HASHing It Out: Medical Uses for Cannabis

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Associate Dean and Professor

Strauss Lecture Series

November 10, 2016

The Story…


OPPORTUNITY AV
KNOCKING ST

Disclosures

Dr. Borgelt has no relevant financial disclosures.

Dr. Borgelt will be discussing unapproved drugs and uses.

Dr. Borgelt has served as a member of six working groups:

- Colorado Department of Public Health and Environment (CDPHE): Amendment 64 (Marijuana Legalization) Task Force Working Group: Consumer Safety and Social Issues
- State Licensing Authority Labeling, Packaging, Product Safety and Marketing
- State Licensing Authority Medical and Retail Marijuana Mandatory Testing and Random Sampling
- State Licensing Authority Serving Size and Product Potency
- CDPHE Retail Marijuana Public Health Advisory Committee
- CDPHE Pregnancy and Breastfeeding Guidelines Committee

Objectives

- Describe the pharmacology of cannabis.
- Evaluate and discuss clinical studies using medical cannabis that have been performed in patients with neuropathic pain.
- Compare and contrast clinical studies that have evaluated medical cannabis use in patients with pediatric epilepsy and other neurologic disorders.
- Review clinical studies that have evaluated medical cannabis use in patients with gastrointestinal disorders.

Audience Question

I know someone who consumes marijuana for medical or recreational purposes.

1. Yes, medical purposes only
2. No, recreational purposes only
3. Yes, both
4. No

Audience Question

I believe the most common reason people seek out marijuana is to...

1. relieve pain
2. improve symptoms of nausea and vomiting
3. relieve muscle spasms associated with multiple sclerosis
4. get high

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Marijuana

- Single molecule pharmaceuticals
  - Dronabinol (Schedule III)
  - Nabilone (Schedule II)
- Liquid extract: nabiximols (Sativex®)
  - Approved in 27 countries; U.S. - Phase III trials
- Liquid extract: cannabidiol (Epidiolex®)
  - FDA: orphan drug status for Dravet and Lennox-Gastaut syndromes
  - Expanded access INDs to several independent investigators
- Phytocannabinoid-dense botanicals
  - *Cannabis sativa* – medicinal plant (Schedule I)

Cannabis

- Plant-derived cannabinoids
  - Δ^9-tetrahydrocannabinol - THC
  - Δ^8-tetrahydrocannabinol - THC
  - Cannabidiol – CBD
  - Cannabinol - CBN
  - Cannabigerol - CBG
  - Cannabichromene - CBC
  - Cannabicyclol - CBL
  - Cannabielsoin - CBE
  - Cannbitriol - CBT
  - Miscellaneous
  - Cannabinodiol (air-oxidation)
- Terpenes
- Flavinoids
- And much more…

Br J Pharmacology 2006;147:S163-71 Br J Pharmacology 2011;163:1344-64

Audience Question

Which of the following receptors is a key target for THC?

1. Cannabinoid-1 receptor (CB1)
2. Cannabinoid-7 receptor (CB7)
3. Peroxisome Proliferator-Activated Receptors (PPAR)
4. G-protein receptor 55 (GPR55)
5. I have no idea ☺

Endogenous Cannabinoid System

- Endocannabinoids and their receptors found throughout body: brain, organs, connective tissues, glands, and immune cells.
- In each tissue, the cannabinoid system performs different tasks; goal is always homeostasis
- When cannabinoid receptors are stimulated, a variety of physiologic processes occur
  - CB1 receptors: nervous system, connective tissues, gonads, glands, organs
  - CB2 receptors: immune system and associated structures
- Endocannabinoids are substances our bodies make naturally to stimulate CB1 and CB2
  - Anandamide
  - 2-arachidonoylglycerol (2-AG)

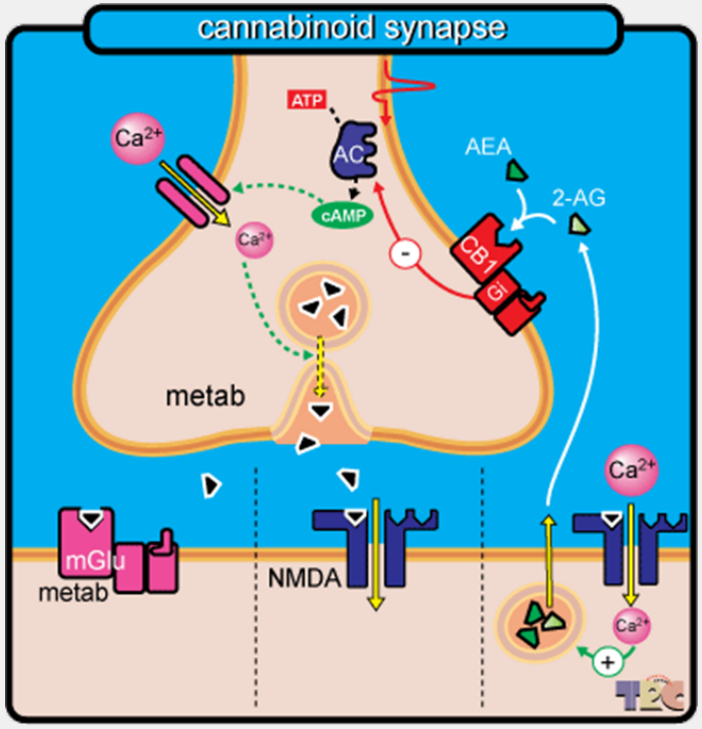
http://norml.org/library/item/introduction-to-the-endocannabinoid-system Accessed June 9, 2015
Neuro Endocrinol Lett. 2008 Apr;29(2):192-200.

