

**4:45 – 5:30 pm**

**Medical Marijuana**

**SPEAKER**  
**Alan M. Ehrlich, MD**

**Presenter Disclosure Information**

The following relationships exist related to this presentation:

- ▶ Alan M. Ehrlich, MD: No financial relationships to disclose.

**Off-Label/Investigational Discussion**

- ▶ In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

**Medical Marijuana: What the Evidence Says**

Alan Ehrlich MD  
Pri-Med Boston  
September 2015

**Case**

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.

Bostwick J et al. NEJM 2013

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.

Bostwick J et al. NEJM 2013

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?

Bostwick J et al. NEJM 2013

## Objectives

- Summarize the evidence for use of marijuana in various medical conditions
- Recognize the adverse effects of marijuana use
- Define the role of the physician in certifying patients for medical marijuana eligibility
- Evaluate evidence-based literature and participate in policy discussions

## Cannabinoid Formulations

Cannabinoid	Dosage and Components	Use In Selected Trials	Cost
Marijuana (Cannabis)	THC content varies THC/cannabidiol varies > 80 cannabinoids May be smoked, vaporized or oral	1%-8% THC 1-3 cigarettes/day	\$8-25 /day
Cannabis extract	$\Delta^9$ -THC 2.5 mg/ CBD 1.25 mg	Max 1.25 mg/kg/d Max 25 mg/d	Not commercially available
Nabiximols	$\Delta^9$ -THC 2.7 mg/ CBD 2.5 mg/spray	Max 65 mg/d Max 120 mg/d	\$40/day
Dronabinol	2.5 mg $\Delta^9$ -THC	Max 10 mg/d Max 20 mg/d	\$1.8/mg \$5-36/day
Nabilone	1 mg synthetic cannabinoid	1 mg bid 0.5-1 mg hs	\$10-40/day

Price data for marinol and marijuana from ProCon.org

## Self-medication rates

- 14-21% of IBD patients<sup>1</sup>
- 13% of patients with fibromyalgia<sup>2</sup>
- 2% general population of Ontario<sup>3</sup>
- 24% with HIV
- 37% of men with chronic prostatitis/CPPS<sup>4</sup>

1. Lal S. et al Eur J Gastroenterol Hepatol 2011
2. Ste-Marie PA et al. Arthritis Care Res (Hoboken) 2012
3. Oghorne AC et al. CMAJ 2000
4. Tripp DA et al. Can Urol Assoc J 2014

## Glaucoma

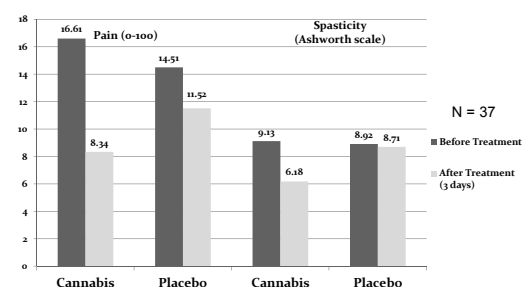
- No evidence from RCTs
- No evidence for improvement in clinical outcomes
- IOP lowered in 60-65%, but effect not sustained
- American Glaucoma Society (AGS)
  - Marijuana can lower IOP
  - Marijuana not currently recommend in any form for treatment of glaucoma

Jampel H. American Glaucoma Society Position Statement 2009

## Multiple Sclerosis - Case

- 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

## Smoked Marijuana for MS



Corey-Bloom et al. CMAJ 2012

## 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 J1 et al. Lancet 2003

## % Reporting Improvement

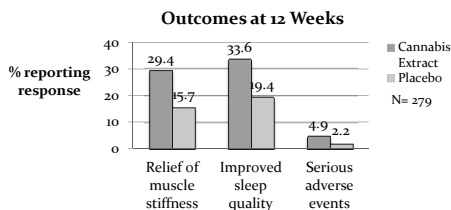
	Cannabis Extract	$\Delta^9$ -THC	Placebo	p-value*
Spasticity (n = 543)	95 (52%)	89 (51%)	67 (37%)	p = 0.010
Pain (n = 419)	68 (46%)	64 (50%)	42 (30%)	p = 0.002
Sleep (n = 479)	82 (50%)	71 (47%)	59 (36%)	p = 0.025
Spasms (n = 520)	96 (53%)	81 (49%)	67 (39%)	p = 0.038

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

Zajicek J1 et al. Lancet 2003

## MUSEC

- RCT of stable MS patients given oral cannabis extract (THC 2.5 mg plus cannabidiol 0.8-1.8 mg)
- Improved muscle stiffness and sleep (p < 0.025)
- No difference in adverse events



Zajicek JP et al. J Neurol Neurosurg Psychiatry 2012

## Collin et al. 2007

- 187 MS patients with painful spasms randomized to oromucosal spray (nabiximols) vs. placebo (2:1) for 6 weeks
- Dose titrated to maximum 48 sprays/day
- Better outcomes on Numerical Rating Scale with spray
- Open label extension for ~ 1 year
  - No significant adverse events
  - No evidence of tolerance developing
  - Average dose 7.3 sprays/day

Collin C et al. European Journal of Neurology 2007.

