Decoding CBD

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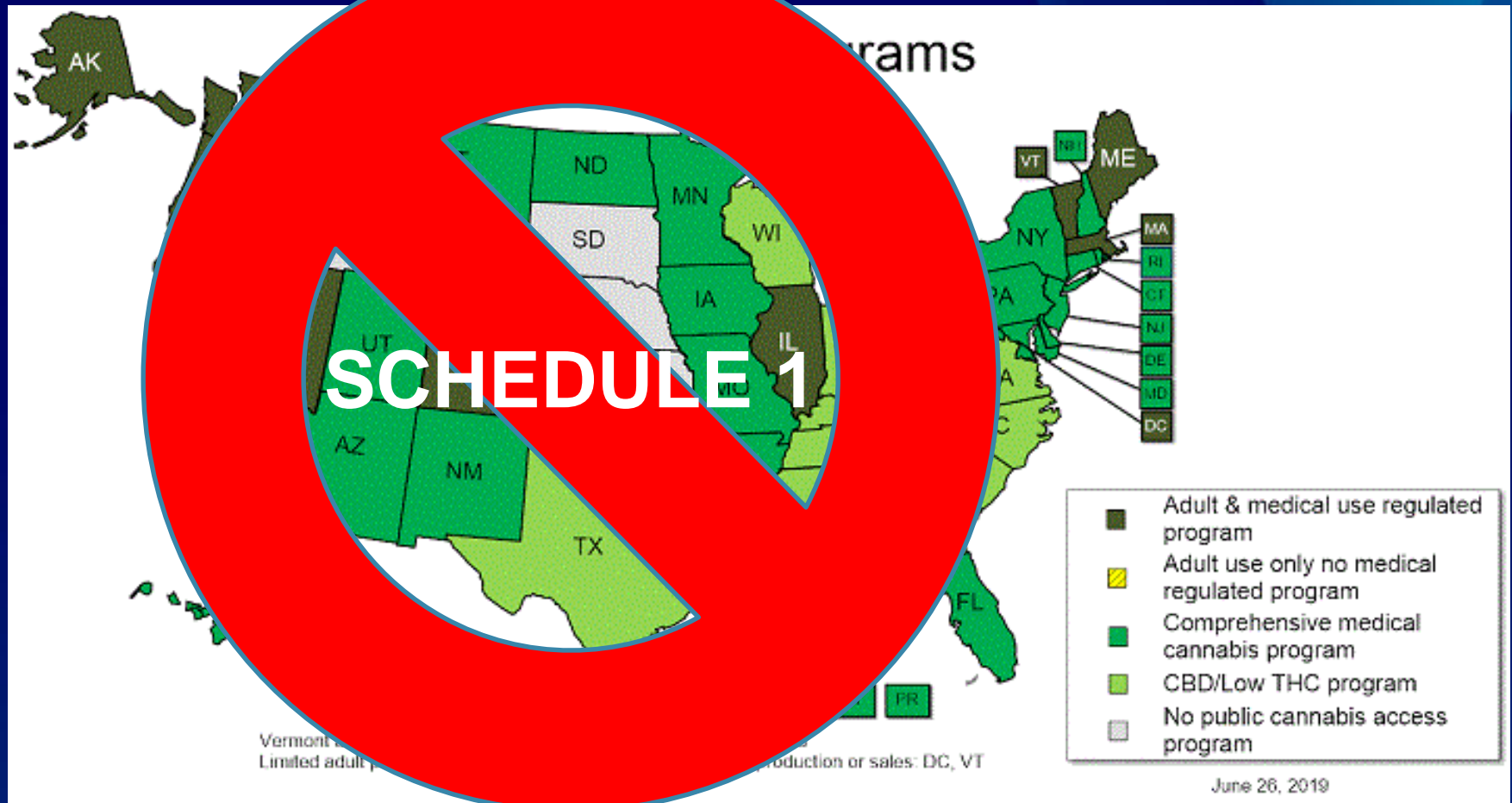
1

Disclosures

- None

Medical cannabis in US

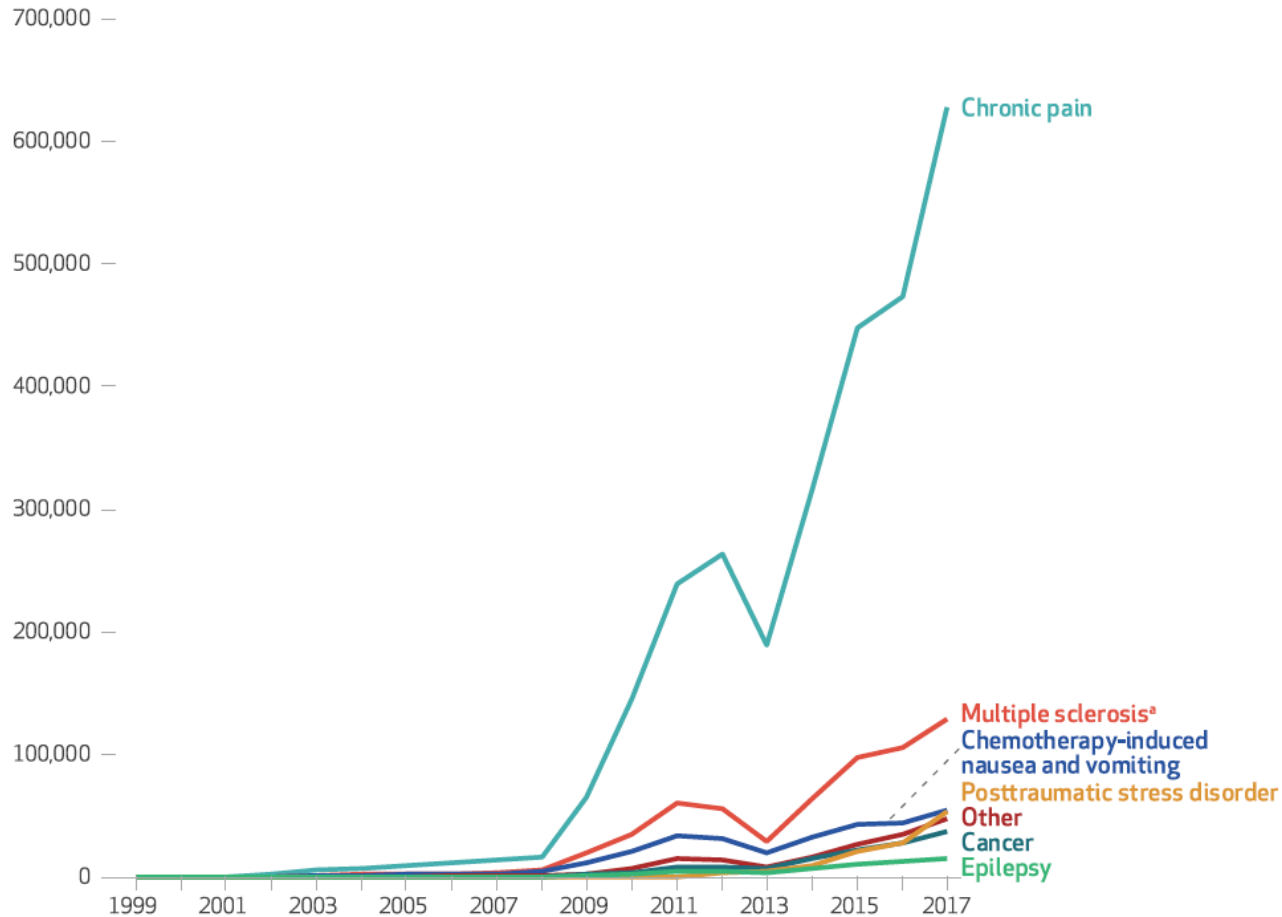# Hemp is officially legalized with President Trump's signature on the Farm Bill