Functional Effects of Anandamide at CB1 & CB2 Receptors

Structure	Anandamide regulates	Resultant effect
Spinal cord	Inhibit GLU & info transfer between body & brain	Decreased pain sensitivity
Parasympathetic system	Inhibit Ach release, HR regulation, urination regulation	HR stimulation, sometimes inhibits urination
Sympathetic system	Inhibit NE release, HR regulation, blood vessel constriction	Delayed reduction in HR and blood pressure
Neuronal cells	Inhibition GLU-induced excitotoxicity	Neuroprotective effect to prevent cell injury
Adipose tissue	Stimulates lipogenesis	Increased adiposity, insulin resistance
Reproductive tissue	Reduces testosterone, luteinizing hormone	Reduced fertility, altered menstrual cycle
Skin	Reduces histamine	Anti-pruritic effect
General	Role in relaxing, eating, sleeping, forgetting protecting	Provide relief from stress, reduction of injury
General	Inhibits immune B lymphocytes, natural killer cells	Anti-inflammatory activity

http://headsup.scholastic.com/students/more-facts-about-how-drug-abuse-puts-your-whole-body-at-risk

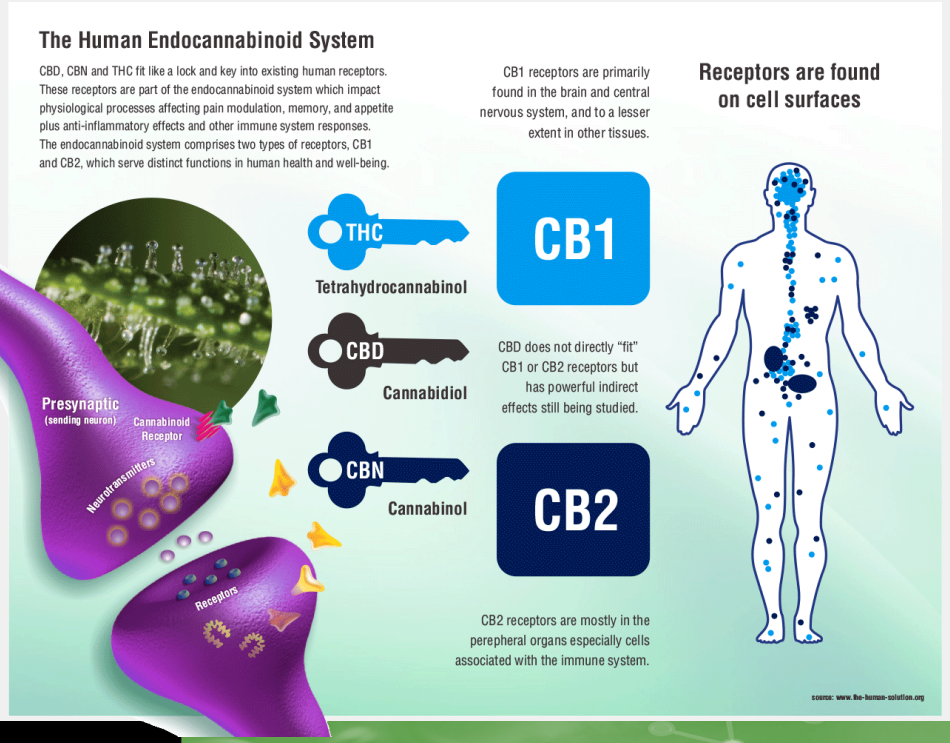
Endocannabinoid System



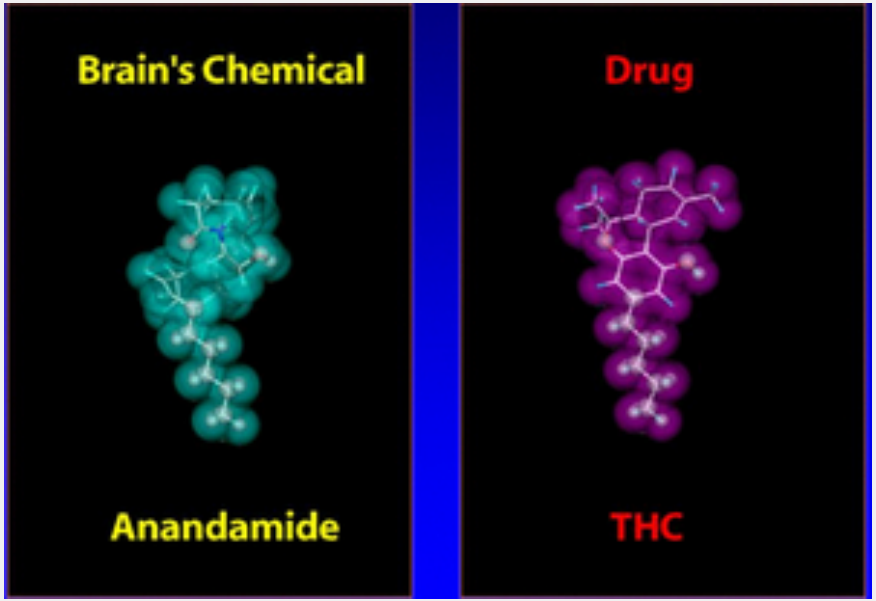
What happens when there is potential endocannabinoid deficiency, dysregulation, destabilization, or decreased binding?

Pertwee RG. Br J Pharmacology 2008;153:199-215.
Smith SC. Neuro Endocrinol Lett. 2014;35(3):198-201.

