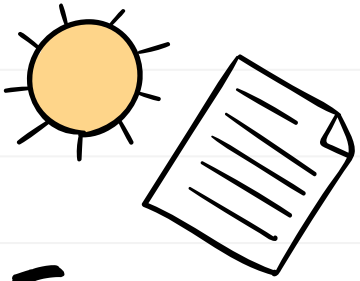
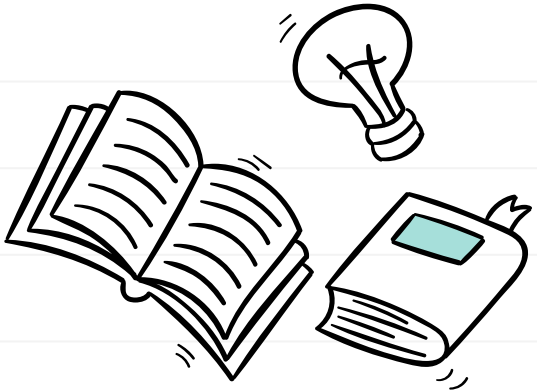
# UPDATE IN THE MEDICAL USE OF CANNABIS

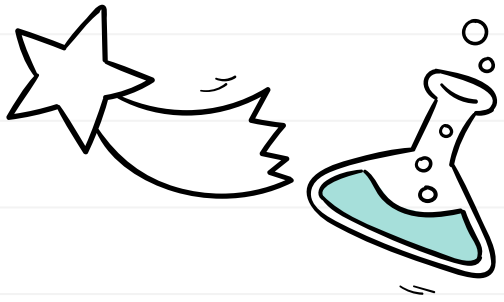


# Update in medical use of cannabis



Chularat Noinonthong
Jirapa Weeranithan

ADVISOR:
Somchai Amornyothin



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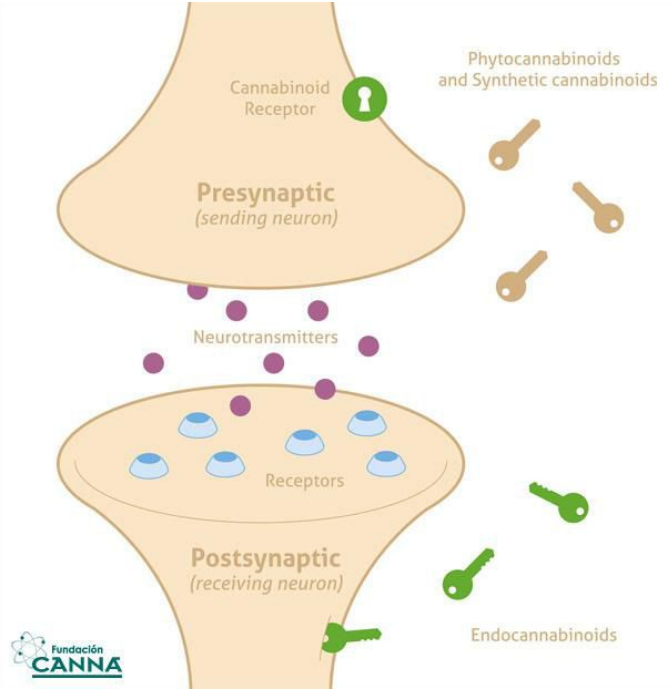
# Definition

- Cannabis “the cannabis plant”
- Cannabinoid “substance that bind to cannabinoid receptors
    - Endocannabinoid “body’s own cannabinoid”
    - Phytocannabinoid “from cannabis plant”
    - Synthetic cannabinoid

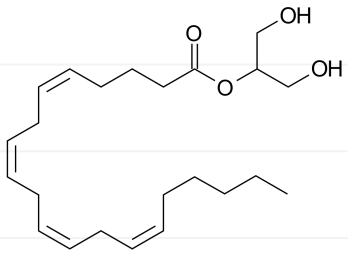
# Endocannabinoid system

- Endocannabinoids
- Cannabinoid receptors (CBr)
- Enzymes from the cannabinoid system  (ECS)

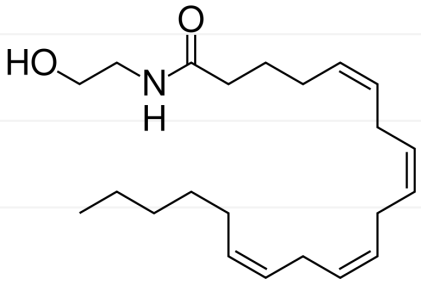


# Endocannabinoid

- 2-archidonoylglycerol (2-AG)




- anandamide



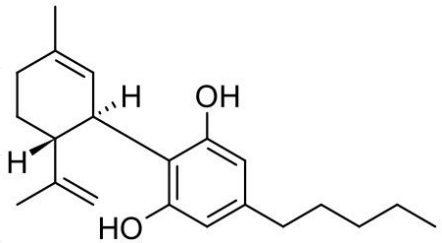
# Endocannabinoid receptors

- CB1 receptors highly concentrated in brain regions related to executive function, memory, cognition, mood, pain perception, and movement. They are also found in the heart, intestines, and bladder.