## Move Improvement-2

- Prospective study of 276 patients with multiple sclerosis spasticity treated with nabiximols
- 221 had f/u at 1 month
- 73% used nabiximols as add on; 27% monotherapy
- Only 55% still using at 3 months
- 30% improvement by numerical rating scale at 1 month in 74.6%

Flachenecker P et al. Eur Neurol 2004

## Urinary Symptoms

- RCT of cannabis extract oral mucosal spray (nabiximols) in 135 patients with MS and OAB (add-on to anticholinergic)
- No difference in number of incontinence episodes
- Nabiximols group had 1 fewer voids/day (p = 0.007)
- Other differences also small but results favored oral mucosal spray for
  - Nocturia (p = 0.01)
  - Overall bladder condition (p = 0.001)
  - Patient global impression of change (p = 0.005)

Kavia RBC et al. Multiple Sclerosis

## 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

## 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

## Additional MS Considerations

- EFNS recommends cannabinoids in MS (level A) only if all other treatments fail<sup>1</sup>
- Cross sectional study of 20 MS patients<sup>2</sup>
  - MS cannabis users more cognitively impaired than nonusers based on fMRI and neuropsych testing
  - Differences found in only 3/16 outcomes assessed

1. Attal N et al. Eur J Neurol 2010  
2. Pavisian B et al. Neurology 2014

## 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)
- AAN finds insufficient evidence to recommend cannabinoids to reduce seizure frequency

Gloss D et al. Cochrane Database Syst Rev 2012

## Epilepsy - Case

34 year old female patients of yours comes in for a visit and tells you she is moving to Colorado.

In passing you ask if this is a job move and she tells you that she has a child with Dravet syndrome that is out of control so they want to get medical marijuana for their child (they saw the CNN special).

Then she asks you if you have an opinion on whether marijuana is good for children like hers.

## 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

## Other Neurologic Conditions

Condition	Reported Benefits	Agents Studied	Study Type	Outcomes
ALS	Appetite Pain Spasticity Drooling	Oral THC 5 mg	Double blind crossover trial N = 27	No benefit
Parkinson Disease	Tremor Bradykinesia Rigidity	Nabilone  Smoked cannabis	Crossover RCT N = 7  Case series N = 22	↓ Dyskinesia  ↓ Tremor Bradykinesia Rigidity
Tourette Syndrome	Reduction in tics	Dronabinol 10 mg	RCT N = 24 (17 completed)	Tic reduction but not significant
Huntington Disease	Decrease in chorea	Nabilone 1-2 mg	Crossover RCT N = 22	UHDRS score ↓ 1.68

## More AAN Recommendations

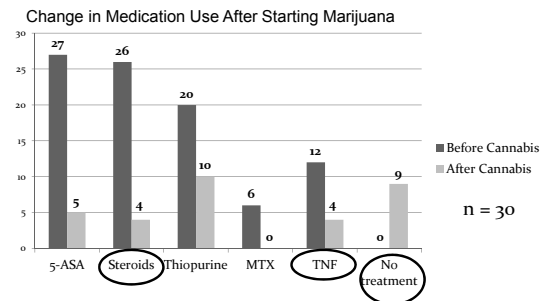
- Nabilone may be prescribed for modest reduction in chorea (AAN level C), but insufficient evidence to recommend long-term use (AAN Level U)
- Oral cannabis extract probably ineffective for levodopa-induced dyskinesias in Parkinson disease (AAN Class I)
- Insufficient evidence to support beneficial effect of THC on tic severity for Tourette Syndrome (AAN Level U)
- Only data comes from very small trials or cohorts

Koppel BS et al. Neurology 2014

## Crohn's Disease - Case

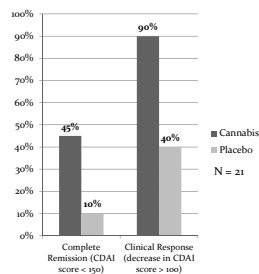
- Carol is a 36 year old computer programmer who has had Crohn's disease for 15 years.
- She has previously had surgery for this and has been treated with MTX, prednisone and mesalamine. She has not tried TNF inhibitors because she has concerns about the risks of cancer and infection.
- She recently 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.