PHARMACEUTICALS & MEDICAL TECHNOLOGY

EXHIBIT 2

Numbers of patient-reported qualifying conditions for medical cannabis licenses, 1999–2017

SOURCE Authors' analysis of data from state medical cannabis registries. NOTES Data were missing for Michigan for 2010 and 2013 and for Rhode Island for 2007, 2009, 2011, 2013, 2015 and 2016. The sharp dip in patient-reported qualifying conditions in 2013 is attributable to the large number of patients in Michigan who were not accounted for in that year. [a]Spasticity symptoms.

Boehnke, Kevin F., et al. "Qualifying Conditions Of Medical Cannabis License Holders In The United States." *Health Affairs* 38.2 (2019): 295-302.

GALLUP®

AUGUST 7, 2019

14% of Americans Say They Use CBD Products

BY **MEGAN BRENAN**

Why Americans Use CBD Products

For what condition or purpose do you use CBD products?

	%
Pain (nonspecific)	40
Anxiety	20
Sleep/Insomnia	11
Arthritis	8
Migraines/Headaches	5
Stress	5
Muscle spasms/Soreness	4
General health (nonspecific)	4
Mental health/PTSD/ADHD/Neurological disorders	4
Recreational	4
Depression	2
Skin care	2
For pet	1
Gastrointestinal/Digestive issues	1
Inflammation	1
Other	7
No opinion	1

Based on U.S. adults who say they use CBD products. Percentages add to more than 100% due to multiple responses.

GALLUP, JUNE 19-JULY 12, 2019

CBD (Cannabidiol)

- Definitions and Background

- CBD Mechanisms and pain-related activity

- Role in Pain management

- Summary

Cannabidiol (CBD): a brief background

- Isolated in 1940 by Roger Adams, chemical structure characterized in 1963 by Raphael Mechoulam

- Small RCT in 1980s showed anti-convulsant activity[1]

- Not your (great great) grandmother's cannabis: changing THC : CBD ratios[2]

- War on Drugs

- Resurgence in 2010s
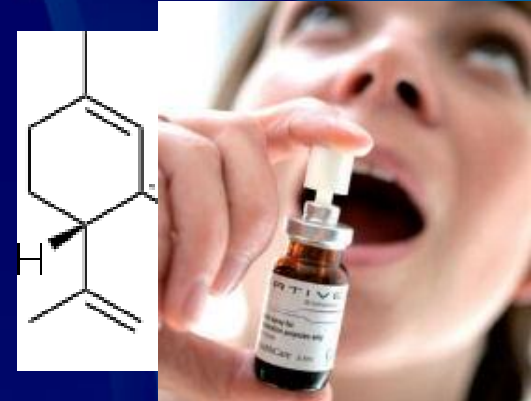
DEA Reclassifies Plant-Derived Marijuana Medicine To Schedule V

⊙ October 5, 2018   ▲ Staff   ⊟ Health and Fitness   ○ 0 Comments

EPIDIOLEX
(cannabidiol) 100 mg/mL
Oral Solution

(Source: Daily Beast)

https://w...
medical...

1. Mechoulam, Raphael, and Elisado A. Carlini. "Toward drugs derived from cann... (1978): 174-179. 2. ElSohly, Mahmoud A., et al. "Changes in cannabis potency o... analysis of current data in the United States." *Biological psychiatry* 79.7 (2016): 613-619.
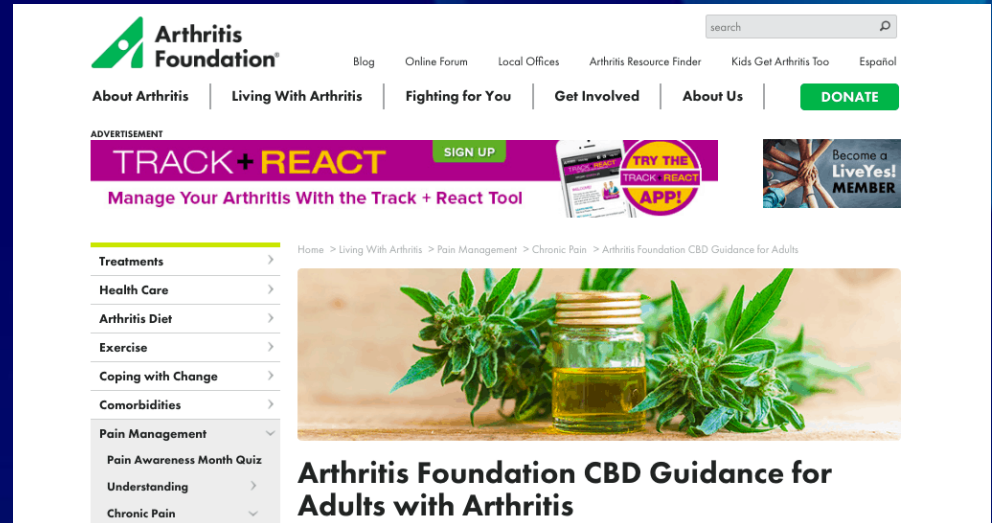
CBD – a legal and regulatory quagmire

Letters

RESEARCH LETTER

Labeling Accuracy of Cannabidiol Extracts Sold Online

There is growing consumer demand for cannabidiol (CBD), a constituent of the cannabis plant, due to its purported medicinal benefits for myriad health conditions.[1] Viscous plant-derived extracts, suspended in oil, alcohol (tincture), or vaporization liquid, represent most of the retail market for CBD. Discrepancies between federal and state cannabis laws have resulted in inadequate regulation and oversight, leading to inac-