- CB2 receptors — found in the spleen, tonsils, thymus gland, bones, skin, and blood (monocytes, macrophages, B-cells and T-cells).

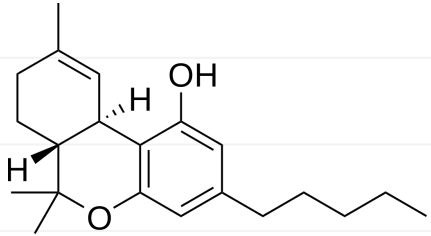
# Phytocannabinoid

- CBD - cannabidiol “non-psycoactive”




  - Very low affinity for CB1 and CB2

- THC -tetrahydrocannabinol “psycoactive”




  - Higher affinity CB1 and CB2 than CBD

# Pharmacokinetics & Pharmacodynamics

- Highly lipid soluble- accumulate in fatty tissue
- THC & CBD are metabolised in liver through CYP450
- Metabolised and excreted via urine and faeces

# Route of administration

**Table 1**
Cannabis routes of administration.

| Cannabis routes of administration | | | |
|---|---|---|---|
| Smoking | Vaporisation | Oral | Other routes |
| • Most common route of administration, but not recommended (joints, bongs, pipes, etc.)<br>• Combustion at 600–900 °C producing toxic biproducts: tar, PAH (polycyclic aromatic hydrocarbons), carbon monoxide (CO), ammonia ($NH_3$).<br>• Chronic use associated with respiratory symptoms (bronchitis, cough, phlegm), but not lung cancer nor COPD (if cannabis only).<br>• Patients may mix with tobacco increasing respiratory/cancer risk<br>• 30–50% of cannabis is lost to 'side-stream' smoke | • Heats cannabis at 160–230 °C. Reduced CO, but not complete elimination of PAH demonstrated to date.<br>• Vaporisation produces significantly less harmful biproducts vs. smoking.<br>• Decreased pulmonary symptoms reported compared to smoking. | • Oils, capsules and other po routes increasingly popular due to convenience and accuracy of dosing.<br>• Edibles (brownies/cookies) may be more difficult to dose.<br>• Juicing and cannabis teas do not allow for adequate decarboxylation of raw plant<br>• Nabiximols oromucosal spray is currently the only cannabis-based prescription that delivers standardised dosage of CBD/THC in a 1:1 ratio with extensive research<br>• Tinctures and lozenges intermediate onset with limited research | • Topicals ideal for localised symptoms (dermatological conditions, arthritis), with limited research evidence<br>• Suppositories possibly indicated for specific populations (cancer, GI symptoms, young/elderly, etc.) with variable absorption. THC-hemisuccinate may allow for best absorption with limited research.<br>• Recreational routes include 'shatter', 'dabs', concentrates. Deliver very high doses of THC with high risk of euphoria, impairment, reinforcement, toxic psychosis, orthostatic hypotension. Inappropriate for medical application. |

MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. Eur J Intern Med. 2018 Mar;49:12-19. doi: 10.1016/j.ejim.2018.01.004. Epub 2018 Jan 4. PMID: 29307505.

# Route of administration

**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 CA, Russo EB. Practical considerations in medical cannabis administration and dosing. Eur J Intern Med. 2018 Mar;49:12-19. doi: 10.1016/j.ejim.2018.01.004. Epub 2018 Jan 4. PMID: 29307505.

