (n = 59)
  - Δ^9-THC:CBD extract was 1:1; Δ^9-THC extract was same Δ^9-THC as in Δ^9-THC:CBD extract
  - Pain outcome: Numerical Rating Scale (NRS) baseline – end-of-study:
    - Δ^9-THC:CBD compared with placebo (improvement of 1.37 vs. 0.69); Δ^9-THC showed a non-significant change (1.01 vs. 0.69).
    - Twice as many patients taking Δ^9-THC:CBD showed a reduction of more than 30% from baseline pain NRS score when compared with placebo (23 [43%] vs. 12 [21%]). The associated odds ratio was statistically significant,
    - Δ^9-THC group responders were similar to placebo (12 [23%] vs. 12 [21%]) and did not reach statistical significance.

Cancer (Therapy)

- **<u>Conclusion 2</u>**: There is insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for cancers, including glioma
- Animal models of solid tumors – cannabis appears to show anti-tumor effects
  - Hepatocellular carcinoma, glioma, non-small cell lung carcinoma, breast cancer, colon cancer, GBM, metastatic cancer
- Results of the animal studies have not been translated to date to human studies with the exception of case reports and case series
- National Cancer Institute (NCI):
  - “Cannabinoids may have benefits in the treatment of cancer-related side effects”

Cancer - ACS

- American Cancer Society has a whole web page devoted to the treatment of cancer symptoms with cannabis and cannabinoids:
  - https://www.cancer.org/treatment/treatments-and-side-effects/complementary-and-alternative-medicine/marijuana-and-cancer.html
- Inhaled cannabis helps for:
  - Nausea and vomiting with cancer chemotherapy
  - Neuropathic pain (caused by cancer or cancer drugs)
  - Improves appetite and food intake
- According to ACS, cannabinoids may help with tumor growth and cause cancer cell death
  - "More recently, scientists reported that Δ^9-THC and other cannabinoids such as CBD slow growth and/or cause death in certain types of cancer cells growing *in lab dishes*. Some animal studies also suggest certain cannabinoids may slow growth and reduce spread of some forms of cancer."

Chemotherapy-induced nausea and vomiting

- **Conclusion 3**: There is conclusive evidence that oral cannabinoids are effective antiemetics in the treatment of chemotherapy-induced nausea and vomiting
- Smith et al., (Cochrane Database: 2015)
  - RCTs showed better control of N/V with Cannabis vs. Placebo
  - RCTs showed patient were more likely to withdraw from study if they were receiving Placebo vs. Cannabis
  - Conclusion: “my be useful for treating refractory chemotherapy-induced nausea and vomiting”

Anorexia and Weight Loss

- **Conclusion 4A**: There is limited evidence that cannabis and oral cannabinoids are effective in increasing appetite and decreasing weight loss associated with HIV/AIDS
- **Conclusion 4B**: There is insufficient evidence to support of refute the conclusion that cannabinoids are an effective treatment for cancer-associated anorexia-cachexia syndrome and anorexia nervosa

Irritable Bowel Syndrome (IBS)

- **<u>Conclusion 5</u>**: There is insufficient evidence to support or refute the conclusion that dronabinol is an effective treatment for the symptoms of IBS
- Lahat et al., 2012 (inhaled cannabis):
  - After 3 months' treatment, patients (N=13) reported improvement in general health perception ($p = 0.001$), social functioning ($p = 0.0002$), ability to work ($p = 0.0005$), physical pain ($p = 0.004$) and depression ($p = 0.007$).
  - Patients had a weight gain of 4.3 ± 2 kg during treatment (range 2-8; $p = 0.0002$) and an average rise in BMI of 1.4 ± 0.61 (range 0.8-2.7; $p = 0.002$).
- Borrelli et al (2013) – Cannabigerol (CBG) reduces inflammatory pathways in murine model of colitis
- Overall, data regarding artisanal cannabis products are insufficient to support or refute efficacy for the treatment of IBS

