

Medical Marijuana: An Evidenced-Based Look at Efficacy and Harms

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Marilyn is a 68-year-old woman with breast cancer metastatic to the lungs and the thoracic and lumbar spine.

She is currently undergoing chemotherapy with doxorubicin.

She reports having very low energy, minimal appetite, and substantial pain in her thoracic and lumbar spine.

NEJM N Engl J Med 2013; 368:866-868

For relief of nausea, she has taken ondansetron and prochlorperazine, with minimal success.

She has been taking 1,000 mg of acetaminophen every 8 hours for the pain.

Sometimes at night she takes 5 mg or 10 mg of oxycodone to help provide pain relief.

During a visit with her primary care physician she asks about the possibility of using marijuana to help alleviate the nausea, pain, and fatigue.

She lives in a state that allows marijuana for personal medicinal use, and she says her family could grow the plants.

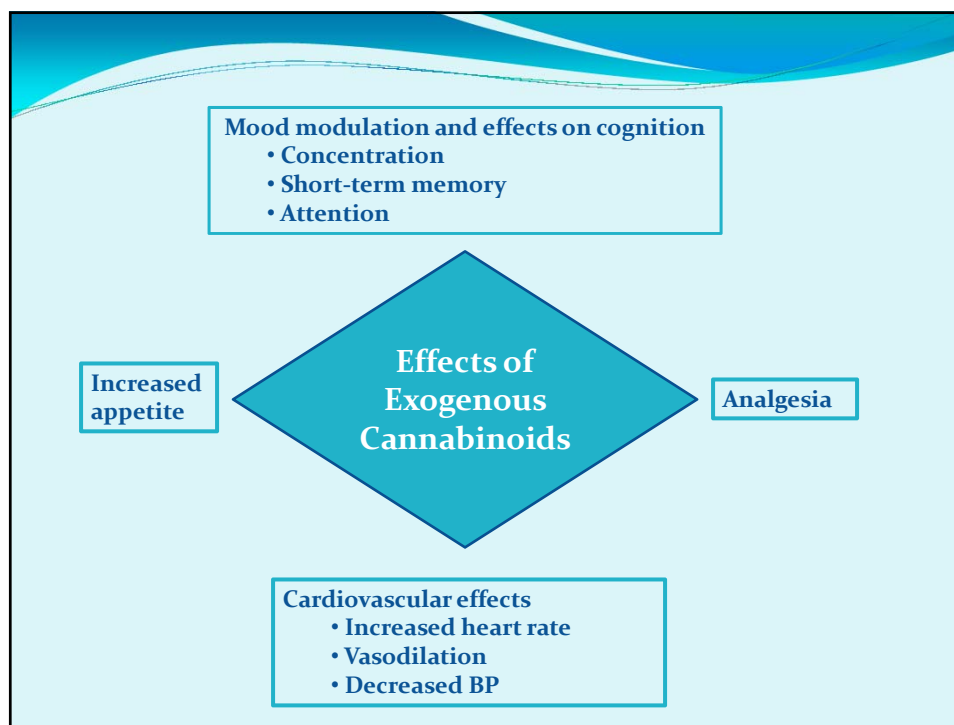
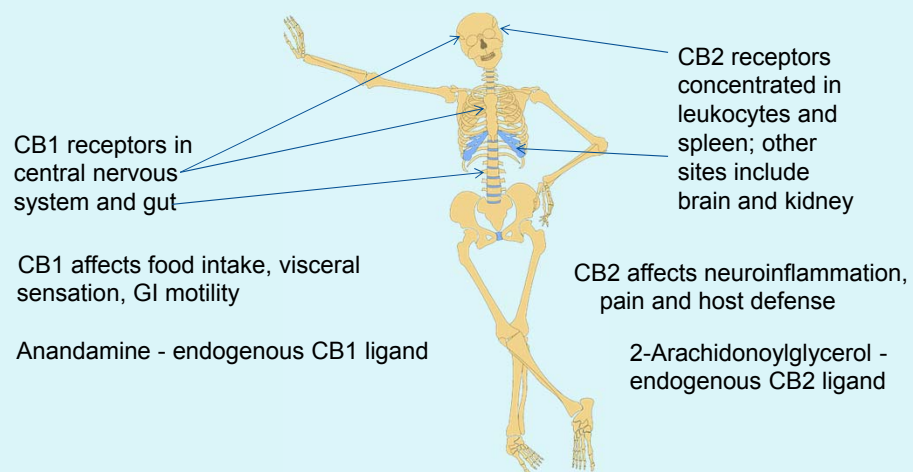
As her physician, what advice would you offer with regard to the use of marijuana to alleviate her current symptoms?