Endogenous Cannabinoid System Interfacing with Exogenous Cannabis

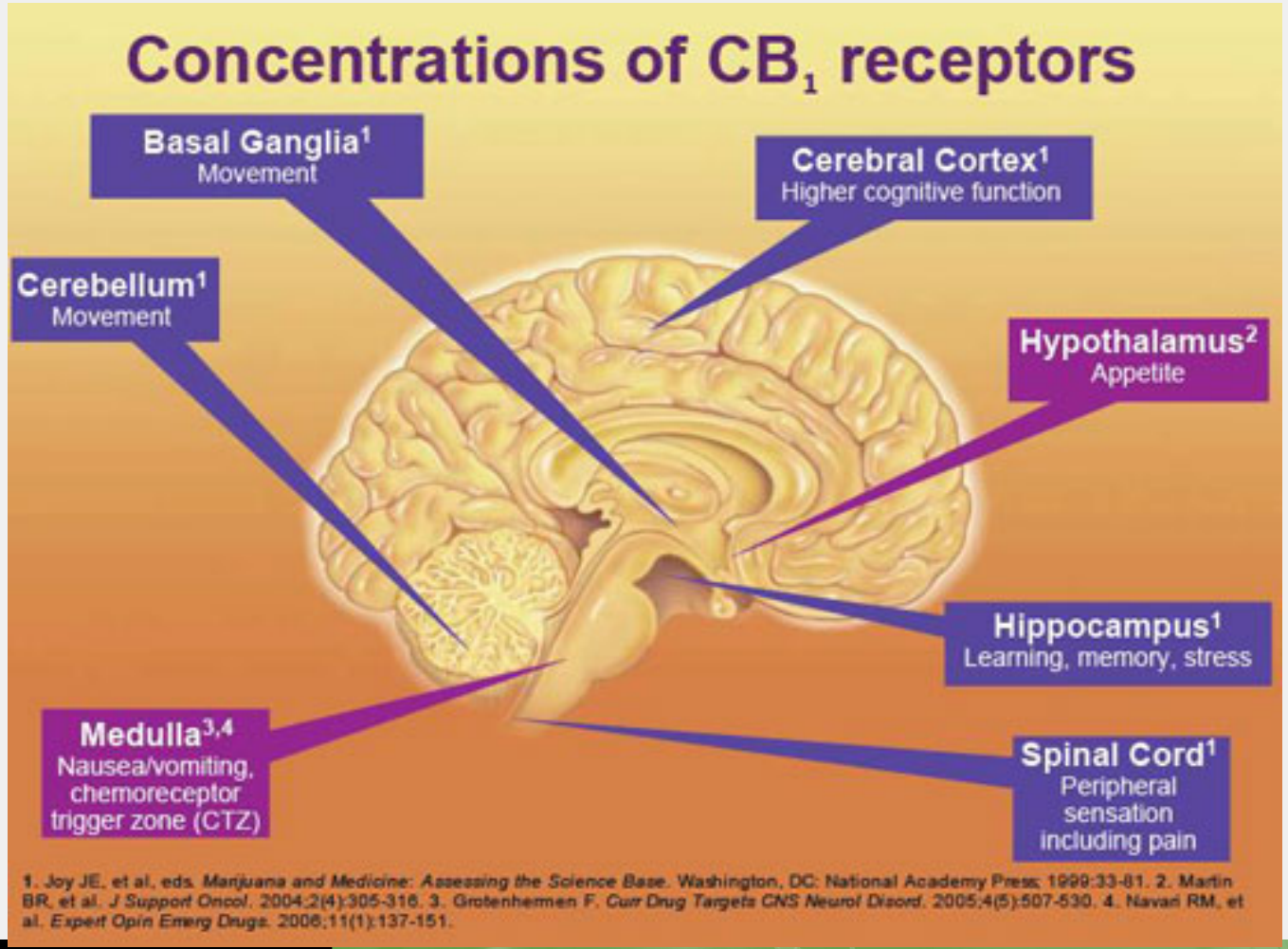


Cannabis Pharmacology



http://www.tokeofthetown.com/2011/03/worth_repeating_bodys_own_cannabinoids_are_the_bli.php

Concentrations of CB_1 receptors



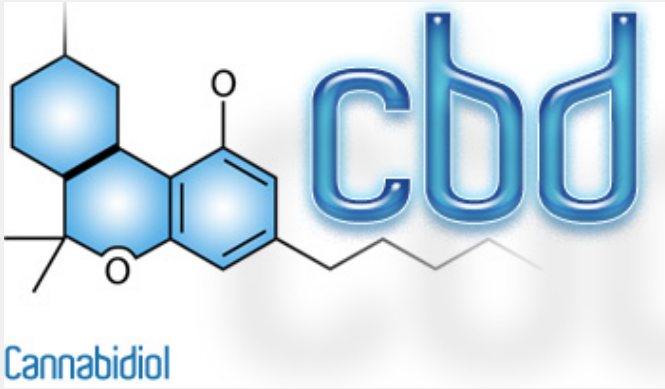
1. Joy JE, et al, eds. *Marijuana and Medicine: Assessing the Science Base*. Washington, DC: National Academy Press; 1999:33-81. 2. Martin BR, et al. *J Support Oncol*. 2004;2(4):305-316. 3. Grotenhermen F. *Curr Drug Targets CNS Neurol Disord*. 2005;4(5):507-530. 4. Navari RM, et al. *Expert Opin Emerg Drugs*. 2006;11(1):137-151.

Non-Cannabinoid Targets Linked to Cannabis

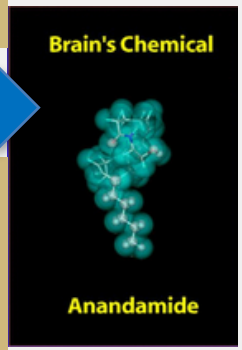
- Other G-protein receptors: GPR55, GPR55940, etc.
- G-protein-coupled receptors: noncompetitive inhibitor at μ- and δ-opioid receptors, NE, DA, 5-HT
- Ligand-gated ion channels: allosteric antagonism at 5-HT3, nicotinic, and enhance activation of glycine receptors
- Transient receptor potential channels (TRPVs): bind and activate TRPV1 *similar to capsaicin*, also CB1 receptors are located near TRPV1
- Ion channels: inhibition of Ca, K, Na channels by non-competitive antagonism
- Peroxisome Proliferator-Activated Receptors: PPARα and PPARγ are activated

N Engl J Med 2015;373:1048-58. Bioorg Med Chem 2015;23:1377-85.

Another Kid on the Block…Cannabidiol (CBD)



Little binding affinity to CB1/CB2

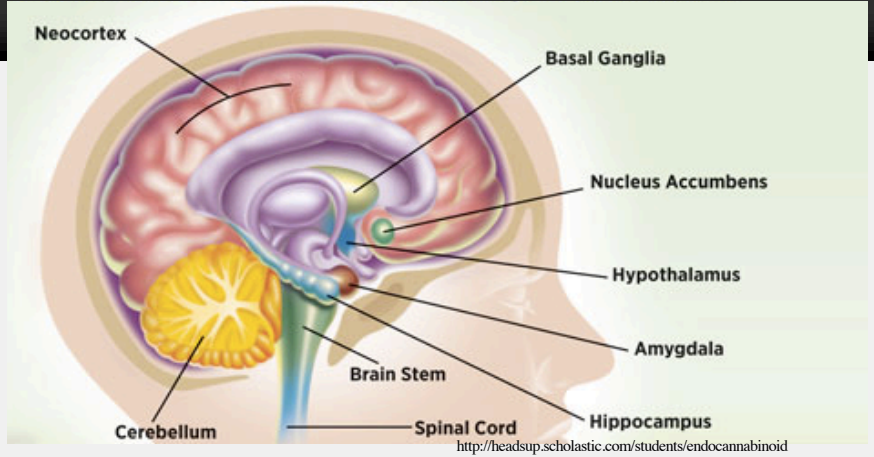


Suppresses enzyme fatty acid amide hydroxylase (“FAAH”) – enzyme that breaks down anandamide

- **Opposes THC at CB1 receptor**
- **Stimulates release of 2-AG**
- **TRPV-1 receptor agonist**
- **5-HT1A receptor activation**
- **GPR55 antagonist**

Epilepsia 2014;55(6):791–802. http://www.projectcbd.org/news/how-cbd-works/ Accessed 06/13/16