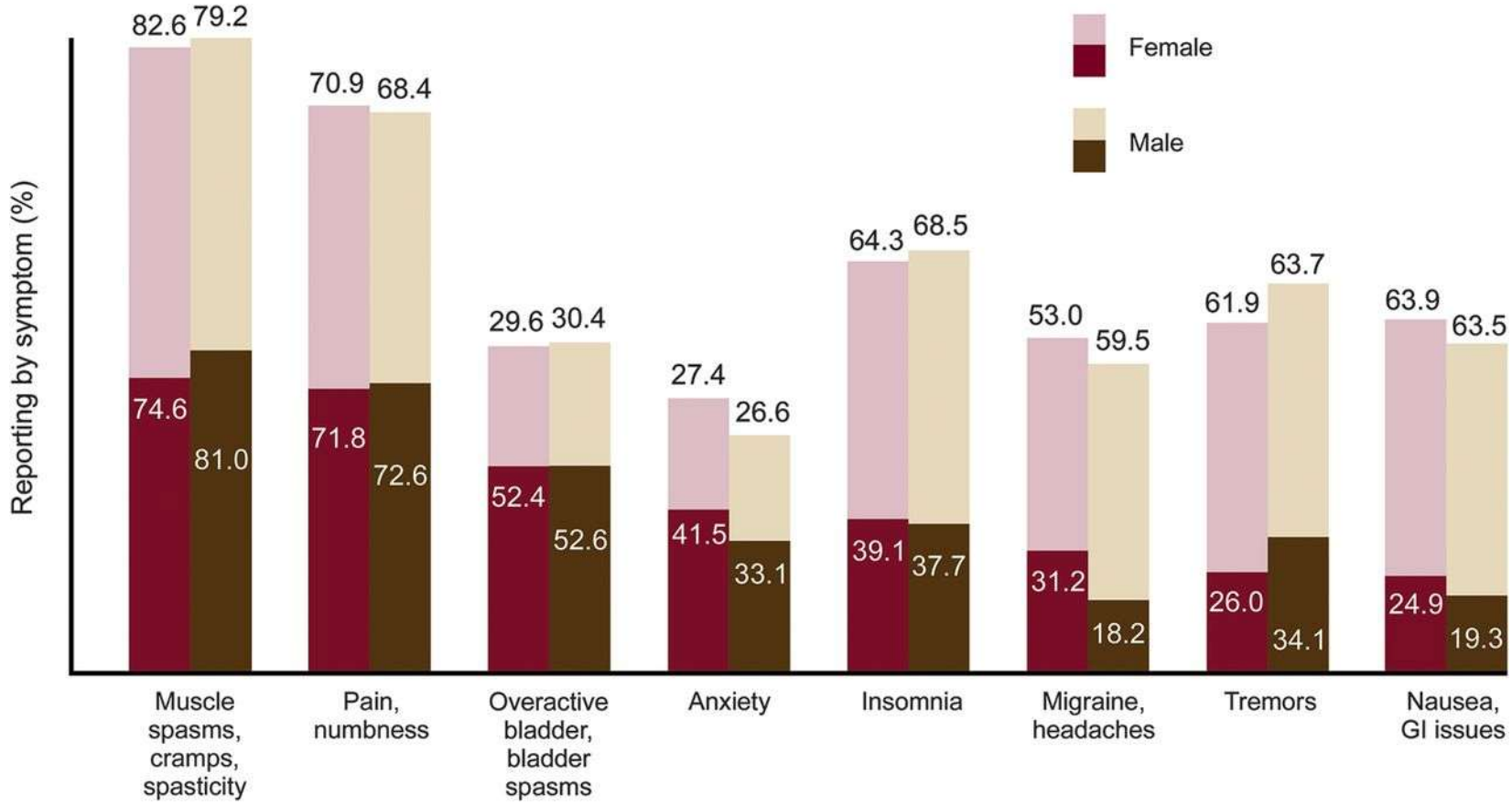
Epilepsy

- **<u>Conclusion 6</u>**: There is insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for epilepsy
- Gaston et al., (2018):
  - 5 placebo-controlled RCTs were completed of highly-purified CBD
  - >10 open-label trials of various artisanal cannabis products were completed
- Pamplona et al., (2018) – meta-analysis:
  - 64% of patients included in cannabis trials report improvement in seizure frequency
  - 71% reported improvement with “CBD-rich extracts” vs. 46% with “purified CBD”
  - Dose needed to achieve – 6 mg/kg/d with “CBD-rich extracts” vs. 25.3 mg/kg/d with “purified CBD”
  - “…the roots of this difference is likely due to synergistic effects of CBD with other phytocannabinoids (aka entourage effect)…”

Spasticity associated with MS and SCI

- **Conclusion 7A**: There is substantial evidence that oral cannabinoids are an effective treatment for improving patient-reported multiple sclerosis spasticity symptoms, but limited evidence for an effect on clinician-measured spasticity
- **Conclusion 7B**: There is insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for spasticity in patients with paralysis due to spinal cord injury

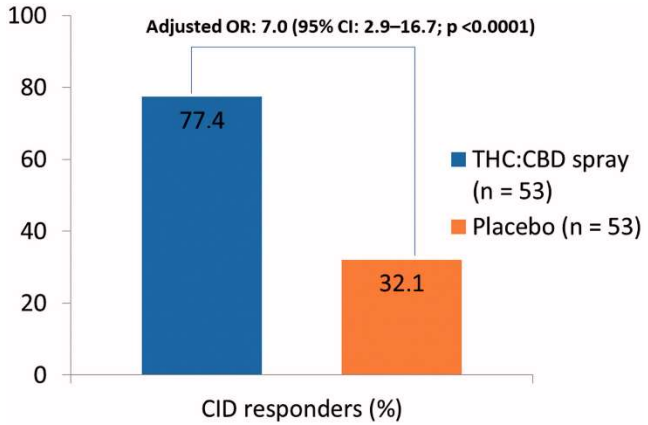
Current symptoms and perceived effectiveness of marijuana in Multiple Sclerosis



Cofield et al., 2017 Neurol Clin Pract

Spasticity associated with MS (Markova et al., 2019)

- SAVANT trial recently published (Sativex as add-on therapy vs. further optimized first-line ANTispastics).
- Eligible patients received add-on Δ^9-THC:CBD spray for 4 weeks to identify responders (≥20% improvement from baseline in spasiticy), then initial responders after wash out were randomized to receive drug or placebo.
- 106/191 patients randomized, 77.4% of patients taking drug had improvement vs. 32.1% with placebo. Also improved changes in mean spasticity, pain, and Ashworth scale (disability)



Hagenbach et al., 2007 (Spinal Cord)

- Dronabinol (synthetic Δ^9-THC) – oral or rectal suppository vs. placebo in SCI
- Mean spasticity for oral Δ^9-THC decreased significantly from 16.72 (±7.60) at baseline to 8.92 (±7.14) on day 43.
- Similar improvement was seen with rectal Δ^9-THC
- Significant improvement of spasticity with active drug (*P*=0.001) over placebo.
- Dose 10-20 mg required for treatment of SCI-related spasticity

- Overall, data regarding synthetic Δ^9-THC are insufficient to support or refute efficacy for the treatment of SCI and there are no good data on the use of artisanal products.