Do you believe that the overall medicinal benefits of marijuana outweigh the risks and potential harms?

Objectives

- Be familiar with the available evidence regarding use of marijuana for treatment of medical conditions
- Be familiar with side effects associated with marijuana use

Endocannabinoid System



Cannabinoid Formulations

Generic Name	Brand Name	Dosage and Components	Dosage Used In Selected Trials
Smoked marijuana	None	1%-8% THC > 80 cannabinoids	1%-8% THC
Cannabis extract	Cannador	Δ^9 -THC 2.5 mg/ CBD 1.25 mg	Max 1.25 mg/kg/d Max 25 mg/d
Nabiximols	Sativex	Δ^9 -THC 2.7 mg/ CBD 2.5 mg/spray	Max 65 mg/d Max 120 mg/d
Dronabinol	Marinol	2.5 mg Δ^9 -THC	Max 10 mg/d Max 20 mg/d
Nabilone	Cesamet	1 mg synthetic cannabinoid	1 mg bid 0.5-1 mg hs



Named Qualifying Conditions (Only If Debilitating)

- Cancer
- Glaucoma
- AIDS
- Hepatitis C
- Multiple sclerosis
- Crohn's disease
- Parkinson's disease
- Amyotrophic lateral sclerosis (ALS)

Self-medication rates

- 14-21% of patients with IBD¹
- 13% of patients with fibromyalgia ²
- 2% general population of Ontario³
 - More than half reported treating pain or nausea
- 24% with HIV
- 10% of patients with ALS⁴



Picture courtesy of tropical Pete's photostream.
<http://www.flickr.com/photos/12023825@N04/wth/2898021822/>

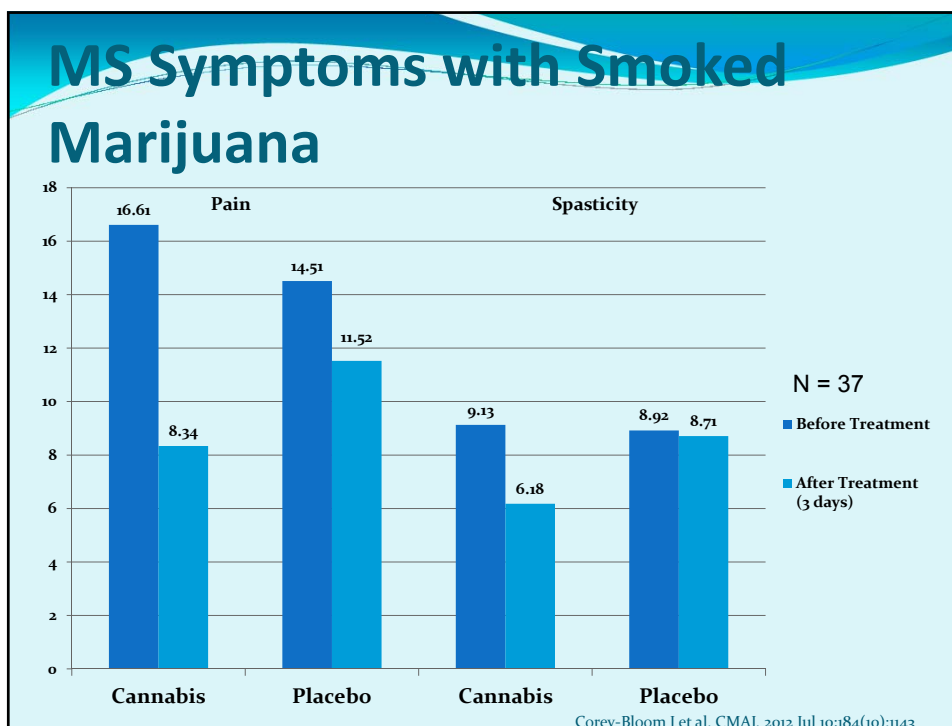
1. Eur J Gastroenterol Hepatol 2011 Oct;23(10):891; 2. Arthritis Care Res (Hoboken) 2012 Aug;64(8):1202;
 3. CMAJ 2000 Jun 13;162(12):1685; 4. Am J Hosp Palliat Care 2004 Mar-Apr;21(2):95

