Pain and Palliative Care PRN—Clinical Controversies of Cannabinoids for Pain Management: Evidence and Political Implications for Pharmacists

Activity No. 0217-0000-14-109-L01, 2.0 contact hours; Knowledge-based activity.

Monday, October 13
1:30 p.m.–3:30 p.m.
Convention Center:
Meeting Room 19

Moderator: Amanda R. McFee Winans, Pharm.D., BCPS
Clinical Pharmacy Specialist, Bassett Medical Center, Cooperstown, New York

Agenda

1:30 p.m.	Medical Use of Cannabinoids: Where's the Evidence? *Laura B. Borgelt, Pharm.D., FCCP, BCPS* Professor, University of Colorado Anschutz Medical Campus, Skaggs School of Pharmacy & Pharmaceutical Sciences, Aurora, Colorado
2:10 p.m.	Medical Use of Cannabinoids: Clinical Pearls *James B. Ray, Pharm.D.* Pharmacy Clinical Coordinator – Pain/Palliative Care, UVA Health System, Charlottesville, Virginia
2:50 p.m.	"My Doctor Gave Me Marijuana … What's the Big Deal?" *Jennifer M. Strickland, Pharm.D., BCPS* Vice President, PGT Business Leader, Millennium Labs, San Diego, California

Conflict of Interest Disclosures

Laura B. Borgelt: no conflicts to disclose.
James B. Ray: no conflicts to disclose.
Jennifer M. Strickland: no conflicts to disclose.
Amanda R. McFee Winans: no conflicts to disclose.

Learning Objectives

1. Explain pharmacological principles for the use of cannabinoids for pain or symptom management.
2. Identify appropriate indications for clinical uses of cannabinoids.

3. Apply evidence-based practices in the approach to managing pain or other symptoms for a patient requesting cannabinoids.
4. Describe the mechanism of action and dosing of the cannabinoid agents utilized in pain and symptom management.
5. Explain pharmacokinetics and pharmacodynamics of the various cannabinoids utilized for pain and symptom management.
6. Recognize common or serious drug interactions and adverse effects associated with medical use of cannabinoids.
7. Relate the use of medical marijuana to possible effects on the associated provider-healthcare professional relationship.
8. Explore the psychosocial and societal aspects of medical use of cannabinoids.
9. Differentiate between medical and non-medical uses of cannabinoids in patients with pain or other distressing symptoms.

Self-Assessment Questions

Self-assessment questions are available online at www.accp.com/am

Medical Use of Cannabinoids: Where's the Evidence?

Laura M. Borgelt, PharmD, FCCP, BCPS
Professor, University of Colorado Anschutz Medical Campus
Departments of Clinical Pharmacy and Family Medicine
American College of Clinical Pharmacy
October 2014

Disclosures

Dr. Borgelt reports no relevant financial relationships.

Dr. Borgelt will be discussing unapproved drugs and unapproved uses for drugs.

Dr. Borgelt has served as a member of five working groups in Colorado:
- Colorado Department of Public Health and Environment: 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
- Colorado Department of Public Health and Environment Public Health Advisory

Objectives

- Explain pharmacological principles for the use of cannabinoids for pain or symptom management
- Identify appropriate indications for clinical uses of cannabinoids
- Apply evidence-based practices in the approach to managing pain or other symptoms for a patient requesting cannabinoids

POLL QUESTION

I live in a state where medical marijuana (MMJ) laws are enacted.

1. True
2. False

POLL QUESTION

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

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

OVERALL goal for this presentation is…

…to help pharmacists better describe the characteristics of marijuana and its effects so you can confidently talk with your patients about the potential benefits and risks of using marijuana.

Patient Case in Colorado

- 47 yo male
- PMH of HTN, diabetes, peripheral neuropathy, and chronic pain
- Pain Treatment Regimen
  - Oxycontin 30mg po BID and oxycodone 5 mg po as needed for breakthrough pain
  - His pain medications have not changed in over one year
  - Today, he admits that he has also been smoking medical marijuana twice daily for the past two years to help his pain (decreased from 8/10 to 4/10).
  - He has been afraid to tell the healthcare team about this because he believes they will not "approve" of this treatment. He states he saw a different physician to get his card and prescription for medical marijuana.