# Adverse effect

**Table 4**
Adverse events associated with cannabis-based medicines.

| Side effect | Most common | Common | Rare |
|---|---|---|---|
| Drowsiness/fatigue | ✓ | | |
| Dizziness | ✓ | | |
| Dry mouth | ✓ | | |
| Cough, phlegm, bronchitis (Smoking only) | ✓ | | |
| Anxiety | ✓ | | |
| Nausea | ✓ | | |
| Cognitive effects | ✓ | | |
| Euphoria | | ✓ | |
| Blurred vision | | ✓ | |
| Headache | | ✓ | |
| Orthostatic hypotension | | | ✓ |
| Toxic psychosis/paranoia | | | ✓ |
| Depression | | | ✓ |
| Ataxia/dyscoordination | | | ✓ |
| Tachycardia (after titration) | | | ✓ |
| Cannabis hyperemesis | | | ✓ |
| Diarrhea | | | ✓ |

MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. Eur J Intern Med. 2018 Mar;49:12-19. doi: 10.1016/j.ejim.2018.01.004. Epub 2018 Jan 4. PMID: 29307505.

# Contraindications

- History of hypersensitivity to any cannabinoid
- Severe and unstable cardio-pulmonary disease
- Current, active drug dependence
- Breasting

# Warnings and Precautions

- patients aged 18 years old and under
- personal or family history of schizophrenia or any psychotic disorder
- severe liver or renal disease
- previous drug dependence

# Warnings and Precautions

- planning to become pregnant or during pregnancy
- concomitant medications, especially sedatives such as opioids and benzodiazepines and medicines metabolised by cytochrome p450 isoenzymes
- elderly

# The therapeutic potential

- Conclusive or substantial evidence
- Moderate evidence effect
- Limited evidence of effect
- No or insufficient evidence

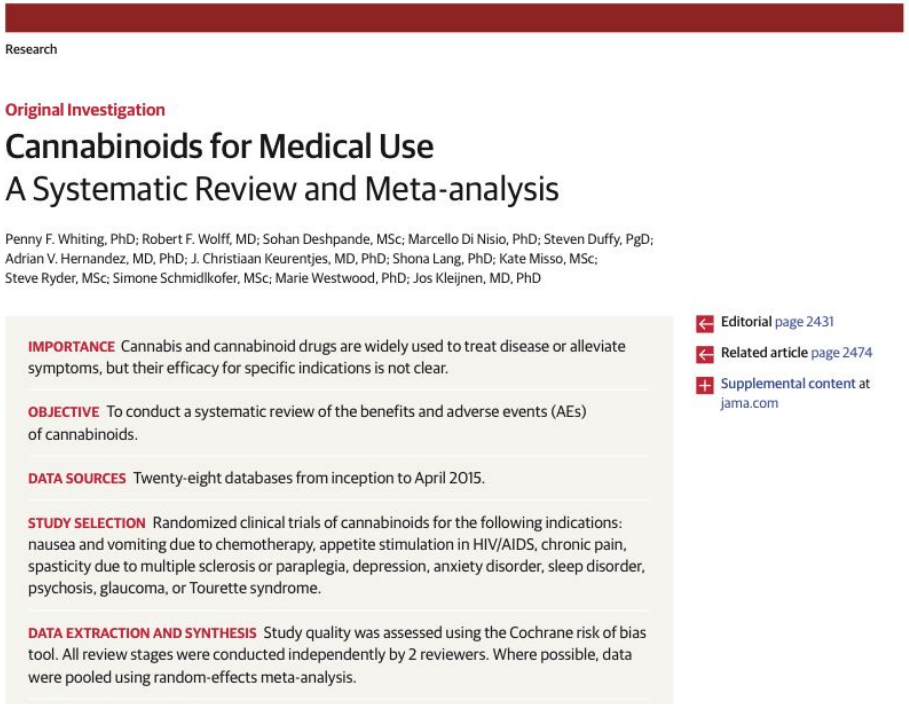
# The therapeutic potential

Conclusive or substantial evidence

- Chronic pain
- Chemotherapy - induced nausea vomitting
- Spasticity associated with multiple sclerosis

# Conclusive or substantial evidence

## Chronic pain



Research

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

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**IMPORTANCE** Cannabis and cannabinoid drugs are widely used to treat disease or alleviate symptoms, but their efficacy for specific indications is not clear.

**OBJECTIVE** To conduct a systematic review of the benefits and adverse events (AEs) of cannabinoids.

**DATA SOURCES** Twenty-eight databases from inception to April 2015.

**STUDY SELECTION** Randomized clinical trials of cannabinoids for the following indications: nausea and vomiting due to chemotherapy, appetite stimulation in HIV/AIDS, chronic pain, spasticity due to multiple sclerosis or paraplegia, depression, anxiety disorder, sleep disorder, psychosis, glaucoma, or Tourette syndrome.

**DATA EXTRACTION AND SYNTHESIS** Study quality was assessed using the Cochrane risk of bias tool. All review stages were conducted independently by 2 reviewers. Where possible, data were pooled using random-effects meta-analysis.