Glaucoma

- American Glaucoma Society (AGS)
 - Marijuana can lower IOP
 - Marijuana not currently recommend in any form for treatment of glaucoma
- No evidence from RCTs
- No evidence for improvement in clinical outcomes
- IOP lowered in 60-65%, but effect not sustained

Multiple Sclerosis

- Daniel is a 59 year old psychiatrist with relapsing-remitting MS for the past 15 years. He is currently working part-time.
- He is on glatiramer 20 mg SQ daily
- His main symptoms are fatigue and muscle spasms which can be quite painful
- He has heard marijuana is good for this and wants certification
- What do you say to him?



CAMS Study

- 657 patient with stable MS and spasticity
- Randomized to oral cannabis extract vs. dronabinol vs. placebo and assessed at 13 weeks
- Primary outcome spasticity on Ashworth scale
- Secondary outcomes included patient reported spasticity, mobility, pain, and sleep quality

Zajicek J et al. Lancet 2003 Nov 8;362(9395):1517

% Reporting Improvement

	Cannabis Extract	Δ^9 -THC	Placebo	p-value*
Spasticity (n = 543)	95 (52%)	89 (51%)	67 (37%)	p = 0.010
Pain (n = 419)	68 (46%)	64 (50%)	42 (30%)	p = 0.002
Sleep (n = 479)	82 (50%)	71 (47%)	59 (36%)	p = 0.025
Spasms (n = 520)	96 (53%)	81 (49%)	67 (39%)	p = 0.038

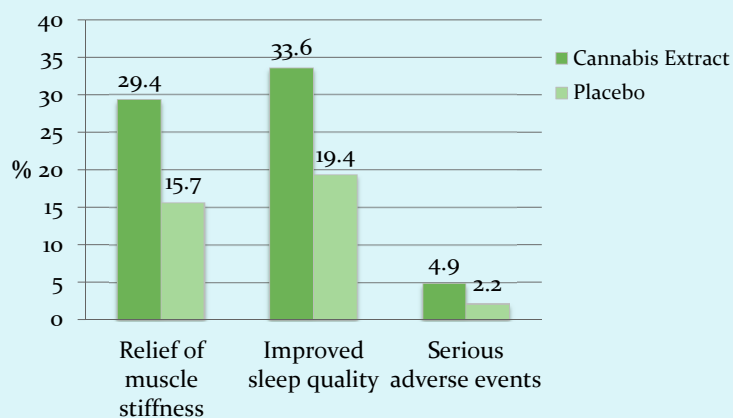
* Comparing 3 treatment groups on original 11-point rating scale.