Tourette Syndrome

- **Conclusion 8**: There is limited evidence that THC capsules are an effective treatment for improving symptoms of Tourette syndrome
- Tourette Association of America (TAA) sponsors several ongoing clinical trials
- Several trials are ongoing internationally but none reported data to date
- TAA web page lists several synthetic cannabinoids under development for the treatment of TS

Amyotrophic Lateral Sclerosis (ALS)

- **Conclusion 9**: There is insufficient evidence that cannabinoids are an effective treatment for symptoms associated with ALS
- Riva et al., (2019) – placebo-controlled RCT of nabiximols in motor neuron disease:
  - Nabiximols is a oro-mucosal spray containing 2.7 mg of Δ^9-THC and 2.5 mg CBD
  - Modified Ashworth Scale (measure of spasticity) scores improved by a mean of 0.11 (SD 0.48) in the nabiximols group and deteriorated by a mean of 0.16 (0.47) in the placebo group (adjusted effect estimate –0.32 [95% CI –0.57 to –0.069]; p=0.013)
  - Nabiximols was well tolerated, and no participants withdrew from the double-blind phase of the study
  - No serious adverse effects occurred.

Huntington's Disease

- **Conclusion 10**: There is insufficient evidence to support or refute the conclusion that oral cannabinoids are an effective treatment for chorea and certain neuropsychiatric symptoms associated with Huntington's disease.

- Preclinical data support development of cannabis products for the treatment of symptoms of HD

Parkinson's Disease (PD)

- **Conclusion 11**: There is insufficient evidence that cannabinoids are an effective treatment for the motor symptoms associated with PD or the levodopa-induced dyskinesia

- Preclinical data support development of cannabis products for the treatment of symptoms of PD
- APA – convened a panel to develop and implement cannabis products for the treatment of PD and its symptoms
- Several states list PD as an "approved condition" however this is based on compassionate use rather than data

Parkinson's Disease

- There are some fairly good quality studies and some anecdotal evidence that symptoms of PD may be improved w/cannabis
- Numerous articles are available e.g.,:
  - Carroll et al (2004 Neurology) – "cannabis extract" vs. PCBO (RCT) in 19 patients with dyskinesia – no effect
  - Lotan et al (2014 Clin Neuropharmacology) – smoked cannabis – improved motor and non-motor scores (sleep and pain)
  - Chagas et al (2014 J Clin Pharmacy and Therapeutics) – CBD may control REM Behavior Disorder
  - Zuardi et al (2008) J Psychopharmacology – CBD decreased psychotic symptoms in patients with psychosis associated with PD
  - Chagas et al (2014) J Psychopharmacology – RCT vs. PCBO of CBD (small dose) – no effect on motor symptoms but PDQ scores much worse in the treatment groups before initiation.
  - Finseth et al (2015) Hindawi – CAM use including cannabis helpful for non-motor symptoms of PD

Dystonia

- **Conclusion 12**: There is insufficient evidence to support of refute the conclusion that nabilone and dronabinol are an effective treatment for dystonia

Dementia

- **<u>Conclusion 13</u>**: There is limited evidence that cannabinoids are ineffective treatments for improving the symptoms associated with dementia

- Van den Elsen et al., 2015 Neurology
  - Δ^9-THC 1.5 mg TID vs. placebo x 3 weeks
  - Primary Outcome: Neuropsychiatric Inventory (NPI) – baseline, 14d and 21d
  - No difference in Neuropsychiatric Inventory between placebo (N=26) and active arm (N=24)
  - No difference in Cohen-Mansfield Agitation Inventory, QoL - AD, or Barthel Index

Glaucoma

- **<u>Conclusion 14</u>**: There is limited evidence that cannabinoids are an ineffective treatment for improving intraocular pressure associated with glaucoma

- **American Academy of Ophthalmology**: "The largest association of eye physicians and surgeons in the world does not endorse cannabis or its derivatives as a glaucoma treatment."
- **Glaucoma Research Foundation**: "…although marijuana can lower the eye pressure, recommending this drug in any form for the treatment of glaucoma at the present time does not make sense…"

TBI

- **<u>Conclusion 15</u>**: There is limited evidence of a statistical association between cannabinoids and better outcomes (i.e., mortality, disability) after TBI or intracranial hemorrhage

Addiction

- **<u>Conclusion 16</u>**: There is no evidence to support or refute the conclusion that cannabinoids are an effective treatment for achieving abstinence in the use of addictive substances

- Socias et al., (2017)
  - Observational study in 122 crack cocaine users
  - Cannabis use resulted in decrease in crack cocaine use (CI 1.02-3.45)
  - "A period of intentional cannabis use to reduce crack cocaine use was associated with decreased frequency of crack use in subsequent periods
- Overall, there are >10 studies that indicate cannabis should be studied as a potential treatment for addiction

Anxiety

- **Conclusion 17**: There is limited evidence that cannabidiol is an effective treatment for the improvement of anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders

- Several trials are registered as starting or ongoing with clinicaltrials.gov

CBD and Anxiety

- Conclusive preclinical evidence of CBD's efficacy in reducing anxiety behaviors relevant to PTSD, GAD, OCD, and SAD, with lack of anxiogenic effects
- CBD reverses anxiogenic effects of THC
- Human studies show 300-600 mg of oral CBD induced anxiety in individuals without anxiety disorders and reduced anxiety in patients with social anxiety disorder
  - No studies for chronic dosing
- CBD associated with greater improvement on anxiety factor compared with placebo during a simulated public speaking test ($p<0.01$)
  - Cannabis or Cannabinoids may be an effective treatment for anxiety symptoms

Whiting et al., JAMA 2015
Blessing et al., Neurotherapeutics 2015

THC and Anxiety

- Four randomized controlled studies (combined 232 participants)
  - Dronabinol 10-20 mg
  - Nabilone max 2 mg daily
  - Nabiximols max 4-8 sprays/day.
- Outcomes typically assessed hours to weeks after randomization. Greater short term benefit with cannabinoids then placebo – no long-term data
- RCT of PCBO vs. Δ^9-THC single capsule of 7.5 mg or 12.5 mg
  - 7.5mg reduced the duration of negative emotional responses to the task and post-task appraisals of how threatening and challenging a stressor was
  - 12.5mg produced small but significant increases in anxiety, negative mood and subjective distress at baseline before and during the stress task
- THC may decrease anxiety at lower doses and increase at higher doses

