CBD for Chronic Pain Management

Michael Saulino, MD, PhD
Physiatrist
MossRehab
Associate Professor,
Department of Rehabilitation Medicine
Thomas Jefferson University
Philadelphia, PA

Michael Saulino, MD, PhD

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- ***Speakers Bureau:*** Ipsen Biopharmaceuticals, Inc.; Medtronic; TerSera Therapeutics LLC

Learning Objective 1

Explain the potential therapeutic benefits of medicinal marijuana for pain management.

Cannabinoid Key

- CBGA = Cannabigerol acid –CBGA is the primary cannabinoid from which all other cannabinoids are derived
- CBDA = Cannabidiol acid—CBDA is the precursor to CBD
- CBD = Cannabidiol—CBD is produced from CBDA through the decarboxylation process
- THCA = Tetrahydrocannabinol acid—THCA is the precursor to THC and is typically most abundant cannabinoid produced in marijuana
- THC = Delta-9-Tetrahydocannabinol—THC is produced from THCA through the decarboxylation process. THC is reported to be the most psychoactive of the cannabinoids

Cannabinoid Key (cont.)

- Delta-8-THC = Delta-8-Tetrahydocannabinol—Delta-8-THC effects are reported to be very similar to delta-9-THC. This compound is almost never produced in any significant amount
- CBG = Cannabigerol—CBG is a non-psychoactive cannabinoid
- CBN = Cannabinol—CBN is the primary product of THC degradation

Pain Definitions

- Pain: An unpleasant sensory and emotional experience associated with actual or potential tissue damage
- Acute pain: pain typically lasting < 3 months, associated with healing of the underlying injury
- Chronic pain: pain typically lasting > 3 months and is independent of tissue status

Pain Definitions (cont.)

- Nociceptive: related to damage of the somatic or visceral tissue
- Neuropathic: related to damage of the peripheral or central nervous system
- Nociplastic: without identifiable nerve or tissue damage, thought to be related to persistent neuronal dysregulation

Stanos S, et al. *Postgrad Med.* 2016;128(5):502-515.

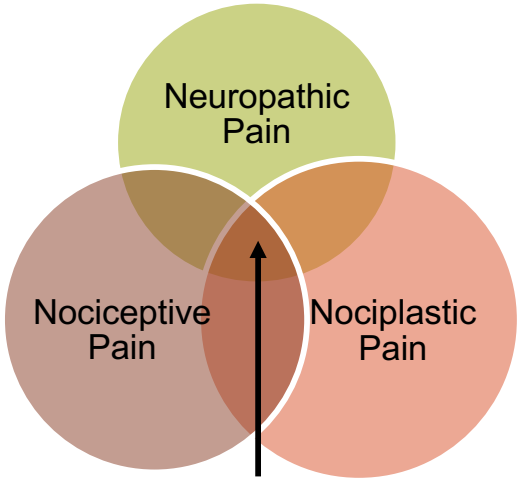
Chronic Pain Presentations

Predominantly Neuropathic

- Postherpetic neuralgia
- Painful diabetic peripheral neuropathy
- Lumbar or cervical radiculopathy
- Spinal Stenosis
- Tumor-related neuropathy
- Chemotherapy-induced neuropathy
- Small fiber neuropathy
- Persistent postoperative pain
- Multiple sclerosis pain
- Post-stroke pain
- Pain associated with spinal cord injury

Predominantly Nociceptive

- Osteoarthritis
- Rheumatoid arthritis
- Tendonitis, bursitis
- Ankylosing spondylitis
- Gout
- Neck and back pain with structural pathology
- Tumor-related nociceptive pain
- Sickle-cell disease
- Inflammatory bowel disease



Mixed pain conditions are frequently associated with multiple pain pathophysiologies once pain becomes chronic

Predominantly Nociplastic

- Fibromyalgia
- Irritable bowel syndrome
- Tension-type pain
- Interstitial cystitis/pelvic pain syndrome
- Tempo-mandibular joint disorder
- Chronic fatigue syndrome
- Restless leg syndrome
- Neck and back pain without structural pathology

Stanos S, et al. *Postgrad Med.* 2016;128(5):502-515.