## Intractable Crohn's Disease



## Cannabis For Intractable Crohn's Disease

- 21 patients with refractory disease
- Cannabis smoking BID vs. placebo
- 8 week study
- Crohn's Disease Activity Index used as outcome
- Differences not significant



## Cannabis For Neuropathic Pain

- 4 placebo-controlled crossover trials
  - Improved pain intensity in 38 patients with spinal cord injury, peripheral neuropathy, nerve injury or CRPS<sup>1</sup>
  - Improved sleep, anxiety, and depression in 23 patients with post traumatic or postsurgical chronic pain<sup>2</sup>
  - >30% pain reduction in 2 trials of 39 patients each<sup>3,4</sup>
- Adverse events
  - Generally mild to moderate
  - Worse at higher doses

1. Panang S et al. J Pain 2008
2. Wilsey B et al. J Pain. 2008
3. Lynch ME et al. Br J Clin Pharmacol 2011
4. Wilsey B et al. J Pain. 2013 February

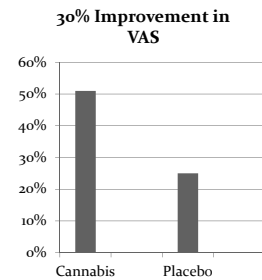
## Cannabis For Neuropathic Pain

- SR of 9 cannabinoid trials > 3 weeks for treatment of neuropathic pain
  - 3 positive results (2 nabiximols, 1 dronabinol)
  - 5 negative results (all nabiximols)
  - 1 mixed results (nabiximols)
  - Mixed results for MS neuropathic pain
  - Negative results for DPN

Finnerup NB et al. Lancet Neurol 2015

## 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;

## HIV-associated Polyneuropathy

- EFNS found efficacy only for
  - Lamotrigine (in patients on ART) (Level B)
  - Smoking cannabis (Level A)
  - Capsaicin patches (Level A)

Attal N et al. Eur J Neurol 2010 Sep;27(9):1113

## Oncology Symptoms

- Israeli survey data of 17,000 cancer patients at single institution
  - 279 (< 1.7%) received a permit for cannabis from an oncologist
  - Median age 60 years
  - 84% had metastatic disease
  - Improvement in pain, general well-being, appetite and nausea were reported by 70%, 70%, 60% and 50%, respectively

Waissengrin B et al. J Pain Symptom Manage. 2014

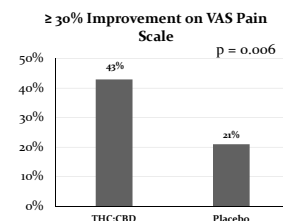
## Cancer Chemotherapy-Induced Nausea and Vomiting (CINV)

- 2 crossover trials of smoked THC vs. placebo
  - 6% vs. 72% in 15 patients with osteogenic sarcoma treated with MTX<sup>1</sup>
  - No benefit in 8 patients with soft tissue sarcoma treated with AC<sup>2</sup>
- Oromucosal spray as add-on therapy to 5-HT<sub>3</sub> receptor antagonists or NK<sub>1</sub> inhibitors in trial of 16 patients with solid tumors<sup>3</sup>
  - Complete response in 71% vs. 22%
  - 1/7 withdrew due to adverse events

1. Chang AE et al. Annals of Internal Medicine 1979  
 2. Chang AE et al. Cancer 1981  
 3. Duran M, et al. British Journal of Clinical Pharmacology. 2010

## Cancer Pain

- No RCTs using smoked cannabis
- RCT of 177 patients<sup>1</sup>
  - oromucosal spray
  - THC
  - Placebo
- Open label extension<sup>2</sup>
  - Median 25 days (2-579)
  - 24/43 stopped for AEs



1. Johnson JR et al. J Pain Symptom Manage 2010  
 2. Johnson JR et al. Journal of Pain and Symptom Management 2013

## Cancer Pain

- Phase 2 trial of nabiximols at varying doses as add-on therapy in 360 patients with advanced cancer
  - Low dose 1-4 sprays/day
  - Medium dose 6-10 sprays/day
  - High dose 11-16 sprays/day
- 263 completed trial
- No significant difference in 30% responder rate

Portenoy RK et al. Journal of Pain 2012

## Cancer Use Recommendations

- American Society of Clinical Oncology (ASCO)<sup>1</sup>
  - Reserve cannabinoids for patients intolerant or refractory to 5HT<sub>3</sub> receptor antagonists, NK-1 receptor antagonists, and dexamethasone
- National Comprehensive Cancer Network (NCCN)<sup>2</sup>
  - synthetic cannabinoids (dronabinol and nabilone) useful as treatment options for breakthrough nausea and vomiting
  - not recommended as part of guidelines for management of antiemesis
- Multinational Association of Supportive Care in Cancer (MASCC) and ESMO<sup>3</sup>
  - Consider cannabinoids a possible option for refractory nausea and vomiting and as rescue antiemetic

1. Kris MG et al. J Clin Oncol 2006  
2. Todaro B. J Natl Compr Canc Netw 2012  
3. Roila F et al. Ann Oncol 2010

## Fibromyalgia

- Rachel is a 43 year old HS math teacher with fibromyalgia.
- She takes duloxetine 60 mg daily and exercises 4 times/week.
- She has problems with sleeping and wakes up feeling "like she was run over by a truck".
- She tried amitriptyline and cyclobenzaprine but stopped due to side effects.
- She tells you she is currently using marijuana to help her sleep and asks you for certification so she can get the marijuana legally.

