



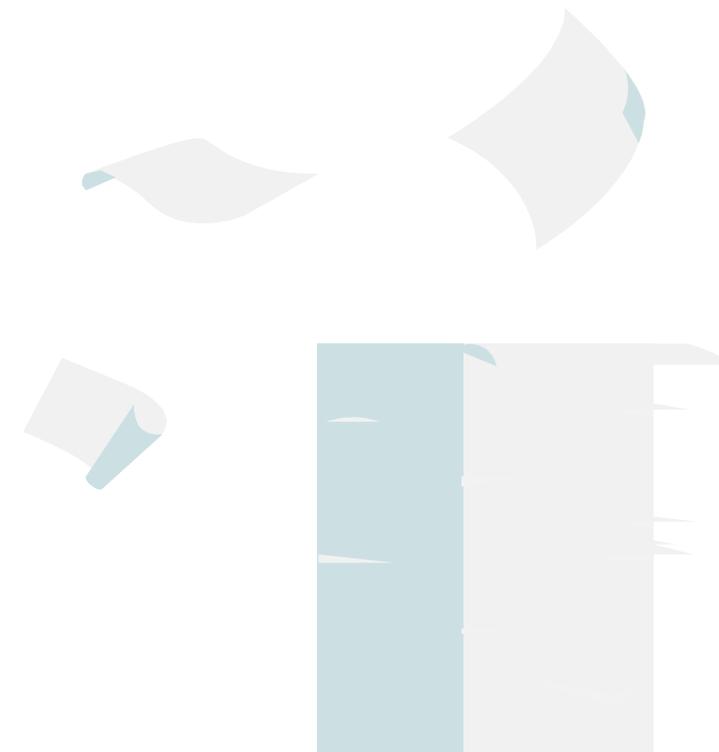
Medical Cannabis

Evidence on Efficacy



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Important information

- ▶ The slides will progress at their own pace.
- ▶ Do not attempt to speed up the video.
- ▶ The Post Test will only unlock after the entire video has been viewed.
- ▶ The video can be paused and resumed later.

Learning objectives

Participants will be able to

- ▶ Compare and contrast CBD (cannabidiol), THC (Δ 9-tetrahydrocannabinol), and medical cannabis.
- ▶ List two conditions for which cannabis or cannabinoids have been shown to be effective.
- ▶ List two conditions for which cannabis or cannabinoids have been shown to be ineffective.
- ▶ Describe the current state of evidence regarding cannabidiol (CBD) and seizures.

Introduction

- ▶ This module will summarize evidence from randomized controlled trials, systematic reviews and meta-analyses of medical cannabis and cannabinoids for treating chronic and acute pain, cancer care, nausea/vomiting, neurologic conditions, glaucoma, and psychiatric conditions.
- ▶ The module will also provide a clinical perspective on medical cannabis and cannabinoids.

Cannabis and Cannabinoids



- ▶ *Cannabis indica* and *Cannabis sativa* are the best-known species.
- ▶ A product's chemical profile is more important than the strain of plant from which it originated.
 - Percentages of cannabinoids determine potency and effects.



Cannabis and Cannabinoids



- ▶ Cannabinoids in cannabis include Δ 9-tetrahydrocannabinol (THC*), cannabidiol (CBD), many minor cannabinoids and terpenoids.
 - THC has psychoactive, antiinflammatory, and analgesic properties.
 - CBD is non-psychoactive and may mitigate THC's effects.
- ▶ FDA-approved prescription products contain only THC.



*THC = delta-9 THC unless otherwise specified

See the DCRx Module, [An Introduction to the Biochemistry and Pharmacology of Medical Cannabis](#) for more information.

Administration and Formulations



Inhalation by smoking or vaporization

(herbal cannabis, resin, concentrates)

Oral

(prescription cannabinoids, edibles, tinctures)

Oro-mucosal or sublingual

(lollipops, lozenges, nabiximols)

Topical or Rectal

(herbal cannabis, resin, concentrates)

Prescription Cannabinoid Preparations



Prescription cannabinoid preparations include

Dronabinol (Marinol)

THC capsule approved for treatment of anorexia associated with weight loss in patients with AIDS, and nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

Nabilone (Cesamet)

THC capsule approved for treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

Nabiximols (Sativex) (Not yet approved in the U.S.)

Whole plant extract containing both THC and CBD, administered sublingually

Adverse Effects



- ▶ Minor adverse effects are common with cannabis and cannabinoids, but major adverse effects are rare.

- ▶ Common side effects include
 - Dizziness
 - Dry mouth
 - Nausea/vomiting
 - Fatigue
 - Somnolence, drowsiness
 - Reduced coordination
 - Ataxia
 - Euphoria
 - Disorientation and confusion
 - Loss of balance
 - Hallucinations
 - Anxiety
 - Sedation
 - Cough

- ▶ Side effects should be weighed against potential benefits for individual patients.



See the DCRx module on [Medical Cannabis, Adverse Effects and Drug Interactions](#) for more information.

Researching Medical Cannabis



- ▶ Although cannabis is legal in some states, it remains a Schedule 1 drug at the federal level. [\(NIDA 2015\)](#)
- ▶ Medical cannabis is not approved by the U.S. Food and Drug Administration as a medicine. [\(NIH 2015\)](#)
- ▶ THC and other constituents of cannabis have been approved as pharmaceutical drugs. [\(NIDA 2014\)](#)
- ▶ The most research has been done on two FDA-approved THC products.
 - Nabilone (Cesamet)
 - Dronabinol (Marinol)
- ▶ Very few studies have been done on inhaled or ingested cannabis.



Researching Medical Cannabis



Cannabis for research is only available from the federal government.

- ▶ The National Institute on Drug Abuse (NIDA) is the primary federal agency that does research on cannabis. (NIDA 2015)
- ▶ Federally-funded research has focused on dependence and other adverse effects. (NYT 2010)
- ▶ NIDA-funded research has focused on THC, CBD, and other cannabinoids, but not medical cannabis. (NIH 2015; NIDA 2014)



Cannabis vs. Cannabinoids

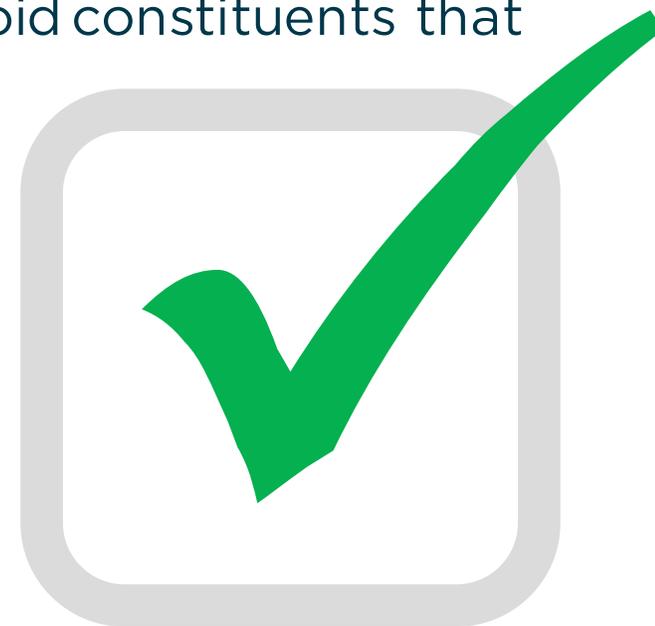
Advantages of cannabis

- ▶ Many clinicians believe cannabis has a different effect than synthesized cannabinoids.
- ▶ Cannabis has many different cannabinoid and non-cannabinoid constituents that may work synergistically (the so-called “entourage effect”).
- ▶ Cannabis is less expensive than prescription forms.