Medicinal Marijuana and Pain

- Considered to be the most prevalent qualifying condition
- Most common conditions include cancer and neuropathic pain
- Most studies are of short duration, low dose and small sample size

Medicinal Marijuana and Pain (cont.)

- Most studies looked at chronic pain
- Significant methodologic problems
- Randomization, blinding, standardization of study product, selection bias, dropout description, short duration, mixed diagnoses, mixed methods of administration

Medicinal Marijuana and Pain (cont.)

- A great deal of case reports and case series
- 43 RCTs with standardized dosing
- NASEM evaluated more than 10,000 abstracts and established that there is “conclusive or substantial evidence” for the use of cannabis in treating chronic pain in adults
- Also concluded that there is “moderate evidence” that cannabinoids are effective in improving short-term sleep outcomes in patients with chronic pain

NASEM = The National Academies of Sciences, Engineering, and Medicine; RCT = randomized controlled trial.

Medicinal Marijuana and Pain (cont.)

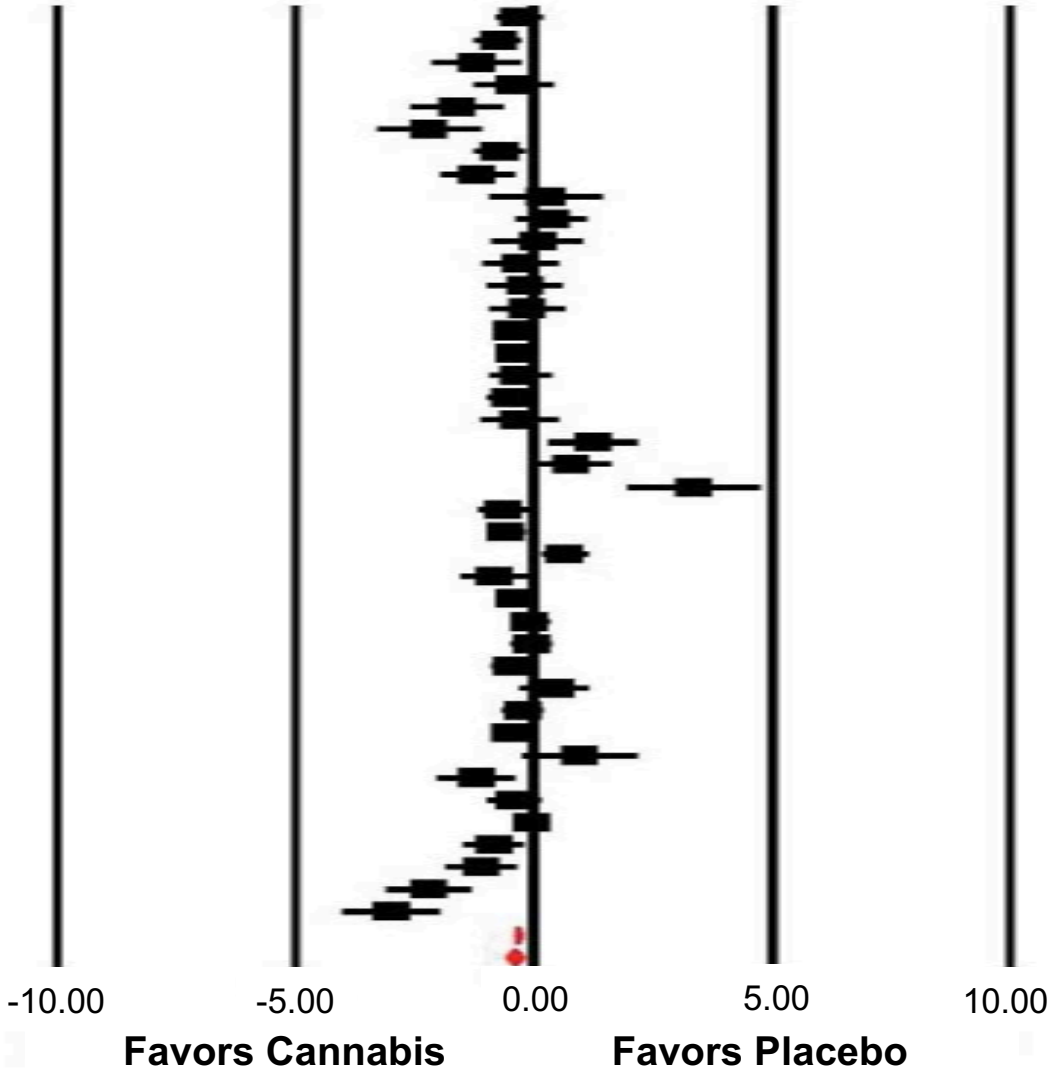
- Mixed results with fibromyalgia, headache and nociceptive pain
- Minimal evidence in acute pain
- Generally well tolerated

Medicinal Marijuana and Pain (cont.)