Zajicek J1 et al. Lancet 2003 Nov 8;362(9395):1517

MUSEC

- RCT of 279 patients with stable MS given cannabis extract orally daily for 12 weeks

Cannabis Extract For Stable MS Symptoms



Zajicek JP et al. J Neurol Neurosurg Psychiatry 2012 Nov;83(11):1125-32

Urinary Symptoms

- RCT of cannabis extract oral mucosal spray in 135 patients with MS and OAB
- All patients continued with anticholinergic medications
- No difference in number of incontinence episodes
- Results favored oral mucosal spray for
 - Nocturia
 - Voids/day
 - Overall bladder condition
 - Patient global impression of change

Kavia RBC et al. Multiple Sclerosis 16(11) 1349-1359

AAN Guidelines

- Oral Cannabis Extract
 - May offer to reduce patient reported symptoms of spasticity and pain (excluding central neuropathic pain) (Level A)
 - Symptomatic benefit is possibly maintained for 1 year (Level C)
 - Ineffective for improving objective spasticity measures (short-term) or tremor (Level B)
- THC: Same as above but benefit is level B

Yadav V et al. Neurology® 2014;82:1083-1092

AAN Guidelines

- Sativex oral mucosal spray
 - May offer to reduce symptoms of spasticity, pain, or urinary frequency (Level B)
 - Probably ineffective for improving objective spasticity measures or number of urinary incontinence episodes (Level B)
 - Ineffective for tremor (Level C)
- Smoked cannabis has inadequate data for spasticity, pain, balance/posture, and cognition (Level U)

Yadav V et al. Neurology® 2014;82:1083-1092

Hepatitis C

- Stephen is a 26 year old former IV drug abuser (clean for 1 year) with Hepatitis C
- He is not in treatment (lost his health insurance)
- Hepatitis C causes nausea
- He comes to you seeking certification for using marijuana
- He doesn't want any testing done because of the cost.
- What do you tell him?

Cannabis Smoking and Progression of Fibrosis

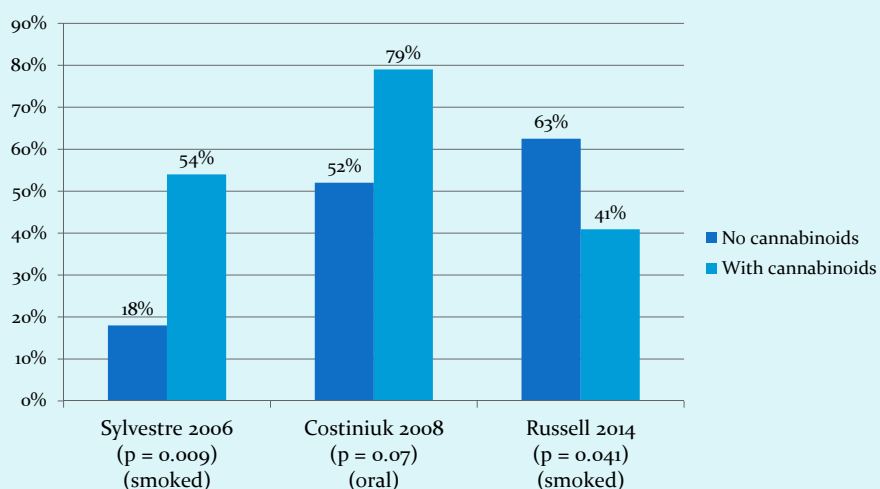
Study	Number of Patients	Outcome	Results
Hezode 2005 ¹	270	Fibrosis stage \geq F3	OR = 3.4
Ishida 2008 ²	204	Fibrosis stage \geq F3	OR = 6.78
Brunet 2013 ³	690	Cirrhosis	HR = 1.12 (0.94-1.34)
		ESLD	HR = 1.07 (0.85-1.34)
		Either	HR = 1.1 (0.95-1.26)

1. Hepatology 12 May 2005 42:1; 63-71
2. Clin Gastroenterol Hepatol. Jan 2008;6:69-75
3. Clin Infect Disease 2013 Sep;57(5):663

Follow-up Visit

- 3 months later Stephen comes back and now has health insurance
- He is getting treated with interferon and ribavirin and getting flu-like symptoms including nausea
- He wants marijuana certification (again)
- What do you tell him?

