What is the evidence?

Pain	Evidence
Pre-clinical	++
Clinical	+++

Pre-clinical data: Pain

- Robust *in vitro* evidence cancer pain responds to cannabinoid treatment
- Use in bone pain/neuropathic pain has strongest evidence
- Direct use of agonists/antagonists and prevention of enzyme degradation
- Peripheral application effective,
- few A/E

Clinical data: Pain

- Trial evidence supports oral use in cancer pain, in addition to usual therapy
- Small studies using smoking/vaporization
- None using edibles or oils
- Reduction in use of pain meds noted

  Few A/E

BJC British journal of Clinical Pharmacology

DOI.10.111/f.1365-2125..2011039 70.x

Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials

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J uroimmunc Phatmacol
DOI 10.1007/s11481.QJ5-9600

INV11ED REVIEW

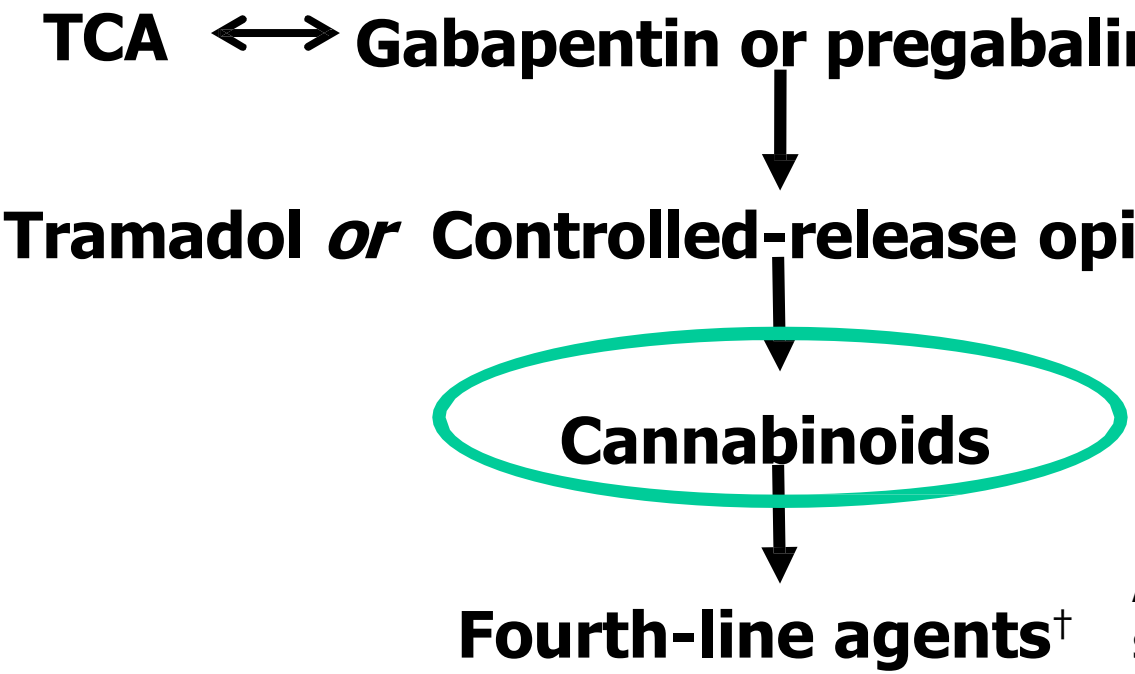
Cannabinoids for the Treatment of Chronic on-Cancer Pain: An Updated ystematic Review of Randomized Controlled Trials

I. E. Lynth [13] · 1ark . \\'ar [2]

Conclusions of reviews

- Studies small, short in duration, modest effect size
- "cannabinoids are safe, demonstrate a modest analgesic effect and provide a reasonable treatment option for chronic non-cancer pain"

CPS neuropathic pain guideline revision



Add additional agents sequentially if partial but inadequate pain relief

†methadone, lamotrigine, topiramate, valproic acid, lidocaine.
‡Do not add SNRIs to TCAs

Pain Res Manage 2014;19(6):328-335

What is the evidence?