Cannabis Activity at CB1 Receptors



http://headsup.scholastic.com/students/endocannabinoid

Structure	THC effect	
Neocortex	Altered thinking, judgement	
Basal ganglia	Slowed reaction time	
Hypothalamus	↑ appetite	1992
Amygdala	Panic, paranoia	
Nucleus accumbens	Euphoria	
Hippocampus	Impaired memory	
Cerebellum	Impaired coordination	
Brain stem	Anti-nausea effects	1985
Hippocampus, forebrain	Anti-epileptic effects ?	
Spinal cord	Altered pain sensitivity	1996

3 Routes of Administration

LUNGS

Vaporized or Smoked

Onset: sec-min
Duration: 2-3 hrs

GUT

Oral Ingestion

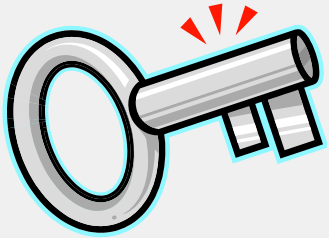
Onset: 0.5-2+ hrs
Duration: 5-8 hrs

SKIN

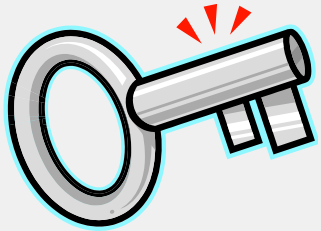
Topical Application

Onset: 15-40 min
Duration: 0.75-2 hrs

Clin Pharmacol Ther 2007;82:572-8. Clin J Pain 2013;29:162-71.



Key Opinion

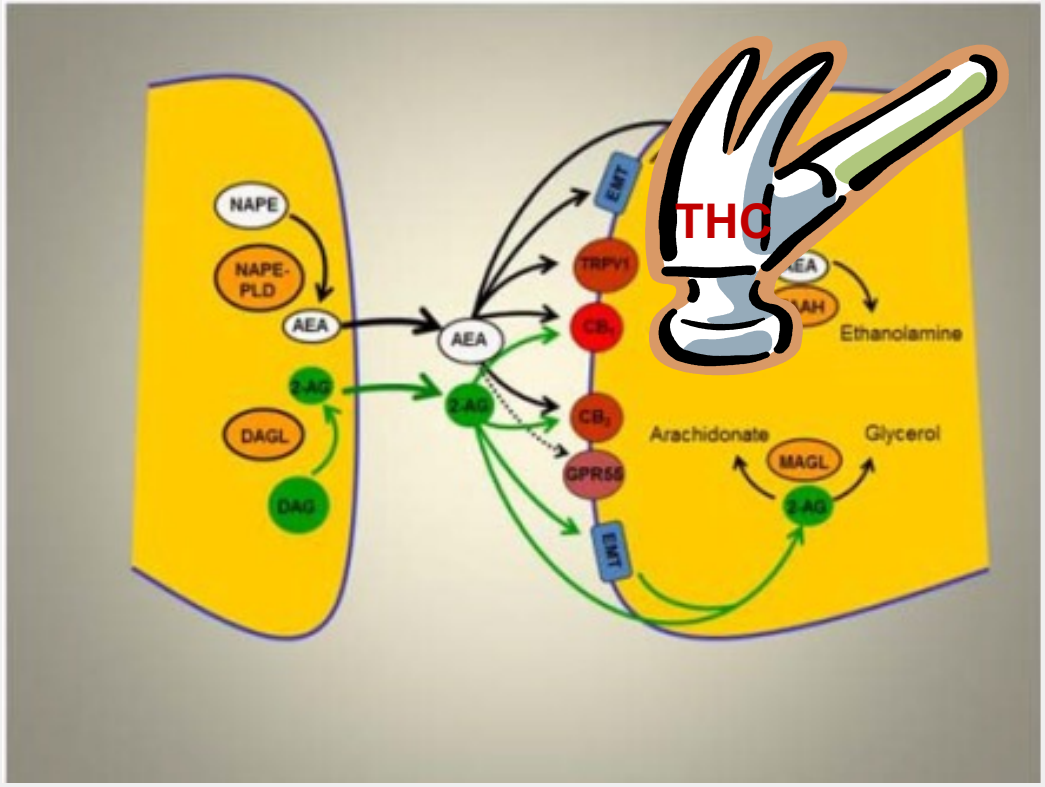


Considerations for medical use of marijuana are different than considerations for recreational use of marijuana.

Medical use: benefit – risk

Recreational use: risk - risk

Summary: Endocannabinoid System and THC



Reprinted with permission. Nat Rev Gastroenterol Hepatol. 2014;11(3):142-3

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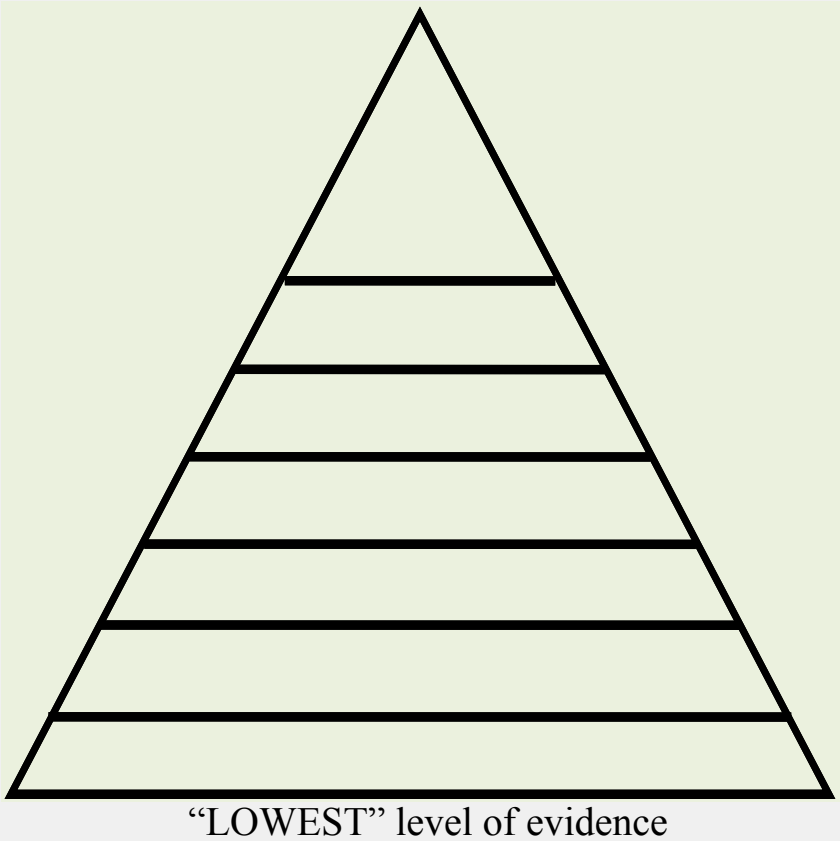
Patient Experience with MMJ

- VIDEO: Teri Robnett

https://www.youtube.com/watch?v=eyw1utFTaug

How Should MMJ Be Studied?