Sustained Virologic Response in HCV

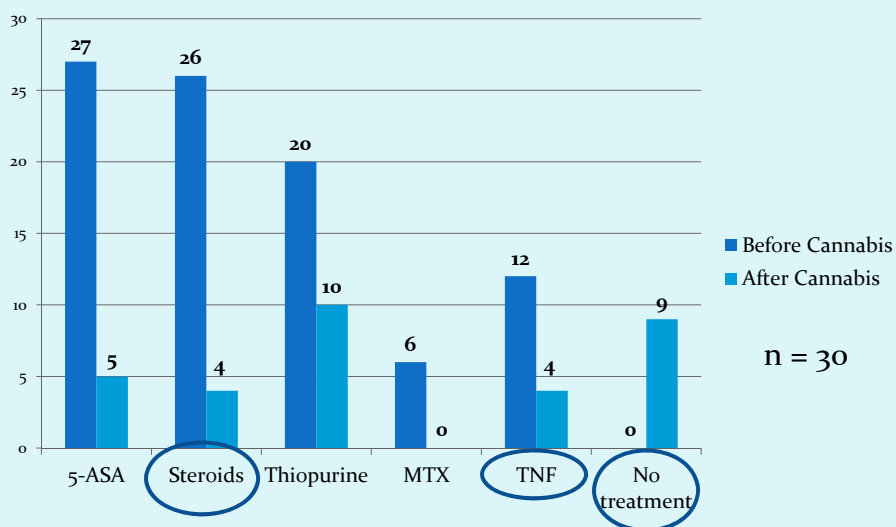


1) Costiniuk CT et al. Can J Gastroenterol 2008 Apr;22(4):376
 2) Sylvestre, Diana; Clements, Barry; Malibu, Yvonne. European Journal of Gastroenterology & Hepatology. Oct 2006. 18(10):1057-1063
 3) Russell M et al. Drug Alcohol Depend. 2014 Jan 1;134:222

Crohn's disease

- Carol is a 36 year old computer programmer who has had Crohn's disease for 15 years.
- She has previously had surgery for this and has been treated with MTX, prednisone and mesalamine. She has not tried TNF inhibitors because she has concerns about the risks of cancer and infection.
- She recently had a flare-up with 6-8 bowel movements a day and abdominal pain/cramping.
- She has heard marijuana can help with Crohn's disease and wants certification. What do you say?

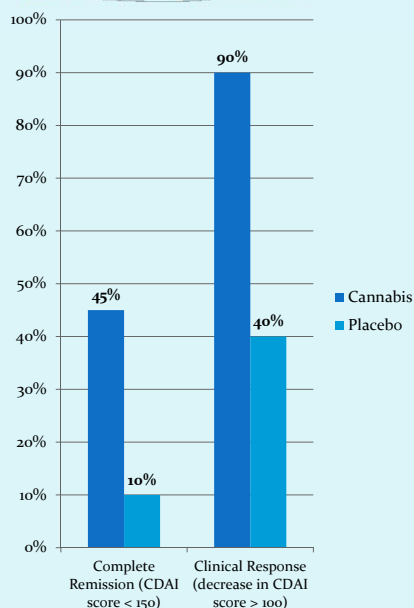
Intractable Crohn's Disease



Naftali T et al. Isr Med Assoc J. 2011 Aug;13(8):455-8

Crohn's RCT

- 21 patients with refractory disease
- Cannabis smoking BID vs. placebo
- 8 week study
- Crohn's Disease Activity Index used as outcome