Nausea	**Evidence**
Pre-clinical	**++**
Clinical	**+++**

Cannabinoids in nausea

Table 2

Clinical Trials With Cannabinoids: Emesis

DRUG(S)	SUBJECTS	OUTCOME	REFERENCES
Nabilone vs prochlorperazine	Pediatric chemotherapy patients	Nabilone more effective	56
Nabilone and prochlorperazine vs metoclopramide and dexamethasone	Chemotherapy patients	Better control of emesis with metoclopramide combination, but nabilone combination better tolerated	57
Nabilone vs metoclopramide	Patients undergoing irradiation	No difference in effectiveness; more adverse effects with nabilone	58
Nabilone vs alizapride	Chemotherapy patients	Nabilone more effective but with more adverse effects (especially at higher doses)	59
Nabilone vs domperidone	Chemotherapy patients	Nabilone more effective	60
Nabilone vs metoclopramide	Chemotherapy patients	No difference in efficacy	61
Oral THC vs prochlorperazine	Chemotherapy patients	No difference in efficacy	62
Oral THC vs prochlorperazine vs placebo	Chemotherapy patients	Oral THC more effective than prochlorperazine or placebo	63
Dronabinol and metoclopramide and prochlorperazine	Chemotherapy patients	No added benefit of dronabinol	64
Dronabinol and prochlorperazine	Chemotherapy patients	Dronabinol effective alone, but combination more effective	65, 53
Nabilone and prochlorperazine	Chemotherapy patients	Nabilone more effective	66
Oral THC vs prochlorperazine	Chemotherapy patients	Oral THC more effective	67

THC = Δ^9-tetrahydrocannabinol

Martin BR & Willey JL. *J Support Onc* 2004;2: 305-16

Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review

Martin R Tramèr, Dawn Carroll, Fiona A Campbell, D John M Reynolds, R Andrew Moore, Henry J McQuay

BMJ 2001, 323:1-8

- CBs may be superior to conventional therapies in low-medium emetogenic setting
- Patient preference for CBs ranged from 38-90% (P 4-20%)
- CBs produced significantly more A/E effects (good & bad), more pt withdrawals

"In selected patients, cannabinoids may be useful as mood enhancing adjuvants for the control of chemotherapy related sickness"

Inhaled marijuana

- Three studies, associated with chemo administration
- Some new users, many previous cannabis users
- All studies showed benefit, but high incidence of side effects
- 25-35% pts prefer marijuana

Vinciguerra et al, *N Y State J Med* 1988 88:525
Chang et al, *Ann Int Med* 1979 91:819
Levitt et al, *JCO* 1984 abstract C-354

What is the evidence?

Appetite/wt loss	Evidence
Pre-clinical	++
Clinical	+

Hypothalamic POMC neurons promote cannabinoid–induced feeding

Marijuana flips appetite switch in brain

Sudden attacks of 'the munchies' triggered by changes in hormone pro-opiomelanocortin (POMC) release by neurons

doi:10.1038/nature.2015.16957
doi: 10.1038/nature14260

Appetite and weight loss

Table 1

Clinical Trials With Cannabinoids: Cachexia and Anorexia

DRUG(S)	SUBJECTS	OUTCOME	REFERENCE
Dronabinol and megestrol	Cancer patients	No effect of dronabinol or combination on appetite or body weight	37
Dronabinol	Cancer patients	Increased appetite	38
Dronabinol and megestrol	AIDS patients	No effect of dronabinol or combination on appetite	39
Dronabinol vs placebo	HIV-positive patients	Increased body fat and increased appetite	40
Dronabinol vs placebo	Alzheimer's patients with anorexia	Increased body weight and decrease in disturbed behavior	41
Dronabinol vs placebo	AIDS patients	Increased appetite; stabilized weight	42
Dronabinol vs placebo	Late-stage AIDS patients	Stable body weight for 7 months	43