Arthritis Foundation CBD Guidance for Adults with Arthritis

Table 1. Label Accuracy by Cannabidiol Extract Type

	Cannabidiol Extract Products			
	Oil (n = 40)	Tincture (n = 20)	Vaporization Liquid (n = 24)	Total (N = 84)
Label accuracy, No. of products (%) [95% CI]				
Accurate[a]	18 (45.00) [30.71-60.17]	5 (25.00) [11.19-46.87]	3 (12.50) [4.34-31.00]	26 (30.95) [22.08-41.49]
Under[b]	10 (25.00) [14.19-40.19]	8 (40.00) [21.88-61.34]	18 (75.00) [55.10-88.00]	36 (42.85) [32.82-53.53]
Over[c]	12 (30.00) [18.07-45.43]	7 (35.00) [18.12-56.71]	3 (12.50) [4.34-31.00]	22 (26.19) [17.98-36.48]
Labeled concentration, mg/mL				
Mean (95% CI)	56.15 (14.23-98.07)	11.14 (5.60-16.60)	26.15 (12.50-39.74)	36.86 (16.21-57.51)
Median (range)	22.26 (2.50-800.00)	8.33 (1.33-50.00)	18.33 (2.00-160.00)	15.00 (1.33-800.00)
Deviation of labeled content from tested value, mg/mL				
Mean (95% CI) [% of deviation]	10.34 (4.95-15.74) [29.01]	3.94 (2.74-5.14) [220.62]	11.52 (8.10-14.94) [1098.70]	9.16 (4.96-13.36) [380.26]
Median (range) [% of deviation]	2.76 (0.13-144.73) [12.11]	1.48 (0.01-22.30) [19.12]	4.62 (0.14-66.07) [67.34]	3.17 (0.10-144.73) [20.42]

[a] Cannabidiol content tested within 10% of labeled value.
[b] Cannabidiol content exceeded labeled value by more than 10%.
[c] Cannabidiol content tested more than 10% below labeled value.

Epidiolex vs. Hemp-derived

Epidiolex

- 100mg/mL

- Oral Solution

- Can be prescribed off-label
  - ~$1,300 per 10,000mg bottle

Hemp-derived

- Variable concentration, price, and standardization

- More formulations

Some grey areas

- FDA: Under Food, Drug, and Cosmetics Act, CBD cannot legally be sold as dietary supplement
  - Is this stopping anyone?
  - Still legal as cosmetics (e.g., topicals)

- Employment implications: Can CBD cause a positive urine drug screen?
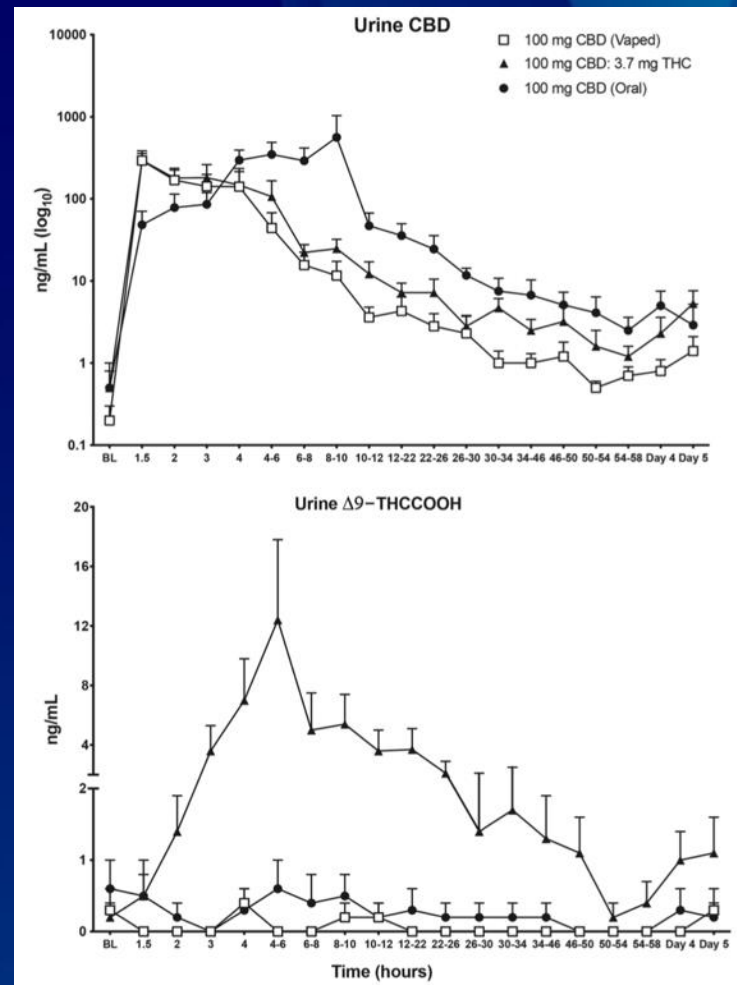
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Preclinical studies of arthritis and inflammation
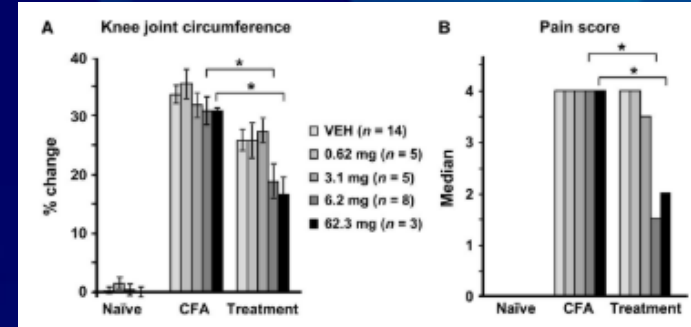
- Various mouse models used:
  - Collagen-induced arthritis (RA)[1]: 2.5-20mg/kg/day I.P., 10-50mg/kg/day oral
  - Freund's adjuvant induced monoarthritic knee (Inflammatory)[2]: 0.6-62.3 mg/day transdermal
  - Sodium monoiodoacetate knee (OA)[3]: intra-articular injection of 100-300ug of CBD

- Reductions in pain: paw withdrawal latency[2] and weight bearing[3]

- Joint swelling and damage[1,2]

- Reductions in Pro-inflammatory biomarkers (TNF- α)[1,2]

From Hammell et al, 2016

From Malfait et al, 2000

1. Malfait AM, Gallily R, Sumariwalla PF, et al. *Proc Natl Acad Sci U S A*. 2000;97(17):9561-9566.PMC16904 2. Hammell DC, Zhang LP, Ma F, et al. *Eur J Pain*. 2016;20(6):936-948.PMC4851925 3. Philpott HT, O'Brien M, McDougall JJ. *Pain*. 2017;158(12):2442-2451.PMC5690292