A Few Questions to Consider

- Are there other ways for him to consume MMJ to avoid the risks of smoking?
- Is MMJ effective for the treatment of pain?
- What adverse effects might this patient experience with chronic use of inhaled MMJ?
- Are there any drug interactions with MMJ?
- How might MMJ impact his opioid use?
- What other issues might this patient need to consider?
- How can I create an environment where patients feel safe to talk with me about any/all treatments they use?

Marijuana

- Single molecule pharmaceuticals
  - Dronabinol (Schedule III)
  - Nabilone (Schedule II)
- Liquid extract: nabiximols (Sativex®)
  - Approved in 24 countries; U.S. - Phase III trials
- Phytocannab
  - *Cannabis* nt (Schedule I)

Cannabis

- Plant-derived cannabinoids*
  - Δ^9-tetrahydrocannabinol - THC
  - Δ^8-tetrahydrocannabinol - THC
  - Cannabidiol – CBD
  - Cannabinol - CBN
  - Cannabigerol - CBG
  - Cannabichromene - CBC
  - Cannabicyclol
  - Cannabielsoin
  - Cannbitriol
  - Miscellaneous
  - Cannabinodiol (air-oxidation)

*Present in varying relative proportions depending on the strain

Br J Pharmacology 2006;147:S163-171
Br J Pharmacology 2011;163:1344-1364

POLL QUESTION

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

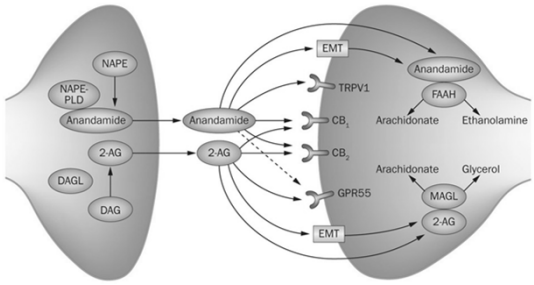
1. Cannabinoid-1 receptor (CB1)
2. Cannabinoid-7 receptor (CB7)
3. Peroxisome Proliferator-Activated Receptors (PPAR)
4. G-protein receptor 55 (GPR55)

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, 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)
- Exogenous cannabinoids stimulate CB1, CB2 and others

http://norml.org/library/item/introduction-to-the-endocannabinoid-system Accessed March 11, 2013

Endocannabinoid System



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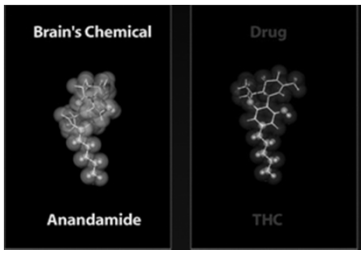
Cannabis Pharmacology



http://www.drugabuse.gov/publications/addiction-science/why-do-people-abuse-drugs/how-are-drugs-able-to-affect-brain-chemicals Accessed August 14, 2014

Targets of Marijuana

CB1 Receptors

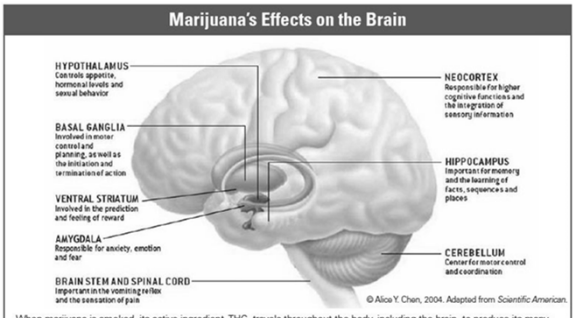
- Basal ganglia
  - Motor activity
- Cerebellum
  - Motor coordination
- Hippocampus
  - Short-term memory
- Neocortex
  - Thinking
- Hypothalamus & limbic
  - Appetite, sedation
- Pertaqueductal gray dorsol horn
  - Pain
- Immune cells

CB2 Receptors

- Immunologic cells
  - B lymphocytes
  - Natural killer cells
- Brain
  - Role not established

Brit J Clin Pharm 2009;67(1):5-21
J Psychopharmacol 2008;22:707–16
J Psychopharmacol 2008;22:717–26.