Jatoi A et al. *J Clin Oncol* 2002;20:567-573
Nelson K et al. *J Pall Care* 1994;10:14-18
Timpone JG et al. *AIDS Res Hum Retroviruses* 1997;13:305-15
Struwe M et al. *Ann Pharmacother* 1993;27:827-31
Beal JE et al. *J Pain Symptom Manage* 1995;10:89-97
Beal JE et al. *J Pain Symptom Manage* 1997;14:7-14

Dronabinol: taste alterations

Pilot trial to improve taste, smell changes in advanced cancer patients

THC 2.5 mg BID or TID vs placebo x 18 days, n=21

Questionnaires / interviews revealed significant improvement in taste / smell, increased appetite and protein intake

QoL measures found improved relaxation, quality of sleep

Adverse effects same in both groups

TD Brisbois Clarkson et al, *Ann Oncol* 2011; 22: 2086-93

What is the evidence?

Neuroprotection	Evidence
Pre-clinical	**+/-**
Clinical	**+**

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Selective Activation of Cannabinoid CB_2 Receptors Suppresses Neuropathic Nociception Induced by Treatment with the Chemotherapeutic Agent Paclitaxel in Rats

Elizabeth J. Rahn, Alexander M. Zvonok, Ganesh A. Thakur, Atmaram D. Khanolkar, Alexandros Makriyannis, and Andrea G. Hohmann

Brief Report

Double-Bli11d .. Placebo control trial Pilot study

What is the evidence?

	Evidence
Insomnia	
Pre-clinical	**-**
Clinical	**++***
Anxiety	
Pre-clinical	**++**
Clinical	**-**

*secondary finding

Cannabinoids and anxiety

Oral cannabinoids used for nausea produces sedation and reduces anxiety

Very low dose cannabis can produce sedation, diminish anxiety without getting high

Cannabidiol can exert anti-anxiety effects, although only demonstrated in acute, experimentally-induced anxiety

Tramer et al, *BMJ* 2001; 323:1-8
Graham and Li, Cannabis and Health, 1976
Bergamaschi et al, *Neuropsychopharmcol* 2011; 36: 1219-26

Psychoneuroendocnnology (2015) 51, 585 - 588

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: .vww.elsevier.com/locateJpsyneuen

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

20 Medical Studies That Prove Cannabis Can Cure Cancer

http://www.collective-evolution.com/2013/08/23/20-medical-studies-that-prove-cannabis-can-cure-cancer/#sthash.H5ypYS6a.dpuf

Cannabis Cures Cancer

https://dl.dropboxusercontent.com/u/27713298/Web/cure/How_It_Works.html

Run From The Cure: How Cannabis Cures Cancer And Why No One Knows

Cannabis sativa hemp, the miracle plant, contains the cure for cancer and other ailments By Rick Simpson - Friday, March 7 2008

http://www.cannabisculture.com/articles/5169.html

What is the evidence?

Cancer	Evidence
Pre-clinical	**+++**
Clinical	**nil**
Clinical trials	**- In Progress**

Cannabis is not a cure for cancer

Actual and Potential Medical Uses

- Indian traditional medicine - claimed effects:
  - sedative, relaxant, anxiolytic
  - analgesic
  - appetite stimulant
  - anticonvulsant
  - antipyretic
  - antibiotic
  - antidiarrheal
  - treatment of withdrawal reactions (alcohol, opiates)

Actual and Potential Medical Uses (cont'd)

- Modern western medicine:

  Accepted uses

  - antinauseant, antiemetic
  - appetite stimulant
  - cancer chemotherapy, AIDS

- Possible uses worth study:
  - analgesia
  - antispasticity (e.g. multiple sclerosis)
  - immunosuppressant
  - glaucoma
  - anticonvulsant, mainly cannabidiol, not THC

Recent Clinical Trials of Cannabinoids for the Treatment of CNS Disorders

Disorder	Target Symptoms	Therapeutic Cannabinoid	Clinical Outcome
Multiple Sclerosis	Spasticity	Oral THC, CBD	In progress
	Neurogenic pain	Sublingual THC, CBD	Phase II trial in progress
	Bladder dysfunction	Sublingual THC, CBD	Phase II trial in progress
Parkinsons's disease	Dystonia	Nabilone	No effect
	Dyskinesia	Nabilone	↓ Dyskinesia
	Tremor	Δ9-THC	No effect
Cancer	Pain	Sublingual THC, CBD	Phase III trial in progress
Postoperative pain	Pain	IM levonantradol	↓ pain, but less effective than existing therapies

