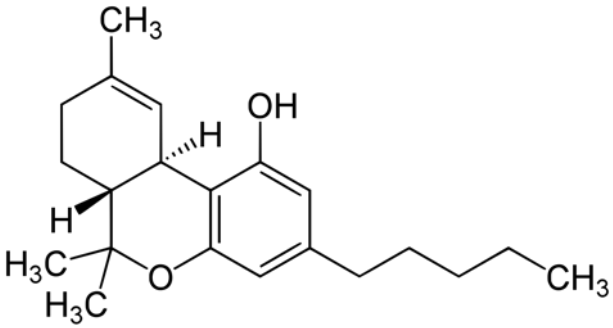
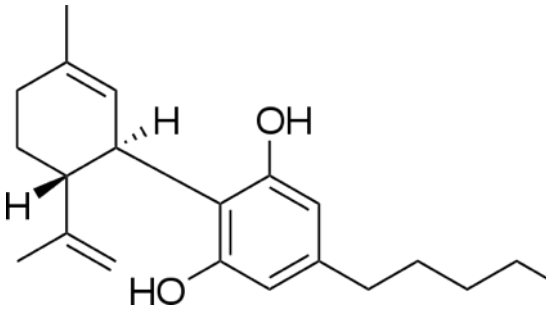
# From Opioid Replacement to Managing Chronic Pain: What is CBD?




Kalev Freeman, MD PhD
Assistant Professor of Surgery and Pharmacology, University of Vermont

Laura Mann Integrative Healthcare Lecture Series
November 8, 2017

# University of Vermont Health Network

DISCLOSURSE:

Is there anything to disclose? Yes

Please list the Potential Conflict of Interest (*if applicable*): Vermont Patients Alliance, PhytoScience Institute, Green State Gardener

All Potential Conflicts of Interest have been resolved prior to the start of this program. Yes

(*If no, credit will not be awarded for this activity.)*

All recommendations involving clinical medicine made during this talk were based on evidence that is accepted within the profession of medicine as adequate justification for their indications and contraindications in the care of patients. Yes

*This lecture will discuss use of investigational drugs not approved for use in the United States.*

# Learning objectives

1. According to the “Cannabinoids for Medical Use: A Systematic Review and Meta-analysis” published in JAMA 2015, there is evidence supporting therapeutic use of cannabinoids for 6 medical conditions. We will discuss the evidence basis for cannabinoids in these conditions. We will also discuss emerging evidence for CBD in pediatric epilepsy.

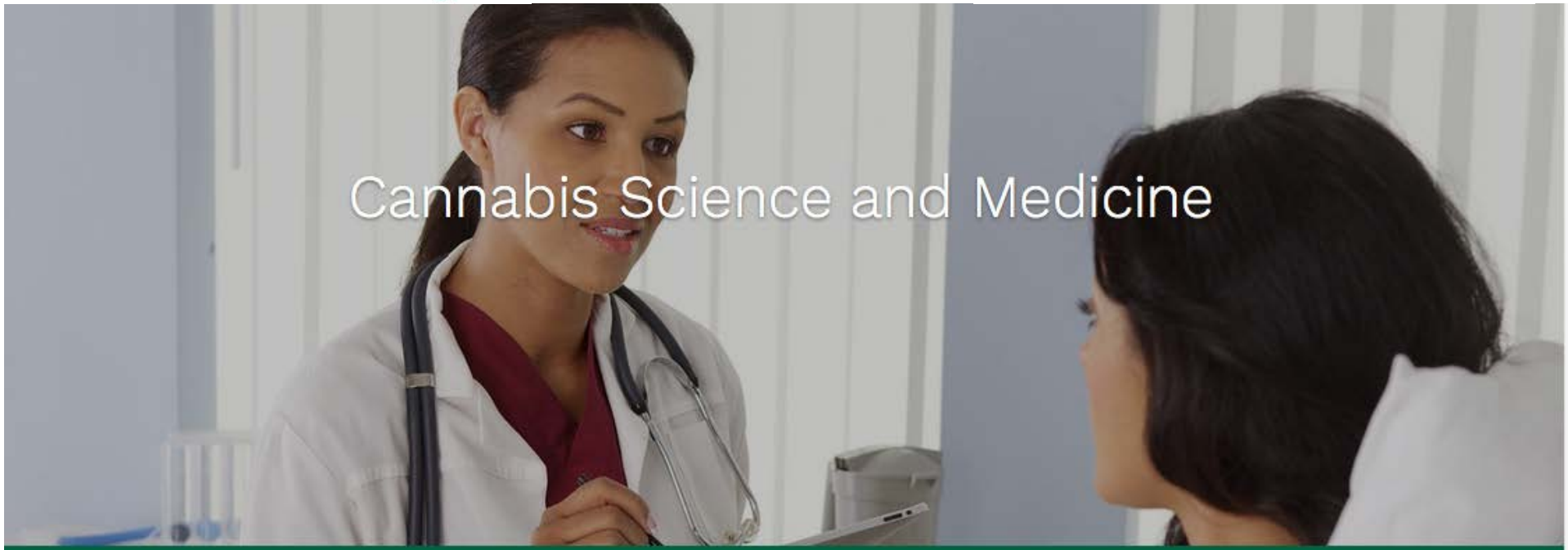
2. The systematic review and meta-analysis also showed that adverse events with cannabis use were significantly higher than placebo. We will review the odds of experiencing adverse events, and the most common events which occurred, after medical use of cannabinoids.

3. We will discuss the potency and quality of medical cannabis, specifically considering hemp-derived CBD products currently available in Vermont and on the internet.

The University of Vermont
LARNER COLLEGE OF MEDICINE

Science Based Education for Therapeutic Use of Cannabis

Graduate and Professional Programs




## Translational *Cannabis* Science and Medicine at the University of Vermont College of Medicine Department of Pharmacology

Through education we help turn observations in the laboratory, clinic and community into interventions that improve health and bridge scientific discoveries in medical *Cannabis* with the needs of health care providers, researchers, students, and professionals.

https://learn.uvm.edu/com/program/cannabis-science-and-medicine/

# Science Based Education for Therapeutic Use of Cannabis

**CME Overview**

Release Date: November 30, 2016

Expiration Date: November 30, 2019

Length: 60-120 minutes per module

Credits: 1.0-2.0 per module

CME processing fee: Included in module fee

Five online modules with 1-2 hours of content focused on *Cannabis* for therapeutic use may be completed a la carte by qualified medical professionals, or interested individuals 18 years of age or older. Medical professionals can earn Continuing Medical Education (CME) units for each module successfully completed. During registration you will be asked to indicate whether you are taking the module(s) for CMEs or not.

LEARN MORE

http://learn.uvm.edu/com/program/cannabis-science-and-medicine/

**Audience:** Designed for Clinicians, Physicians, Nurse Practitioners, Physician Assistants, and Pharmacists.
**Frequency:** Available on-demand throughout the year by UVM's Department of Pharmacology

**Online Modules:**

1. MEDICO-LEGAL (1.25 hours) – Register for this Module
   - Cannabis History, Policy and Law
   - Public Health – Risks and Potential Benefits

2. BIOLOGY AND BASIC SCIENCE (1.75 hours) – Register for this Module
   - The Endocannabinoid System
   - The Phytocannabinoids and Terpenes

3. CLINICAL PRACTICE 1 – PHYSIOLOGY AND PHARMACOLOGY (2 hours) – Register for this Module
   - Physiological and Adverse Effects
   - Preparations and Dosage

4. CLINICAL PRACTICE 2 –PAIN SYNDROMES (1.5 hours) – Register for this Module
   - Clinical Practice – Chronic pain
   - Clinical Practice – Cancer and Palliative care

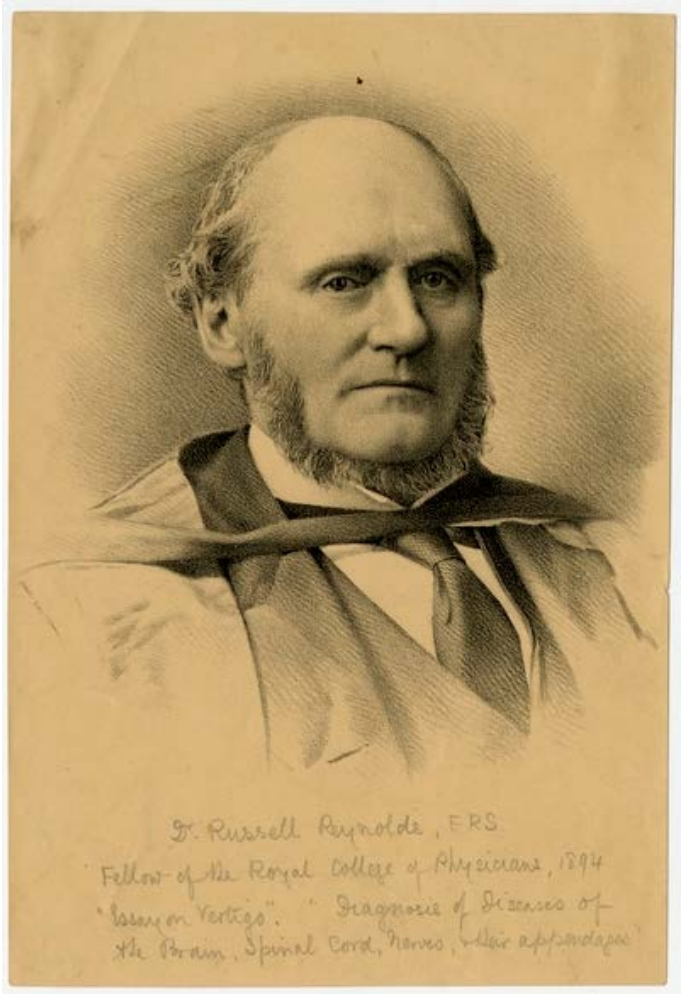
5. CLINICAL PRACTICE 3 – MOTOR DISORDERS (1.25 hours) – Register for this Module
   - Clinical Practice – MS and Parkinson's disease
   - Clinical Practice – Seizures

http://learn.uvm.edu/com/program/cannabis-science-and-medicine/

# “Indian hemp”

In almost all painful maladies I have found Indian hemp by far the most useful of drugs. *The bane of many opiates and sedatives is this, that the relief of the moment, the hour, or the day, is purchased at the expense of tomorrow's misery.* In no one case to which I have administered Indian hemp, have I witnessed any such results.