- Little evidence that CBD alone can be effective
- Some data to support pain relieving capacity of THC
- However, higher THC levels are associated with higher prevalence of adverse effects
- CBD ”cools” the THC “fire”

RCTs in Chronic Pain

Study Name	Outcome
Noyes 1975aI	THC10mg vs. Placebo
Noyes 1975aII	THC 20mg vs. Placebo
Noyes 1975bI	THC 5mg vs. Placebo
Noyes 1975bII	THC 10mg vs. Placebo
Noyes 1975bIII	THC 15mg vs. Placebo
Noyes 1975bIV	THC 20mg vs. Placebo
Staquet 1978a	NIB 4mg vs. Placebo
Staquet 1978b	NIB 4mg vs. Placebo
Buggy 2003a**	THC 5mg vs. Placebo
Buggy 2003b**	THC 5mg vs. Placebo, 2h
Buggy 2003c**	THC 5mg vs. Placebo, 4h
Wade 2003a	THC 2.5mg vs. Placebo
Wade 2003b	CBD 2.5mg vs. Placebo
Wade 2003c	THC\CBD 2.5mg vs. Placebo
Berman 2004a	GW-2000-02 (THC) vs. Placebo
Berman 2004b	GW-1000-02 (sativax) vs. Placebo
Wade 2004	Sativax vs. Placebo
Rog 2005*	Sativax vs. Placebo
Wissel 2006	Nabilone 1mg vs. Placebo
Beaulieu 2006a**	Nabilone 1mg vs. Placebo, movement
Beaulieu 2006b**	Nabilone 1mg vs. Placebo, rest
Beaulieu 2006c**	Nabilone 2mg vs. Placebo, movement
Blake 2006	CBM vs. Placebo
Nurmikko 2007*	Sativax vs. Placebo
Frank 2008	Nabilone 2mg vs. Dihydrocodeine 240mg
Skrabek 2008	Nabilone 0.5mg vs. Placebo
Wilsey 2008	3.5+7% cannabis cigarete vs. Placebo
Ware 2010a	2.5% cannabis cigarete vs. Placebo
Ware 2010b	6% cannabis cigarete vs. Placebo
Ware 2010c	9.4% cannabis cigarete vs. Placebo
Selvarajah 2010*	Sativax vs. Placebo
Johnson 2010a*	THC 2.7mg vs. Placebo
Johnson 2010b*	THC 2.5mg\CBD 2.5mg vs. Placebo
Rintala 2010	Dronabinol vs. Diphenhydramine
Toth 2012	Nabilone 1-4mg vs. Placebo
Pini 2012	Nabilone 0.5mg vs. Ibuprufen 400mg
Langford 2013a	THC 2.5mg\CBD 2.5mg vs. Placebo
Langford 2013b	THC 2.5mg\CBD 2.5mg vs. Placebo
Wallace 2015a	1% THC vaporizer vs. Placebo
Wallace 2015b	4% THC vaporizer vs. Placebo
Wallace 2015c	7% THC vaporizer vs. Placebo



CBM = cannabis-based medicine; CI = confidence interval;
NIB = nitrogen analog of tetrahydrocannabinol.
Aviram J, Samuelly-Leichtag G. *Pain Physician.* 2017;20(6):E755-E796.