A. Blog
B. Case control study
C. Case report
D. Case series
E. Cohort study
F. Meta-analysis
G. My opinion
H. Randomized controlled trial
I. Review article



Cannabinoids for Medical Use: Systematic Review and Meta-Analysis

CONDITION	# TRIALS*	Result vs. placebo % efficacy	Conclusion
Nausea/vomiting due to chemotherapy	3	Complete response OR 3.82 (95% CI 1.55-9.42) 47% vs 20%	Low-quality evidence suggesting improvements
Chronic pain	8	Reduction of 30% or more in pain OR 1.41 (95% CI 0.99-2.00) 37% vs 31%	Moderate-quality evidence to support use
Spasticity related to MS or paraplegia	8	Ashworth spasticity scale WMD** -0.12 (95% CI -0.24 to 0.01)	Moderate-quality evidence to support use

*Variety of cannabinoid products evaluated

**WMD: weighted mean difference

**Common AEs of cannabinoids included dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucination.

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

Inhaled Cannabis for Neuropathic Pain: Meta-Analysis of Individual Data

- Synthesizes the individual participants' original data obtained from the studies' principal investigators
- Five randomized controlled trials evaluating inhaled cannabis
- Compared proportion of patients experiencing >30% clinical improvement in chronic neuropathic pain assessed with a continuous patient-reported instrument (e.g., visual analog scale) at baseline and after inhaled cannabis

RESULTS

- 178 patients with 405 observed responses
- Estimated OR (CRI) for >30% ↓ in pain score: 3.22 (1.59-7.24)
- Number needed to treat (CRI): 5.55 (3.35-13.7)

Note: gabapentin NNT 5.9 (4.6-8.3) for diabetic neuropathy

J Pain 2015;16:1221-32. Cochrane Database of Systematic Reviews 2014, Issue 4. Art. No.: CD007938.

Adverse Effects

- Serious Adverse Effects (SAEs)
  - Placebo: 1 (psychosis)
  - Cannabis: 2 (hypertension, increased pain)
- Mild adverse effects
  - Anxiety, disorientation, difficulty concentrating, headache, dry eyes, burning sensation, dizziness, and numbness
  - Psychoactive effects (such as feeling “high”) were statistically significantly associated with treatment allocation in 2 studies and increased in frequency with increasing dose

J Pain. 2015 Dec;16(12):1221-32. doi: 10.1016/j.jpain.2015.07.009. Epub 2015 Sep 9.

Limitations and Conclusions

- Ineffective participant blinding
- Placebo effects likely
- Different causes of neuropathy
- Small number of studies and participants
- Difficult to estimate bioavailable cannabis
- Short-term data only (up to two weeks)

Inhaled cannabis results in short-term reductions in chronic neuropathic pain for 1 in every 5 to 6 patients treated.

J Pain. 2015 Dec;16(12):1221-32. doi: 10.1016/j.jpain.2015.07.009. Epub 2015 Sep 9.

Crossover Study: Low-dose Vaporized Cannabis

- Objective: evaluate analgesic efficacy in patients with neuropathic pain despite traditional treatments
- Visual analog scale (0-100)
- 39 patients with previous cannabis exposure
  - 28 male/11 female
  - Avg age 50 years
- Vaporized cannabis
  - Medium-dose (3.53%)
  - Low-dose (1.29%)
  - Placebo

INHALED CANNABIS	
Number of episodes	111
≥30% ↓ in VAS Placebo Low-dose Med-dose	Number [% (95%CI)} 10/38 [26% (15-42%)] 21/37 [57% (41-71%)] 22/36 [61% 45-75%)]
Statistical significance P vs Low: p=0.0069 P vs Med: p=0.0023 Low vs Med: p=0.7	
NNT: Low	3.2
NNT: Med	2.9

J Pain. 2013 Feb;14(2):136-48. doi: 10.1016/j.jpain.2012.10.009.

Smoked Cannabis for Chronic Neuropathic Pain

- 21 adults post-traumatic or post-surgical neuropathic pain
- Cannabis 25 mg at 0%, 2.5%, 6%, and 9.4% THC smoked 3x/day
- Four 14-day periods in crossover trial
- Primary outcome: pain intensity (11-item scale)

RESULTS

- Pain intensity
  - 9.4%: score = 5.4
  - 0%: score = 6.1
  - (p=0.023; difference 0.7, 95% CI 0.02-1.4)
- Sleep (more drowsiness, getting to sleep more easily, faster, and with less wakefulness)
  - 9.4% vs 0%: $p<0.05$
- Anxiety and depression improved (EQ5D)
  - 9.4% vs 0%: $p<0.05$
- Adverse events
  - 248 mild; 6 moderate (fall, ↑pain, numbness, drowsiness, pneumonia)

CMAJ. 2010 Oct 5;182(14):E694-701. doi: 10.1503/cmaj.091414

MMJ in Painful HIV-Associated Sensory Neuropathy: Systematic Review and Meta-Analysis

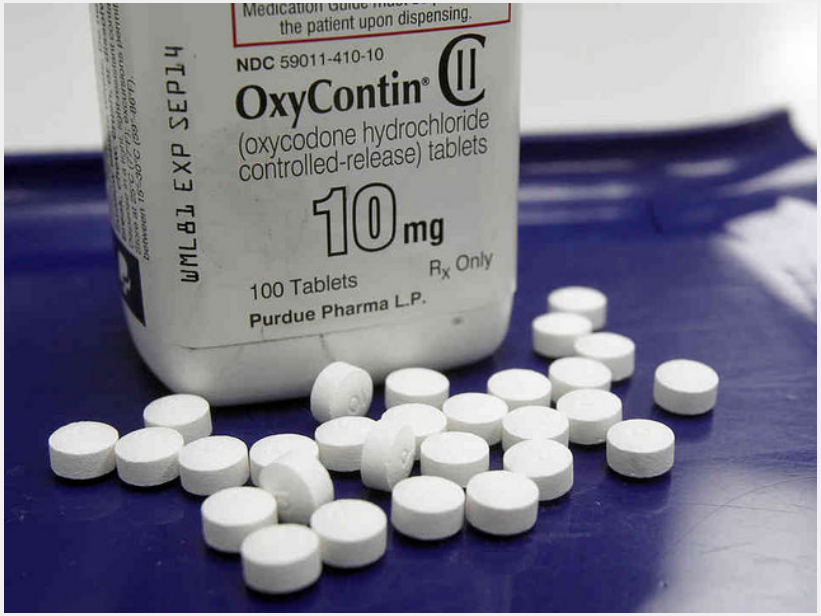
- Objective: evaluate clinical effectiveness of various analgesics
- Total of 14 trials evaluated
- Smoked cannabis 1-8% and capsaicin 8% found to be effective