Whiting et al., JAMA 2015
Childs et al., 2017 Drug Alcohol Dependence

Registry data on Anxiety

- 1,746 patients (9 medical cannabis clinics in CA)
  - Pain, insomnia, anxiety – most frequent reasons for cannabis use
  - **37.8% of patients reported using cannabis to relieve anxiety**
  - 16.9% to relieve panic attacks
  - 55.1% to improve relaxation
  - Anxiety/depression was identified as a reason for authorizing MM card for 13% of patients
- 1,429 cannabis users (social media) in WA from 2013-2016 about conditions treated, use patterns, perceptions of efficacy and physical and mental health
  - Pain (61.2%), **anxiety (58.1%)**, depression (50.3%), headache/migraine (35.5%)....
  - 86% reduction in symptoms as a result of Cannabis use
  - 59.8% reported using cannabis as an alternative to pharmaceutical prescriptions.
  - **More than half (58%) reported they used cannabis for anxiety with symptom improvement**

Reinarman et al, J Psychoactive Drugs , 2011
Sexton et al, Cannabis and Cannabinoid Research, 2016

Depression

- **Conclusion 18**: There is limited evidence that nabiximols, dronabinol, and nabilone are ineffective treatments for the reduction of depressive symptoms in individuals with chronic pain or MS

Registry data on Depression

- 1,746 patients (9 medical cannabis clinics in CA)
  - Pain, insomnia, anxiety – most frequent reasons for cannabis use
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Sexton et al, Cannabis and Cannabinoid Research, 2016

Sleep Disorders

- **Conclusion 19**: There is moderate evidence that cannabinoids, primarily nabiximols, are an effective treatment to improve short-term sleep outcomes in individuals with sleep disturbance associated with OSA, fibromyalgia, chronic pain, and MS

PTSD

- **<u>Conclusion 20</u>**: There is limited evidence that nabilone is effective for improving symptoms of PTSD
- Fraser at al., (2009)
  - 72% of patients receiving nabilone experienced cessation or improvement of nightmares
- Roitman et al., (2014)
  - 10 patients received Δ^9-THC 5 mg bid
  - Significant improvement in global symptom severity, sleep quality, frequency of nightmares, and PTSD hyperarousal symptoms
- MAPS study – completed 2/2019
  - Approved by FDA, DEA, and NIDA
  - Data analysis is ongoing

Schizophrenia and other psychoses

- **Conclusion 21**: There is insufficient evidence to support or refute the conclusion that cannabidiol is an effective treatment for the mental health outcomes in individuals with schizophrenia
- Since then 2 major RCTs were published:
  - #1: 33 antipsychotic medication-naive participants at clinical high risk of psychosis – CBD 600mg vs. PCBO
  - fMRI – increased activation in cognitive task with CBD in caudate, parahippocampal gyrus, and midbrain compared to PCBO
  - #2: 43 patients with schizophrenia randomized 1:1 to CBD 1000 mg/day or PCBO x 6 weeks
  - CBD – significantly lower levels of positive psychotic symptoms (PANSS), improved CGI-I, AE were similar to PCBO
- Overall, CBD studies show likely efficacy in treating psychosis and schizophrenia

Bhattacharyya et al., 2018 JAMA Psychiatry
McGuire et al., 2018 Am J Psychiatry

- Several major conditions were not mentioned in the “Report”:
  - Autism Spectrum Disorder (ASD)
  - Crohn’s Disease
  - End-of-life / palliative care
  - Fibromyalgia
  - Migraine / Headache

Autism Spectrum Disorder

- Schleider et al., (2019)
  - Prospective observational study of 188 children with ASD treated with 20:1 CBD:Δ^9-THC
  - Of 155 with 6-months data, 83.7% reported a significant or moderate improvement
- Bonni Goldstein, MD
  - 17/27 patients aged 3-18 years treated with CBD-rich showed improved behavior, calmer, reduced self-mutilation, better focus etc.
  - Lower CBD:THC ratio (high CBD may be overstimulating)
- Several studies listed on clinicaltrials.gov
  - CBD for ASD (NYU – recruiting)
  - Placebo, CBD, CBDV (King's College London – active)
  - CBD vs. Placebo for behavioral problems in ASD (Jerusalem, Israel – completed – no data)