- Sir John Russell Reynolds, *The Lancet,* 1890




Sir John Russell Reynolds, 1828-1896. British neurologist, president of the Royal College of Physicians, house physician to Queen Victoria. Digital Library- Yale University

Greg Miller. Pot and pain. Science 04 Nov 2016: Vol. 354, Issue 6312, pp. 566-568. DOI: 10.1126/science.354.6312.566

*Hemp Farm, Hardwick VT – Courtesy of Green Mountain CBD*

# Endocannabinoid system

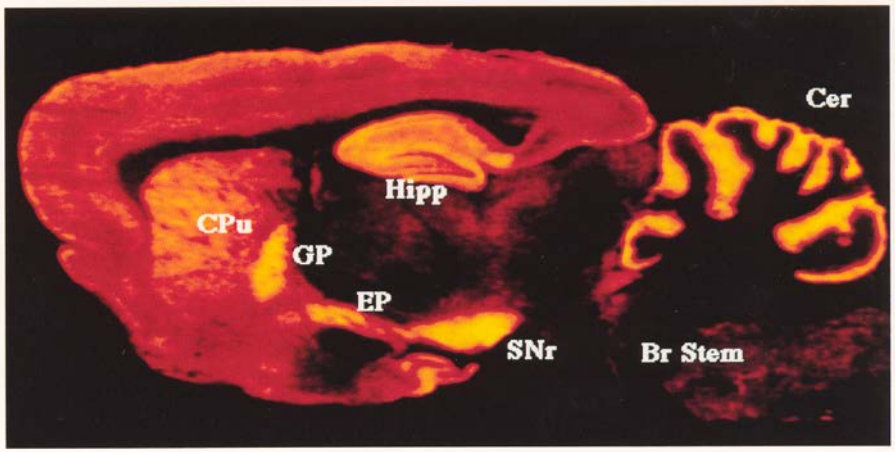
*Cannabis* contains phytocannabinoids which act on the endocannabinoid (eCB) system

The eCB system consists of:

- cannabinoid receptors (CBs)
- endogenous agonists (endocannabinoids)
- agonist-metabolizing enzymes

# Cannabinoid Receptors: $CB_1$ and $CB_2$

- $CB_1$ is primarily expressed in neurons
- $CB_1$ is found in adipose tissue, blood vessels, gut, testes, uterus
- $CB_1$ is *not found* in the brainstem's cardiorespiratory drive centers – which explains the lack of lethal overdoses from cannabis
  - ➢ Unlike opioid receptor distribution




Autoradiograph of rat brain exposed to [$^3$H]CP55,940 (Herkenham *et al.,* 1990).

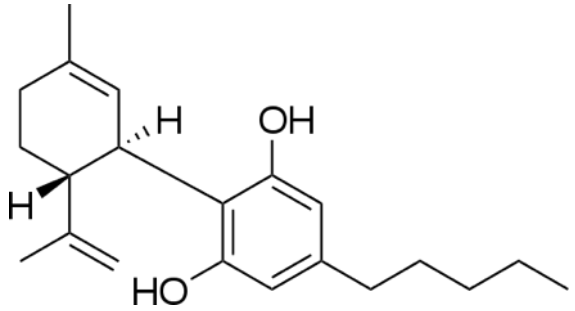
= highest densities in memory centers, limbic system, basal ganglia, cerebellum

= lower densities in cerebral cortex

= lowest densities in the brain stem

$CB_2$ is primarily expressed in the immune system

# Cannabidiol (CBD)




- CBD is the primary naturally-occurring medical compound in hemp and hemp oil
- CBD oils are now widely available in Vermont and on the internet
- It is a cannabinoid -- like THC – but mechanism of action and clinical effects are markedly different
- There is mounting evidence supporting anti-epileptic use of cannabis-derived extracts containing CBD
- CBD alone is used for chronic pain, insomnia, muscle relaxant, and as a health supplement

# Cannabidiol (CBD) activates non-endocannabinoid receptors

- TRPV1 is found in neurons
- TRPV1 involved in pain signal pathways
- Activity decreased with overactivity (desensitization), leading to analgesic effects

Iannotti, F.A. et al., 2014. Chem Neurosci. 5(11):1131-41. doi: 10.1021/cn5000524.

# GW pharmaceuticals phase 3 trials

Sativex® (CBD:THC sublingual spray) trials have provided evidence for therapeutic benefit in cancer pain

American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 13, No 5 (May), 2012: pp 438-449
*Available online at www.jpain.org and www.sciencedirect.com*

# Nabiximols for Opioid-Treated Cancer Patients With Poorly-Controlled Chronic Pain: A Randomized, Placebo-Controlled, Graded-Dose Trial

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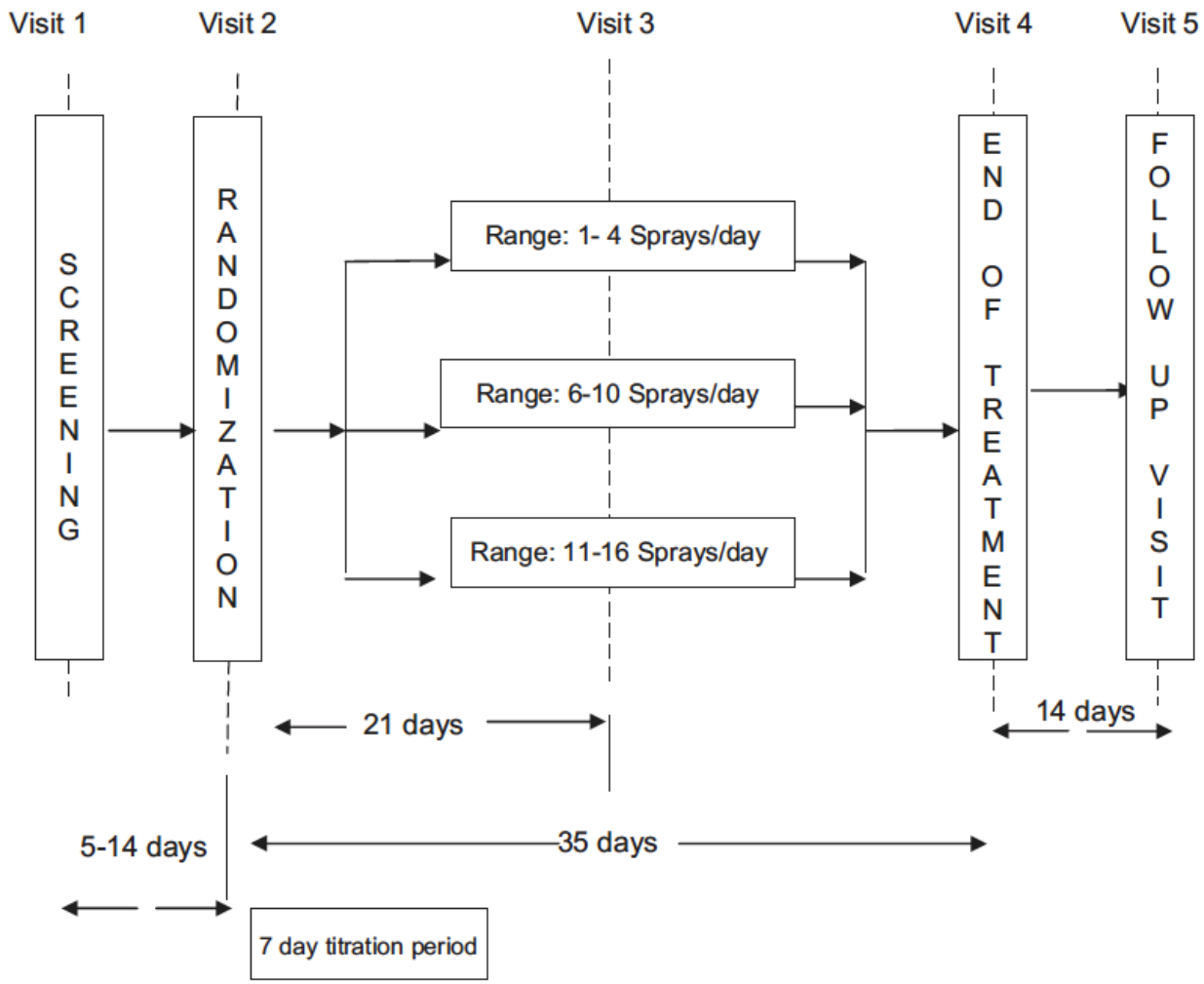



**Figure 1.** Study design.

Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain. 2012 May;13(5):438-49.