## Fibromyalgia

- Cohort of 28 patients with fibromyalgia
- Reported improvements 2 hours after smoking marijuana

Symptoms	Change in VAS in mm
Pain	↓ 37.1 (p < 0.001)
Stiffness	↓ 40.7 (p < 0.001)
Relaxation	↑ 27.6 (p < 0.01)
Somnolence	↑ 20 (p < 0.00)
Well-being	↑ 40 (p < 0.001)

Fiz J et al. PLoS One. 2011

## Nabilone for Fibromyalgia

- RCT with 40 patients with FM pain for 4 weeks<sup>1</sup>
  - Nabilone 1-2 mg/day vs. placebo
  - Significant improvement in pain, anxiety, and Fibromyalgia Impact Questionnaire (FIQ) score
- Crossover trial of FM patients with insomnia<sup>2</sup>
  - Nabilone 0.5-1 mg vs. Amitriptyline 10-20 mg
  - Nabilone associated with improved sleep quality, improved restfulness, more AE

1. Skrabek RQ et al. J Pain. 2008  
2. Ware MA et al. Anesth Analg. 2010

## 2012 Canadian Pain Society 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)**

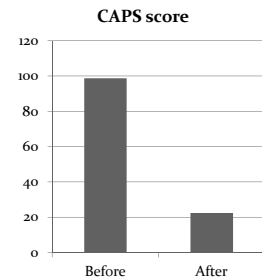
[http://www.canadianpainsociety.ca/pdf/Fibromyalgia\\_Guidelines\\_2012.pdf](http://www.canadianpainsociety.ca/pdf/Fibromyalgia_Guidelines_2012.pdf)

## Hepatitis C

- All data regarding use with hepatitis C predate newer medications (ledipasvir, sofosbuvir, paritaprevir, ritonavir, ombitasvir, simeprevir)
- Benefits of marijuana appear limited to improving tolerance for interferon based regimens
  - Benefit only found in 2 of 3 cohorts
  - Concerns about fibrosis progression in 2 of 3 observational studies

## PTSD

- New Mexico Medical Cannabis Program
  - 80 patients treated for PTSD with marijuana
  - Symptom severity assessed with Clinician Administered Posttraumatic Scale (CAPS) (0-136)
  - Retrospective reporting by patients



Greer GR et al. J Psychoactive Drugs. 2014 Jan-Mar;46(1):73-7

## Adverse Effects of Cannabis

- Short-term cognitive effects
  - Dizziness
  - Impaired motor coordination
  - Altered judgment
  - Paranoia
  - Euphoria
  - Disorientation
  - Dissociation
- Increased appetite

1. Volkow ND et al. NEJM 2014  
2. Wilcock A et al. Journal of Pain and Symptom Management 2013

## Other Adverse Effects of Cannabis

- Recurrent cyclic vomiting (cannabinoid hyperemesis syndrome)
- Fertility issues
- 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 ↑ 2-2.6X
- Dose-response curve
- Risk higher in studies of fatal crashes
- fMRI indicate no safe level of acute marijuana smoking

1. Li M et al. Epidemiol Rev 2012  
2. Ashbridge M et al. BMJ 2012  
3. Battistella G et al. PLoS ONE 2013

## Diversion

- Major concern with medical marijuana
- 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%)

Salomonsen-Sautel S et al. J Am Acad Child Adolesc Psychiatry. 2012

## Evidence Summary

- Best evidence for efficacy is for MS spasms, HIV neuropathic pain, Crohns disease, chemo-induced nausea and vomiting
- May help other painful conditions including fibromyalgia, cancer, and certain seizure disorders
- Uncertain benefit: Adult epilepsy, Tourette Syndrome, PTSD, Parkinson disease, ALS
- No clinical benefit for glaucoma

## Practice Recommendations

- Marijuana is not first-line treatment for any medical condition
- Always optimize standard medical therapy first
- Marijuana should only be a supplement to medical care, not a substitute
- Certification should be part of ongoing doctor-patient relationship. Follow up to monitor for adverse effects
- Assess individual risks and benefits
- Consider written agreement outlining expectations