Advantages of cannabinoids

- ▶ Pharmaceutical preparations have excellent quality control.
- ▶ Pharmaceutical preparations enable precise dosing.

{ For both cannabis and cannabinoids }
“Start low and go slow.”

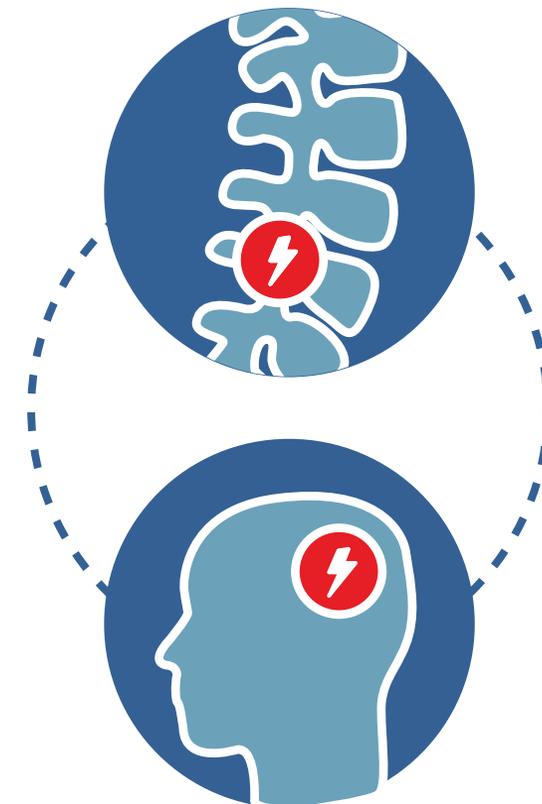


Chronic Pain

A systematic review of 18 randomized controlled trials (RCTs) with a total of 766 participants with chronic non-cancer pain found that 15/18 trials showed a significant analgesic effect of cannabinoids, compared to placebo.

- ▶ Conditions studied included neuropathic pain, “chronic pain”, rheumatoid arthritis, fibromyalgia, and central pain in multiple sclerosis.
- ▶ No serious adverse events were reported.

(Lynch and Campbell 2011)



Chronic Pain

A systematic review identified 28 studies (27 placebo-controlled, 1 treatment-controlled) of cannabis in a total of 2454 participants with chronic pain.

- ▶ 12 studies of neuropathic pain
- ▶ 6 trials of other types of pain
- ▶ 3 for cancer pain
- ▶ 3 for diabetic neuropathy
- ▶ 2 for fibromyalgia
- ▶ 2 for HIV-associated sensory neuropathy

Preparations tested included nabiximols, nabilone, inhaled cannabis, THC (oral or oromucosal), and dronabinol. (Whiting 2015)

{ Studies generally showed improvements in pain measures with cannabis and cannabinoids. }

Chronic Pain

Neuropathic Pain



STUDY	POPULATION	TREATMENT	OUTCOME
Rog (2005)	RCT (parallel group) in 66 patients with central neuropathic pain due to MS	Whole plant cannabis spray (2.7 mg THC and 2.5 mg CBD) up to 48 sprays/24 h for 4 weeks.	The treatment was superior to placebo in reducing the intensity of pain as measured by an (NRS) (p=.005).
Serpell (2014)	RCT (parallel group) in 246 patients with peripheral neuropathic pain with allodynia	Nabiximols (2.7 mg THC and 2.5 mg CBD) up to 24 sprays/24 h for 15 weeks.	The THC/CBD group, compared to placebo, experienced reduced pain severity measured on an 11 point NRS in (p=.034).
Turcotte (2015)	RCT (parallel group) in 15 patients with neuropathic pain due to MS	Nabilone or placebo titrated over 4 weeks starting with initial dose of 0.5 mg (0.5 mg/week increase) followed by oral nabilone (1 mg) or placebo twice daily for 5-weeks.	The nabilone group, compared to placebo, experienced less pain (as measured by VAS) (p<0.001).
Ware (2010)	RCT (crossover) in 23 adults with post-traumatic postsurgical neuropathic pain.	4 potencies of cannabis cigarettes (0%, 2.5%, 6% and 9.4% THC) inhaled through a pipe 3 times a day over four 14-day periods.	Cannabis cigarettes containing 9.4% THC (but not 2.5% or 6%) were superior to placebo in reducing average daily pain intensity on the 11-point NRS was lower for 9.4% vs. placebo cigarette (0%). There was no effect of 2.5% and 6% THC cigarettes over placebo.
Wilsey (2013)	RCT (crossover) in 39 patients with peripheral neuropathic pain	Vaporized cannabis (3.53% or 1.29%) or placebo.	Cannabis (3.53% and 1.29%) reduced pain intensity (measured by VAS) after 120 minutes compared to placebo (p=.0002). There was no significant difference between the two active doses.
Wilsey (2008)	RCT (crossover) in 38 patients with neuropathic pain	Low dose cannabis (3.5%), high dose (7%) cannabis, or placebo cigarette for 4 hours on 3 separate days.	The 3.5% and 7% cannabis group experienced spontaneous pain relief (measured by VAS) in compared to placebo (p=.016). There was no difference between the low and high-dose cigarettes.

Chronic Pain

Neuropathic Pain



STUDY	POPULATION	TREATMENT	OUTCOME
Berman (2007)	RCT (crossover) in 117 patients with central neuropathic pain (non-acute spinal cord injury). (unpublished abstract of conference presentation)	Nabiximols (Sativex) (2.7 mg THC and 2.5 mg CBD); THC spray, or placebo up to 48 sprays/24 h for 2 weeks each.	There was no difference between nabiximols (Sativex) and placebo for NRS pain scores.
Berman (2004)	RCT (crossover) in 48 patients with central neuropathic pain (brachial plexus avulsion)	Nabiximols (Sativex) (2.7 mg THC and 2.5 mg CBD); THC spray, or placebo up to 48 sprays/24 h for 2 weeks each.	Nabiximols (Sativex) was superior to placebo in reduction in pain score (by diary entry (p<.005).
Frank (2008)	RCT (crossover) in 96 patients with mixed neuropathic pain	Dihydrocodeine (30mg-240mg) or nabilone (250 mcg-2mg) for 7 weeks each.	Dihydrocodeine was significantly better than nabilone as measured by the visual analogue score (VAS) (p=.01).
Karst (2003)	RCT (crossover) in 21 patients with chronic neuropathic pain	CT-3 (a synthetic cannabinoid) 20 mg orally or placebo 2x/day for 4 days, then 40 mg 2x/day for 3 days.	Treatment and placebo in pain measured by visual analog scale 3 hours after intake, but differences were less pronounced after 8 hours (p=.02).
Langford (2013)	RCT (parallel group) in 339 patients with central neuropathic pain due to MS	THC/CBD spray (2.7 mg THC and 2.5 mg CBD) or placebo, self-titrated for 14 weeks.	THC/CBD spray was not superior to placebo in mean NRS pain score.
Nurmikko (2007)	RCT (parallel) in 125 patients with neuropathic pain characterized by allodynia	Nabiximols spray (2.7 mg THC and 2.5 mg CBD) up to 48 sprays/24 h for 7-10 days.	Nabiximols (Sativex) was superior to placebo in mean reduction in pain intensity scores by VAS (p=.004)