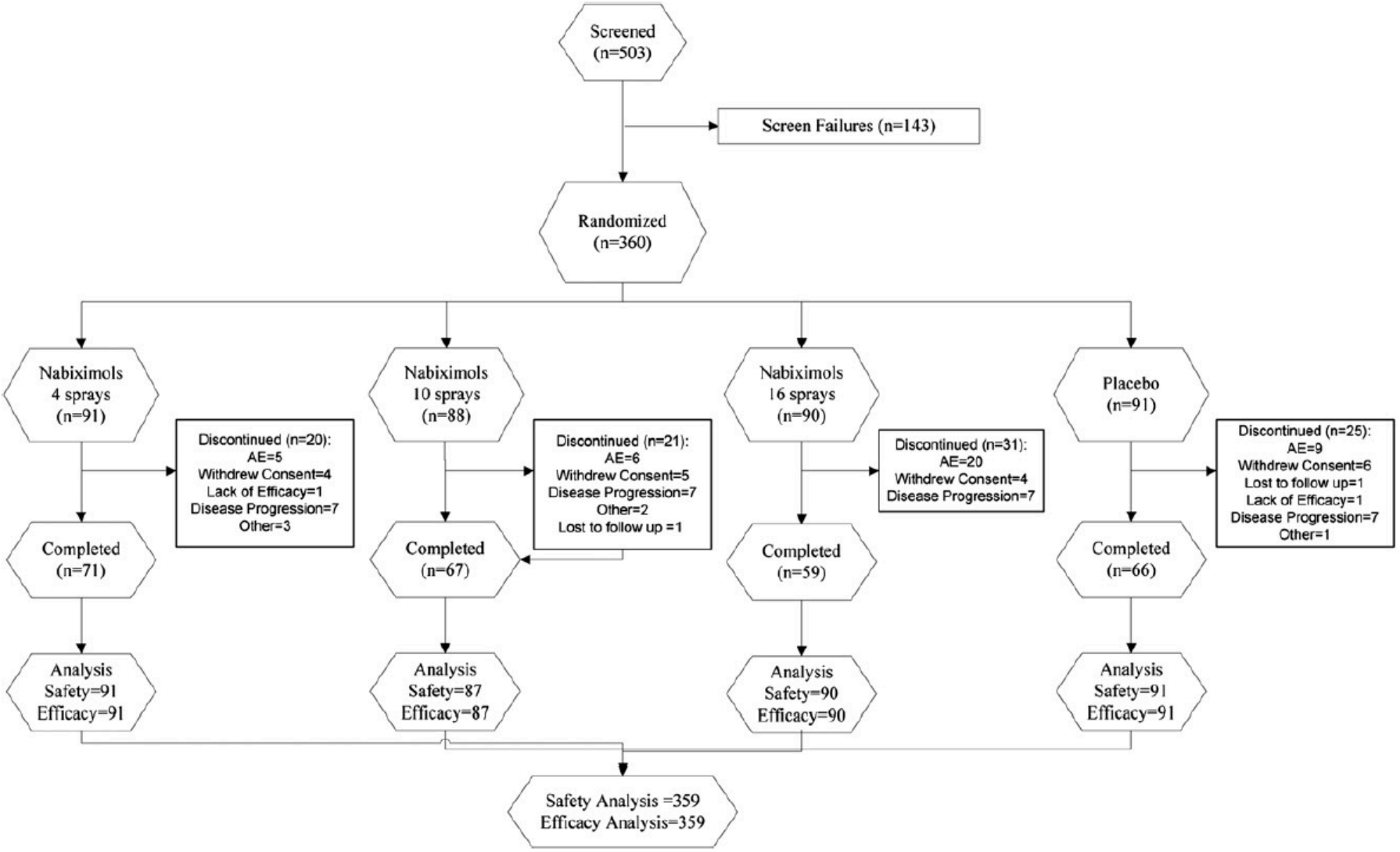



**Figure 2.** Study design CONSORT diagram.

Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain. 2012 May;13(5):438-49.

## Table 3. Primary Cancer Site and Pain Classification

| | Number (Percentage) of Patients | | | | |
|---|---|---|---|---|---|
| | Nabiximols 1–4 Sprays (N = 91) | Nabiximols 6–10 Sprays (N = 88) | Nabiximols 11–16 Sprays (N = 90) | Placebo (N = 91) | Total (N = 360) |
| Primary cancer sites | | | | | |
| Breast | 15 (16.5) | 11 (12.5) | 15 (16.7) | 13 (14.3) | 54 (15.0) |
| Gastrointestinal | 15 (16.5) | 17 (19.3) | 16 (17.8) | 16 (17.6) | 64 (17.8) |
| Lung | 13 (14.3) | 17 (19.3) | 14 (15.6) | 20 (22.0) | 64 (17.8) |
| Prostate | 10 (11.0) | 8 (9.1) | 14 (15.6) | 12 (13.2) | 44 (12.2) |
| Other | 35 (38.5) | 30 (34.1) | 28 (31.1) | 29 (31.9) | 122 (33.9) |
| Unknown | 3 (3.3) | 5 (5.7) | 3 (3.3) | 1 (1.1) | 12 (3.3) |
| Pain classification | | | | | |
| Bone | 20 (22.0) | 15 (17.0) | 34 (37.8) | 17 (18.7) | 86 (23.9) |
| Mixed | 42 (46.2) | 37 (42.0) | 32 (35.6) | 39 (42.9) | 150 (41.7) |
| Neuropathic | 8 (8.8) | 12 (13.6) | 7 (7.8) | 11 (12.1) | 38 (10.6) |
| Somatic | 1 (1.1) | 13 (14.8) | 7 (7.8) | 11 (12.1) | 32 (8.9) |
| Visceral | 20 (22.0) | 11 (12.5) | 10 (11.1) | 13 (14.3) | 54 (15.0) |

Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain. 2012 May;13(5):438-49.

Best results with 4 sprays per day (10mg THC / 10 mg CBD)
Higher doses were not well-tolerated

- more adverse events
- higher drop-out rates.

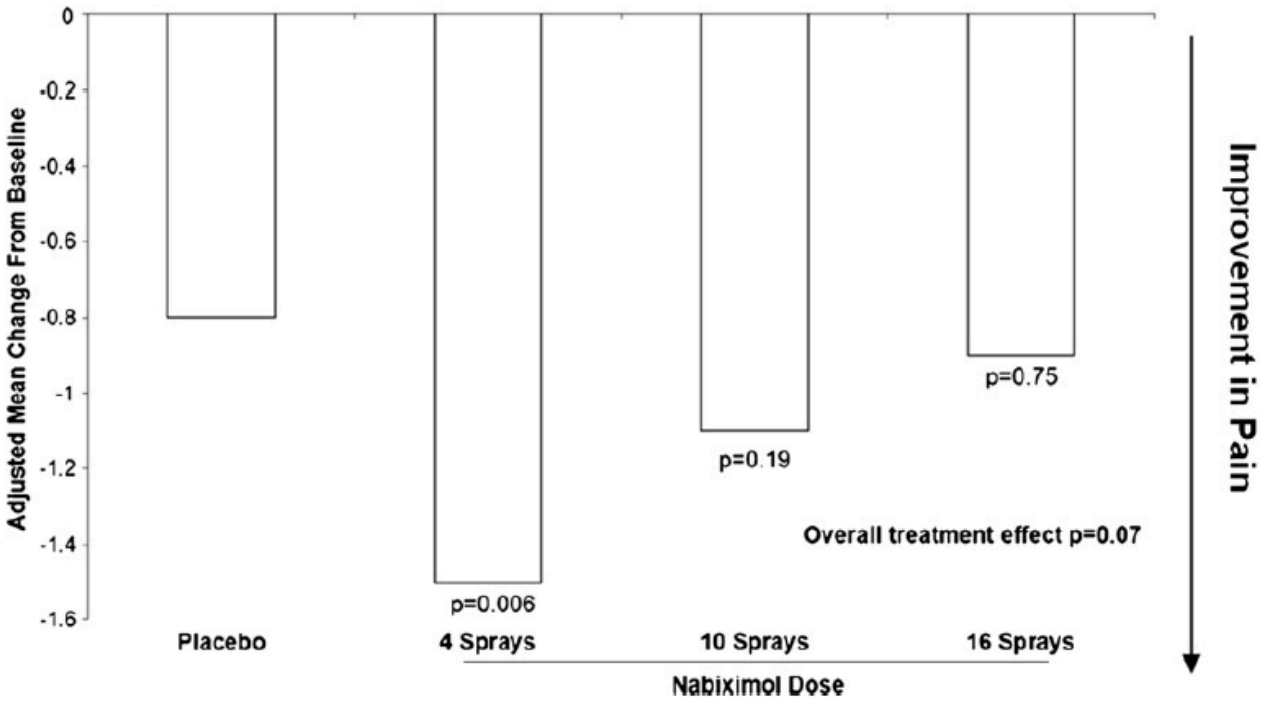



**Figure 4.** Analysis of change from baseline in NRS average pain score.

Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain. 2012 May;13(5):438-49.