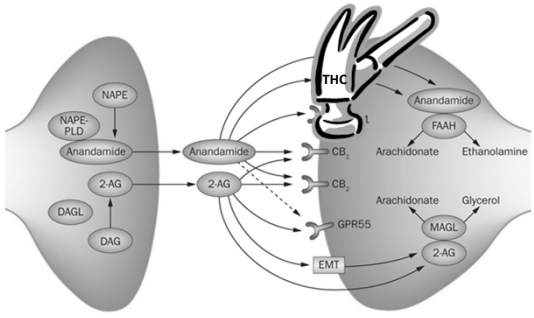
Marijuana's Effects on the Brain



When marijuana is smoked, its active ingredient, THC, travels throughout the body, including the brain, to produce its many effects. THC attaches to sites called cannabinoid receptors on nerve cells in the brain, affecting the way those cells work. Cannabinoid receptors are abundant in parts of the brain that regulate movement, coordination, learning and memory, higher cognitive functions such as judgment, and pleasure.

http://www.drugabuse.gov/publications/research-reports/marijuana/how-does-marijuana-produce-its-effects Accessed August 14, 2014

Endocannabinoid System



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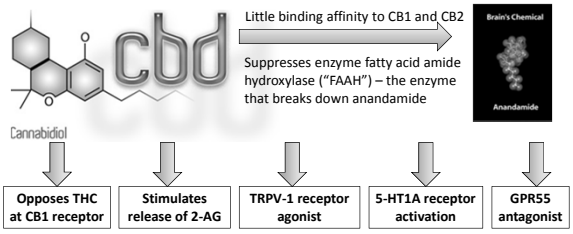
Non-Cannabinoid Targets Linked to Cannabis

- 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

Another Kid on the Block…

Other cannabinoids found in the plant are also providing effects. The cannabinoid that has sparked the most interest is a non-psychoactive component called cannabidiol (CBD).



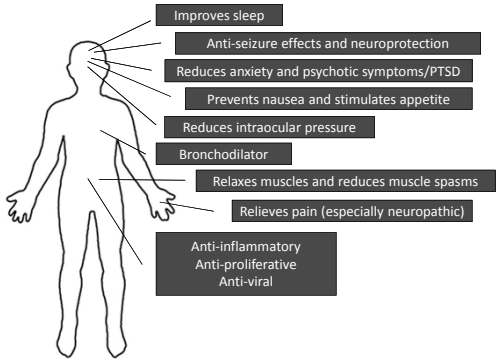
Epilepsia 2014;55(6):791–802. http://www.projectcbd.org/news/how-cbd-works/ Accessed 7/13/14

Receptor Response to Cannabinoids

- Ligand concentration
- Presence of other cannabinoid ligand molecules
- Receptor density and state of activation
- Levels of signaling proteins

Expert Opin Drug Metab Toxicol 2013;9(9):1219-28. Immunobiology 2010;215(8):588-97. Nature 2001;410(6828):588-92

Potential Physiologic Responses to Cannabis

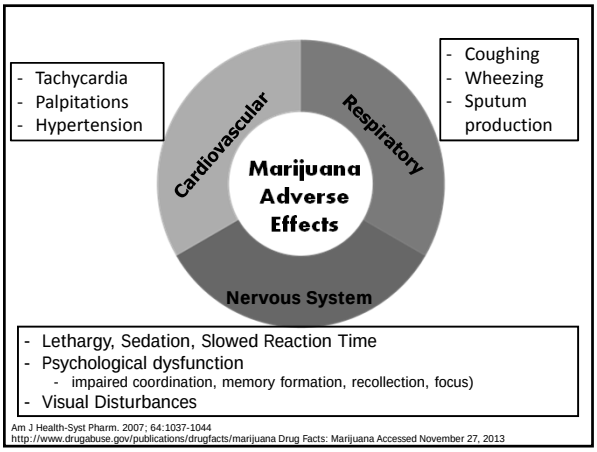


Minnesota Medicine 2014:4:18-27.
http://www.cancer.gov/cancertopics/pdq/cam/cannabis/patient/page1/AllPages/Print. Accessed 7/14/14.