- The average number of patients who reported a reduction in pain of at least 30% was greater with cannabinoids than with placebo (OR, 1.41 [95% CI, 0.99-2.00])

# Conclusive or substantial evidence

## Chronic pain

European Journal of Internal Medicine 49 (2018) 7–11

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- There were five fair-to-good quality systematic reviews that contributed to the conclusion that there is substantial evidence that Cannabis is an selective treatment for chronic pain in adults.

# Conclusive or substantial evidence

## Chronic pain

Cannabis and Cannabinoid Research
Volume 1.1, 2016
DOI: 10.1089/can.2016.0007

Cannabis and Cannabinoid Research
Mary Ann Liebert, Inc. publishers

ORIGINAL RESEARCH Open Access

### A Cross-Sectional Survey of Medical Cannabis Users: Patterns of Use and Perceived Efficacy

Michelle Sexton,[1,*] Carrie Cuttler,[2] John S. Finnell,[3] and Laurie K. Mischley[4]

**Abstract**

**Background:** The political climate around Cannabis as a medicine is rapidly changing. Legislators are adopting policies regarding appropriate medical applications, while the paucity of research may make policy decisions around conditions for which Cannabis is an effective medicine difficult.

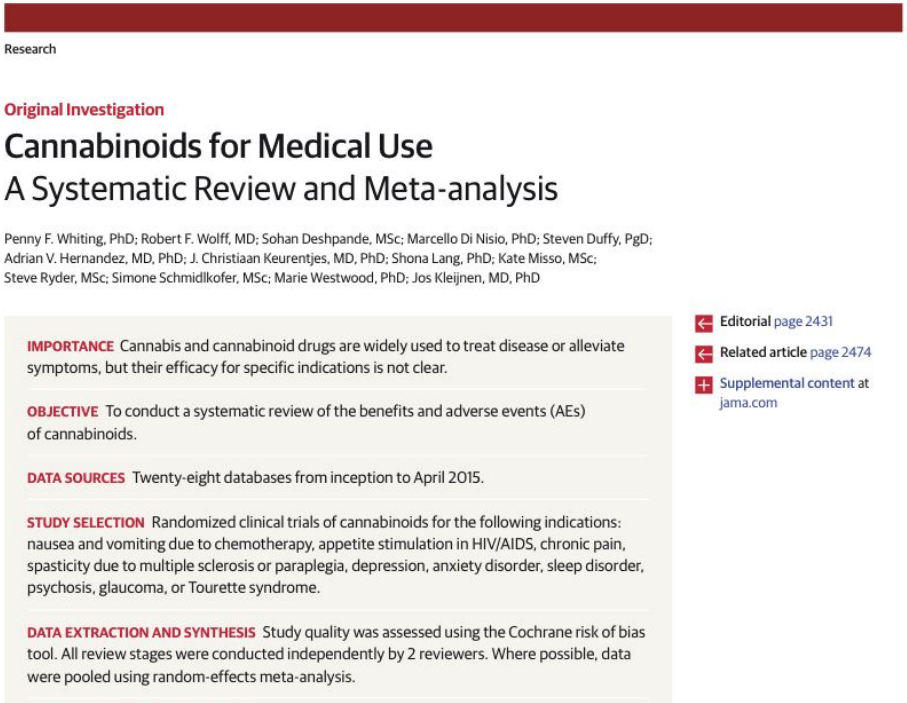
**Methods:** An anonymous online survey was developed to query medical Cannabis users about the conditions they use Cannabis to treat, their use patterns, perception of efficacy, and physical and mental health. Participants were recruited through social media and Cannabis dispensaries in Washington State.

**Results:** A total of 1429 participants identified as medical Cannabis users. The most frequently reported conditions for which they used Cannabis were pain (61.2%), anxiety (58.1%), depression (50.3%), headache/migraine (35.5%), nausea (27.4%), and muscle spasticity (18.4%). On average, participants reported an 86% reduction in symptoms as a result of Cannabis use; 59.8% of medical users reported using Cannabis as an alternative to pharmaceutical prescriptions. Global health scores were on par with the general population for mental health and physical health.

**Conclusions:** While patient-reported outcomes favor strong efficacy for a broad range of symptoms, many medical users are using Cannabis without physician supervision and for conditions for which there is no formal research to support the use of Cannabis (e.g., depression and anxiety). Future research and public policy should attempt to reduce the incongruence between approved and actual use.