RCTs in Chronic Neuropathic Pain

Wade 2003a	THC 2.5mg vs. Placebo
Wade 2003b	CBD 2.5mg vs. Placebo
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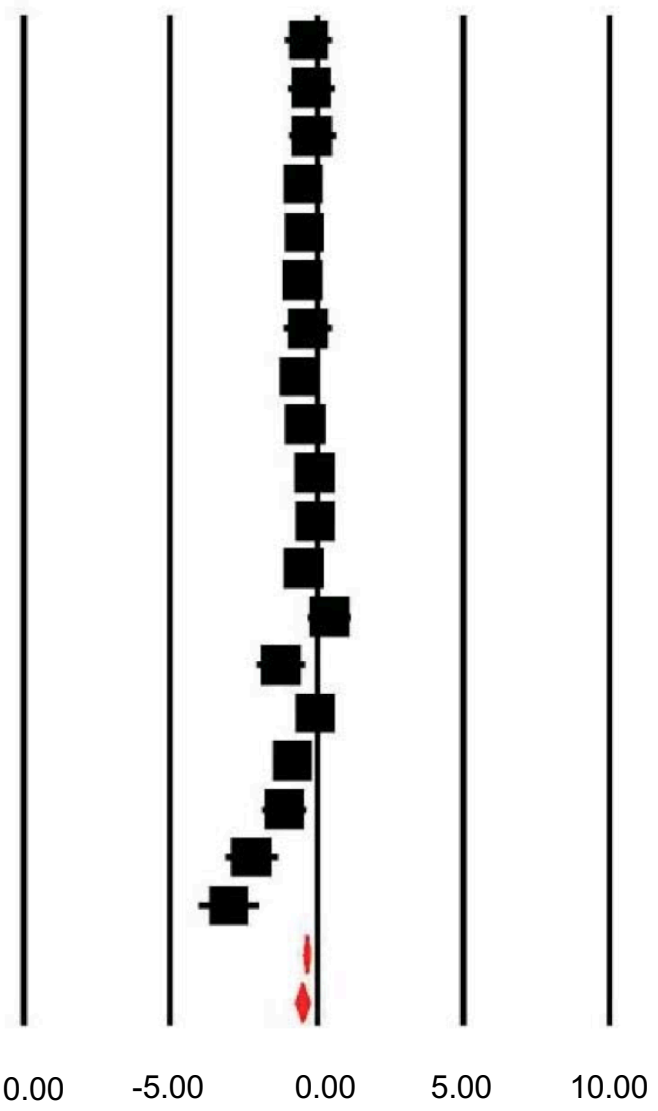

Aviram J, Samuelly-Leichtag G. *Pain Physician.* 2017;20(6):E755-E796.

RCTs in Chronic Cancer Pain

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Noyes 1975aII	THC 20mg vs. Placebo
Noyes 1975bI	THC 5mg vs. Placebo
Noyes 1975bII	THC 10mg vs. Placebo
Noyes 1975bIII	THC 15mg vs. Placebo
Noyes 1975bIV	THC 20mg vs. Placebo
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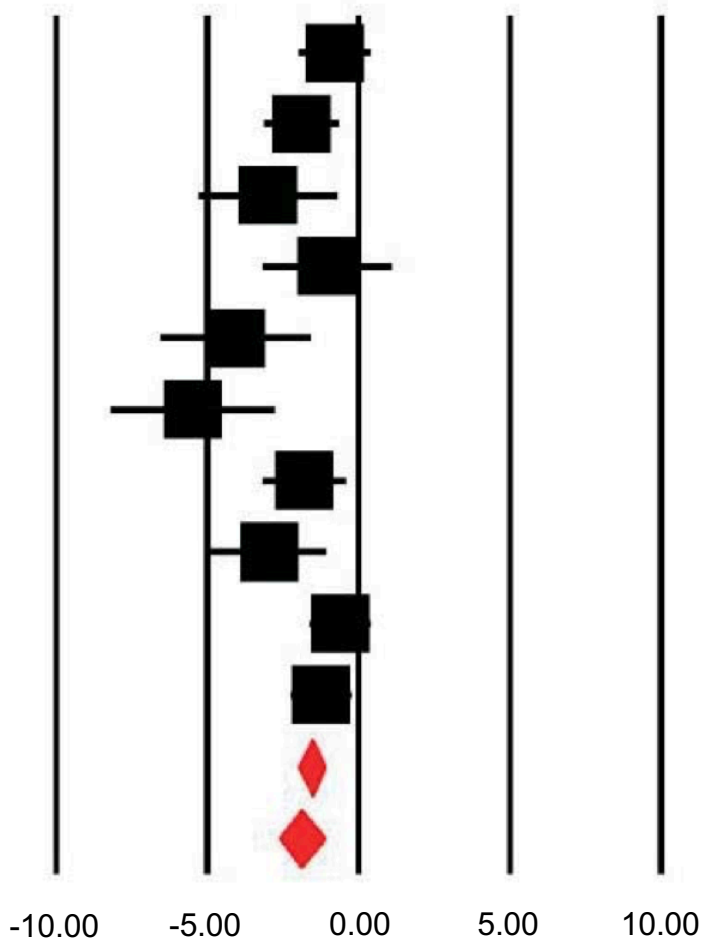

Aviram J, Samuelly-Leichtag G. *Pain Physician.* 2017;20(6):E755-E796.