CBD = cannabidiol

THC = tetrahydrocannabinol

Croxford, JL. CNS Drugs 2003; 17(3)

Recent Clinical Trials of Cannabinoids for the Treatment of CNS Disorders (cont'd)

Disorder	Target Symptoms	Therapeutic Cannabinoid	Clinical Outcome
Spinal cord injury	Pain	Sublingual THC, CBD	Phase II trial in progress
GI tract pain	Pain	THC	↓ Morphine requirement
Traumatic Brain Injury / Stroke	Neurodegeneration	IV dexanabinol (HU-211)	↓Intracranial pressure, ↓ mortality, phase III trial in progress
	Neurodegeneration	CBD	In progress
HIV wasting syndrome	Appetite loss, nausea	Smoked cannabis	In progress
	Appetite loss, nausea	Dronabinol	↑ appetite, ↓ nausea
TIC (Tourette's syndrome)	Behavioural disorders	THC	undetermined

Croxford, JL. CNS Drugs 2003; 17(3)

Analgesia

CB_1-selective agonists reduce pain

receptors in periaqueductal gray mainly (direct local injection effective)

separate from opioid analgesia mechanism

- naloxone blocks morphine analgesia but not THC analgesia
- CB_1 blocker (SR 141716A) blocks THC but not morphine analgesia

but THC and morphine augment each other's effects - possibility of combined use

Analgesia (cont'd)

- both oral THC and smoked marijuana work
  - onset of action faster with smoking
  - for chronic pain, speed not necessary
- new water-soluble esters of THC-acid analogs
  - analgesic and anti-inflammatory action
  - no psychoactivity, no gastric irritation
  - possible replacement for NSAIDs?
- migraine – only anecdotal evidence
  - no controlled comparison of oral vs smoked

Relief of Spasticity (e.g., Multiple Sclerosis)

- one double-blind crossover study with oral THC, 2.5 to 15 mg daily
  - doses of 7.5 mg or more gave subjective and objective improvement of spasm

- self-report by 112 MS patients in UK and USA
  - smoked marijuana
  - main benefits reported: decreased spasticity and pain
  - also claimed other benefits, including improved balance and walking

Relief of Spasticity (e.g., Multiple Sclerosis)

- but experiment with 10 MS patients, 10 normal controls, smoking one marijuana cigarette
  - objective measures
  - worse posture and balance in both groups, more so in MS patients than controls

- no controlled studies of smoked vs. oral THC, no controlled comparisons with other drugs used for relief of spasm

Glaucoma

- THC shown to reduce intraocular pressure (IOP) in both normals and glaucoma patients
- both smoked marijuana and oral THC effective
- after smoking, fall in IOP greatest at 2 hrs, gone by 3-4 hrs.
  - to maintain clinically useful reduction, would have to smoke 8-10 times a day

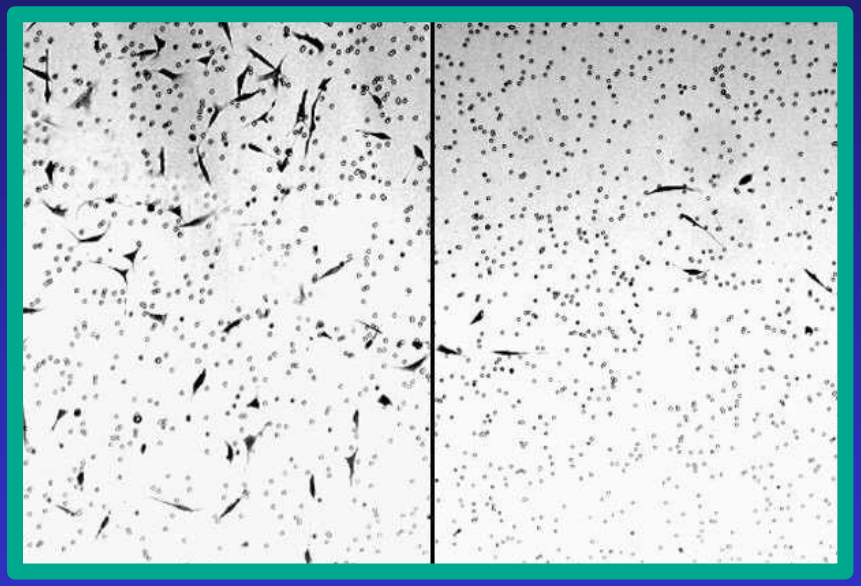
Glaucoma (cont'd)