# Conclusive or substantial evidence

## Nausea and Vomiting Due to Chemotherapy



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- Studies suggested a greater benefit of cannabinoids compared with both active comparators and placebo
- Complete nausea and vomiting response was greater with cannabinoids (dronabinol or nabiximols) than placebo (OR, 3.82 [95% CI, 1.55-9.42]

# Conclusive or substantial evidence

## Nausea and Vomiting Due to Chemotherapy

European Journal of Internal Medicine 49 (2018) 7–11

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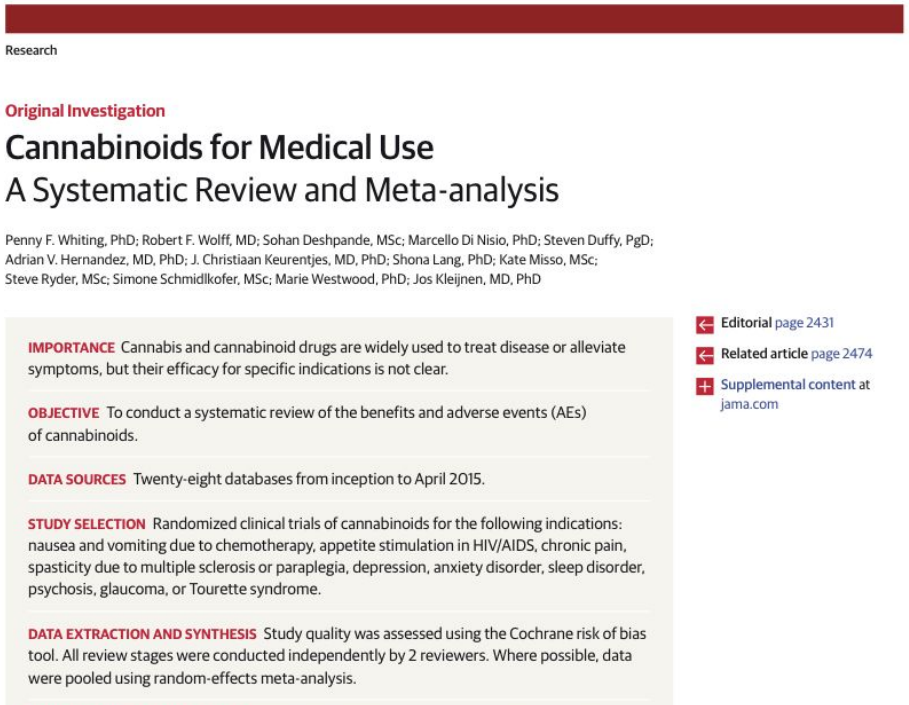
- All trials suggested a greater benefit for cannabinoids than for both active agents and for the placebo
- FDA-approved cannabinoids dronabinol or nabilone to treat nausea and vomiting that is resistant to standard antiemetic therapies.

# Conclusive or substantial evidence

## Spasticity Due to MS or Paraplegia



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- Studies generally suggested that cannabinoids were associated with improvements in spasticity
- Cannabinoids (nabiximols, dronabinol, and THC/CBD) were associated with a greater average improvement on the Ashworth scale for spasticity compared with placebo