Overcoming the Bell-Shaped Dose-Response of Cannabidiol by Using *Cannabis* Extract Enriched in Cannabidiol

- Zymos
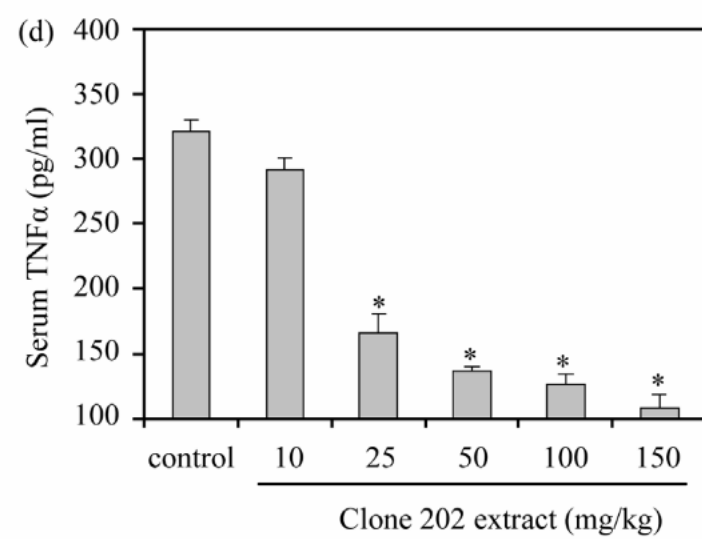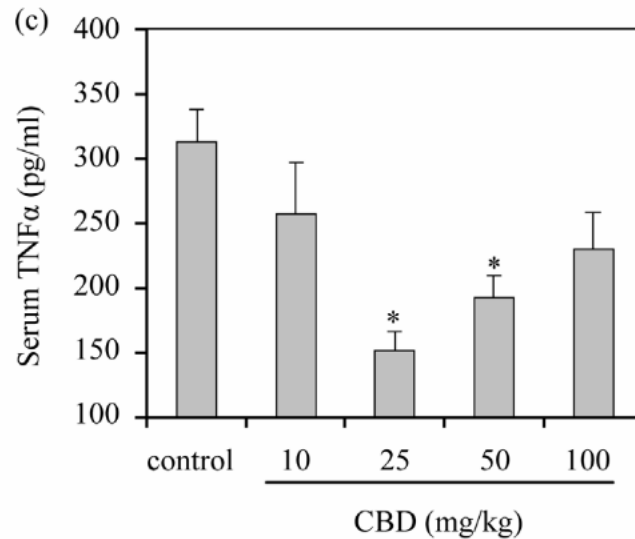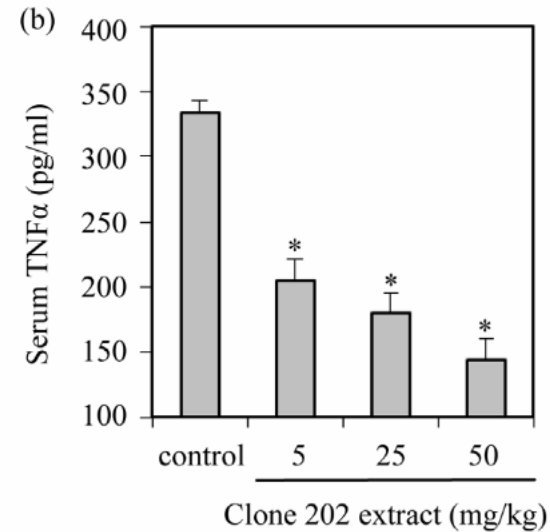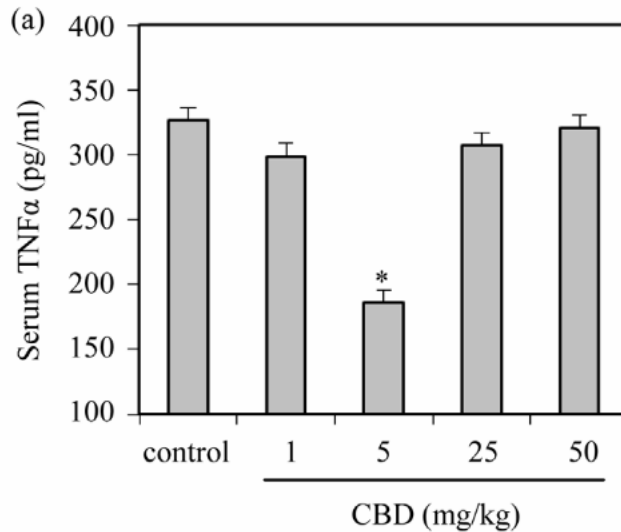
Anxiety: Short-term human studies

- Acute dosing paradigms: single day, 100-800mg/CBD used

- Decreased anxiety[1-4]