Neuropathic Pain (Associated with HIV or Diabetes)



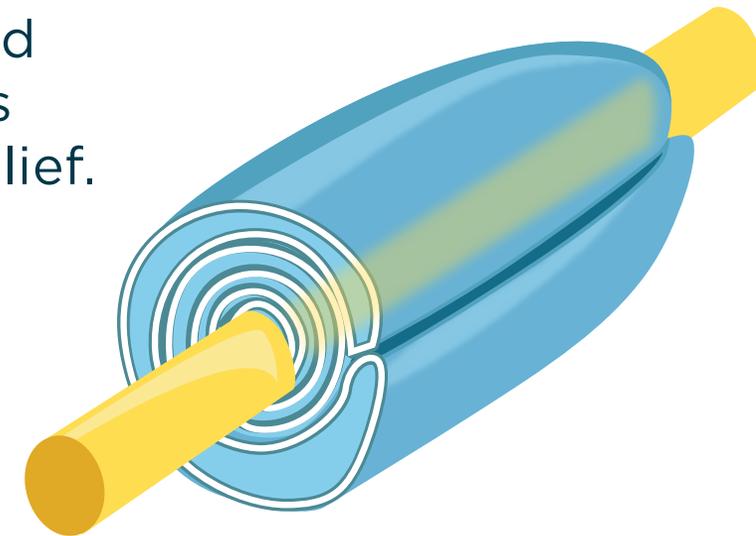
STUDY	POPULATION	TREATMENT	OUTCOME
Abrams (2007)	RCT (parallel group) in 55 patients with HIV-associated neuropathy.	Smoked cannabis (3.56% THC) or placebo cigarettes without cannabinoids 3 times/day for 5 days.	Smoked cannabis reduced daily pain by 34% vs. 17% in placebo group (p=0.03); greater than 30% reduction in pain was reported by 52% in cannabis group vs. 24% in control (p=0.04). The first cigarette reduced chronic pain by 72% in cannabis group vs. 15% in control (p<.001).
Ellis (2009)	RCT (crossover) in 34 patients with HIV-associated neuropathy.	Cannabis (1-8% THC) or placebo 4 times/day for 5 consecutive days/week for two weeks.	The proportion with pain reduction greater than 30% was 0.46 with cannabis vs. 0.18 with placebo; pain reduction was greater with cannabis than placebo (p=.016).
GW Pharma Ltd (2005)	RCT (parallel group) in 297 patients with diabetic peripheral neuropathy.	Nabiximols (Sativex) or placebo up to 24 sprays/day over 14 weeks.	There was no benefit of nabiximols over placebo in proportion of patients with pain reduction greater than 30%.
Selvarajah (2010)	RCT (parallel group) in 30 patients with diabetic peripheral neuropathy.	Nabiximols (Sativex) or placebo up to 4 sprays/day over 2 weeks.	There was no benefit of nabiximols over placebo on mean daily pain scores.
Wallace (2013)	RCT (crossover) in 16 patients with diabetic peripheral neuropathy.	Oromucosal spray (1%, 4%, and 7% THC) or placebo in single doses	There was a significant difference between placebo and all doses (p<.05) for spontaneous pain. High doses were significantly better than low/medium doses (p=.001). Only high doses were effective for evoked pain (p<.001).

Neuropathic Pain



- ▶ Another systematic review and meta-analysis of 18 double-blind randomized placebo-controlled trials of cannabis and cannabinoid treatments for chronic neuropathic pain also showed that cannabis and cannabinoids appear to reduce pain intensity. ([Martin-Sanchez 2009](#))
- ▶ 6 double-blind randomized controlled trials (n=226) studied the use of medical cannabis in neuropathic pain. All studies showed a statistically significant benefit in terms of pain relief. ([Deshpande 2015](#))

{ Cannabinoids are effective for the treatment of neuropathic pain. }



Rheumatoid Arthritis



A randomized, double-blind, placebo-controlled study in 58 patients with RA found that nabiximols oromucosal spray (Sativex) once daily for 5 weeks improved morning pain on movement, pain at rest and sleep quality. (Blake 2006)

Pain Endpoints after 5 Weeks of Treatment

EFFICACY ENDPOINTS	Baseline (mean/median)		Endpoint (mean/median)		Difference (mean/median)	P (95% CI)
	CBM	PLACEBO	CBM	PLACEBO		
Morning Pain on Movement	7.0	6.7	4.8	5.3	-0.95	0.044 (-1.83,-0.02)
Morning Pain at Rest	5.3	5.3	3.1	4.1	-1.04	0.018 (-1.90,-0.18)
Sleep Quality	5.7	5.8	3.4	4.6	-1.17	0.027 (-2.20,-0.14)

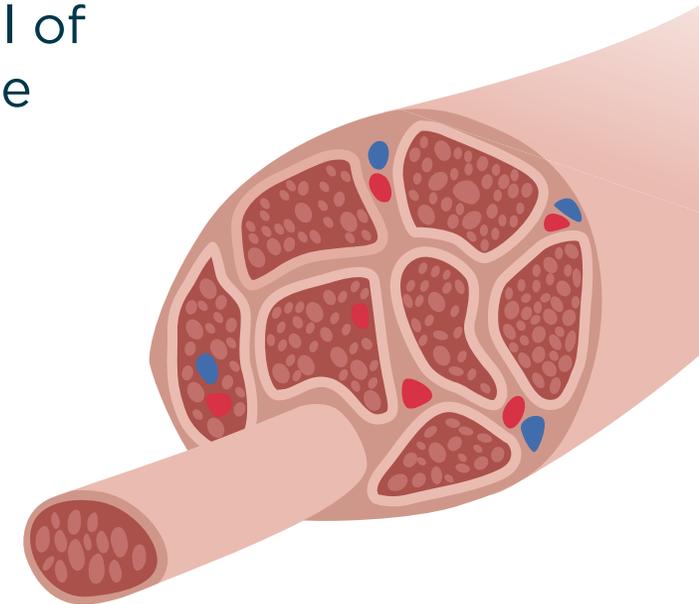
*a score derived from 15 adjectives describing pain Adapted from Blake 2006

Fibromyalgia



- ▶ A randomized placebo-controlled trial of 40 fibromyalgia patients found that nabilone (0.5 mg q.d. titrated up to 1 mg b.i.d. over 4 weeks) reduced pain and improved quality of life. (Skrabek 2008)
- ▶ A randomized double-blind placebo-controlled crossover trial of 32 fibromyalgia patients with neuropathic pain found nabilone (0.5-1.0 mg) equivalent to amitriptyline (10-20 mg) for pain. (Ware 2010)

{ There is evidence that cannabinoids are effective for pain associated with fibromyalgia. }



Acute Pain

RCTs have shown

- ▶ No effect of intravenous THC on dental extraction pain. (Raft 1977)
- ▶ No effect of THC capsules or sublingual spray on post-operative pain after abdominal hysterectomy. (Buggy 2003)
- ▶ Levonantradol* was to be no more effective than codeine for acute post-operative pain. (Campbell 2001)



*Levonantradol is a synthetic, potent analog of THC, usually given intramuscularly. Levonantradol is no longer used clinically.