POLL QUESTION

Which of the following is/are common adverse effects of marijuana?

1. Low blood pressure
2. Slowed reaction time
3. Decreased heart rate
4. Insomnia
5. All of the above



Am J Health-Syst Pharm. 2007; 64:1037-1044
http://www.drugabuse.gov/publications/drugfacts/marijuana Drug Facts: Marijuana Accessed November 27, 2013

Psychiatric Implications

- Acute cannabis psychosis
  - Very large dose of cannabinoid botanical consumed
  - Typically through oral ingestion (concentrated preparation)
  - Agitation, confusion, sedation
  - Self-limiting and generally disappears after metabolism/excretion
- Acute schizophreniform reaction
  - Young adults under stress and have other vulnerabilities to schizophreniform illness
  - Early and heavy cannabis exposure may increase the risk of developing a psychotic disorder such as schizophrenia
  - Carefully monitor or avoid in early teens or preteens with preexisting symptoms of mental illness or patients with significant family or personal history of mental illness

J Psychiatr Res 2013 Apr;47(4):438-44
J Clin Psychiatry 2012 Nov;73(11):1463-8
Clin J Pain 2013;29:164-71

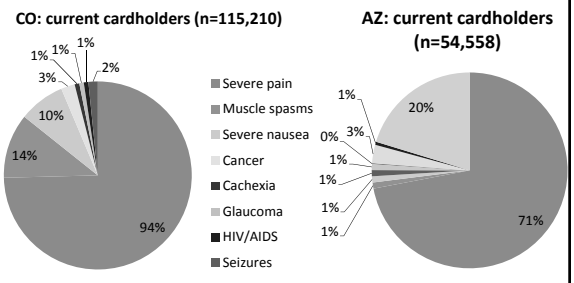
Summary of Cannabis Pharmacology

- Cannabinoids may have a role for the treatment of many conditions involving the endocannabinoid system
- Although several possibilities, most well-studied target receptors are CB1 and CB2 found throughout the body
- Adverse effects include central nervous system, cardiovascular, and respiratory effects
- Benefit and risk of cannabis should be evaluated for individual patients
- More research is needed

Therapeutic Effectiveness of MMJ

What Should Be Studied?

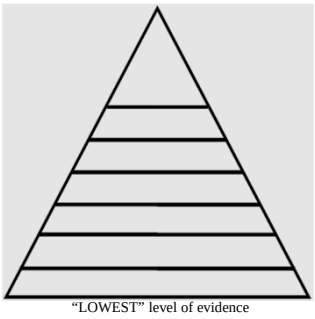
MMJ Registrants in CO and AZ: Qualifying Conditions



https://www.colorado.gov/pacific/sites/default/files/CHEIS_MMJ_05_2014_%20MMR_report.pdf Accessed Aug 13, 2014..
http://www.azdhs.gov/medicalmarijuana/documents/reports/2014/medical-marijuana-quarterly-report-july-2014.pdf