- Inverted U-shaped curve?[2]
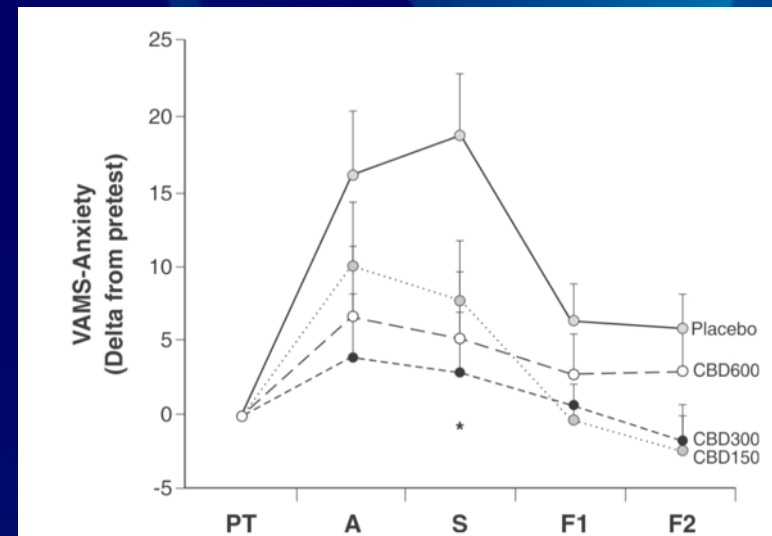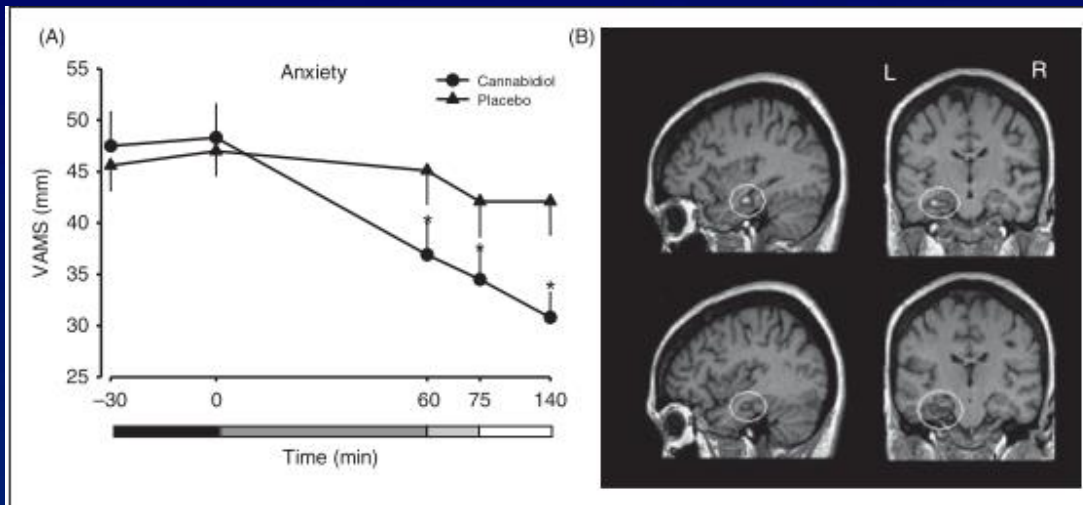
Figure 1 Visual Analogue Mood Scale (VAMS) anxiety factor scores in each phase of the simulated public speaking test (SPST) for groups treated with cannabidiol (CBD) 150, 300, and 600 mg or placebo (points in the curve refer to mean scores and vertical lines refer to mean standard errors).* Lower anxiety levels in the group treated with CBD 300 mg relative to the placebo phase (p = 0.042). PT = pre-test; A = anticipatory anxiety; S = speech; F1= post-test 1; F2 = post-test 2.

1. Linares IM, Zuardi AW, Pereira LC, et al. *Braz J Psychiatry.* 2019;41(1):9-14 2. Zuardi AW, Rodrigues NP, Silva AL, et al *Front Pharmacol.* 2017;8:259.PMC5425583 3. Crippa JA, Derenusson GN, Ferrari TB, et al.. *J Psychopharmacol.* 2011;25(1):121-130 4. Masataka, Nobuo. *Frontiers in Psychology* 10 (2019): 2466.

CBD opioid-sparing?

Cannabidiol for th...
Craving and Anxie...
Heroin Use Disorc...
Placebo-Controll...

Yasmin L. Hurd, Ph.D., Sharron Spriggs...
Chris Kudrich, D.H.Sc., Anna M. Opres...

- Three doses:
  - Placebo, 400mg, 800 mg
- Administered 3 days in row
- Primary outcomes
  - Craving and anxiety (VAS)
- Secondary outcomes
  - Affect
  - Cognitive performance
  - Physiological measures
  - Safety

FIGURE 3. Change from baseline scores on the visual analogue scale for craving in a study of cannabidiol (CBD) for the reduction of craving and anxiety in heroin use disorder[a]
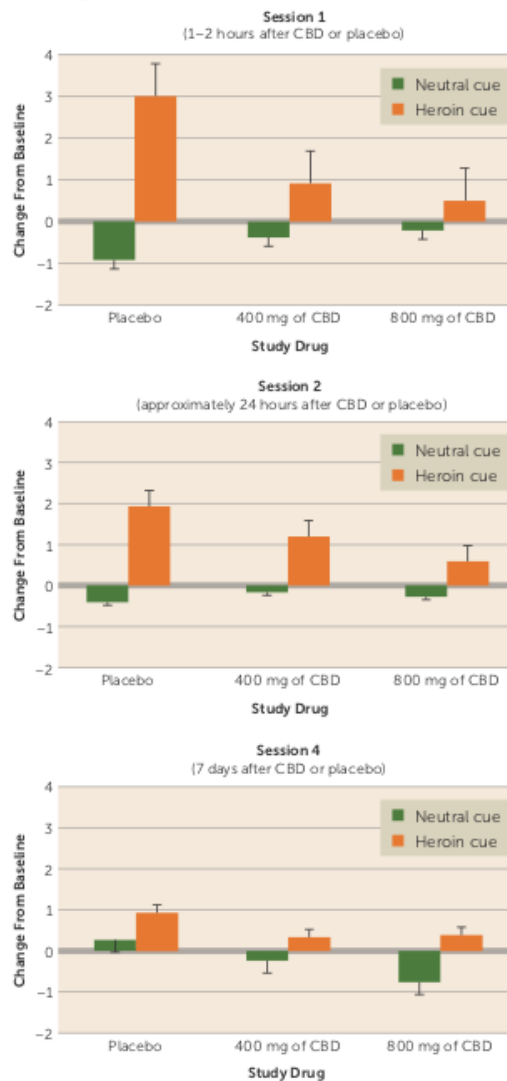
[a] The change in scores was recorded after the presentation of neutral or heroin-associated cues 1–2 hours (session 1) and 24 hours (session 2) after the first CBD or placebo administration, as well as 7 days after the third daily CBD or placebo administration (session 4). Error bars indicate standard deviation.

FIGURE 4. Change from baseline scores on the visual analogue scale for anxiety in a study of cannabidiol (CBD) for the reduction of craving and anxiety in heroin use disorder[a]

[a] The change in scores was recorded after the presentation of neutral or heroin-associated cues 1–2 hours (session 1) and 24 hours (session 2) after the first CBD or placebo administration, as well as 7 days after the third daily CBD or placebo administration (session 4). Error bars indicate standard deviation.

CBD + THC: Synergism?

- Allosteric modulator of cannabinoid receptor 1, alters CB1 binding of THC[1]

- When co-administered, CBD widens therapeutic window of THC in preclinical studies of neuropathic pain[2]

- Associated with decreases THC-related psychoactivity and adverse events[3,4]

Figure 3. Dose–response curves for the effect of combined THC and CBD treatment on allodynia. Dose–response curves showing the effect of administration of THC and CBD in a fixed ratio (THC:CBD at 1:1.13 fixed weight ratio) on (A) mechanical PWT and (B) acetone-induced responses. The biphasic sigmoidal fit for the combination THC:CBD data is shown (ED$_{50}$ and E$_{Max}$ estimates shown in Table 1). Also shown are the predicted additive dose response curves for combination THC:CBD, and the sigmoidal fits for THC and CBD alone (reproduced from Fig. 2). **, ***, and **** denote $P < 0.01$, 0.001, and 0.0001, respectively, for THC:CBD experimental combination vs predicted additive at equivalent doses. CBD, cannabidiol; ED$_{50}$, median effective dose; PWT, paw withdrawal threshold; THC, Δ9-tetrahydrocannabinol.