{ Cannabis and cannabinoids are not recommended for acute pain. }



Cannabinoid-Opioid Interactions

- ▶ An RCT of dronabinol (10 or 20 mg) in patients taking opioids for chronic pain found that, compared to placebo, dronabinol reduced pain ($p < 0.01$) and increased patient satisfaction ($p < 0.05$).
 - There was no difference between 10 and 20 mg. ([Narang 2008](#))
- ▶ An RCT in 359 cancer patients with poorly controlled pain despite a stable opioid regimen (253 completed) found that Sativex (4, 10, or 16 sprays/day x 5 weeks) decreased pain and reduced sleep disruption.
 - The highest dose was less effective than the two lower doses. ([Portenoy 2012](#))
- ▶ An experimental pain study found that THC was ineffective as an analgesic on its own, but THC slightly augmented the effect of morphine in 2 of 3 measures. ([Naef 2003](#))

Cannabis-Opioid Interactions

- ▶ Only one study of opioid interactions tested cannabis instead of cannabinoids.
- ▶ A study of 21 patients with chronic pain treated with sustained-release morphine or oxycodone found that adding inhaled cannabis for 5 days
 - Significantly decreased pain by 27% (95% CI 9-46)
 - Had no significant effect on plasma opioid levels.

(Abrams 2011)

{ Co-administration of cannabis or cannabinoids with opioids is safe and may allow for use of lower doses of opioids. }



Chemotherapy-Induced Nausea and Vomiting (CINV)



A systematic review identified 28 RCTs (8 placebo-controlled, 20 treatment-controlled) with 1772 participants that examined the effects of cannabinoids on CINV.

- ▶ 14 studies tested nabilone (which mimics THC)
- ▶ 9 studies tested dronabinol (THC)
- ▶ 4 studies tested levonantradol (no longer used in medicine)
- ▶ 1 study tested nabiximols (THC and CBD)

(Whiting 2015)

**{ Studies generally showed a benefit
of cannabinoids for CINV. }**



Chemotherapy-Induced Nausea and Vomiting (CINV)



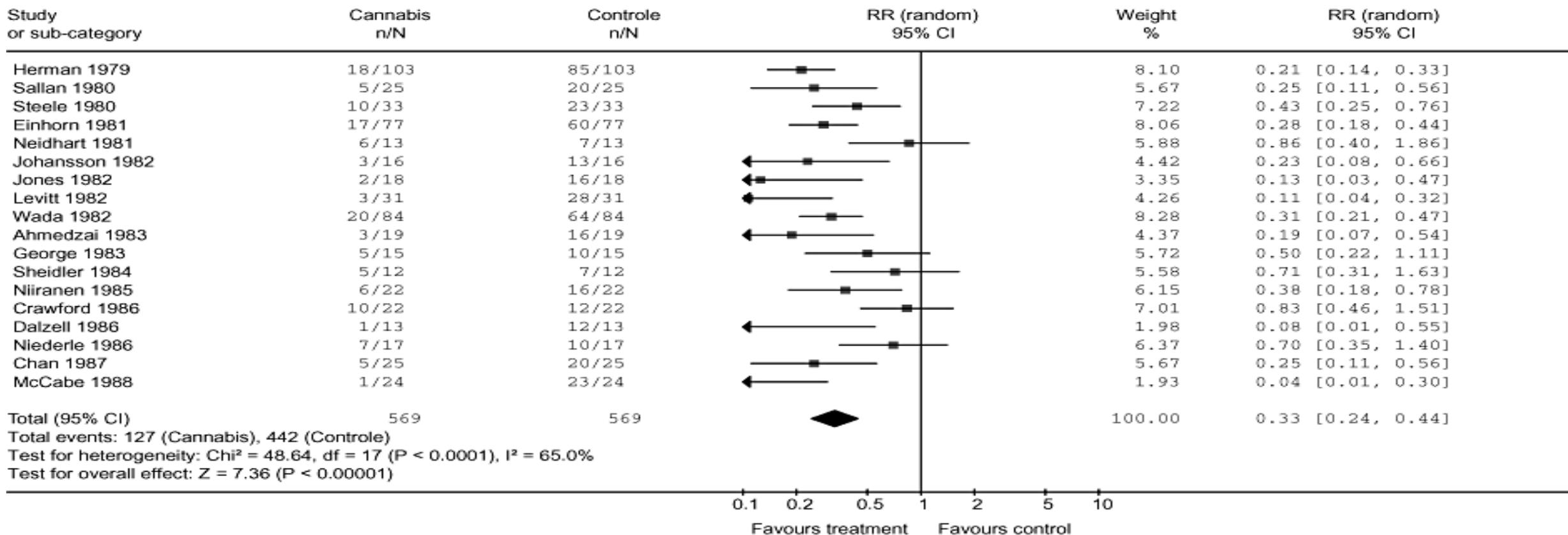
Another systematic review and meta-analysis of 30 randomized controlled trials with a total of 1,138 patients also found that

- ▶ Cannabinoids were more effective than placebo or neuroleptic drugs in reducing chemotherapy-associated nausea and vomiting.
 - ▶ Patients preferred cannabinoids.
- (Machado Rocha 2008)

In a Cochrane review, 23 RCTs compared cannabinoids to placebo or other anti-emetic drugs and found that

- ▶ People were more likely to report a complete absence of vomiting (n=168) or nausea/vomiting (n=288) with cannabinoids compared to placebo.
 - ▶ Cannabinoids were equivalent to prochlorperazine in four trials. There was no evidence of an additive effect when cannabinoids were added to other anti-emetics.
- (Smith 2015)

Chemotherapy-Induced Nausea and Vomiting (CINV)



(Machado Rocha 2008)

Induced Nausea and Vomiting

An RCT (not included in the review above) of 13 healthy patients found that for ipecac-induced nausea and vomiting.

- ▶ Smoked cannabis, compared with placebo, reduced “queasiness”; low doses also reduced vomiting.
- ▶ Ondansetron was more effective for both nausea and vomiting. (Soderpalm 2001)

Inhaled cannabis has modest anti-emetic effects in chemotherapy-induced nausea and vomiting and possibly other types of nausea/vomiting.