Naftali T et al. Clin Gastroenterol Hepatol. 2013 Oct;11(10):1276-1280

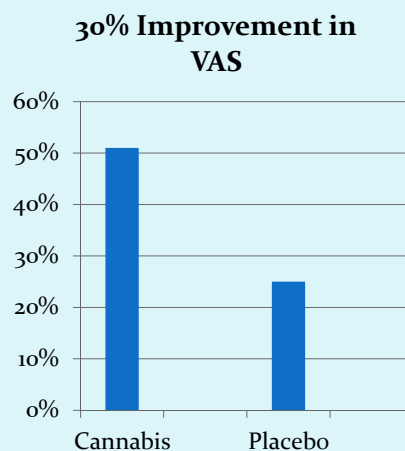
HIV-Related Disorders

- HIV-associated Pain
- Anorexia and loss of muscle
- No adverse changes in viral load CD4 or CD8 counts with short-term marijuana use

Haney M et al. Psychopharmacology (Berl). 2005 Aug;181(1):170-8

HIV-associated Pain

- Systematic review
- 2 placebo-controlled RCTs with 122 patients of smoked cannabis
- NNT 3 (95% CI 2.2-7.5)



Philips TJ et al. PLoS One. 2010; 5(12): e14433

Anorexia and Loss of Muscle

- Crossover trial of 30 patients with smoked marijuana, dronabinol, and placebos
- Increase appetite in patients with clinically significant muscle mass loss
- Dronabinol 10-20 mg dose used

Abrams DI et al. Ann Intern Med. 2003;139:258-266.

Cancer Chemotherapy-Induced Nausea and Vomiting

- No RCTs of smoked cannabis vs. placebo
- 1 crossover trial of 20 patients used smoked cannabis vs. oral synthetic THC
 - 25% had improvement in emesis
 - 35% had significant adverse events
 - 7 patients preferred oral THC
 - 4 patients preferred smoked cannabis
 - 9 patients had no preference

Levitt M et al. Proceedings of the American Society of Clinical Oncology 1984; 391

Cancer Chemotherapy-Induced Nausea and Vomiting

- Dronabinol equally effective as ondansetron in small RCT
- Systematic review of 30 RCTs found cannabinoids better than
 - prochlorperazine (12 trials)
 - metoclopramide (4 trials)
 - chlorpromazine (2 trials)
 - domperidone (2 trials) (1 trial)
 - haloperidol, thiethylperazine, and alizapride (1 trial each)

Meiri E et al. Curr Med Res Opin. 2007 Mar;23(3):533-43
 Tramer MR et al BMJ. 2001 Jul 7;323(7303):16-21

Other Cancer Uses

- Extremely limited evidence for pain reduction
- No RCTs using smoked cannabis
- In RCT of 177 patients of oromucosal spray vs. THC vs. placebo, oromucosal spray twice as effective as either other option
- Minimal efficacy for treating cachexia

Johnson JR et al. J Pain Symptom Manage 2010 Feb;39(2):167
 Strasser F et al. J Clin Oncol 2006;24(21):3394-400
 Jatoti A et al. Journal of Clinical Oncology 2002;20(2):567-573

Parkinson's Disease & ALS

- PD patient reported benefit in (30-44%)
 - Resting tremor
 - Bradykinesia
 - Muscle rigidity
- ALS patients report benefits in
 - Appetite
 - Pain
 - Spasticity
 - Drooling
 - Depression (for 2-3 hours)

Parkinson Disease

- No studies of smoked cannabis
- Crossover study with 7 patients with PD treated with nabilone
 - Nabilone reduced levodopa induced dyskinesia
 - No difference in ON time period
- Crossover trial with 19 patients with PD using cannabis extract of THC and cannabidiol
 - No difference in dyskinesia (UPDRS score) or PDQ 39
 - Improvement on MMSE (1.5 points, $p < 0.01$)

Amyotrophic Lateral Sclerosis

- Double blind crossover trial of 5 mg THC orally for spasticity in 27 ALS patients
- Cramps assessed using VAS
- No adverse effects
- No benefit

Weber M, Goldman B, Truniger S. J Neurol Neurosurg Psychiatry. 2010 Oct;81(10):1135-40