1. Laprairie, R. B., et al. *British journal of pharmacology* 172.20 (2015): 4790-4805.
2. Casey, Sherelle L., Nicholas Atwal, and Christopher W. Vaughan. *Pain* 158.12 (2017): 2452-2460. 3. Russo, Ethan B. *British journal of pharmacology* 163.7 (2011): 1344-1364.

Risks of CBD

An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies

Kerstin Iffland and Franjo Grotenhermen

- Generally well tolerated: multiple studies demonstrate safety of ≥600mg/day CBD in several different conditions[1]

- Drug-drug interactions: Can inhibit or affect liver enzyme activity which can affect CBD plasma concentrations[1,2]

- Epidiolex effects (high doses): Drowsiness, decreased appetite, diarrhea, fatigue, malaise, weakness/lethargy, rash, difficulty sleeping, infections[2]

- Quality control!
  - Pesticides, solvents, heavy metals can be left behind by sloppy manufacturing

The risk of contaminants and false labeling in the exploding CBD industry

by Lisa Fletcher/ABC7 | Wednesday, May 15th 2019

Iffland, Kerstin, and Franjo Grotenhermen. "An update on safety and side effects of cannabidiol: a review of clinical data and relevant animal studies." *Cannabis and cannabinoid research* 2.1 (2017): 139-154. 2. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf

CBD (Cannabidiol)

- Definitions and Background

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Mechanistic Characterization of Pain
Variable degrees of any mechanism can contribute in any disease

	Nociceptive	Neuropathic	Nociplastic
Cause	Inflammation or damage	Nerve damage or entrapment	CNS or systemic problem
Clinical features	Pain is well localized, consistent effect of activity on pain	Follows distribution of peripheral nerves (i.e. dermatome or stocking/glove), episodic, lancinating, numbness, tingling	Pain is widespread and accompanied by fatigue, sleep, memory and/or mood difficulties as well as history of previous pain elsewhere in body
Screening tools		PainDETECT	Body map or FM Survey
Treatment	NSAIDs, injections, surgery, ? opioids	Local treatments aimed at nerve (surgery, injections, topical) or CNS-acting drugs	CNS-acting drugs, non-pharmacological therapies
Classic examples	Osteoarthritis Autoimmune disorders Cancer pain	Diabetic painful neuropathy Post-herpetic neuralgia Sciatica, carpal tunnel syndrome	Fibromyalgia Functional GI disorders Temporomandibular disorder Tension headache Interstitial cystitis, bladder pain

Mixed Pain States

CBD clinical trials for chronic pain

> **30**
> SYNTHETIC TRANSDERMAL CANNABIDIOL FOR THE TREATMENT OF
>
> **Systematic Reviews and Meta-Analyses**
>
> **PAIN**®
>
> **Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies**
>
> Emily Stockings[a,*], Gabrielle Campbell[a], Wayne D. Hall[b,c], Suzanne Nielsen[a], Dino Zagic[a], Rakin Rahman[a], Bridin Murnion[d,e], Michael Farrell[a], Megan Weier[a], Louisa Degenhardt[a]
>
> average weekly improvement in worst pain score of ≥ 30% and decrease in WOMAC physical function sub scale of at least 20% at last observation.

- Limited: short length and small sample size
  - Many used THC alone or THC + CBD
- Most support in neuropathic pain (THC+CBD).
- Increased risk of short term AEs (mostly minor) for study participants
- Recent clinical trials suggest that CBD may be useful in nociceptive pain[3] but not centralized pain[4]

1. Whiting, Penny F., et al. *Jama* 313.24 (2015): 2456-2473. 2. Nugent, Shannon M., et al. *Annals of internal medicine* 167.5 (2017): 319-331. 3. Hunter, D., et al. *Osteoarthritis and Cartilage* 26 (2018): S26. 4. van de Donk, Tine, et al. *Pain* (2018).

Pharmacokinetics

Pharmacokinetics
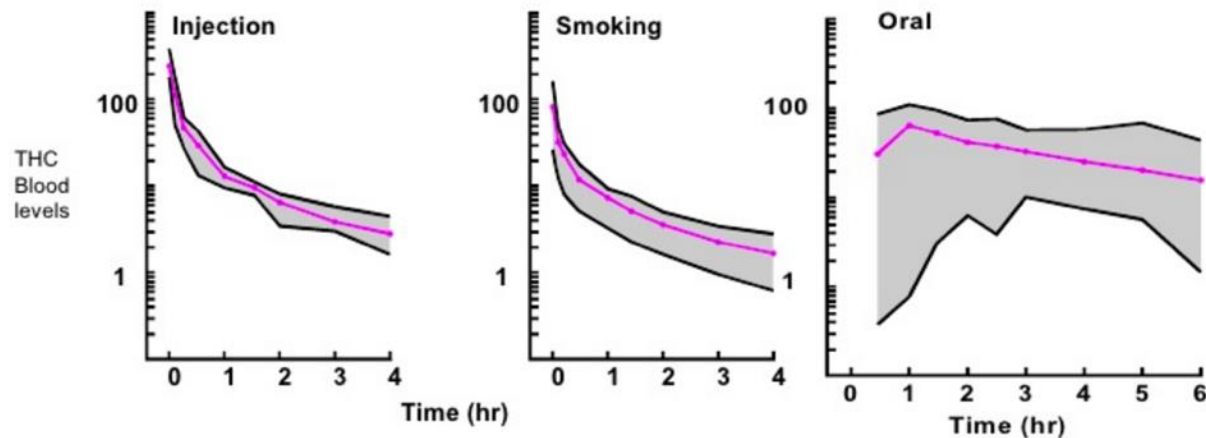
Route of administration influences THC pharmacokinetics, left = 5 mg i.v. injection, center = smoking 13.0 mg, or right =consuming cookie with 20 mg (Agurell et al. 1986).

From Agurell, Stig, et al. *Pharmacological Reviews* 38.1 (1986): 21-43.

Table 2

Administration factors in cannabis delivery methods.

Issue	Smoking/vaporisation	Oral	Oromucosal	Topical
Onset (min)	5–10	60–180	15–45	Variable
Duration (h)	2–4	6–8	6–8	Variable
Pro	Rapid action, advantage for acute or episodic symptoms (nausea/pain)	Less odor, convenient and discrete, advantage for chronic disease/symptoms	Pharmaceutical form (nabiximols) available, with documented efficacy and safety.	Less systemic effect, good for localised symptoms
Con	Dexterity required, vaporisers may be expensive, and not all are portable	Titration challenges due to delayed onset	Expensive, spotty availability	Only local effects

MacCallum, Caroline A., and Ethan B. Russo. "Practical considerations in medical cannabis administration and dosing." *European journal of internal medicine* (2018).