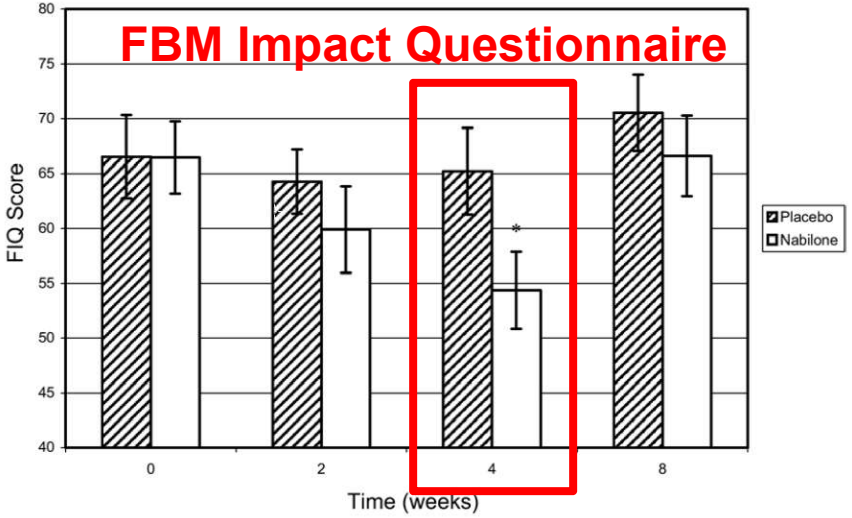
Crohn's Disease

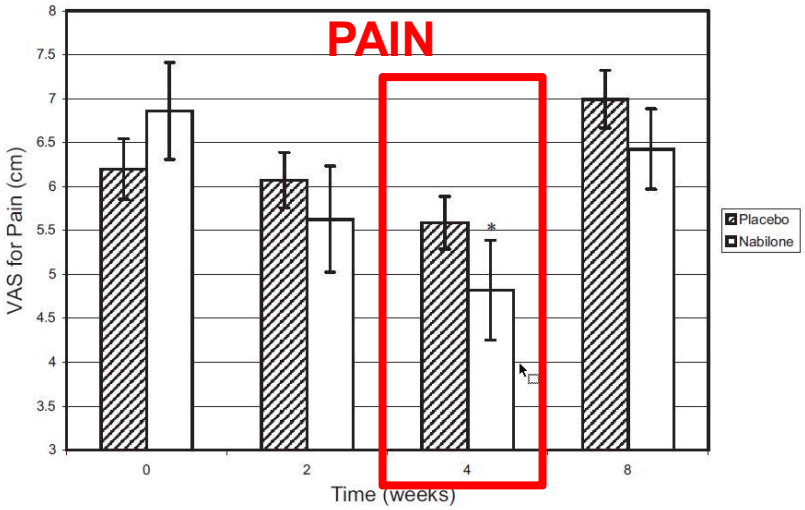
- Overall, studies are very limited but there is some anecdotal evidence that symptoms of Crohn's disease may be improved w/cannabis
- Non-scientific data:
  - Cannabis improves symptoms of Crohn's disease (e.g., cramps, diarrhea, improved appetite) but not the gut inflammation
  - Improves QOL in Crohn's disease
- There is no clear evidence that cannabis can treat symptoms associated with Crohn's disease

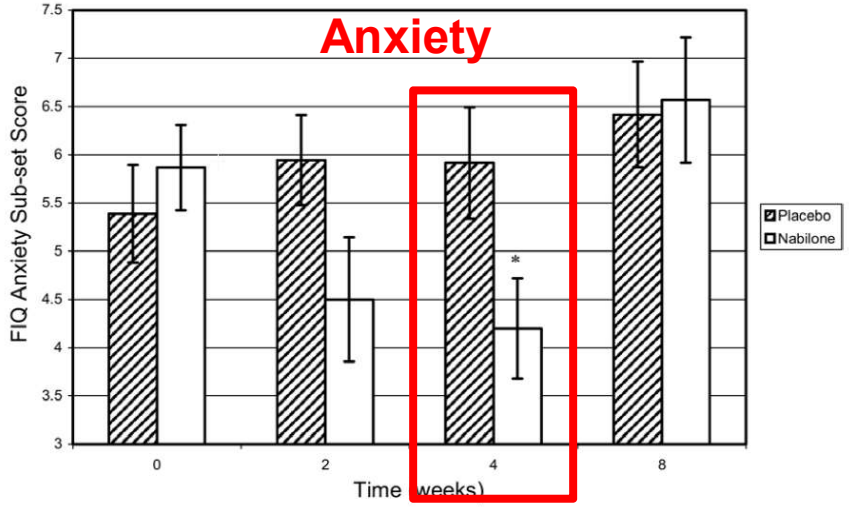
End-of-life / palliative care

- Aggarwal (2016) Current Oncology:
  - “Cannabinoid Integrative Medicine” should be a part of end-of life palliative care
- Luba et al (2018) J Psychoactive Drugs:
  - Palliative care providers (N = 426) completed a one-time online survey assessing these attitudes, beliefs, and practices.
  - Results demonstrated that palliative care providers endorse cannabis for a wide range of palliative care symptoms, end-of-life care generally, and as an adjuvant medication.
- Bar-Sela et al (2013)
  - 106/131 continued treatment with all cancer or anticancer treatment-related symptoms improvemed ($P < 0.001$). No significant side effects except for decrease in memory ($P = 0.002$).
- “Although studies with a control group are missing, the improvement in symptoms should push the use of cannabis in palliative treatment of oncology patients.”

Fibromyalgia (CED)