# Conclusive or substantial evidence

## Spasticity Due to MS or Paraplegia

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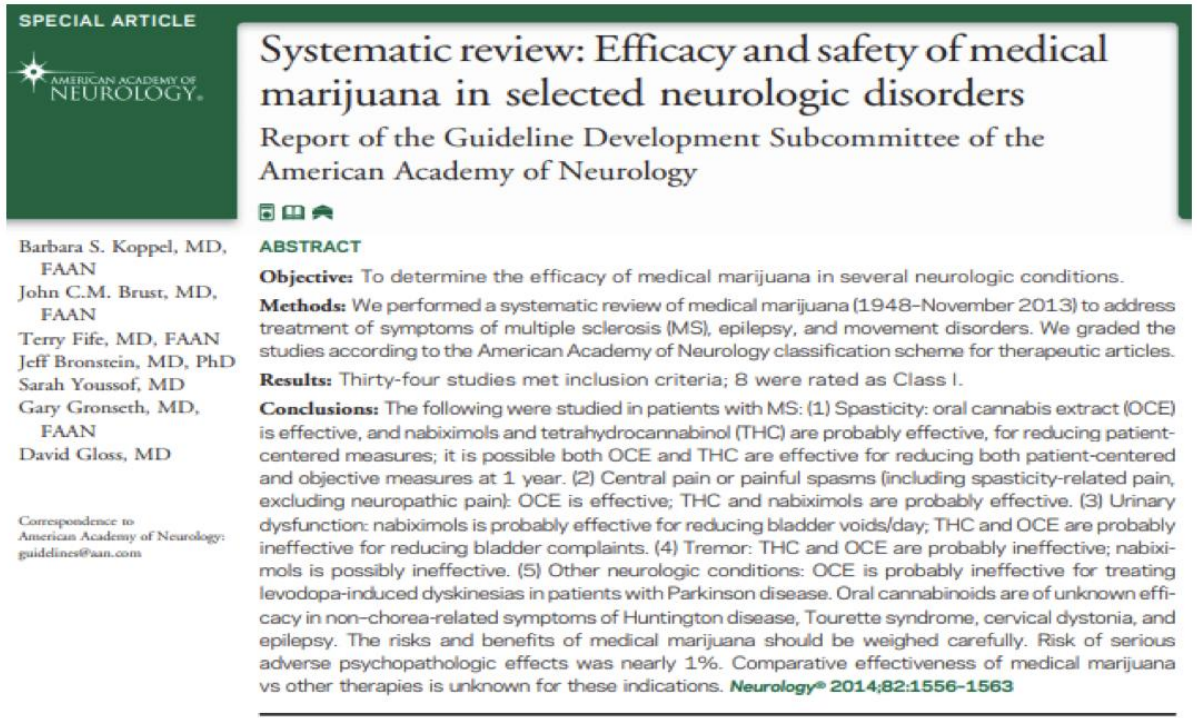
- Cannabinoids decreased the patient self- reported spasticity score by -0.76 (95% CI: -1.38 to -0.14) on a 0 to 10 scale that was statistically greater than placebo.
- Nabiximols and oral THC were “probably effective” and oral Cannabis extract was “established as effective”

# Conclusive or substantial evidence

## Spasticity Due to MS or Paraplegia



SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY

# Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders

## Report of the Guideline Development Subcommittee of the American Academy of Neurology


Barbara S. Koppel, MD, FAAN
John C.M. Brust, MD, FAAN
Terry Fife, MD, FAAN
Jeff Bronstein, MD, PhD
Sarah Youssof, MD
Gary Gronseth, MD, FAAN
David Gloss, MD

Correspondence to American Academy of Neurology: guidelines@aan.com



**ABSTRACT**

**Objective:** To determine the efficacy of medical marijuana in several neurologic conditions.

**Methods:** We performed a systematic review of medical marijuana (1948–November 2013) to address treatment of symptoms of multiple sclerosis (MS), epilepsy, and movement disorders. We graded the studies according to the American Academy of Neurology classification scheme for therapeutic articles.

**Results:** Thirty-four studies met inclusion criteria; 8 were rated as Class I.

**Conclusions:** The following were studied in patients with MS: (1) Spasticity: oral cannabis extract (OCE) is effective, and nabiximols and tetrahydrocannabinol (THC) are probably effective, for reducing patient-centered measures; it is possible both OCE and THC are effective for reducing both patient-centered and objective measures at 1 year. (2) Central pain or painful spasms (including spasticity-related pain, excluding neuropathic pain): OCE is effective; THC and nabiximols are probably effective. (3) Urinary dysfunction: nabiximols is probably effective for reducing bladder voids/day; THC and OCE are probably ineffective for reducing bladder complaints. (4) Tremor: THC and OCE are probably ineffective; nabiximols is possibly ineffective. (5) Other neurologic conditions: OCE is probably ineffective for treating levodopa-induced dyskinesias in patients with Parkinson disease. Oral cannabinoids are of unknown efficacy in non–chorea-related symptoms of Huntington disease, Tourette syndrome, cervical dystonia, and epilepsy. The risks and benefits of medical marijuana should be weighed carefully. Risk of serious adverse psychopathologic effects was nearly 1%. Comparative effectiveness of medical marijuana vs other therapies is unknown for these indications. *Neurology*® 2014;82:1556–1563