**Table 4. Summary of Main Efficacy Results**

| | Treatment Difference/Odds Ratio (P value) | | |
|---|---|---|---|
| | Nabiximols 1–4 Sprays | Nabiximols 6–10 Sprays | Nabiximols 1–16 Sprays |
| 30% Responder rate analysis | 1.37 (.33)* | 1.19 (.61)* | .90 (.76) |
| Cumulative responder analysis | −12.5 (.008)* | −8.75 (.038)* | −1.97 (.675)* |
| Daily average pain NRS | −.75 (.006)* | −.36 (.187)* | −.09 (.750)* |
| Daily mean worst pain NRS | −.73 (.011)* | −.24 (.397)* | −.06 (.829)* |
| Sleep disruption NRS | −.88 (.003)* | −.33 (.260)* | −.08 (.784)* |
| BPI-SF pain severity composite score | −1.30 (.236)* | −1.40 (.119)* | −1.00 (.861)* |
| BPI-SF pain interference composite score | −.90 (.871)* | −1.50 (.088)* | −.90 (.956) |
| PAC-QoL overall score | −.10 (.226)* | −.10 (.493)* | .00 (.139)* |
| PGIC | 1.40 (.268)* | .88 (.664) | .83 (.538) |
| MADRS | −2.40 (.480) | −1.50 (.151) | −1.10 (.083) |
| Opioid composite score | 1.87 (.038)* | 1.70 (.079)* | 1.16 (.622)* |

*Treatment in favor of nabiximols.

Best odds of achieving 30% improvement in pain with Nabiximols (1-4 Sprays) but this was not statistically significant.

In absolute terms, treatment with Nabiximols achieved a 26% improvement in pain.

- Reduction in daily average pain
- Reduction in mean worst pain
- Reduction in sleep disruption

Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain. 2012 May;13(5):438-49.

Original Investigation

# Cannabinoids for Medical Use
## A Systematic Review and Meta-analysis

Penny F. Whiting, PhD; Robert F. Wolff, MD; Sohan Deshpande, MSc; Marcello Di Nisio, PhD; Steven Duffy, PgD; Adrian V. Hernandez, MD, PhD; J. Christiaan Keurentjes, MD, PhD; Shona Lang, PhD; Kate Misso, MSc; Steve Ryder, MSc; Simone Schmidlkofer, MSc; Marie Westwood, PhD; Jos Kleijnen, MD, PhD

*JAMA*. 2015;313(24):2456-2473. doi:10.1001/jama.2015.6358

- Meta-analysis provides compilation of data from randomized clinical trials (RCTs) comparing cannabinoids to placebo for chronic pain and other conditions.
- Also provides best available information about potential for adverse events (AEs) with cannabis [1].
- “Moderate-quality evidence” to support the use of cannabinoids for the treatment of chronic pain and spasticity.
- “Low-quality evidence” suggesting that cannabinoids were associated with improvements in nausea and vomiting due to chemotherapy, weight gain in HIV, sleep disorders, and Tourette syndrome.

Cannabinoids for Medical Use: A Systematic Review and Meta-analysis.JAMA. 2015 Jun 23-30;313(24):2456-73.

- Includes 28 studies of chronic pain (63 reports, 2454 individual participants)

Table 2. Summary Estimates From Meta-analyses of Parallel-Group Studies and Results for Primary Outcomes With Associated GRADE Ratings

| Indication[a] | No. of Studies (No. of Patients) | Cannabinoid (No. of Studies) | Comparator | Outcome[b] | Summary Estimate | Favors | $I^2$, % | GRADE Rating[c] |
|---|---|---|---|---|---|---|---|---|
| Chronic pain (neuropathic and cancer pain) | 8 (1370) | Smoked THC (1), Nabiximols (7) | Placebo | Pain reduction ≥30% NRS or VAS scores Follow-up 2-15 weeks | OR (95% CI), 1.41 (0.99 to 2.00) | CBM | 48 | Moderate |
| | 6 (948) | Nabiximols (6) | Placebo | Pain NRS scores (0-10) Follow-up 2-14 weeks | WMD (95% CI), −0.46 (−0.80 to −0.11) | CBM | 59 | Moderate |
| | 3 (613) | Nabiximols (3) | Placebo | Pain Brief Pain Inventory-Short Form scale (0 to 10) Follow-up 3-15 weeks | WMD (95% CI), −0.17 (−0.50 to 0.16) | CBM | 0 | Moderate |
| | 6 (267) | Nabiximols (5), Nabilone (1) | Placebo | Patient global impression of change Follow-up 3-14 weeks | OR (95% CI), 2.08 (1.21 to 3.59) | CBM | 68 | Low |
| | 5 (764) | Nabiximols (5) | Placebo | Neuropathic pain Neuropathic Pain Scale (0-100) Follow-up 5-15 weeks | WMD (95% CI), −3.89(−7.32 to −0.47) | CBM | 41 | Moderate |
| | 3 (573) | Nabiximols (3) | Placebo | Quality of life EQ-5D scale (0 to 100) Follow-up 12-15 weeks | WMD (95% CI), −0.01 (−0.05 to 0.02) | Placebo | 0 | Moderate |

Abbreviations: ADL, activities of daily living; CBM, cannabis based medicine; EQ-5D, EuroQol Five Dimension Scale; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NA, not applicable; NRS, numerical rating scale; OR, odds ratio; THC, tetrahydrocannabinol; VAS, visual analog scale; WMD, weighted mean difference.

[a] No studies for glaucoma were included in the study estimate. The authors note that THC and cannabidiol were the interventions used in the reviewed glaucoma studies.

[b] Outcome includes the specific indication that was assessed, the means by which assessment was made, and follow-up (not shown for all studies).

[c] GRADE Working Group grades of evidence: (1) high quality, further research is very unlikely to change the group's confidence in the estimate of effect; (2) moderate quality, further research is likely to have an important impact on the group's confidence in the estimate of effect and may change the estimate; (3) low quality, further research is very likely to have an important impact on the group's confidence in the estimate of effect and is likely to change the estimate; (4) very low quality, the group is very uncertain about the estimate.

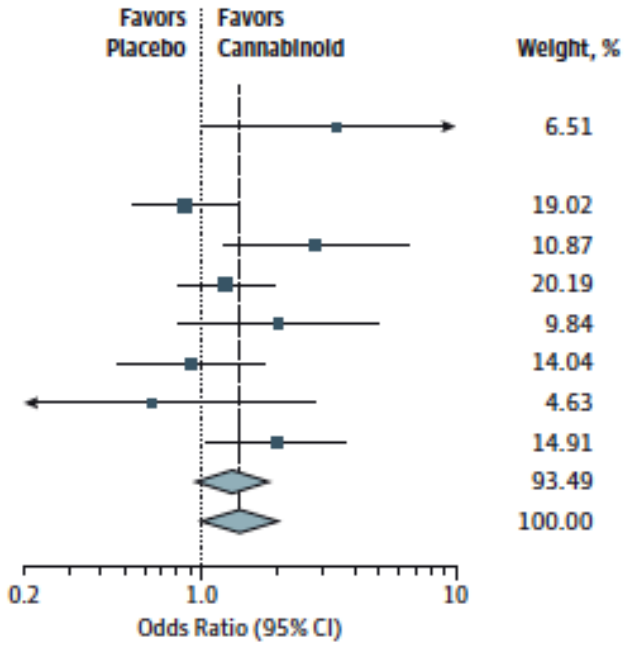
- Interventions including smoked cannabis flower, synthetic THC (Nabilone) and sublingual THC / CBD mix (Nabiximols) compared to placebo.

Cannabinoids for Medical Use: A Systematic Review and Meta-analysis.JAMA. 2015 Jun 23-30;313(24):2456-73.

# “Moderate quality” evidence that cannabis-based medicine reduces pain

**Figure 2. Improvement in Pain**

| Improvement in Pain With Cannabinoid vs Placebo by Study | Cannabinoid Events No. | Cannabinoid Events Total No. | Placebo Events No. | Placebo Events Total No. | Odds Ratio (95% CI) |
|---|---|---|---|---|---|
| Tetrahydrocannabinol (smoked) | | | | | |
| Abrams et al,[77] 2007 | 13 | 25 | 6 | 25 | 3.43 (1.03-11.48) |
| Nabiximols | | | | | |
| GW Pharmaceuticals,[22] 2005 | 54 | 149 | 59 | 148 | 0.86 (0.54-1.37) |
| Johnson et al,[69] 2010 | 23 | 53 | 12 | 56 | 2.81 (1.22-6.50) |
| Langford et al,[65] 2013 | 84 | 167 | 77 | 172 | 1.25 (0.81-1.91) |
| Nurmikko et al,[76] 2007 | 16 | 63 | 9 | 62 | 2.00 (0.81-4.96) |
| Portenoy et al,[67] 2012 | 22 | 90 | 24 | 91 | 0.90 (0.46-1.76) |
| Selvarajah et al,[70] 2010 | 8 | 15 | 9 | 14 | 0.63 (0.14-2.82) |
| Serpell et al,[88] 2014 | 34 | 123 | 19 | 117 | 1.97 (1.05-3.70) |
| Subtotal $I^2$=44.5%, ($P$=.0.94) | 241 | 660 | 209 | 660 | 1.32 (0.94-1.86) |
| **Overall** $I^2$=47.6%, ($P$=.0.64) | 254 | 685 | 215 | 685 | 1.41 (0.99-2.00) |




Odds indicate 30% or greater improvement in pain with cannabinoid compared with placebo, stratified according to cannabinoid. The square data markers indicate odds ratios (ORs) from primary studies, with sizes reflecting the statistical weight of the study using random-effects meta-analysis. The horizontal lines indicate 95% CIs. The blue diamond data markers represent the subtotal and overall OR and 95% CI. The vertical dashed line shows the summary effect estimate, the dotted shows the line of no effect (OR = 1).

Cannabinoids for Medical Use: A Systematic Review and Meta-analysis.JAMA. 2015 Jun 23-30;313(24):2456-73.