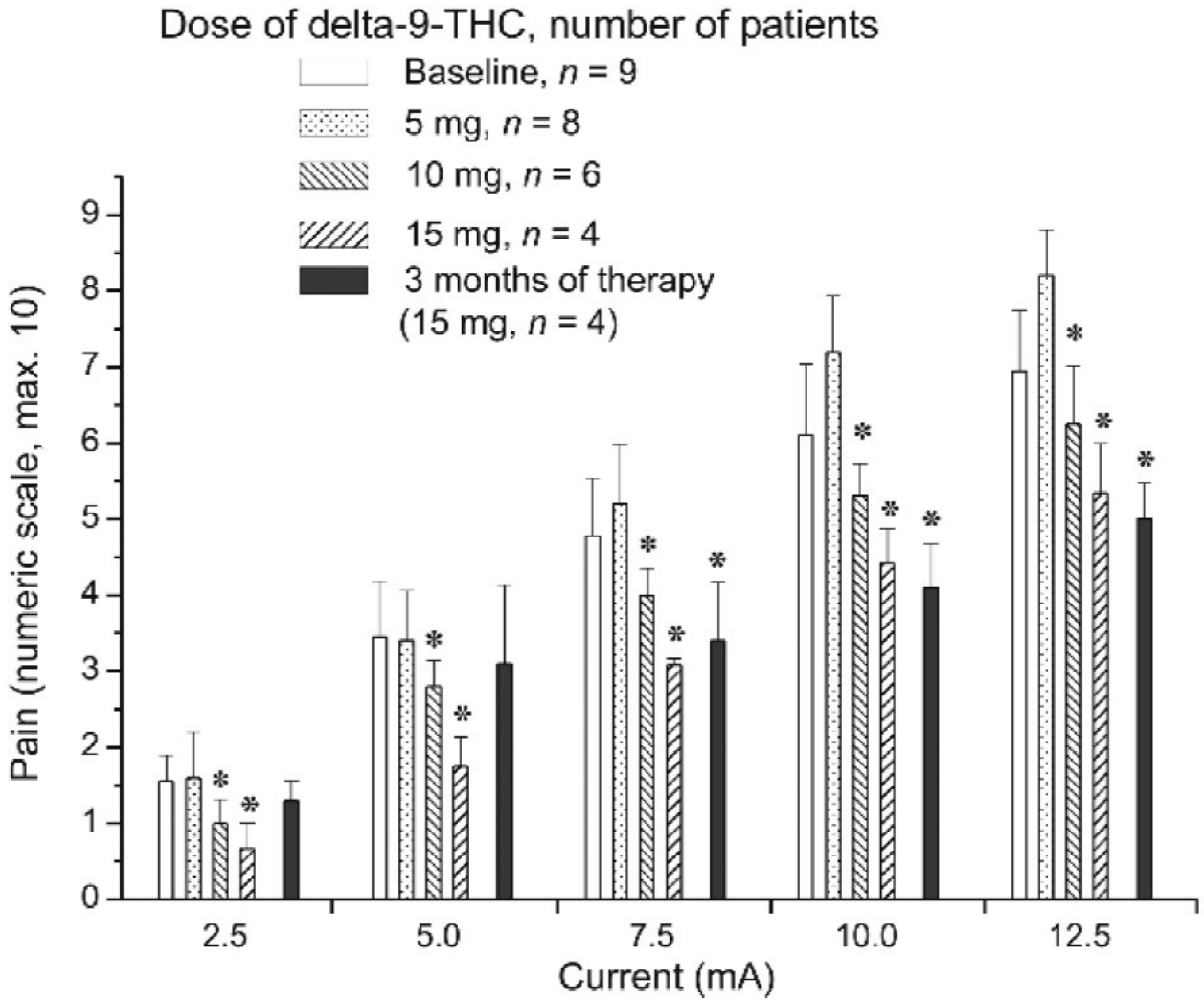




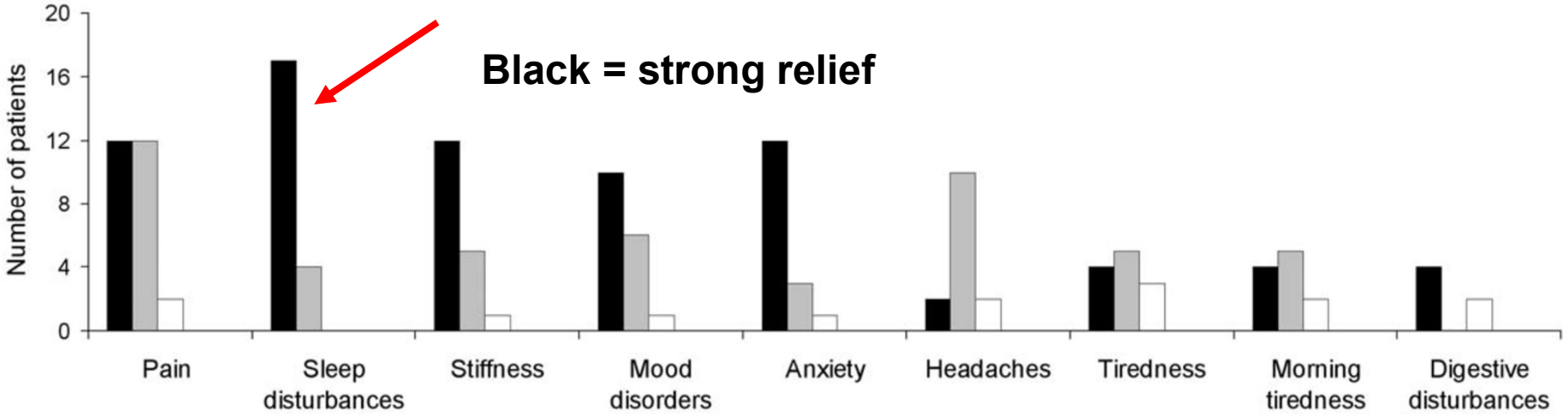
- 40 patients w/FBM
- **RCT** 1 mg bid Nabilone (Cesamet – synthetic THC) vs. PCBO
- 4-week Tx and 4-week washout