SMOKED CANNABIS	
Number of episodes	122
≥30% improvement in VAS	31/61
≥50% improvement in VAS	15/61
RR (95% CI)	2.38 (1.38 to 4.10)
NNT (95% CI)	3.38 (2.19 to 7.50)

*NNT for capsaicin 8% = 6.46 (3.86-19.69)

PLoS ONE [Electronic Resource]. 5(12):e14433, 2010

Medical Cannabis and Opioid Use



The JAMA Network

From: **Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010**

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.

This association strengthened over time

Year 1 (–19.9%; 95% CI,–30.6% to -7.7%; *P* = .002)
Year 2 (–25.2%; 95% CI,–40.6% to –5.9%; *P* = .01)
Year 3 (–23.6%; 95% CI,–41.1% to –1.0%; *P* = .04)
Year 4 (–20.2%; 95% CI,–33.6% to –4.0%; *P* = .02)
Year 5 (–33.7%; 95% CI,–50.9% to -10.4%; *P* = .008)
Year 6 (–33.3%; 95% CI,–44.7% to -19.6%; *P* < .001)

JAMA Intern Med. 2014;174(10):1668-1673. doi:10.1001/jamainternmed.2014.4005

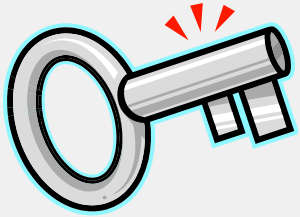
Medical Cannabis and Opioid Use

- 244 medical cannabis patients with chronic pain in Michigan
- Survey of 46 questions
  - Medical condition(s) for which cannabis was used
  - Method/frequency of cannabis use
  - Changes in noncannabis medication use
  - Changes in medication side effects
  - Quality of life changes since starting cannabis use
  - Demographic information
  - 2011 Fibromyalgia Survey Criteria (0-31 score)

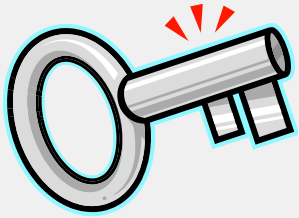
J Pain. 2016 Jun;17(6):739-44. doi: 10.1016/j.jpain.2016.03.002. Epub 2016 Mar 19.

OUTCOME OF INTEREST	PATIENT RESPONSES (n=244) Mean (SD)
Fibromyalgia score (0-31)	9.23 (5.52)
Opioid use change	−63% (46%)
Degree to which side effects of medication affect daily function (before using medical cannabis); scale from 1 to 10	6.44 (2.91)
Degree to which side effects of medication affect daily function (after using medical cannabis); scale from 1 to 10	2.77 (2.35)
Number of medication classes used (before cannabis use)	2.35 (1.43)
Number of medication classes used (after cannabis use)	1.82 (.94)
Quality of life change	45% (28%)

J Pain. 2016 Jun;17(6):739-44. doi: 10.1016/j.jpain.2016.03.002. Epub 2016 Mar 19.



Summary



Cannabis may have a role in chronic pain, especially neuropathic pain when patients have failed other treatments. Mortality from and use of opioids appears to decrease with cannabis use. Adverse effects do occur so benefits and risks should be weighed for individual patients while considering patient safety and public health concerns.

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Pediatric Epilepsy: AES Annual Meeting 2015

- 261 children (average age 11 years)
- Severe epilepsy not responding to other treatments
- Epidiolex given in increasing doses with other AEDs (avg=3)
- After 3 months of treatment
  - 45% lower frequency of seizures
  - 47% experienced ≥50% reduction in seizures
  - 9% seizure-free
  - Dravet syndrome patients: 62% reduction in seizures, 13% seizure free
  - Lennox-Gastaut patients: 71% reduction in atonic seizures
- Adverse effects (>10%)
  - Sleepiness, diarrhea, fatigue (4% discontinued treatment)
- Serious adverse effects: 5% treatment-related
  - Altered liver enzymes, status epilepticus, diarrhea and others
- Lack of efficacy caused 12% withdrawal

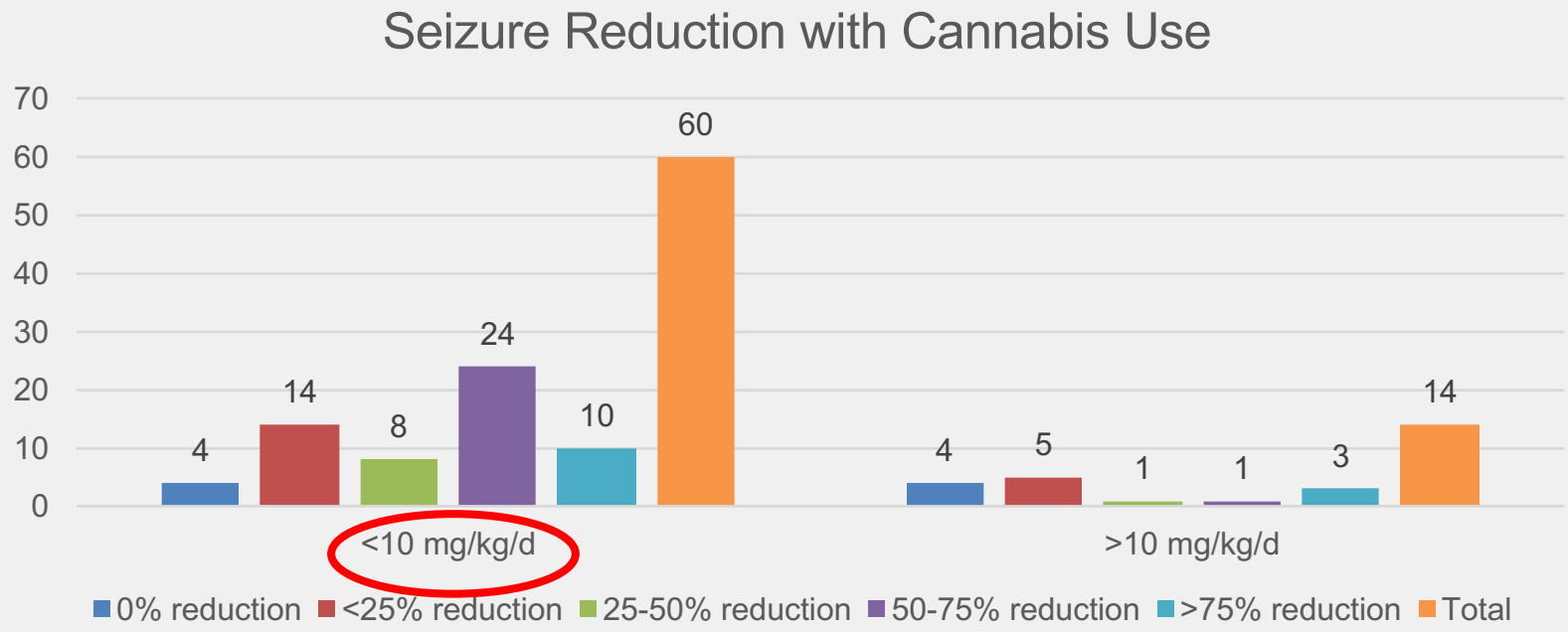
http://www.medicalnewstoday.com/articles/303725.php Accessed 6/13/16