# Summary Estimates of Adverse Events (AEs)

Meta-analysis provides a pooled analysis for adverse events (AE) associated with medical trials using cannabinoids.

*Results: cannabinoids were associated with approximately 3x increased odds of any AE compared to placebo.*

Odds of most common AEs, relative to placebo:

- Dizziness (5x)
- Disorientation (5x)
- Confusion (4x)
- Drowsiness (4x)
- Euphoria (4x)
- Dry Mouth (3x)
- Somnolence (3x)
- Asthenia (2x)
- Anxiety (2x)
- Balance (2x)
- Hallucination (2x)
- Paranoia (2x)

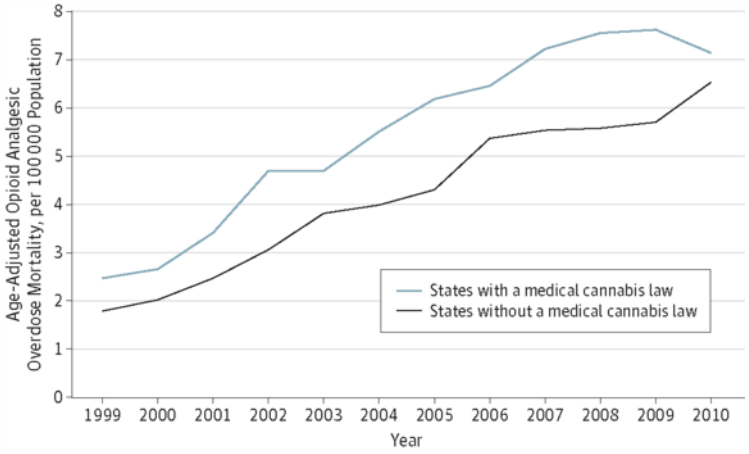
**Table 3. Summary Estimates From Meta-analyses for Each AE Assessed: Odds of Participants Experiencing AE With Cannabinoid vs Placebo or Active Comparison**

| | No. of Studies (No. of Patients) | Summary OR (95% CI) | $I^2$, % |
|---|---|---|---|
| General AE categories | | | |
| Any | 29 (3714) | 3.03 (2.42-3.80) | 31 |
| Serious | 34 (3248) | 1.41 (1.04-1.92) | 0 |
| Withdrawal due to AE | 23 (2755) | 2.94 (2.18-3.96) | 2 |
| MedDRA high-level grouping[164] | | | |
| Gastrointestinal disorders | 10 (1960) | 1.78 (1.43-2.22) | 0 |
| Infections and infestations | 7 (1681) | 1.13 (0.87-1.46) | 0 |
| Psychiatric disorders | 8 (1672) | 3.10 (1.81-5.29) | 55 |
| Nervous system disorders | 10 (1521) | 3.17 (2.20-4.58) | 46 |
| Musculoskeletal and connective tissues disorders | 7 (1310) | 1.32 (0.75-2.32) | 34 |
| General disorders and administration site conditions | 6 (1208) | 1.78 (1.34-2.36) | 0 |
| Death | 5 (929) | 1.01 (0.51-2.00) | 0 |
| Ear and labyrinth disorders | 3 (922) | 2.72 (1.55-4.75) | 0 |
| Respiratory, thoracic, and mediastinal disorders | 5 (851) | 0.80 (0.46-1.39) | 0 |
| Cardiac disorders | 7 (833) | 1.42 (0.58-3.48) | 0 |
| Blood disorders | 3 (543) | 1.42 (0.20-10.25) | 18 |
| Injury, poisoning and procedural complications | 3 (543) | 1.18 (0.48-2.93) | 0 |
| Renal and urinary disorders | 3 (470) | 2.45 (2.27-2.65) | 0 |
| Investigations | 2 (427) | 1.55 (0.36-6.71) | 0 |
| Metabolism and nutrition | 2 (427) | 2.37 (1.00-5.61) | 0 |
| Neoplasms, benign, malignant, and unspecified | 2 (427) | 0.99 (0.47-2.08) | 0 |
| Skin and subcutaneous | 3 (405) | 0.85 (0.34-2.13) | 0 |
| Eye disorders | 1 (339) | 1.42 (0.46-4.33) | NA |
| Reproductive system | 1 (246) | 1.55 (0.20-11.92) | NA |
| Hepatobiliary disorders | 1 (181) | 3.07 (0.12-76.29) | NA |
| Mental status change | 3 (106) | 2.49 (0.49-12.64) | 0 |
| Other body systems | 1 (42) | 2.59 (0.34-19.47) | NA |
| Injection site pain | 1 (32) | 2.49 (0.92-6.68) | NA |
| Individual AEs | | | |
| Dizziness | 41 (4243) | 5.09 (4.10-6.32) | 18 |
| Dry mouth | 36 (4181) | 3.50 (2.58-4.75) | 28 |
| Nausea | 30 (3579) | 2.08 (1.63-2.65) | 0 |
| Fatigue | 20 (2717) | 2.00 (1.54-2.62) | 0 |
| Somnolence | 26 (3168) | 2.83 (2.05-3.91) | 27 |
| Euphoria | 27 (2420) | 4.08 (2.18-7.64) | 49 |
| Depression | 15 (2353) | 1.32 (0.87-2.01) | 0 |
| Vomiting | 17 (2191) | 1.67 (1.13-2.47) | 0 |
| Diarrhea | 17 (2077) | 1.65 (1.04-2.62) | 15 |
| Disorientation | 12 (1736) | 5.41 (2.61-11.19) | 0 |
| Asthenia | 15 (1717) | 2.03 (1.35-3.06) | 0 |
| Drowsiness | 18 (1272) | 3.68 (2.24-6.01) | 44 |
| Anxiety | 12 (1242) | 1.98 (0.73-5.35) | 54 |
| Confusion | 13 (1160) | 4.03 (2.05-7.97) | 0 |
| Balance | 6 (920) | 2.62 (1.12-6.13) | 0 |
| Hallucination | 10 (898) | 2.19 (1.02-4.68) | 0 |
| Dyspnea | 4 (375) | 0.83 (0.26-2.63) | 0 |
| Paranoia | 4 (492) | 2.05 (0.42-10.10) | 0 |
| Psychosis | 2 (37) | 1.09 (0.07-16.35) | 25 |
| Seizures | 2 (42) | 0.91 (0.05-15.66) | 0 |

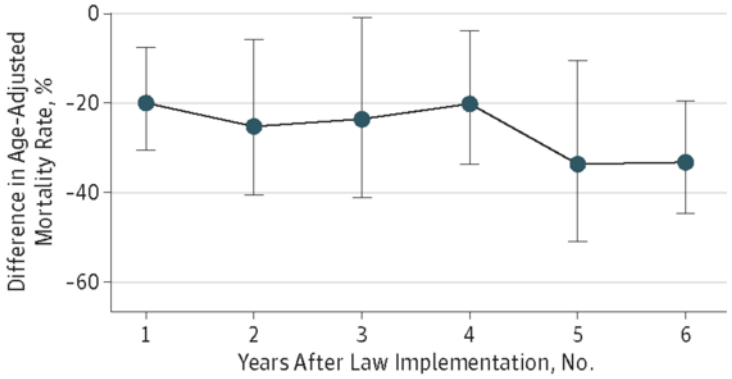
Cannabinoids for Medical Use: A Systematic Review and Meta-analysis.JAMA. 2015 Jun 23-30;313(24):2456-73.

# States with medical *Cannabis* laws have significantly lower state-level opioid overdose mortality rates

- A time-series analysis was conducted of medical cannabis laws and state-level death certificate data in the United States from 1999 to 2010; all 50 states were included.
- Results showed states with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate (95% CI, −37.5% to −9.5%; *P* = .003) compared with states without medical cannabis laws.
- The association between medical cannabis laws and opioid analgesic overdose mortality in each year after implementation of the law strengthened over time




Mean Age-Adjusted Opioid Analgesic Overdose Death Rate. States with medical cannabis laws compared with states without such laws in the United States, 1999-2010.




Association Between Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in Each Year After Implementation of Laws in the United States, 1999-2010. Point estimate of the mean difference in the opioid analgesic overdose mortality rate in states with medical cannabis laws compared with states without such laws; whiskers indicate 95% CIs.

Bachhuber MA et al. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. JAMA Intern Med. 2014 Oct;174(10):1668-73.

# Substitution of cannabis for opioids in chronic pain

- Online survey of 244 medical cannabis patients with chronic pain to examine whether medical cannabis changed individual patterns of opioid use
- N=184 analyzed
- Found that cannabis was associated with
  - Decrease in opioid use (65%)
  - Decreases in other medications
  - Improved quality of life (45%)



Boehnke KF, et al. Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain. J Pain. 2016 Jun;17(6):739-44. doi: 10.1016/j.jpain.2016.03.002. PMID: 27001005

# Cannabis as a substitute for opioids

- Opioids are ineffective for chronic pain and yet they are widely prescribed
- Chronic pain patients may successfully substitute cannabis for opioids and other drugs used for chronic pain
- Patients have improved side effect profile and benefits with cannabis-based medicine compared to other classes of medications

1. Boehnke KF, et al. Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain. J Pain. 2016 Jun;17(6):739-44. doi: 10.1016/j.jpain.2016.03.002. PMID: 27001005

# Cannabidiol in treatment-resistant epilepsy

- Multicenter study of 10 centers treating children with CBD (average age 10.5 years)
- Total enrollment of 214 subjects
- Open-label (no placebo control or randomization)
- Patients received 99% pure oil-based CBD extract (Epidiolex, GW Pharmaceuticals, London, UK) in a 100 mg per mL sesame oil-based solution orally or by gastric tube.
- 2–5 mg/kg/day divided in twice-daily dosing added to baseline antiepileptic drug regimen, then up-titrated by 2–5 mg/kg once a week until intolerance or a maximum dose of 25 mg/kg/day was reached.