A Cross-Sectional Study of Cannabidiol Users
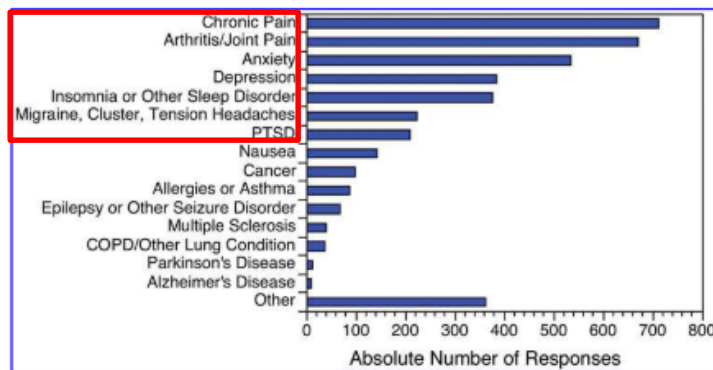
Jamie Corroon[1,2] and Joy A. Phillips[3]

FIG. 1. Number of medical conditions for which respondents reported using CBD, by medical condition (n = 3963). CBD, cannabidiol; COPD, chronic obstructive pulmonary disease; PTSD, post-traumatic stress disorder.
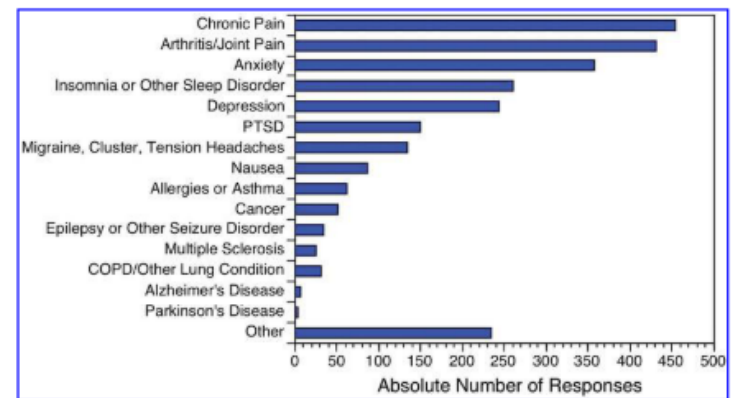

FIG. 3. Number of medical conditions for which respondents report CBD treating "Very Well by Itself" or "Moderately Well by Itself," by medical condition (n = 2557).

Corroon, Jamie, and Joy A. Phillips. "A cross-sectional study of cannabidiol users." *Cannabis and cannabinoid research* 3.1 (2018): 152-161.

Arthritis Foundation®

79% surveyed are currently using CBD, have used it in the past or are considering using it.

94% of those who report using CBD used it to relieve pain.

71% of patients report that using CBD has improved their ability to sleep.

67% of patients report that using CBD has been effective in improving their mental health/depressed mood.
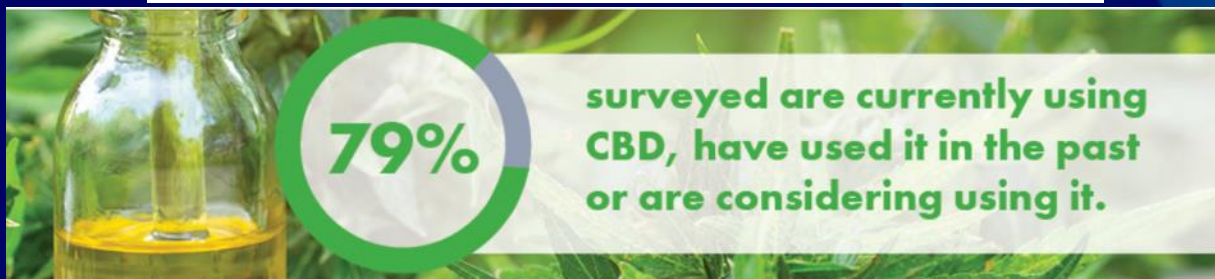
Figure 1. Self reported effectiveness of CBD for managing FM-related symptoms