Pediatric Epilepsy: Israeli Experience

- Retrospective review of 74 patients (1-18 years) with intractable epilepsy using CBD-enriched medical cannabis
- Resistant to >7 antiepileptic drugs
- Treated with CBD-enriched product for at least 3 months
  - CBD:THC – 20:1
  - CBD dose ranged from 1-20 mg/kg/day
- Seizure frequency assessed by parental report

Seizure. 2016 Feb;35:41-4. doi: 10.1016/j.seizure.2016.01.004. Epub 2016 Jan 6.

Results (n=74 patients)



Seizure. 2016 Feb;35:41-4. doi: 10.1016/j.seizure.2016.01.004. Epub 2016 Jan 6.

Adverse Effects

- Reported in 34/74 patients
  - » Seizure aggravation: 13 (18%)
  - » Somnolence/fatigue: 16 (22%)
  - » Gastrointestinal problems and irritability: 5 (7%)

  Note: side effects led to withdrawal in 5 patients

Seizure. 2016 Feb;35:41-4. doi: 10.1016/j.seizure.2016.01.004. Epub 2016 Jan 6.

Limitations and Conclusions

- Lack of a control group
- No consistent rate of dosage elevation
- Reliance upon parental report on seizure frequency
- Short duration of the study
- Lack of long-term outcome
- No EEG results and no measurement of other drug levels

Results of this multicenter study on CBD treatment for intractable epilepsy in a population of children and adolescents are highly promising

Seizure. 2016 Feb;35:41-4. doi: 10.1016/j.seizure.2016.01.004. Epub 2016 Jan 6.

Systematic Review: Efficacy and Safety of Medical Marijuana in Selected Neurologic Disorders Report of the Guideline Development Subcommittee of the American Academy of Neurology

In Patients with Multiple Sclerosis

Condition	Effective	Possibly effective	Probably or possibly ineffective
Spasticity	OCE	Nabiximols, THC	
Central pain or painful spasms	OCE	Nabiximols, THC	
Urinary dysfunction		Nabiximols	THC, OCE
Tremor			THC, OCE, nabiximols

*OCE= oral cannabis extract

"The risks and benefits of medical marijuana should be weighed carefully."
"Comparative effectiveness of medical marijuana vs other therapies is unknown for these indications."

Neurology. 2014;82(17):1556-63

Indications for Whole Plant Extracts

Nabiximols (Sativex®)

- Spasticity (muscle stiffness/spasm) due to MS
- Neuropathic pain in MS
- Adjunctive analgesic treatment in patients with advanced cancer who experience moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain

Cannabidiol (Epidiolex®)

- Pediatric epilepsy
  - Lennox-Gastaut Syndrome
  - Dravet Syndrome

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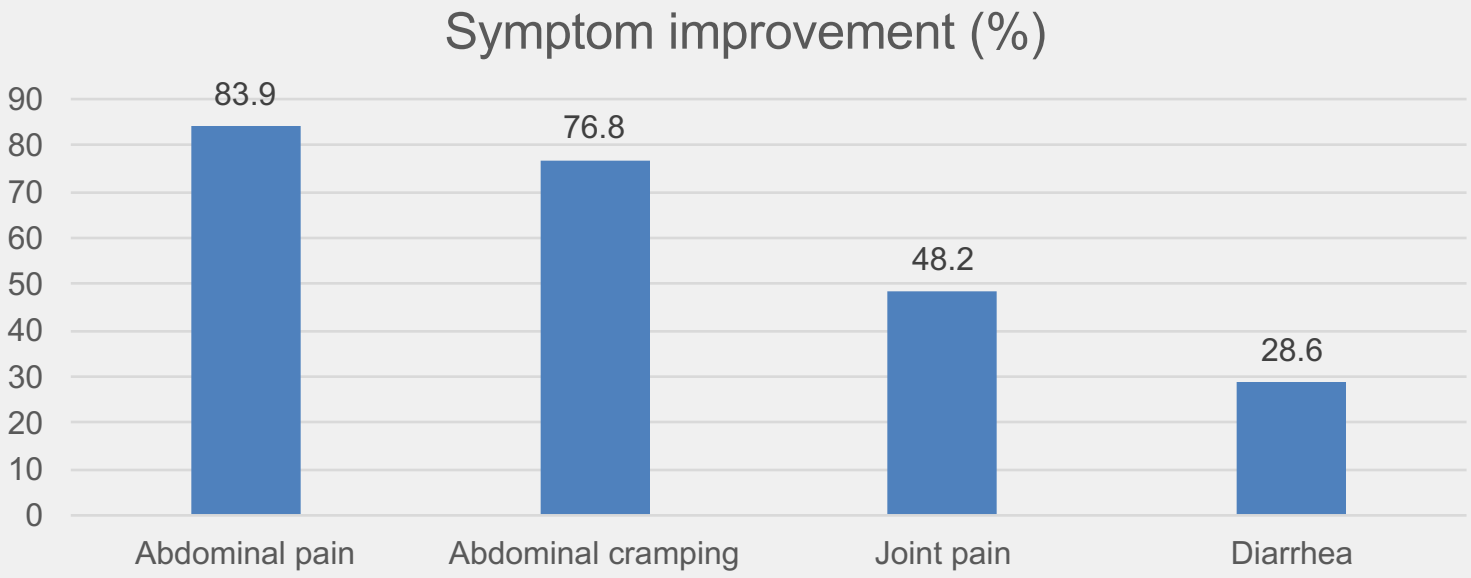
Irritable Bowel Syndrome & Crohn's Disease

- 313 patients with irritable bowel disease surveyed at University of Calgary
- Comparison of patients that used cannabis and those that did not

- 17.6% of respondents used cannabis to relieve IBD symptoms
- Most chose inhalation route of administration (96.4%)
- Improved symptoms of IBD (next slide)
- Cannabis use >6 months at any time for IBD symptoms was a strong predictor of requiring surgery in patients with Crohn's disease (OR = 5.03, 95% CI = 1.45–17.46)

Inflamm Bowel Dis. 2014 Mar;20(3):472-80. doi: 10.1097/01.MIB.0000440982.79036.d6.