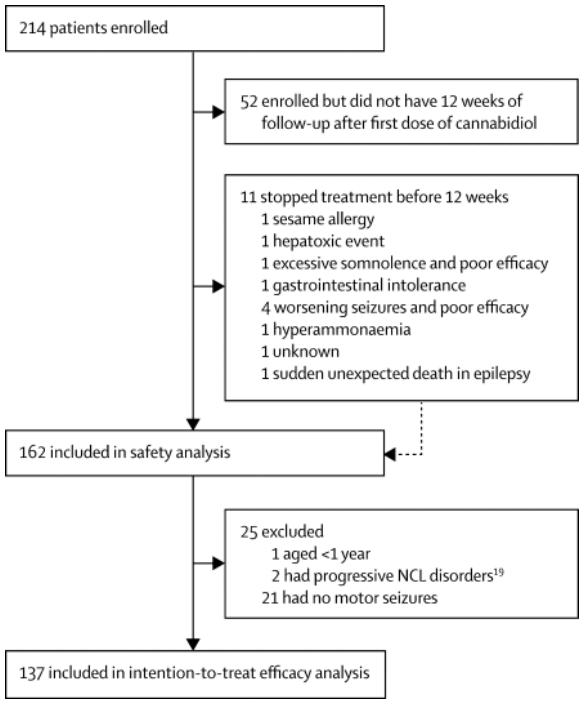



Figure 1. Trial profile NCL=neuronal ceroid lipofucinosis.

Devinsky O, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. Lancet Neurol. 2016 Mar;15(3):270-8. doi: 10.1016/S1474-4422(15)00379-8. PMID: 26724101

# Efficacy

- Among all subjects, the median frequency of motor seizures dropped from 30·0 per month (IQR 11·0–96·0) at baseline to15·8 per month (5·6–57·6) over the 12 week treatment period (Figure 2).
- For individual subject, the median reduction in monthly motor seizures was 36·5% (IQR 0–64·7) (Figure 3).

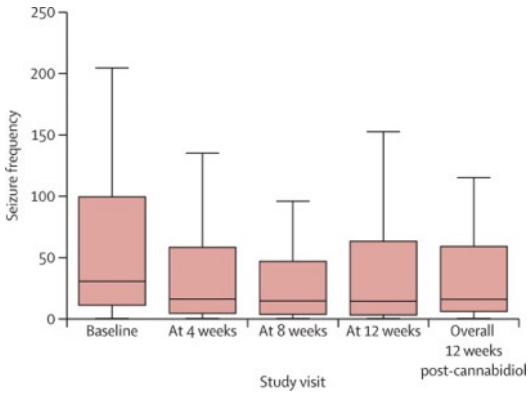



Figure 2. Monthly frequency of motor seizures in patients in the efficacy analysis group (n=137). Boxplots show median values, with 25th and 75th percentiles. The whiskers denote the 25th percentile – 1·5 × IQR and the 75th percentile + 1·5 × IQR.

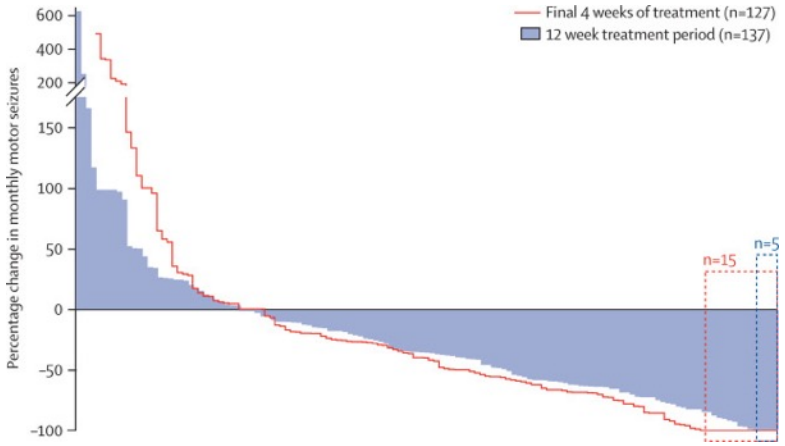



Figure 3. Percentage change in monthly frequency of motor seizures in patients in the efficacy analysis group (n=137). Percentage changes for each patient are ordered from greatest increase to greatest decrease. The dashed boxes indicate patients who became free of that seizure type during the 12 week treatment period (blue) or the last 4 weeks of treatment (red).

1. Devinsky O, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. Lancet Neurol. 2016 Mar;15(3):270-8. doi: 10.1016/S1474-4422(15)00379-8. PMID: 26724101

# Safety

- Adverse events reported in 128 (79%) of 162 patients within the safety group.
- AEs that occurred in more than 10% of patients:
  somnolence (n=41 [25%]) decreased appetite (n=31 [19%]) diarrhea (n=31 [19%])
  fatigue (n=21 [13%])
  convulsion (n=18 [11%])
- Five (3%) patients discontinued
- Serious AEs were reported in 48 (30%) patients, including one death—a sudden unexpected death in epilepsy regarded as unrelated to study drug.
- 20 (12%) patients had severe adverse events possibly related to cannabidiol use.

Table 3.
Adverse events and treatment-emergent serious adverse events

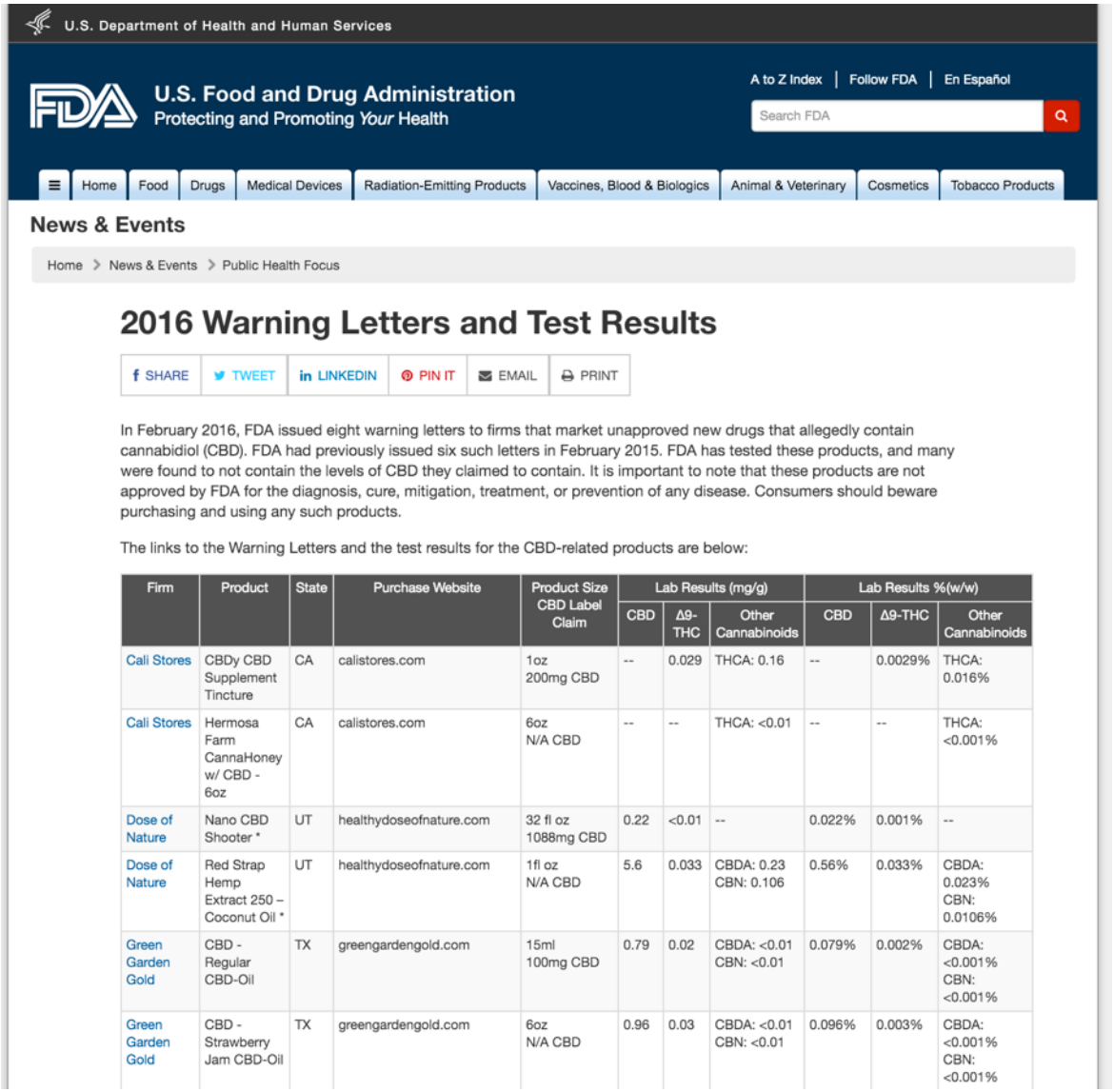
| | Safety analysis group (n=162) |
|---|---|
| **Adverse events (reported in >5% of patients)** | |
| Somnolence | 41 (25%) |
| Decreased appetite | 31 (19%) |
| Diarrhoea | 31 (19%) |
| Fatigue | 21 (13%) |
| Convulsion | 18 (11%) |
| Increased appetite | 14 (9%) |
| Status epilepticus | 13 (8%) |
| Lethargy | 12 (7%) |
| Weight increased | 12 (7%) |
| Weight decreased | 10 (6%) |
| Drug concentration increased | 9 (6%) |
| **Treatment-emergent serious adverse events*** | |
| Status epilepticus | 9 (6%) |
| Diarrhoea | 3 (2%) |
| Weight decreased | 2 (1%) |
| Convulsion | 1 (<1%) |
| Decreased appetite | 1 (<1%) |
| Drug concentration increased | 1 (<1%) |
| Hepatotoxicity | 1 (<1%) |
| Hyperammonaemia | 1 (<1%) |
| Lethargy | 1 (<1%) |
| Unspecified pneumonia | 1 (<1%) |
| Aspiration pneumonia | 1 (<1%) |
| Bacterial pneumonia | 1 (<1%) |
| Thrombocytopenia | 1 (<1%) |

Data are n (%). One patient might have had more than one serious adverse event.