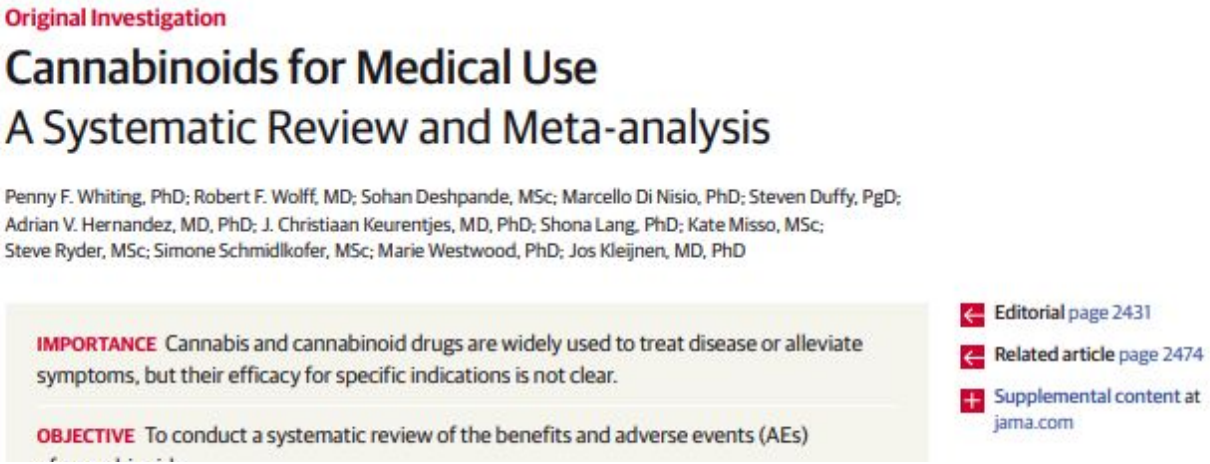
# The therapeutic potential

Moderate evidence effect

- Sleep disturbance

# Moderate evidence effect

## Sleep disturbance



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- Two studies evaluated cannabinoids specially for the treatment of sleep problem.

# Moderate evidence effect

## Sleep disturbance

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# Moderate evidence effect

## Sleep disturbance

- Moderate evidence that cannabinoids, predominantly nabiximols, are effective in improving the short-term sleep outcomes in individuals with sleep disturbances associated with

    - Obstructive sleep apnea
    - Fibromyalgia
    - Chronic pain
    - Multiple sclerosis.

# The therapeutic potential

Limited evidence of effect

- Appetite and weight gain
- Post traumatic stress disorder
- Tourette syndrome

# LIMITED EVIDENCE EFFECT

## APPETITE AND WEIGHT GAIN

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- One randomized trial in HIV patients did show weight gain in the Cannabis smoking and dronabinol recipient groups compared to placebo

# LIMITED EVIDENCE EFFECT

## APPETITE AND WEIGHT GAIN

Clinical Trial › J Clin Oncol. 2002 Jan 15;20(2):567-73. doi: 10.1200/JCO.2002.20.2.567.

### Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study

Aminah Jatoi [1], Harold E Windschitl, Charles L Loprinzi, Jeff A Sloan, Shaker R Dakhil, James A Mailliard, Sarode Pundaleeka, Carl G Kardinal, Tom R Fitch, James E Krook, Paul J Novotny, Brad Christensen

**Conclusion:** In the doses and schedules we studied, megestrol acetate provided superior anorexia palliation among advanced cancer patients compared with dronabinol alone. Combination therapy did not appear to confer additional benefit.

# LIMITED EVIDENCE EFFECT

## POST TRAUMATIC STRESS DISORDER

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Review Article

The therapeutic effects of *Cannabis* and cannabinoids: An update from the National Academies of Sciences, Engineering and Medicine report

Donald I. Abrams

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- Nabilone was statistically better than placebo for improving night- mares, global clinical state and general well-being ($p < 0.05$).

# LIMITED EVIDENCE EFFECT

## POST TRAUMATIC STRESS DISORDER

The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: A preliminary randomized, double-blind, placebo-controlled cross-over design study

Rakesh Jetly[a,*], Alexandra Heber[a], George Fraser[b], Denis Boisvert[b]

# LIMITED EVIDENCE EFFECT

## TOURETTE SYNDROME

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- Tic severity and global clinical outcome scores were improved in the treatment groups, but the tic severity improved by less than one point on a zero to six point scale .

# LIMITED EVIDENCE EFFECT

## TOURETTE SYNDROME

brain sciences

MDPI

*Case Report*

# Significant Tic Reduction in An Otherwise Treatment-Resistant Patient with Gilles de la Tourette Syndrome Following Treatment with Nabiximols

**Ahmad Seif Kanaan [1,2,†], Ewgeni Jakubovski [1,†] and Kirsten Müller-Vahl [1,*]**

1 Clinic of Psychiatry, Socialpsychiatry and Psychotherapy, Hannover Medical School, Carl-Neuberg-Str. 1, Hannover 30625, Germany; amadeus.kanaan@gmail.com (A.S.K.); jakubovski.ewgeni@mh-hannover.de (E.J.)