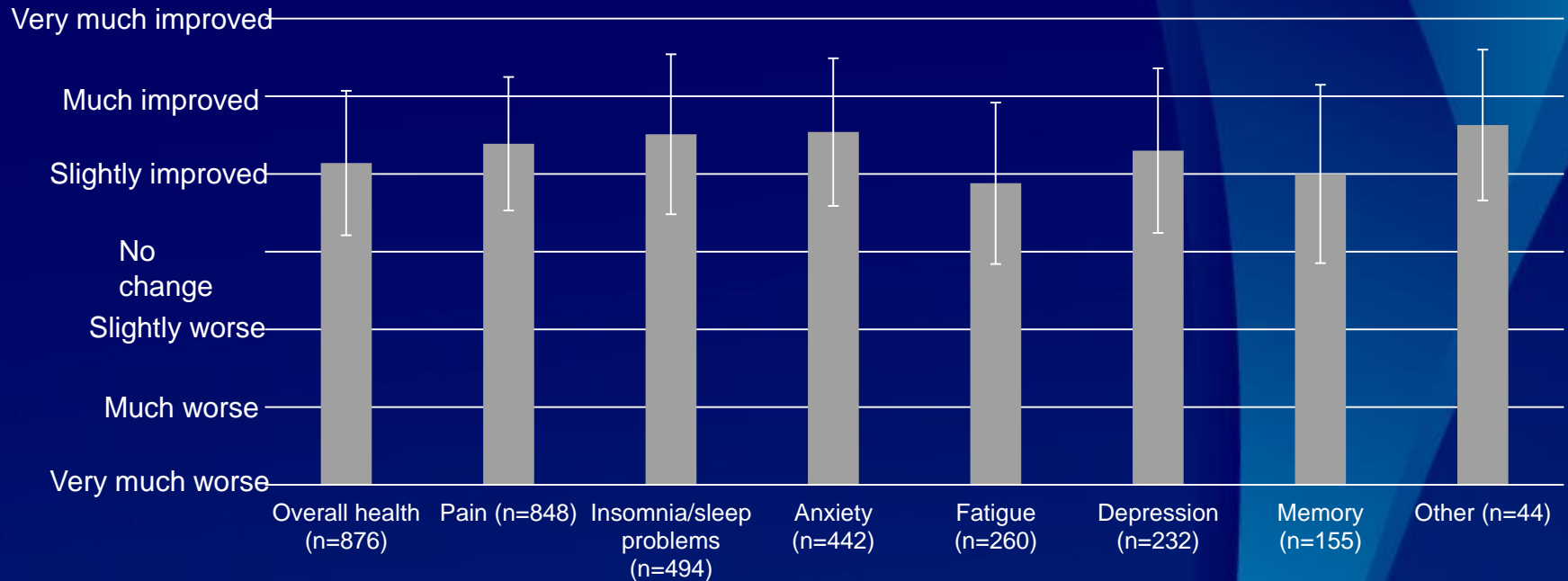

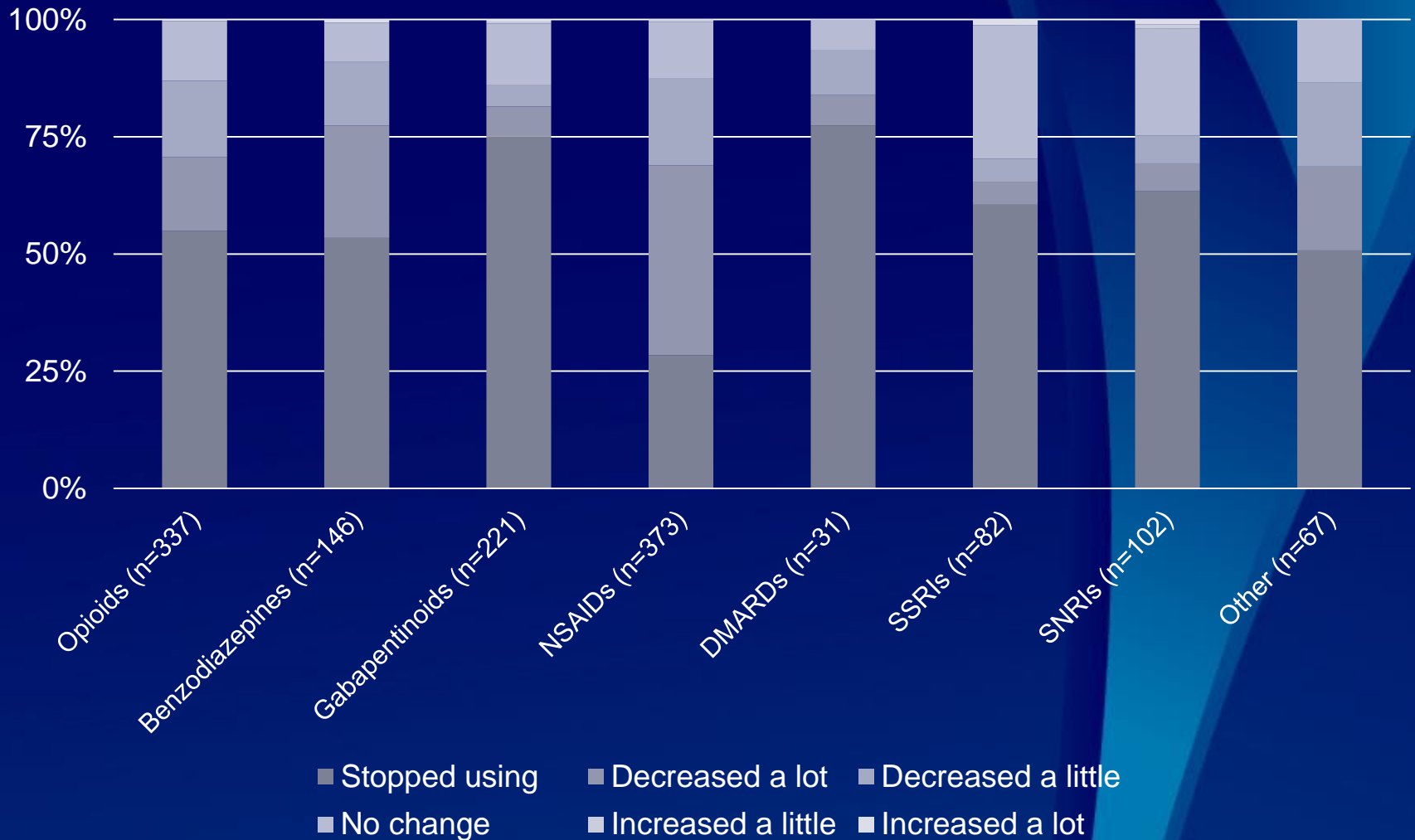Figure 1. Changes were assessed using the Patient Global Impression of Change for each symptom. Error bars are ± Standard Deviation. 30-40% of study population reported much to very much improvement across each symptom.

Boehnke et al, under review

Figure 1. Substituting CBD for pain medications (n=878)

Boehnke et al, under review.

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Summary and Practical Tips

- CBD clinical trials are very limited or non-existent. Most plausibility in nociceptive pain and pain-related symptoms (e.g., anxiety, inflammation)

- Patients are using CBD regardless: How to effectively communicate?

  - Come up with a treatment plan with your patient.

  - Consider using as an adjuvant

  - "Start low, go slow"[1]

  - Minimize harm: Quality control and avoiding inhalation

  - Consider pharmacokinetics of different administration routes for dose layering: e.g., edibles for XR, tinctures for PRN

- THC?

  - Can add through FDA-approved Marinol (schedule III) or medical cannabis license

1. MacCallum, Caroline A., and Ethan B. Russo. "Practical considerations in medical cannabis administration and dosing." *European journal of internal medicine* (2018).

Brief Commentary: Cannabinoid Dosing for Chronic Pain Management

Kevin F. Boehnke, PhD, and Daniel J. Clauw, MD

Editors' Note: This commentary was selected for publication from among 100 submitted manuscripts in response to a call for readers' perspectives on prescribing or recommending marijuana.

As pain researchers, we are underwhelmed by systematic reviews of clinical trials of cannabinoids, which report modest effect sizes for chronic neuropathic pain but limited or insufficient efficacy in other pain conditions (1). These reviews also report substantial adverse events (1). Nevertheless, we cannot ignore the reality of cannabis's growing use as medicine, especially for chronic pain.

We endorse this paradigm because conservative titration, delayed introduction to THC, and flexible administration allow patients to find their optimal personal dosing strategy without being prematurely pushed into using high-dose THC products—some of which contain more than 100 mg of THC per serving (4). Given the growing understanding of how long-term, high-dose opioid use dysregulates the endogenous opioid system (5), we are concerned that consistent, high doses of THC might do the same to the endogenous cannabinoid system. We are satisfied with how our paradigm mitigates such exposure.

Questions?