* Reported by the investigator to be possibly related to cannabidiol use.

1. Devinsky O, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. Lancet Neurol. 2016 Mar;15(3):270-8. doi: 10.1016/S1474-4422(15)00379-8. PMID: 26724101

# How does a patient in VT get CBD?



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## 2016 Warning Letters and Test Results

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In February 2016, FDA issued eight warning letters to firms that market unapproved new drugs that allegedly contain cannabidiol (CBD). FDA had previously issued six such letters in February 2015. FDA has tested these products, and many were found to not contain the levels of CBD they claimed to contain. It is important to note that these products are not approved by FDA for the diagnosis, cure, mitigation, treatment, or prevention of any disease. Consumers should beware purchasing and using any such products.

The links to the Warning Letters and the test results for the CBD-related products are below:

| Firm | Product | State | Purchase Website | Product Size CBD Label Claim | Lab Results (mg/g) | | | Lab Results %(w/w) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | CBD | Δ9-THC | Other Cannabinoids | CBD | Δ9-THC | Other Cannabinoids |
| Cali Stores | CBDy CBD Supplement Tincture | CA | calistores.com | 1oz 200mg CBD | -- | 0.029 | THCA: 0.16 | -- | 0.0029% | THCA: 0.016% |
| Cali Stores | Hermosa Farm CannaHoney w/ CBD - 6oz | CA | calistores.com | 6oz N/A CBD | -- | -- | THCA: <0.01 | -- | -- | THCA: <0.001% |
| Dose of Nature | Nano CBD Shooter * | UT | healthydoseofnature.com | 32 fl oz 1088mg CBD | 0.22 | <0.01 | -- | 0.022% | 0.001% | -- |
| Dose of Nature | Red Strap Hemp Extract 250 – Coconut Oil * | UT | healthydoseofnature.com | 1fl oz N/A CBD | 5.6 | 0.033 | CBDA: 0.23 CBN: 0.106 | 0.56% | 0.033% | CBDA: 0.023% CBN: 0.0106% |
| Green Garden Gold | CBD - Regular CBD-Oil | TX | greengardengold.com | 15ml 100mg CBD | 0.79 | 0.02 | CBDA: <0.01 CBN: <0.01 | 0.079% | 0.002% | CBDA: <0.001% CBN: <0.001% |
| Green Garden Gold | CBD - Strawberry Jam CBD-Oil | TX | greengardengold.com | 6oz N/A CBD | 0.96 | 0.03 | CBDA: <0.01 CBN: <0.01 | 0.096% | 0.003% | CBDA: <0.001% CBN: <0.001% |

# FDA and Dietary Supplements

- State medical cannabis programs provide CBD products
- Warnings and regulatory challenges with sales of CBD oil that do not actually contain CBD
- Dietary supplements cannot claim to “treat, prevent or cure a disease”.
- The FDA has granted “Investigational New Drug” status to CBD for GW Pharma’s research program
- Because of this IND ruling, the “FDA has concluded that cannabidiol products are excluded from the dietary supplement definition under section 201(ff)(3)(B)(ii) of the FD&C Act”.
- Under that provision, if a substance (such as cannabidiol) has been authorized for investigation as a new drug for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, then products containing that substance are outside the definition of a dietary supplement.

*CBD is not yet FDA approved as a drug; yet, it cannot be considered a dietary supplement, since it is currently being studied.*

# CBD products available in VT in 2017



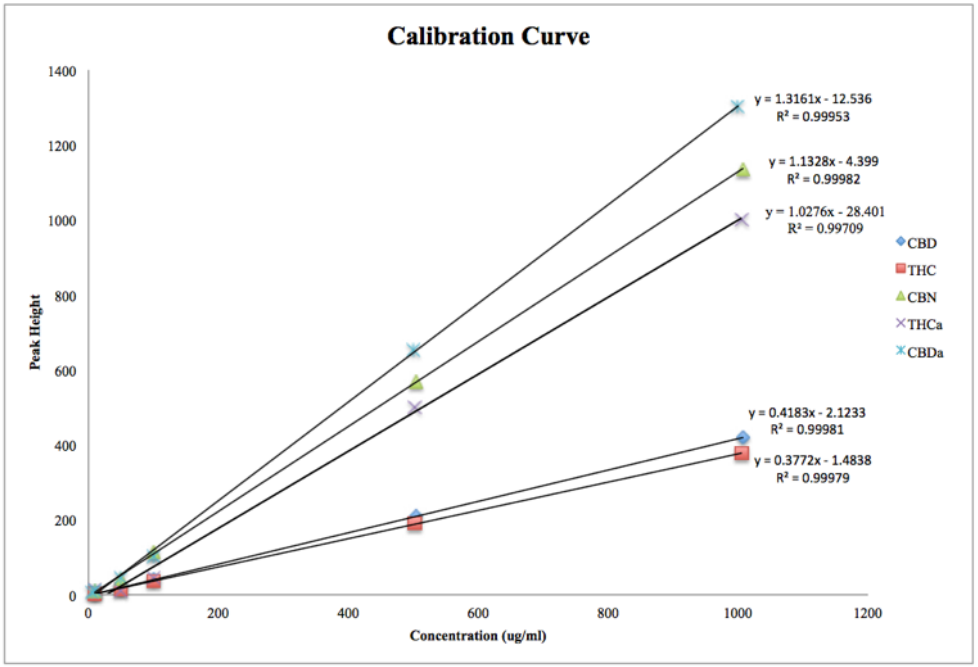

# Research Objective

- Previous studies have shown wide variability in dosing and accuracy of labeling in medical cannabis products [1].
- There is currently no state or federal oversight of the labeling or the composition of marketed products.
- The objective of this research was to examine the cannabinoid potency of CBD products available in Vermont and the accuracy of the dosage suggested on their product labels.

[1] Vandrey R, et al. Cannabinoid Dose and Label Accuracy in Edible Medical Cannabis Products. *JAMA*. June 23/30, 2015 Volume 313, Number 24.

# Methods

- Twenty-four CBD products were purchased in Vermont and tested for potency.
- Analysis of cannabinoid content performed using Investigator SFC system equipped with an auto injector (Waters Corp). Each sample was tested three times.
- Analytical results were compared to the product labels.



# Results (1) (*unpublished*)

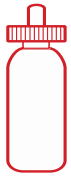
**Sample size:** Out of 28 stores surveyed, 22 carried CBD products, 6 did not. A total (n) of 24 products were purchased from 11 stores, including 14 national brands and 10 Vermont brands.

**Delivery methods:** Of 24 products, 7 were capsules, 11 were tinctures, 3 were cartridges, and 3 were concentrates.

**CBD presence in products:** 24/24 products contained CBD or CBDa.

**Bioavailability of CBD:** 24/24 products contained bioavailable CBD. Measurable CBDa, which is not bioavailable, was found in 13/24 products. 1/24 products was predominantly composed of CBDa.

**THC presence in products:** Generally, THC levels were below 0.3%. 11/ 24 products had measurable THC. 1/24 products measured above 0.3%, at 0.8%.