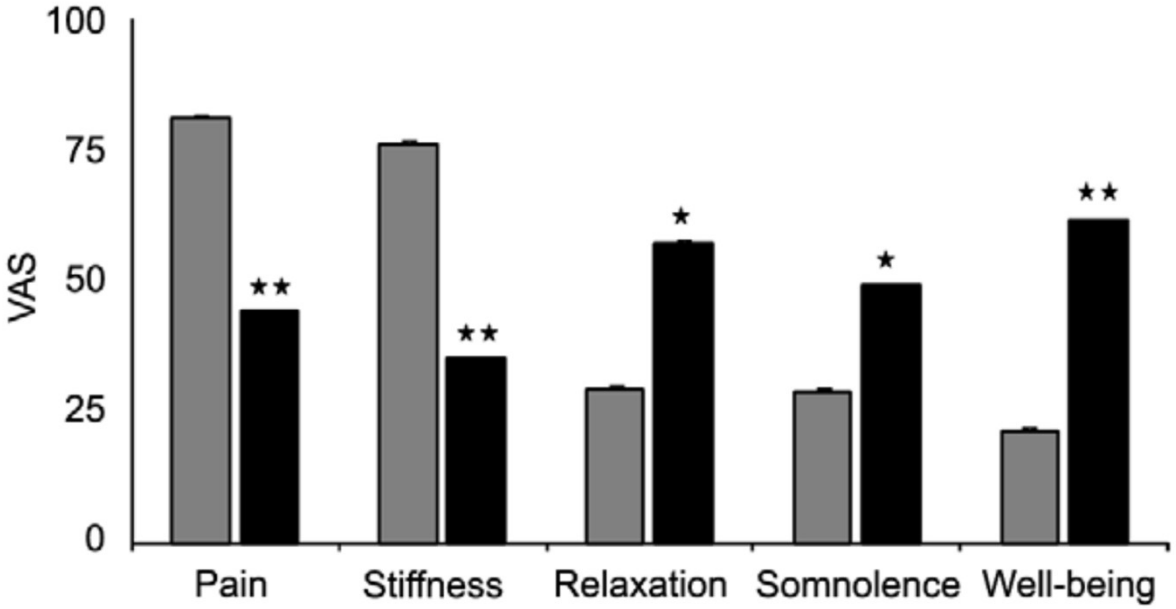
Skrabek et al., 2008; J Pain

Fibromyalgia



Schley et al., 2006; Curr Med Res Op



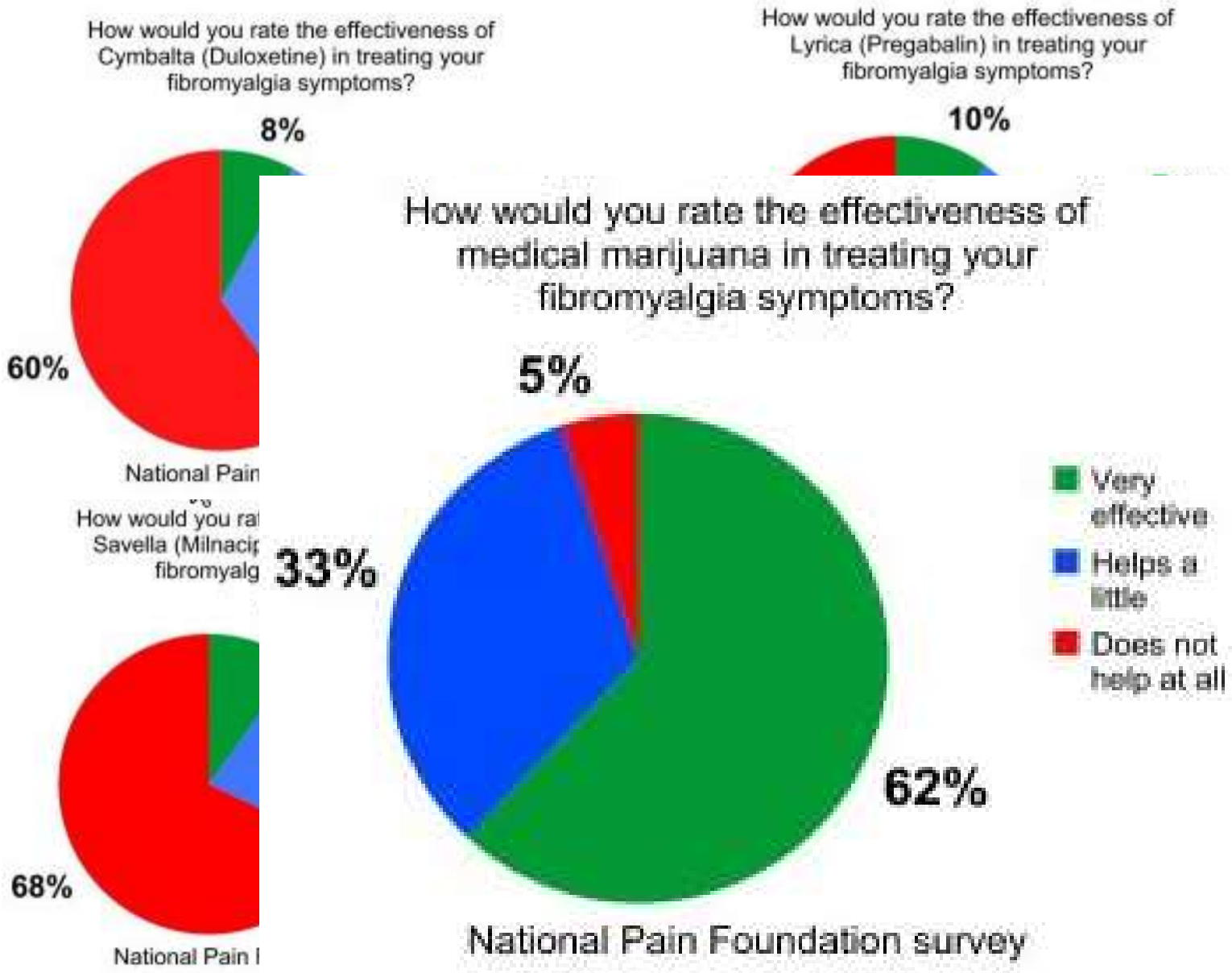


- 28 w/FBM using cannabis self-administration

Fiz et al., 2011; PLoS One

Fibromyalgia – National Pain Report Survey

http://nationalpainreport.com/marijuana-rated-most-effective-for-treating-fibromyalgia-8823638.html