Urine Drug Testing

- THC vs. THCV vs. CBD
- Typical cutoff is 50 ng/ml
- Single marijuana use: urine testing will remain positive for up to 3 days
- Moderate use: positive urine testing for up to 4 days
- Heavy use: positive for up to 10 days
- Chronic heavy use: positive for 30 days or more
- Passive exposure: typically results in < 10 ng/ml, NOT a valid explanation for a positive test result

THCV = tetrahydrocannabivarin.

Blood/Plasma Testing

- Smoking marijuana leads to peak plasma levels of 100-200 ng/ml within minutes
- Levels often drop below 5 ng/ml within 3 hours
- Oral preparations have lower peak and longer duration
- Washington State: Blood THC level of 5 ng/ml or greater is statutorily defined as driving under the influence – could potentially be positive with passive exposure
- Pennsylvania and New Jersey: defined on behavior

Salivary Analysis

- Reasonably good approximation to plasma level unless tested immediately after oral/buccal administration
- Commercially available
- Relatively inexpensive
- Point of care testing available for simple screening
- Quantitative testing takes 24-48 hours
- Some issues with false positives have been reported

Breath Analysis

- Not commercially available yet
- Will be available soon
- Unclear relationship to impairment

Perioperative Considerations with Medicinal Marijuana

- Vascular – tachycardia, ischemic stroke
- Higher risk of respiratory complications
- Postoperative hypothermia
- Difficulties with depth of anesthesia
- Variable effects on coagulation
- Perhaps some synergies with opiates
- Potentiate/prolong NMJ blockade
- Cannabis hyperemesis syndrome
- Cannabis withdrawal syndrome

NMJ = neuromuscular junction.

Medicinal Marijuana and Spasticity

- Most studied disease entity is MS, followed by SCI
- Typically evaluated in “moderate to severe” disease
- Mostly open label studies
- Perhaps the most positive take home point is tolerability and safety
- Fairly clear positive effects on patient self report of spasticity intensity
- Less clear evidence of objective decrease in spasticity
- Very little drop out – better compared to the current oral options
- Very few major adverse effects

MS = multiple sclerosis; SCI = spinal cord injury.

Cannabinoids in Multiple Sclerosis (CAMS) Study

- Randomized, placebo-controlled, 15-week trial
- 630 patients with stable MS and muscle spasticity in UK
- Positive effects on patient-reported spasticity and pain
- No evidence of treatment effects on change in Ashworth score or other measures of disability
- Some evidence of improvement in walking time for ambulatory patients
- Similar findings were seen in smaller open-label studies
  - Some subjective, but no observer-verified, improvement in disease-related spasticity

Zajicek JP, et al. *Lancet*. 2003;362(9395):1517-1526

CAMS Extension Study

- Double-blind trial out to 12-months
- Continued positive effects on patient-reported spasticity and pain
- Small treatment effect on objective measures at 12-months
- Extremely well tolerated

Zajicek JP, et al. *J Neurol Neurosurg Psychiatry*. 2005;76(12):1664-1669.

Nabiximols

- THC plus CBD (1:1) fixed ratio oromucosal spray
- Regulatory approval in about 30 countries outside of the U.S. for MS spasticity (some countries also have indication for MS neuropathic pain)
- About 12 RCTs are available for review in the literature with about 3 dozen open label studies to supplement
- Good evidence to support decreased subjective severity of spasticity – most of the trials use NRS as the primary outcome measure
- Far less conclusive evidence with objective measures

NRS = numerical rating scale.
Perras C. *Issues Emerg Health Technol*. 2005;(72):1-4.


PATIENTS


MON
TUE
WED
THU

Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.