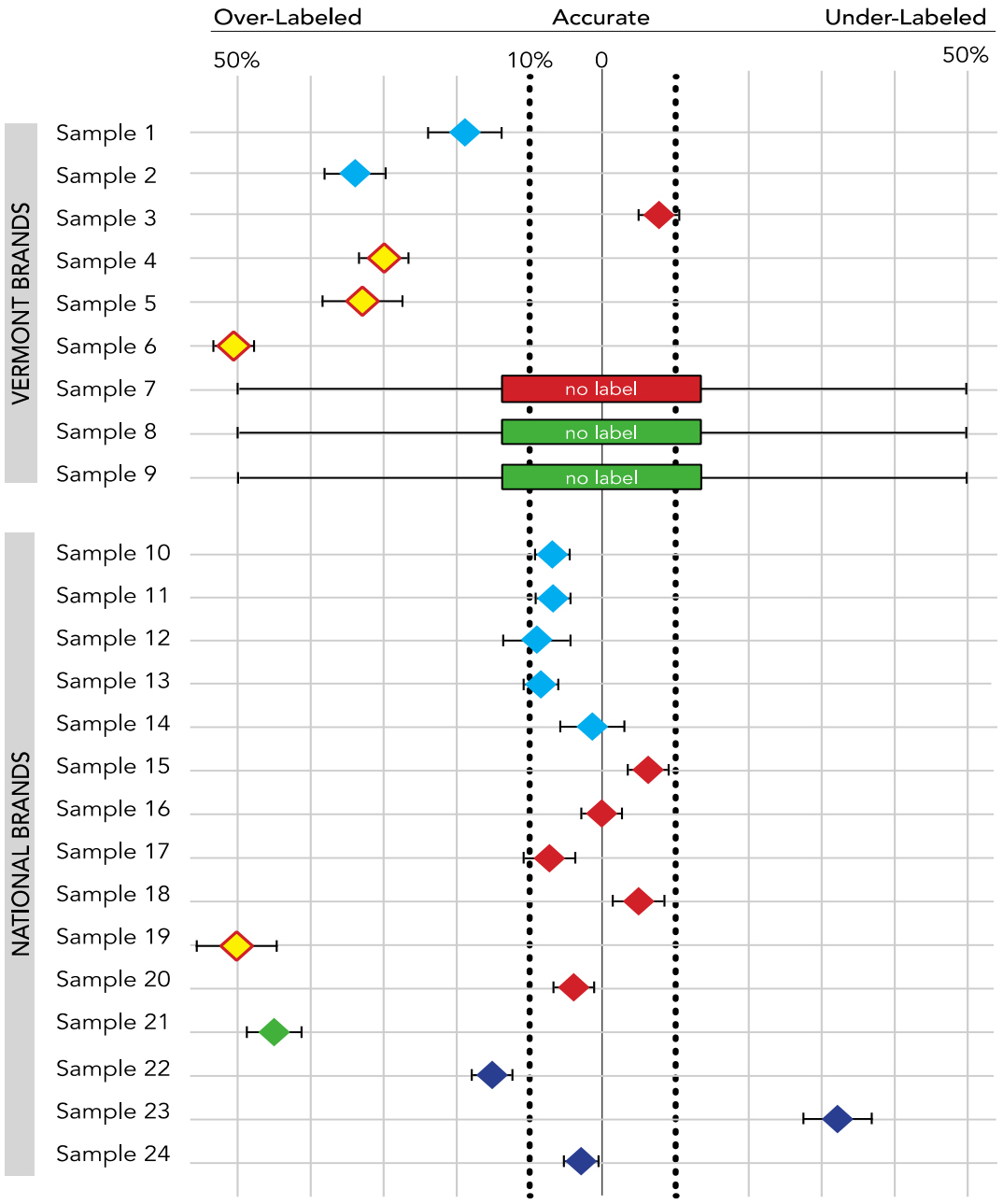
g

**concentrates**
n=3
dose range: unlabeled
% potency range: 47.99-77.07%
mean: 63.81%

# Results (2) (*unpublished*)

**Accuracy of labels:**
50% of products were labeled accurately (within 10% of the reported potency)

- 12/24 products were accurately labeled (test results were within 10% of CDB reported on label)
- 1/24 products were under labeled (test results were 10% more than CBD reported on label)
- 8/24 products were over labeled (test results were 10% less than CBD reported on label)
- 3/24 products were un-labeled



# Conclusions – CBD extracts in VT

- All products contained measurable CBD - *but not all bioavailable* – and only 50% were accurately labeled.
- Delivery method appears to impact accuracy of the labeled dose.
  - Capsules were the most accurate, followed by tinctures.
  - Concentrates and cartridges were difficult to compare due to limited labeling.
  - Tinctures with labels that recommended a dose of “one full dropper” or “a single drop” were more accurate than tinctures with labels that that recommended a multi-drop dose.
- National-brand labels were more accurate than Vermont-brand labels.
  - Of the 14 national-brand products, 11 were labeled accurately, 3 were over-labeled, and 1 was under-labeled.
  - Of the 10 Vermont-brand products, 1 product was labeled accurately, 9 were over-labeled, and 3 had no labels.

Further research and testing is required to assess additional quality measures and safety of products. This study did not include analysis of pesticides, residual solvents, heavy metals, toxins, or microbes.

# Labeling Accuracy of Cannabidiol Extracts Sold Online

## Eighty-four products were purchased and analyzed (from 31 companies)

**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.

Marcel O. Bonn-Miller, PhD et al. JAMA. Nov 7, 2017;318(17):1708-1709.

**Table 2. Observed Cannabinoid Concentration of 84 Tested Extract Products Sold Online**

| Cannabinoid | Average Observed Concentration Across Tests, mg/mL | |
|---|---|---|
| | Mean (SD) | Median (Range) |
| Cannabidiol[a] | 30.96 (80.86) | 9.45 (0.10-655.27) |
| Cannabidiolic acid | 1.35 (6.74) | 0 (0-55.73) |
| Cannabigerol | 0.08 (0.55) | 0 (0-4.67) |
| Cannabinol | 0 | 0 |
| Δ-9-Tetrahydrocannabinol | 0.45 (1.18) | 0 (0-6.43) |
| Δ-9-Tetrahydrocannabibolic acid | 0 | 0 |

[a] The mean labeled concentration for cannabidiol was 36.86 mg/mL (SD, 96.56) and the median was 15.00 mg/mL (range, 1.33-800.0).

Marcel O. Bonn-Miller, PhD et al. JAMA. Nov 7, 2017;318(17):1708-1709.

# Discussion

- Wide range of CBD concentrations / lack of an accepted dose.
- 26% of products contained less CBD than labeled
- “Overlabeling of CBD products similar in magnitude to levels that triggered warning letters to 14 businesses from the US Food and Drug Administration (eg, actual CBD content was negligible or less than 1% of the labeled content)”
- “Underlabeling is less concerning as CBD appears to neither have abuse liability nor serious adverse consequences at high doses, but the THC content observed may be sufficient to produce intoxication or impairment, especially among children.”
- Continued need for regulatory agencies (federal, state?) to take steps to ensure label accuracy of consumer products.

Marcel O. Bonn-Miller, PhD et al. JAMA. Nov 7, 2017;318(17):1708-1709.

# Learning objectives

1. According to the “Cannabinoids for Medical Use: A Systematic Review and Meta-analysis” published in JAMA 2015, there is evidence supporting therapeutic use of cannabinoids for 6 medical conditions. We will discuss the evidence basis for cannabinoids in these conditions. We will also discuss emerging evidence for CBD in pediatric epilepsy.

2. The systematic review and meta-analysis also showed that adverse events with cannabis use were significantly higher than placebo. We will review the odds of experiencing adverse events, and the most common events which occurred, after medical use of cannabinoids.

3. We will discuss the potency and quality of medical cannabis, specifically considering hemp-derived CBD products currently available in Vermont and on the internet.

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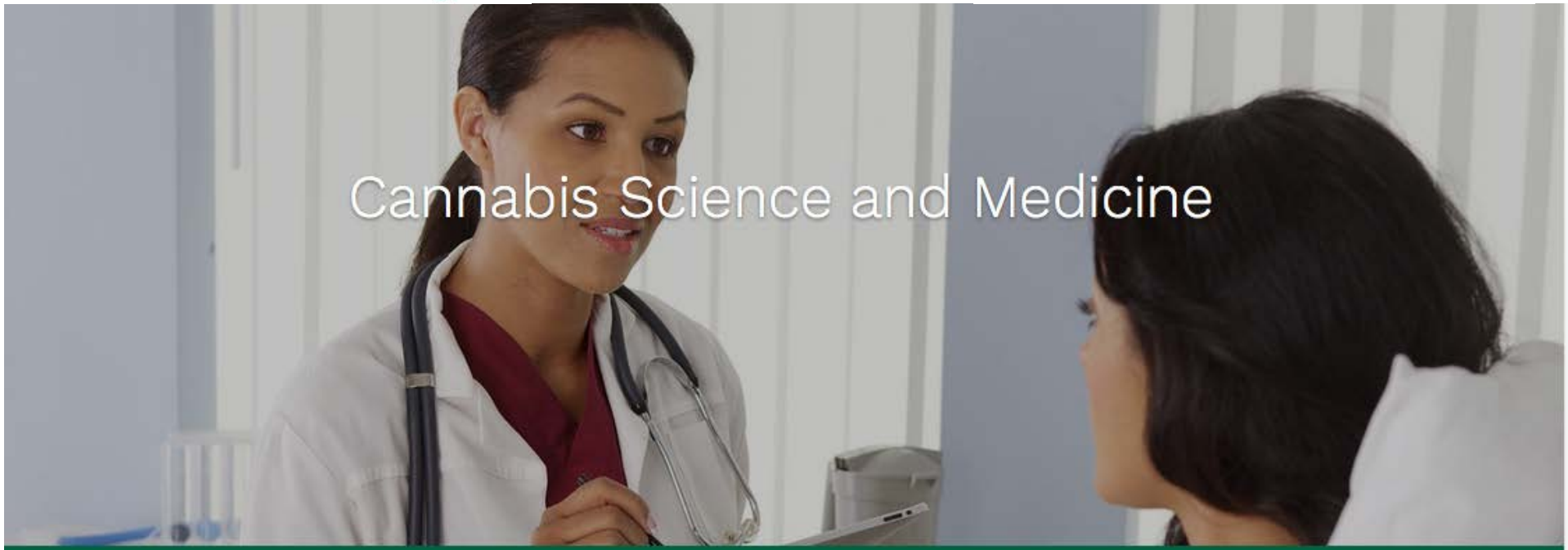


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Through education we help turn observations in the laboratory, clinic and community into interventions that improve health and bridge scientific discoveries in medical *Cannabis* with the needs of health care providers, researchers, students, and professionals.

https://learn.uvm.edu/com/program/cannabis-science-and-medicine/