- oral THC more prolonged, but psychoactive effects still not separable from IOP reduction
- topical THC drops in eye not feasible - too irritating to eye
- potential future drugs:
  - dexanabinol (CH211) lowers IOP but has no psychoactivity
  - other synthetics with high water-solubility may permit topical use (eye-drops)

National Cancer Institute

Preclinical studies of cannabinoids indicate potential in these areas:

- Antitumor activity
- Stimulating appetite
- Pain relief
- Nausea & vomiting
- Anxiety & sleep



Breast cancer cells in a lab specimen, before (L) & after (R) application of CBD.

Source: Pacific Medical Center

Source: National Cancer Institute. *Cannabis and Cannabinoids.* https://www.cancer.gov/about-cancer/treatment/cam/patient/cannabis-pdq#link/_13

How Does Cannabis Help?

The endocannabinoid system

Receptors found on cells throughout the body

Purpose appears to relate to homeostasis, wherever in the body the receptors are activated by either endo- or phyto-cannabinoids

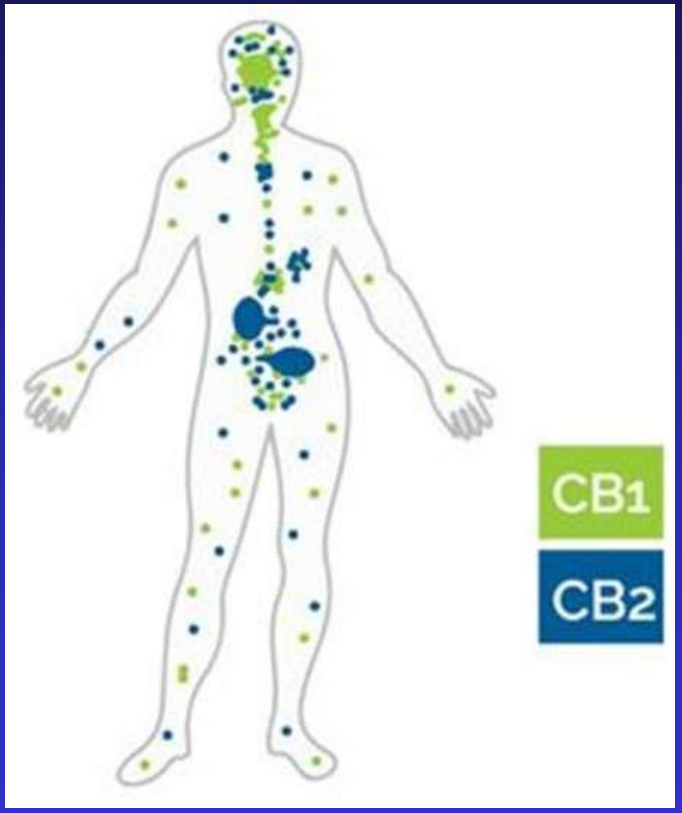
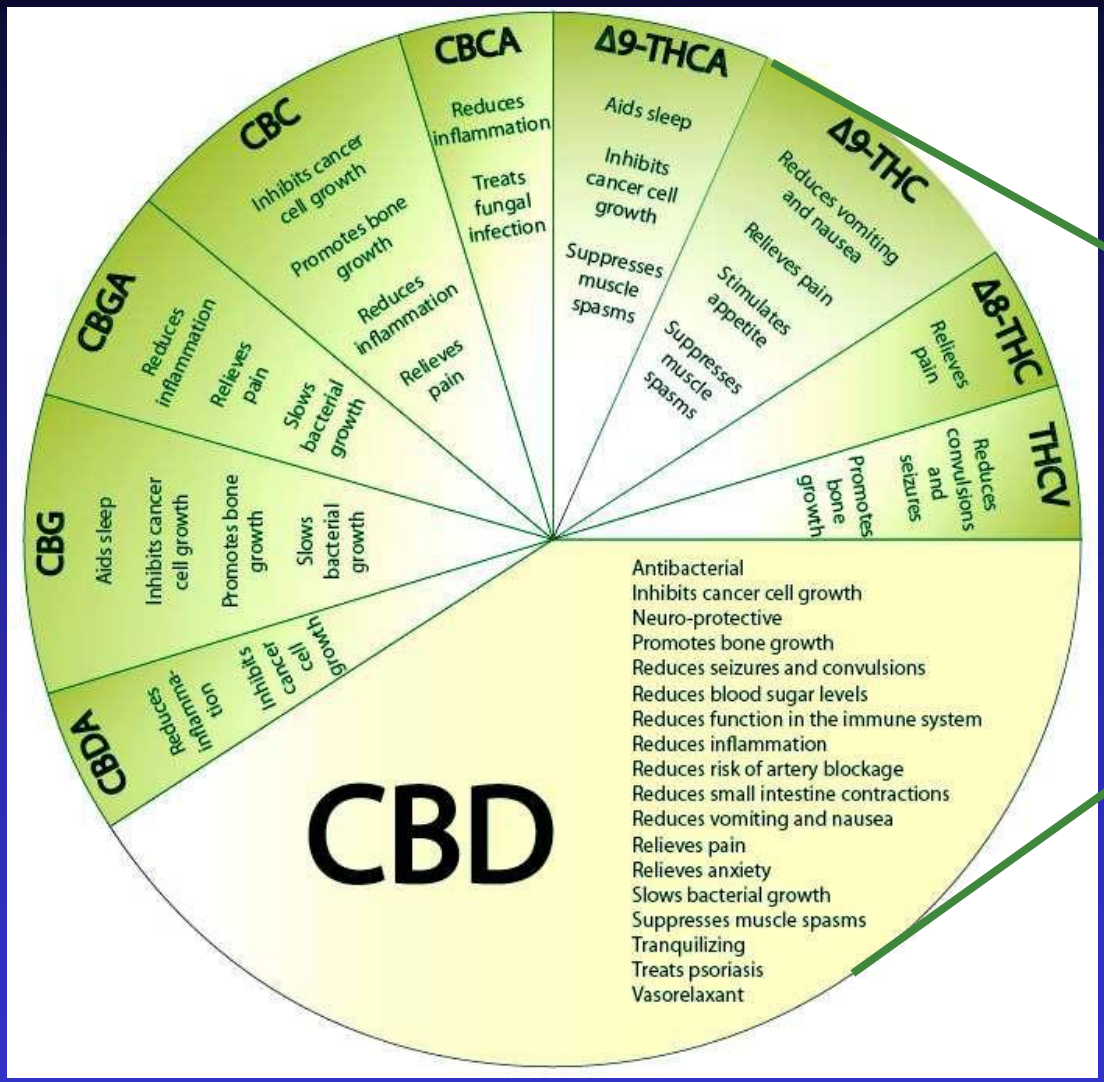


Image source: David Guzman, "The Endocannabinoid System"



Cannabis Indica

Cannabis Sativa

Proposed Action of Cannabis for different symptom.

THC	CBD
• Eases pain esp. in cancer • Nausea vomiting • Sleep disorders • Mood disorders • Relaxation คลายเครียด • Suppress muscle spasm • Reduce wasting	• Reduce dravet seizure • Kill breast cancer cells มะเร็ง • Stop inflammation • Anti oxidant • Anti psychotic • Increase appetite • Change in weight