- ▶ Dronabinol (Marinol) is indicated for the treatment of anorexia associated with weight loss in patients with AIDS. (AbbVie 2015)
- ▶ A Cochrane systematic review of seven RCTs in patients with HIV/AIDS, ranging from 21-84 days, found variable effects of cannabis on appetite, weight, performance and mood. (Lutge 2013)
- ▶ One treatment-controlled trial found megestrol acetate more effective than dronabinol.
 - The combination was no more effective than megestrol alone. (Timpone 1997)



Cancer-related Anorexia Cachexia Syndrome (CACS)



- ▶ An RCT of 243 patients (164 completed) with CACS found no superiority of cannabis extract or THC over placebo for affecting appetite or quality of life. (Strasser 2006)
- ▶ A double-blind, RCT of 469 patients with CACS found that megestrol acetate was more effective than dronabinol for stimulating appetite and increasing weight gain.
 - Combined treatment was no more effective than megestrol acetate alone. (Jatoi 2002)



{ The effect of dronabinol on appetite and weight gain are small; megestrol acetate is superior. }

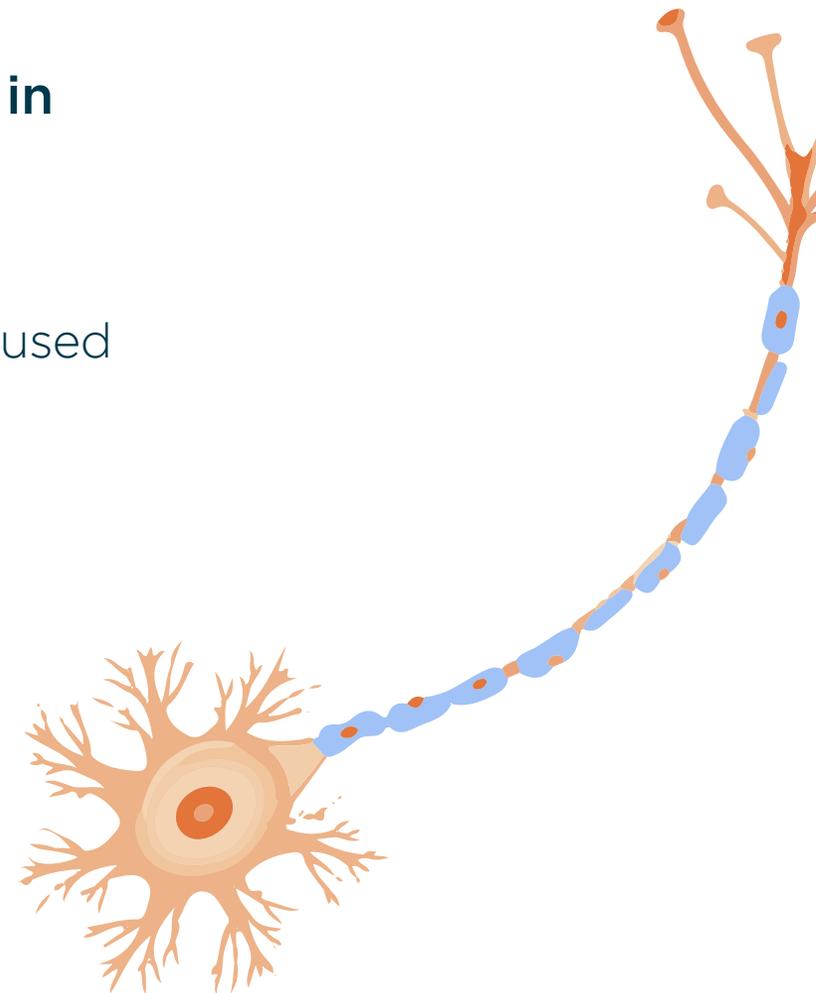
Spasticity

A systematic review identified 14 placebo-controlled trials in 2280 participants with spasticity. (Whiting 2015)

- ▶ 11 studies with 2138 subjects examined MS-associated spasticity
- ▶ 3 studies with 142 subjects examined spasticity in paraplegia caused by spinal cord injury.
- ▶ Studies tested nabiximols, dronabinol, nabilone, THC/CBD, ECP002A (THC) and smoked cannabis.

Studies tested nabiximols, dronabinol, nabilone, THC/CBD, ECP002A (THC) and smoked cannabis.

- ▶ No preparation seemed superior to other preparations.



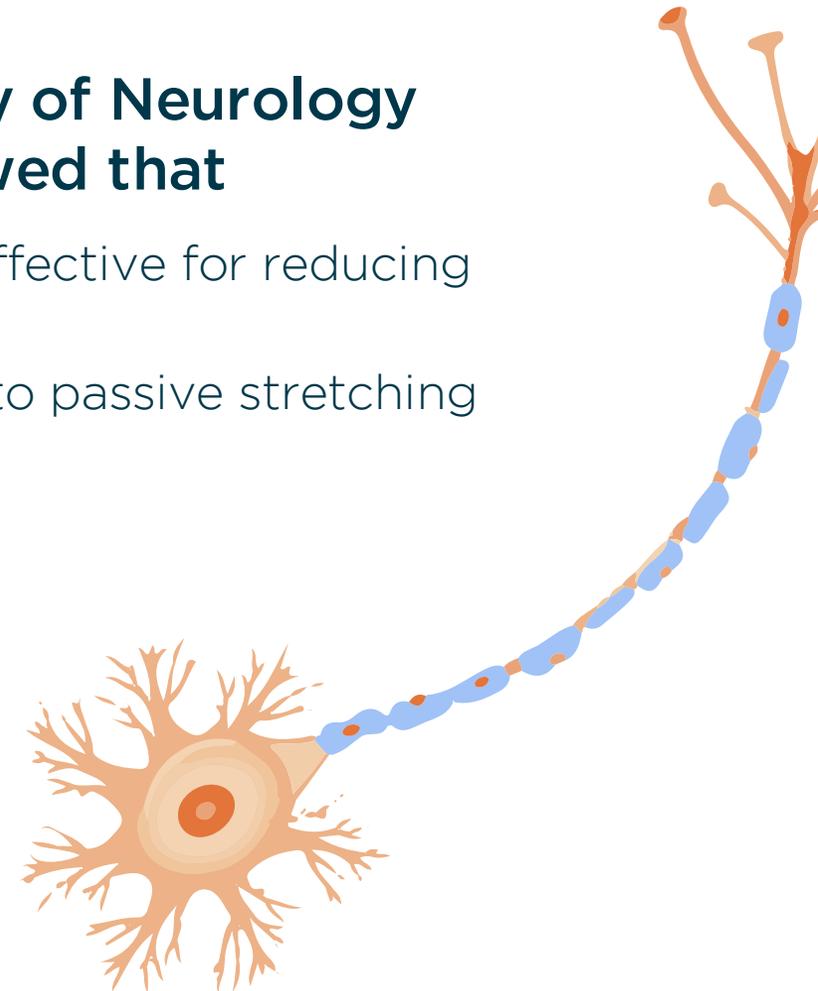
Spasticity

Another systematic review by the American Academy of Neurology included 17 studies of 1177 patients. The analysis showed that

- ▶ Oral cannabis extract, THC, and nabiximols were shown to be effective for reducing patient-reported spasticity.
- ▶ There was no effect on Ashworth Spasticity scores (resistance to passive stretching of soft tissues).