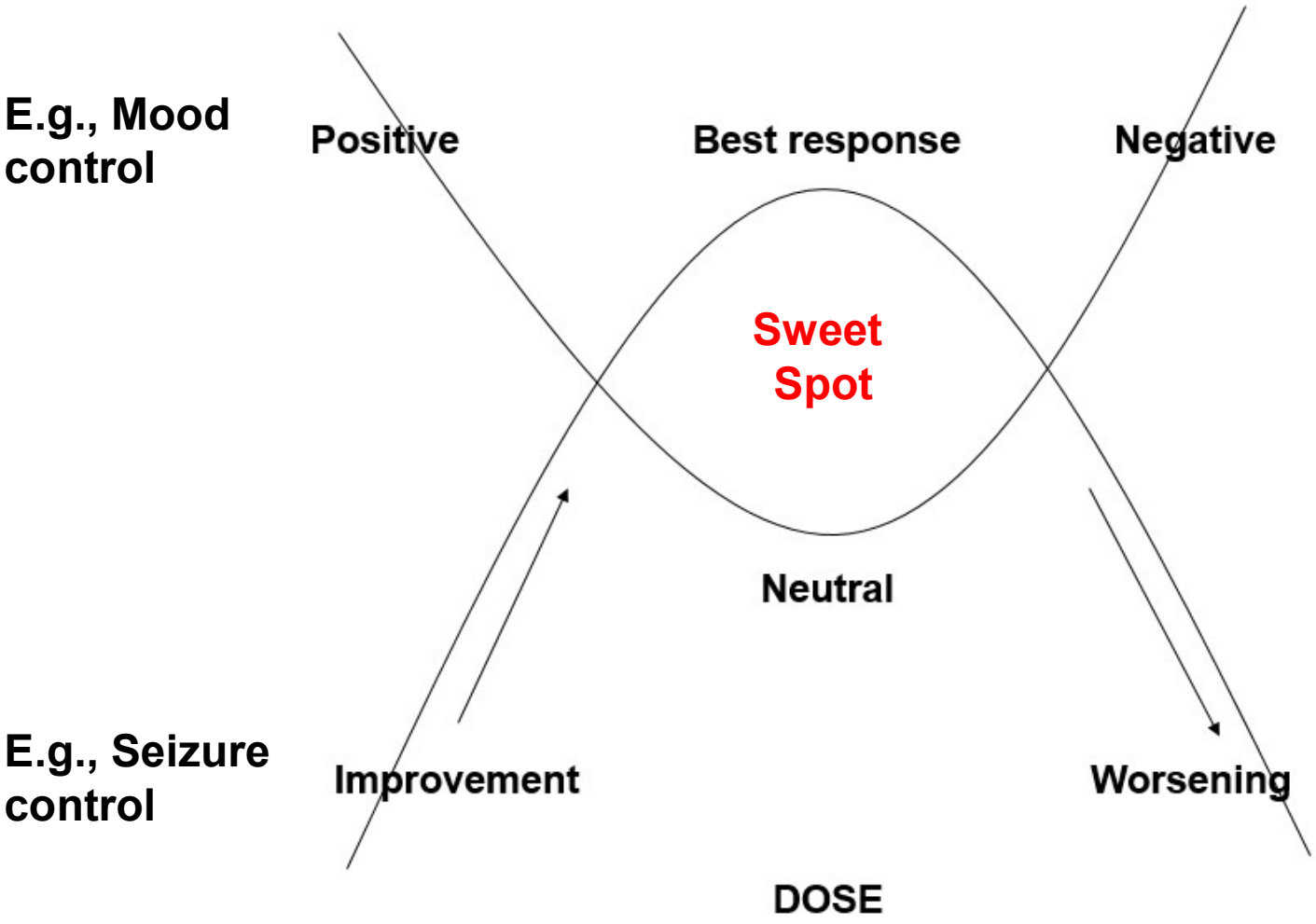
Migraine

- Observational study in 121 patients with migraines (in CO) – retrospective chart review
  - Migraine frequency decreased from 10.4 to 4.6 per month ($p<0.0001$)
  - Most patients used more than one form of cannabis and used it daily
  - Inhaled forms of cannabis were commonly used for acute migraine treatment and were reported to abort migraine headache.
- Medication overuse headache – RCT in 30 patients with daily analgesic intake for at least 5 years and failed at least 3 detoxification attempts.
  - Randomized to ibuprofen 400 mg or nabilone 0.5 mg daily for 8 weeks, followed by 1 week washout, and then 8 weeks of the other medication.
  - Nabilone superior in reducing daily analgesic intake, pain intensity, level of medication dependence, and improved quality of life.

Rhyne et al., 2016; Pharmacotherapy
Pini et al J Headache Pain 2012

Cannabis Dosing and Variation in Response

- Psychological effects of cannabis are biphasic and bidirectional



Cannabis Dosing and Variation in Response

- **“Sweet spot”**
  - Cannabinoids upregulate ECS at acute and lower doses via increased EC production, CR expression, and/or affinity
  - Cannabinoids can downregulate ECS upon persistent agonism (long-term high doses) via membrane receptor endosome internalization

- Individual differences in objective and subjective effects of cannabis vary by variety/strain, dosage, route of administration, personality, and/or degree of tolerance (Pacher, 2006)
- Tolerance develops as a function of CB_1R downregulation (Volkow, 2017); with chronic use any benefit derived from THC with regard to mental health could result in symptom exacerbation when not using THC

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A case for a pharmaceutical grade product

- Dispensaries in San Francisco, Los Angeles, Seattle (randomly selected)
- 75 edible products of different brands
- 17% labelling of content was accurate
  - 23% under-labelled
  - 60% over-labelled
- For non-THC content:
  - 17% were labelled as (+)
  - 59% had non-THC content

Vandrey et al., 2015 JAMA

A case for a pharmaceutical grade product

Label accuracy, No. of products (% [95% CI]	
Accurate[a]	
Under[b]	
Over[c]	
Labeled concentration, mg/mL	
Mean (95% CI)	
Median (range)	
Deviation of labeled content from tested value, mg/mL	
Mean (95% CI) [% of deviation]	
Median (range) [% of deviation]	

Bon-Miller et al., 2017 JAMA

Proposed Recommendations

- Cannabis or cannabinoids are or may be effective for the treatment of symptoms associated with the following conditions:
  - Anxiety
  - ASD (behavior)
  - Chemotherapy-induced (treatment-induced) nausea and vomiting
  - Chronic Pain (including fibromyalgia and ± headache / migraine)
  - Epilepsy / seizure disorders
  - HIV / AIDS related nausea and weight loss
  - PTSD
  - Sleep disorders
  - Spasticity associated with motor neuron disease / ALS
  - Spasticity associated with MS and SCI
  - Tourette syndrome