2 Max Planck Institute for Human Cognitive and Brain Sciences, Stephanstraße 1a, Leipzig 04103, Germany

* Correspondence: mueller-vahl.kirsten@mh-hannover.de; Tel.: +49-511-532-3551; Fax: +49-511-532-3187

† These authors contributed equally to this study.

Academic Editors: Kieron O'Connor and Marc Lavoie

Received: 7 March 2017; Accepted: 19 April 2017; Published: 26 April 2017

**Abstract:** Early anecdotal reports and preliminary studies suggested that cannabinoid-based medicines such as delta-9-tetrahydrocannabinol (THC) are effective in the treatment of Gilles de la Tourette syndrome (TS). We report a single case study of a patient with otherwise treatment-resistant TS successfully treated with nabiximols. Our patient was a 22-year-old male suffering from severe and complex TS. Treatment with nabiximols was commenced at a dose of 1 puff/day (=100 µL containing 2.7 mg THC and 2.5 mg cannabidiol (CBD)) and slowly increased up to a dosage of 3 × 3 puffs/day (=24.3 mg THC and 22.5 mg CBD). Several clinical measures for tics, premonitory urges, and global impairment were acquired before and after two weeks of treatment. Treatment with nabiximols resulted in major improvements of both tics and premonitory urges, but also global impairment and health-related quality of life according to all used measurements without causing relevant adverse effects. Our results provide further evidence that treatment with nabiximols may be effective in the treatment of patients with TS. Given the positive response exhibited by the patient highlighted in this report, further investigation of the effects of nabiximols is proposed on a larger group of patients in a clinical trial setting.

# The therapeutic potential

No or insufficient evidence

- Cancer
- Epilepsy
- Neurodegenerative disorder
- Irritable bowel syndrome
- Addiction

# No evidence effect

## Cancer

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- There is only one published clinical trial investigating cannabis as anticancer agent in vitro with glioma cell.
- In human trial , there was no clinical benefit above that provided by chemotherapy alone.

# No evidence effect

## Epilepsy

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- The lack of blinding and control groups were deemed to make the evidence insuficient to support a benefit for cannabinoids in the treatment of seizures at this time.

# No evidence effect

## Epilepsy

THE LANCET
Neurology
Volume 15, Issue 3, March 2016, Pages 270-278

Articles

### Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial

Dr Prof Orrin Devinsky MD [a, †], Eric Marsh MD [b, †], Daniel Friedman MD [a, †], Prof Elizabeth Thiele MD [c], Linda Laux MD [d], Joseph Sullivan MD [e], Ian Miller MD [f], Robert Flamini MD [g], Angus Wilfong MD [h], Francis Filloux MD [i], Matthew Wong MD [j], Nicole Tilton CRNP [e], Patricia Bruno RN [c], Judith Bluvstein MD [a], Julie Hedlund RN [a], Rebecca Kamens [b], Jane Maclean MD [b], Srishti Nangia MD [d] ... Prof Maria Roberta Cilio MD [e]

- Our findings suggest that cannabidiol might reduce seizure frequency and might have an adequate safety profile in children and young adults with highly treatment-resistant epilepsy. Randomised controlled trials are warranted to characterise the safety profile and true efficacy of this compound.

# No evidence effect

## Neurodegenerative disorder

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- Insufficient evidence to support the use of Cannabis or cannabinoids in the treatment of amyotrophic lateral sclerosis, chorea and certain neuropsychiatric symptoms associated with Huntington's disease, motor symptoms associated with Parkinson's disease or the levodopa-induced dyskinesia, spasticity associated with paralysis in patients with spinal cord injury and dystonia.

# No evidence effect

## Irritable bowel syndrome

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- No systematic reviews located in the literature.
- A single randomized trial of two doses of dronabinol versus placebo in adults with diarrhea related to irritable bowel syndrome was identified. No effect of dronabinol on gastric, small bowel or colonic transit as measured by radioscintigraphy was seen.

# No evidence effect

## Addiction

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journal homepage: www.elsevier.com/locate/ejim

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- 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.

# Take home message

- Endocannabinoid system
- Phytocannabinoid are exogenous cannabinoid
- Conclusive therapeutic effect
    - Chronic pain
    - Chemotherapy induced nausea and vomiting
    - Spastic associated with multiple sclerosis

# THANK YOU