(Koppel 2014)

{ There is moderate evidence that cannabinoids are effective for spasticity. }



Pain and Tremor



Studies of patients with MS found that

- ▶ Nabiximols were effective for reducing central pain (pain initiated or caused by a primary lesion or dysfunction of the CNS) (Rog 2005), but not effective at reducing spasms. (Collin 2007)
- ▶ One study of smoked cannabis in 37 patients found that it reduced pain as a secondary outcome. (Corey-Bloom 2012)
- ▶ Six studies that included information on tremor found no improvement with THC, oral cannabis extract, or nabiximols. (Koppel 2014)



{ Evidence shows that nabiximols are effective for pain in MS patients, but have no effect on tremor. }

Bladder Dysfunction



An American Academy of Neurology systematic review included four studies on bladder dysfunction in MS. ([Koppel 2014](#))

- ▶ A study of 135 patients found no difference between nabiximols and placebo on incontinence, but showed a benefit of nabiximols on nocturia, overactive bladder symptoms, voids per day, and patient ratings. ([Kavia 2010](#))
- ▶ Three other studies that looked at bladder complaints as a secondary outcome found no benefit of nabiximols, THC or oral cannabis extract when compared to placebo. ([Wade 2004](#); [Vaney 2004](#); [Zajicek 2003](#))



{ Cannabinoids may be effective for some bladder conditions associated with MS. }

Huntington's Disease



An American Academy of Neurology systematic review included two double-blind crossover RCTs for symptomatic Huntington's Disease (HD). (Koppel 2014)

- ▶ A study in 44 patients compared nabilone (1 or 2 mg) to placebo and found no difference in effectiveness. (Curtis 2009)
- ▶ Another study evaluated 15 patients receiving CBD (10 mg/kg/d in 2 divided doses) or placebo and found no difference in effectiveness. (Consroe 1991)



{ Cannabinoids do not appear to be effective for Huntington's Disease. }

Parkinson's Disease



- ▶ An uncontrolled, observational study of 22 Parkinson's Disease patients found that motor symptoms improved from 33.1 at baseline to 23.2 after smoking cannabis, assessed by the Unified Parkinson's Disease Rating Scale. (Lotan 2014)
- ▶ A double-blind RCT of 7 Parkinson's disease patients found that nabilone administered prior to levodopa significantly reduced total levodopa-induced dyskinesia by 22.2%. (Sieradzan 2001)
- ▶ A double-blind crossover study of CBD extract found no beneficial effect in 19 patients with levodopa induced dyskinesias; some patients symptoms worsened. (Carroll 2004)

{ Insufficient evidence is available for the effect of cannabis or cannabinoids on Parkinson's symptoms. }

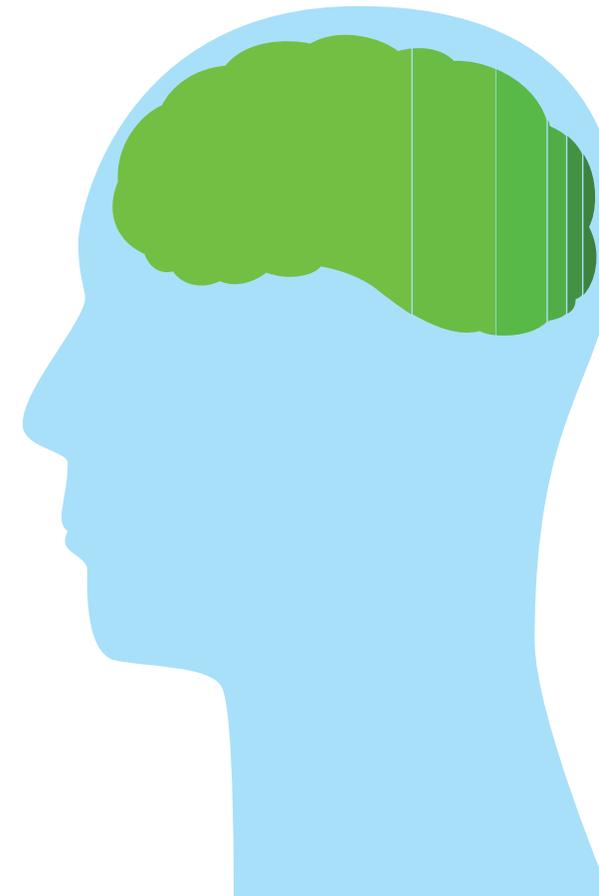


Alzheimer's Disease



No clinical trials of cannabinoids for dementia were identified, but cannabinoids have properties that may make them prospects for treating Alzheimer's disease.

- ▶ Cannabinoids reduce oxidative stress, inflammation, and formation of beta-amyloid plaques and neurofibrillary tangles. ([Ahmed 2015](#); [Eubanks 2006](#))
- ▶ THC binds to allosteric sites where beta-amyloid binds, and also promotes microglial migration, which permits removal of deposited beta-amyloid peptide. ([Martin-Moreno 2011](#); [Ramirez 2005](#))
- ▶ CBD has neuroprotective effects on beta-amyloid stimulated rat pheochromocytoma PC12 cells, inhibiting hyperphosphorylation of protein, which leads to formation of neurofibrillary tangles. ([Esposito 2006](#))
- ▶ CBD may reduce apoptosis. ([Iuvone 2004](#))



Tourette's Syndrome



A Cochrane review identified two RCTs of THC for Tourette's Syndrome (TS). [\(Curtis 2009\)](#)

- ▶ A double-blind placebo-controlled study in 24 TS patients (17 completed) found that THC (up to 10 mg/day x 6 weeks) was more effective than placebo on a self-rated symptom list and several other scales. [\(Muller-Vahl 2003\)](#)
- ▶ A double-blind placebo-controlled single dose crossover study in 12 TS patients found that THC (5.0, 7.5, or 10.0 mg) was more effective than placebo at decreasing motor tics and obsessive-compulsive behavior. [\(Muller-Vahl 2002\)](#)

**{ Limited evidence is available, but THC may be considered }
{ when treating patients with Tourette's Syndrome. }**

Seizures (Surveys and Case Studies)

- ▶ **Cannabis preparations are commonly used and recommended for seizure disorders.**
- ▶ A survey of parents belonging to a Facebook group that focused on the use of cannabidiol-enriched cannabis for seizures in children with early-onset, severe forms of epilepsy found that 16/19 parent respondents reported reduced seizure frequency in their children during treatment with cannabidiol-enriched cannabis.
 - Two reported complete seizure freedom, and eight reported > 80% reduction in seizure frequency. ([Porter and Jacobson 2013](#))
- ▶ A case report of a child with Dravet syndrome found that a high concentration CBD:THC strain of cannabis, now known as Charlotte's Web, reduced seizure frequency from nearly 50 seizures per day to 2-3 nocturnal convulsions per month.
 - This effect has persisted for almost 2 years, and Charlotte was weaned off of other antiepileptic drugs. ([Maa and Figi 2014](#))

Seizures (RCTs)

There have been four small trials of CBD for seizures.

STUDY	POPULATION	DOSE/DURATION	OUTCOME
Trembly (1990) Consroe (1992)	RCT (crossover) in 12 patients (unpublished abstract of conference presentation)	After 6 month placebo run-in, CBD 300 mg or placebo x 12 months.	There were no statistics performed; Consroe apparently states that 10/12 patients had no change in seizure frequency.
Cunha (1980)	RCT in 15 treated epilepsy patients (age 14-49) with frequent seizures	CBD 200-300 mg/day or placebo for 8-18 weeks	4/8 CBD-treated subjects remained seizure-free compared to 1/7 subjects receiving placebo. 3 treated subjects had partial improvement. At study end, 1 CBD-treated patient experienced no benefit, compared to 6/7 placebo-treated subjects.
Ames & Cridland (1985)	RCT in 12 institutionalized patients with mental retardation and uncontrolled seizures	CBD (300 mg x 1 week, then 200 mg x 2 weeks) or placebo	There was no difference in seizure frequency between CBD and placebo.
Mechoulam (1978)	RCT in 9 treated patients with seizures	CBD 200 mg or placebo x 3 months	2/4 CBD treated patients became seizure-free, compared to 0/5 placebo-treated patients.