Symptom Improvement in IBD Patients



Inflamm Bowel Dis. 2014 Mar;20(3):472-80. doi: 10.1097/01.MIB.0000440982.79036.d6.

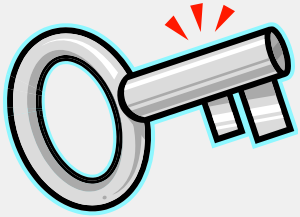
Other IBD Studies

- Prospective cohort survey study of 292 patients
  - Among current and past users (51.3%), 16.4% of patients used marijuana for disease symptoms
    - Majority felt marijuana was "very helpful" for relief of abdominal pain, nausea, and diarrhea
- Observational study of 30 patients with Crohn's disease (CD),
  - Medical cannabis associated with improvement in disease activity
  - Reduction in the use of other medications
- Placebo-controlled study in 21 chronic CD patients
  - Decrease in CD activity index >100 in 10 of 11 subjects on cannabis compared to 4 of 10 on placebo
  - Complete remission was achieved in 5 of 11 subjects on cannabis group and 1 of 10 on placebo
- Observational study (number of participants not provided)
  - Low-dose cannabidiol did not have an effect on CD activity.

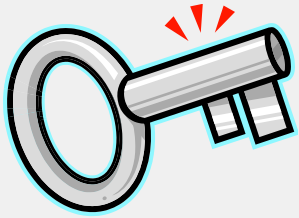
Dig Dis. 2014;32(4):468-74. doi: 10.1159/000358155. Epub 2014 Jun 23.
Inflamm Bowel Dis. 2013 Dec;19(13):2809-14. doi: 10.1097/01.MIB.0000435851.94391.37

Other Interesting Clinical Findings

- Migraine
  - Pharmacotherapy. 2016;36(5):505-10
- Pediatric treatment-resistant epilepsy: parental reports
  - Epilepsy Behav 2015;47:138-41
  - Epilepsy Behav 2015;45:49-52
  - Epilepsy Behav 2013;29:574-7
- PTSD: cannabis used more frequently for sleep and coping
  - Drug and Alcohol Dependence 2014;136:162–5
  - J Psychoactive Drugs 2014;46:73-7
- Alzheimer's Disease
  - Clin Pharmacol Ther. 2015 Jun;97(6):597-606
  - J Neuroimmune Pharmacol. 2015 Jun;10(2):268-80
- Bladder Cancer
  - Urology. 2015 Feb;85(2):388-92



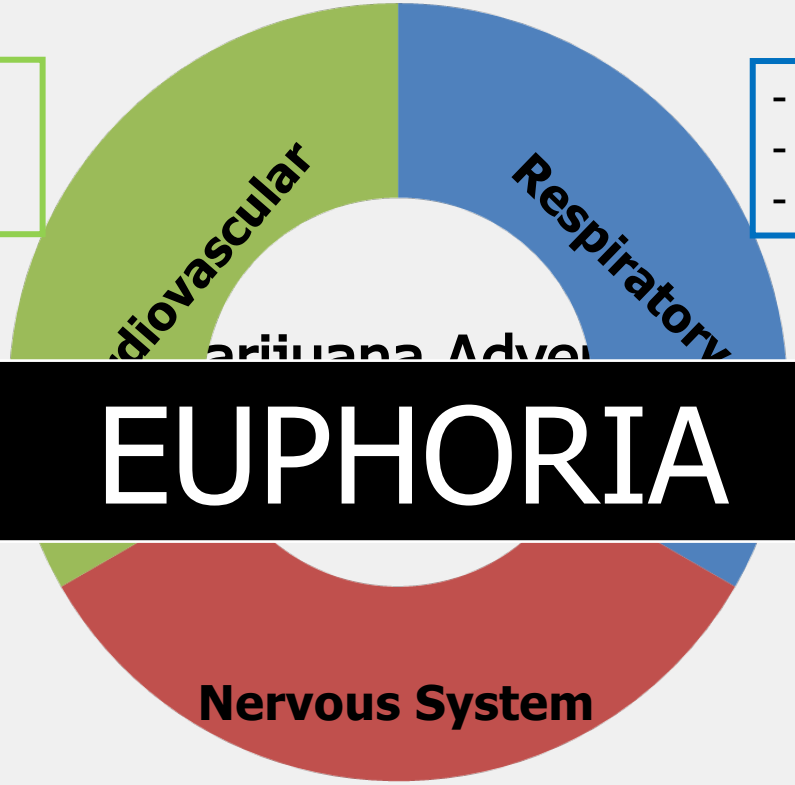
Summary



Cannabis may have a role in a variety of conditions when patients have failed other FDA-approved treatments. Adverse effects do occur so benefits and risks should be weighed for individual patients while considering patient safety and public health concerns.

- Tachycardia
- Palpitations
- Hypertension

- Coughing
- Wheezing
- Sputum production



EUPHORIA

- Lethargy, Sedation, Slowed Reaction Time
- Psychological dysfunction: impaired coordination, memory formation, recollection, focus)
- Visual Disturbances

Am J Health-Syst Pharm. 2007; 64:1037-1044. Pharmacotherapy 2013;33:195-209.
http://www.drugabuse.gov/publications/drugfacts/marijuana Drug Facts: Marijuana Accessed 12/23/15

Conclusions

- Marijuana and its active components impact the endocannabinoid system to provide various effects.
- Many dosage formulations of marijuana available to patients.
- Clinical studies performed in children and adults demonstrate some effectiveness for certain conditions including neuropathic pain, epilepsy, and gastrointestinal conditions.
- Adverse effects are reported in all studies so benefits and risks must be carefully weighed.

QUESTIONS?

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