Cannabis For Neuropathic Pain

- 3 placebo-controlled crossover trials
 - Improved pain intensity in 38 patients with spinal cord injury, peripheral neuropathy, nerve injury or CRPS
 - Improved sleep, anxiety, and depression in 23 patients with post traumatic or postsurgical chronic pain
 - >30% pain reduction in 39 patient trial
- Adverse events generally mild to moderate, worse at higher doses

Panang S et al. J Pain 2008 Mar;9(3):254
 Wilsey B et al. Wilsey B et al, J Pain. 2008 Jun;9(6):506-21
 Lynch ME, Campbell F. Br J Clin Pharmacol 2011 72:5 735-744

Fibromyalgia

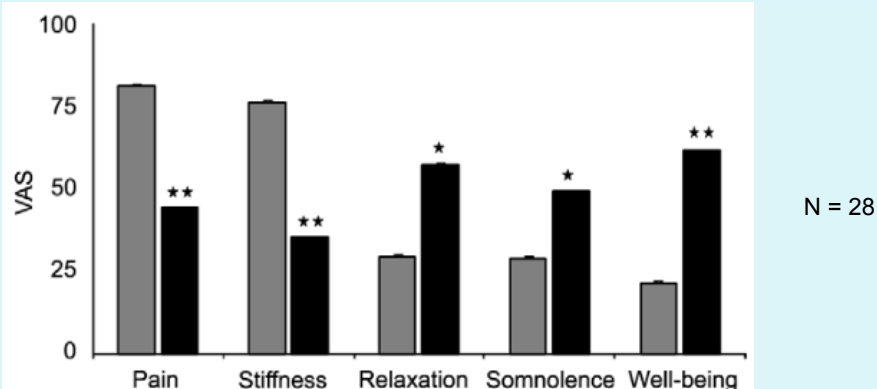


Figure 2. Perceived effects of cannabis self-administration.
 Note: Perceived benefits of cannabis recorded by patients on a range of symptoms using 100-mm VAS scales before and at 2 hours of cannabis consumptions. Grey bars: pre-cannabis; black bars: post-cannabis.
 * * = $p < 0.001$; * = $p < 0.05$.
 doi:10.1371/journal.pone.0018440.g002

Fiz J et al. PLoS One. 2011 Apr 21;6(4):e18440

Canadian 2012 fibromyalgia guideline

A trial of a prescribed pharmacologic cannabinoid may be considered in a patient with fibromyalgia, particularly in the setting of important sleep disturbance (Level 3, Grade C)

Epilepsy

- Most data from case reports and pre-clinical studies
- Cochrane review found 4 placebo-controlled studies of cannabidiol 200-300 mg/day
- Only 48 total patients
- 2 trials found benefit (no statistics done)

Gloss D et al. Cochrane Database Syst Rev 2012 Jun
13;(6):CD009270

Severe Childhood Seizures

- Dravet Syndrome, Lennox-Gastaut syndrome, Doose Syndrome
- Survey of 19 parents on Facebook group
- 12 = Average number of AEDs tried before cannabis
- 84% reported significant reduction in seizures with cannabidiol-enriched cannabis
 - 11% complete freedom from seizures
 - 42% reported > 80% reduction in seizures
 - 32% reported 25-60% reduction in seizures

Porter BE et al. Epilepsy and Behavior 2013 Dec;29(3):574-7

Adverse Effects

I don't need pot to be hungry, lazy, and paranoid.