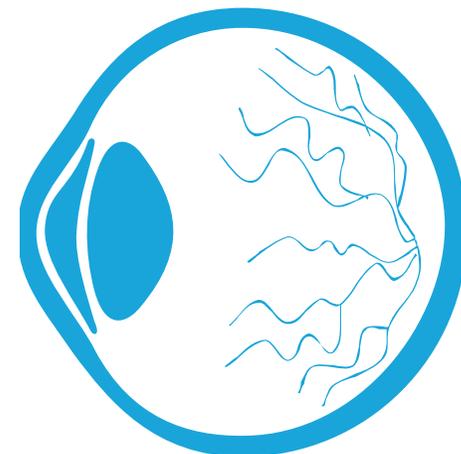
Seizures

- ▶ Larger studies of CBD for seizures are needed.
- ▶ Although robust evidence for the effectiveness of CBD for seizures is lacking, controlled clinical trials are ongoing.
 - ▶ For example, Epidiolex, a liquid form of CBD made by GW Pharmaceuticals, is being tested in a clinical trial that plans to enroll 150 pediatric patients age 1-18 with Dravet syndrome and other intractable epilepsies.

{ Cannabis can be considered for intractable seizures not controlled with medications, or when patients are unable to tolerate seizure medications. }

Glaucoma

- ▶ A small placebo-controlled crossover trial in 6 participants found smoking cannabis briefly reduces intraocular pressure (IOP).
 - A single dose of THC (5 mg sublingually) reduced IOP for less than 2 hours.
 - A single dose of CBD 40 mg (but not 20 mg) increased IOP transiently. (Tomida 2006)
- ▶ Smoking marijuana or ingesting THC may reduce IOP for several hours in patients with glaucoma, but sustaining this effect is not practical.
- ▶ Future research should include ocular cannabis formulations.



{ Oral or smoked cannabis for glaucoma is not recommended since effective medical treatments are available. }

Schizophrenia/Psychosis



A review of 19 studies examined the cognitive effects of cannabis compared to a placebo in schizophrenia patients.

- ▶ 11 studies reported better cognitive functions among cannabis users
- ▶ 5 found little or no difference between the groups
- ▶ 3 found poorer cognitive functions among cannabis users than non-users.

(Segev and Lev-Ran 2012)

**{ There is inconsistent evidence regarding
cannabis and schizophrenia/psychosis. }**

Anxiety



- ▶ A randomized controlled trial (RCT) of 10 patients with generalized Social Anxiety Disorder found that 400 mg CBD significantly decreased anxiety. (Crippa 2011)
- ▶ Two RCTs, one of 36 patients with generalized social anxiety disorder and another of 40 healthy volunteers, found that pretreatment with CBD reduced anxiety associated with a simulated public speaking test. (Bergamaschi 2011; Zuardi 1993)

**{ CBD may decrease anxiety
in patients. }**



Post-Traumatic Stress Disorder



- ▶ In a retrospective chart review of 80 Post-Traumatic Stress Disorder (PTSD) patients, cannabis use reduced symptom scores in the Clinician Administered Posttraumatic Scale. (Greer 2014)
- ▶ Another retrospective chart review of 47 PTSD patients found nabilone reduced or stopped nightmares in the majority of patients (72%). (Fraser 2009)

{ Anecdotal information suggests that cannabis may be effective as a treatment for PTSD, but no randomized controlled trials have been conducted. }



Depression



- ▶ No studies have been done using cannabinoids as treatment for depression.
- ▶ Five studies of cannabinoids for other conditions that reported depression as a secondary outcome measure found no benefit of cannabinoids on depression. (Whiting 2015)

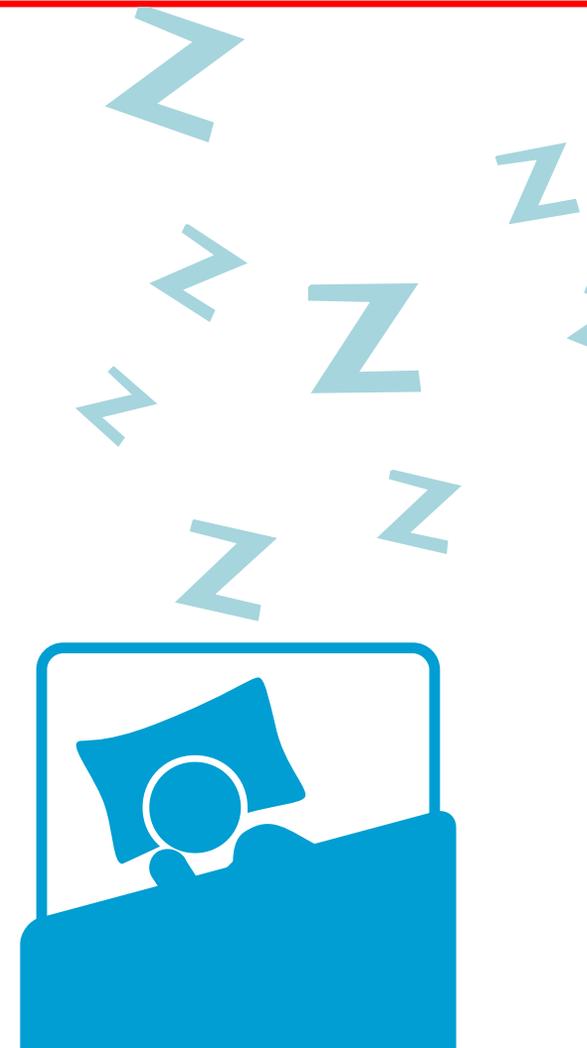
**{ Cannabinoids are ineffective
for treating depression. }**



Sleep Disorders

- ▶ A randomized treatment-controlled crossover trial in 29 fibromyalgia patients with chronic insomnia found that nabilone 0.5-1 mg/kg before bedtime was superior to amitriptyline for improving sleep. ([Ware 2010](#))
- ▶ A placebo-controlled study in 22 patients with obstructive sleep apnea syndrome found that dronabinol was superior to placebo on a sleep apnea/hypopnea index. ([Prasad 2011](#))
- ▶ 19 other studies that assessed sleep as a secondary outcome measure found that cannabinoids (primarily nabiximols) improved sleep quality. ([Whiting 2015](#))

{ Cannabinoids may help with some measures of sleep quality. }



Clinical Recommendations

CONDITIONS WITH EVIDENCE OF EFFICACY

- ▶ Cannabis is recommended for neuropathic pain.
- ▶ Cannabis can be a useful adjunct in treating cancer pain.
- ▶ Cannabis is effective for nausea and vomiting.
- ▶ Cannabis may be useful in some patients for stimulating appetite.
- ▶ Cannabis may help treat anxiety.
- ▶ There is moderate evidence that cannabinoids are effective for spasticity.



Clinical Recommendations

CONDITIONS WHERE THE EVIDENCE DOES NOT SUPPORT THE USE OF CANNABIS/CANNABINOIDS

- ▶ Acute pain
- ▶ Tremor in MS
- ▶ Huntington's disease
- ▶ Glaucoma
- ▶ Schizophrenia
- ▶ Depression

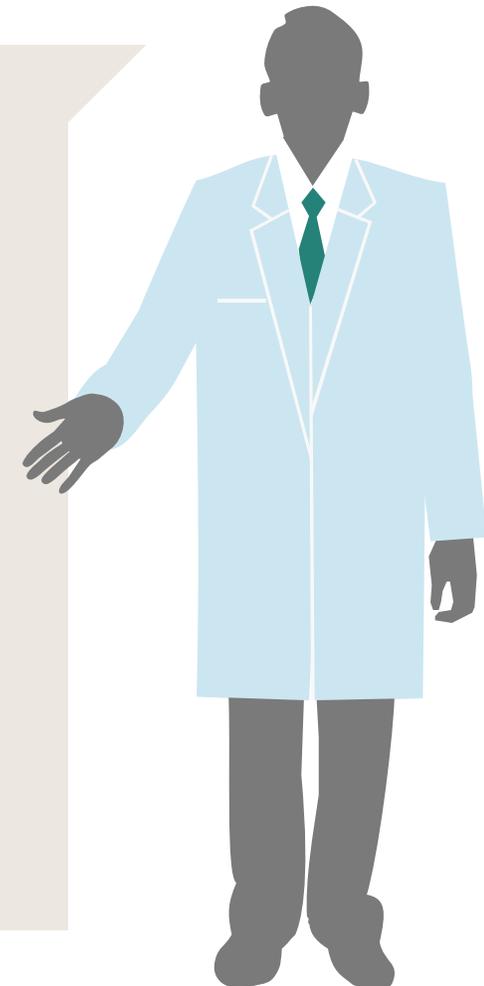


Clinical Recommendations

AREAS OF CAUTION

- ▶ Cannabis is contraindicated in those with a history of psychosis; current or past substance use disorder, cardiovascular or respiratory disease; pregnancy.
- ▶ Use caution in patients younger than 25.
- ▶ Use caution in patients with active mood disorders, those with risk factors for cardiovascular disease, and those who use high doses of alcohol or benzodiazepines.

{“Start low, go slow”}



Resources



DC Department of Health

doh.dc.gov



National Cancer Institute (NCI)

www.cancer.gov



International Cannabinoid Research Society (ICRS)

www.icrs.co



International Association for Cannabinoid Medicines (IACM)

www.cannabis-med.org

Resources



**University of California's Center
for Medicinal Cannabis Research**

www.cmcr.ucsd.edu



**The Canadian Consortium
for the Investigation of Cannabinoids**

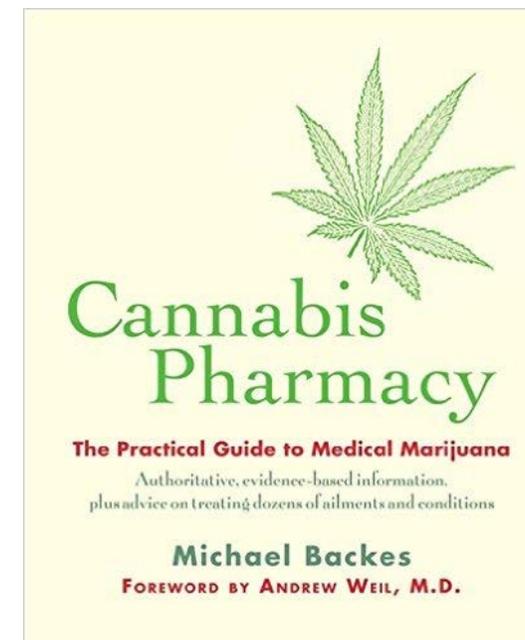
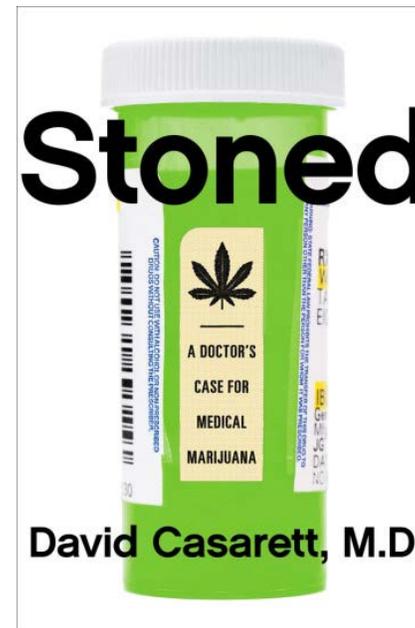
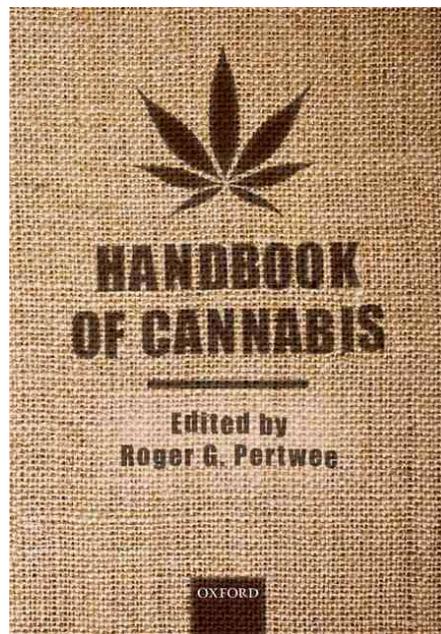
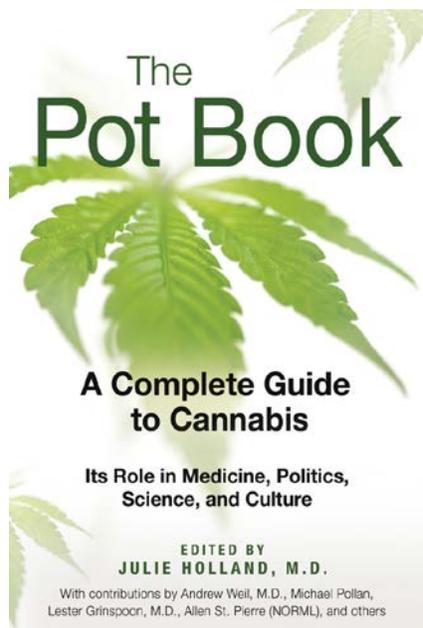
www.ccic.net



Patients Out of Time

www.medicalcannabis.com

Resources



Resources

For more information on prescribing in the District and to become a recommending physician visit:



doh.dc.gov/mmp

Please visit DCRx for a full list of references and more information on these and other treatment-related subjects.



doh.dc.gov/dcrx

Questions can be sent by email to doh.mmp@dc.gov or by regular mail to:

Medical Marijuana Program
Health Regulation and Licensing Administration
899 N. Capitol Street, NE
2nd Floor
Washington, DC 20002