Adverse Effects of Cannabis

- Short-term cognitive effects
 - Dizziness
 - Memory dysfunction
 - Sense of slowed time
 - Increased body awareness
 - Difficulty focusing
 - Incoordination
 - Sleepiness

Other Adverse Effects of Cannabis

- Recurrent cyclic vomiting (cannabinoid hyperemesis syndrome)
- Increased cough, phlegm, and wheezing
- Psychosis – degree of risk unclear
- Potential for abuse and can be addictive
- May have withdrawal symptoms (anxiety, insomnia)
- Lethal overdose in humans has not been reported
 - THC spares autonomic nervous system
 - CB₁ receptors generally absent in brain stem

Pulmonary Issues

- THC causes acute bronchodilation
- Chronic use associated with symptoms of chronic bronchitis
- Chronic use
 - No increase in airway obstruction
 - Not associated with COPD
 - No clear association with lung or upper airway cancer
 - May increase risk for pneumonia
 - Overall significantly lower risks than tobacco

Tashkin DP. Ann Am Thorac Soc 2013;10:239–247

Driving Issues

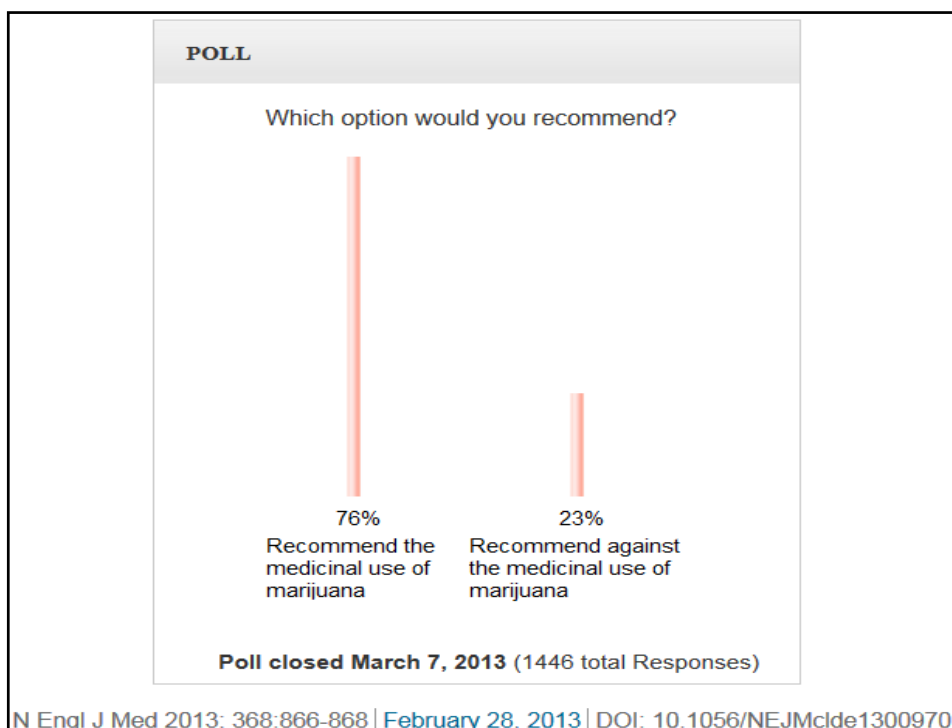
- 2 systematic reviews
- Risk of MVA \uparrow 2-2.6X
- Dose-response curve
- Risk higher in studies of fatal crashes
- fMRI indicate no safe level of acute marijuana smoking



Li M et al. Epidemiol Rev 2012;34:65-72;
Asbridge M et al. BMJ 2012;344:e536 doi: 10.1136/bmj.e536;
Battistella G et al. PLoS ONE 8(1): e52545. doi:10.1371/journal.pone.0052545

Diversion

- Major concern with medical marijuana
- In Denver substance abuse clinic
 - 74% of adolescents used someone else's medical marijuana
 - Marijuana dependence more likely with access to diverted medical marijuana (89% vs. 67%)



Recommendations

- Marijuana is not first-line treatment for any medical condition
- Best evidence for efficacy is for HIV, Crohns disease, MS, neuropathic pain and Hepatitis C
- May be helpful with some other painful conditions such as fibromyalgia
- Little benefit for glaucoma, ALS, Parkinson
- All else is anecdotal



Questions?