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



Treatment of Chronic Non-Cancer Pain: Systematic Review of Randomized Trials

Cannabinoid	Overall result
Smoked cannabis (n=4)	**All trials found positive effect** by improving neuropathic pain vs placebo with no serious adverse effects.
Oromucosal extracts (n=7)	**6/7 trials demonstrated positive analgesic effects** for neuropathic pain, RA, mixed chronic pain. In one trial evaluating RA, **significant decrease in disease activity** (28 joint disease activity score).
Nabilone (n=4)	**Three showed significant analgesic effect** in spinal pain, fibromyalgia, and spasticity related pain vs placebo. One showed **similar effect in neuropathic pain vs dihydrocodeine**.
Dronabinol (n=2)	**Significant reduction in central pain** (MS) vs placebo. **Significantly greater analgesia** vs placebo for mixed chronic pain on opioids.
THC-11-oic acid analogue - CT-3 or ajulemic acid (n=1)	Ajulemic acid led to **significant improvement** in neuropathic pain intensity **at 3 hours, but no difference at 8 hours** compared with placebo.

Br J Clin Pharmacol 2011;72(5):735-44

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

Cannabis Treatment for Chronic Pain

Systematic Review and Meta-Analysis

- 18 double-blind RCTs
- Synthetic derivatives included
- Efficacy outcome: "intensity of pain" by VAS
- Harms: number of adverse events
- Concluded moderate efficacy, but risks may be greater than benefit

OUTCOME	OR (95% CI)
Intensity of pain	**-0.61 (-0.84, -0.37)**
Euphoria	**4.11 (1.33, 12.72)**
Dysphoria	2.56 (0.66, 9.92)
Blurred vision	**8.34 (4.63, 15.03)**
Tinnitus	2.18 (0.93, 5.11)
Disorientation/Confusion	**3.24 (1.51, 6.97)**
Dissociation/ Acute psychosis	3.18 (0.89, 11.33)
Speech disorders	**4.13 (2.08, 8.20)**
Ataxia, muscle twitching	**3.84 (2.49, 5.92)**
Numbness	**3.98 (1.87, 8.49)**
Impaired memory	**3.45 (1.19, 9.98)**
Attention disturbances	**5.12 (2.34, 11.21)**

Pain Medicine 2009; 10(8):1353-68)

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)

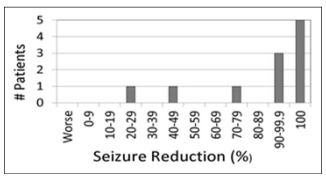
RESULTS

- 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;182:E694-701.

High Concentration Cannabidiol in Highly Refractory Pediatric Epilepsies

- Charlotte's Web (CW Realm Oil, or Realm Oil)
  - CBD at a ratio of >16:1 relative to other cannabinoids
- 11 patients with severe, medically refractory epilepsy and who had received Realm Oil for at least 3 months
  - 4 Doose syndrome, 2 Dravet syndrome, 1 Lennox-Gastaut syndrome, 1 metachromatic leukodystrophy, 1 cortical dysplasia and 2 idiopathic epilepsy
  - Average of 10 AEDs in their lifetime
  - Average dose was 4 to 12 mg/kg/day, in 2 or 3 divided doses



- Side effects:
  - Sedation
  - Unsteadiness

In Press with the American Epilepsy Society, 67th Annual Meeting, December 6-10, 2013

Parent Survey of Cannabidiol-enriched Cannabis use in Pediatric Treatment-Resistant Epilepsy

- 19 responses from parents belonging to Facebook group
  - Children age 2-16 years with epilepsy and current use of CBD-enriched cannabis (dose ranging from 0.5-28.6 mg/kg/day)
- Avg # of AEDs prior to CBD-enriched cannabis = 12
- Results
  - 16/19 (84%) reported a reduction in child's seizure frequency
    - 2/19 (11%) = complete seizure freedom
    - 8/19 (42%) = >80% reduction in seizure frequency
    - 6/19 (32%) = 25-60% reduction in seizure frequency
    - 12/19 parents weaned their child from another AED
  - Other benefits: better mood (79%), increased alertness (74%), improved sleep (68%), decreased self-stimulation (32%)
  - Side effects: drowsiness (37%) and fatigue (16%)

Epilepsy Behav. 2013;29(3):574-7

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 Apr 29;82(17):1556-63

Other Interesting Clinical Findings

- PTSD: cannabis used more frequently for sleep and coping
  - Drug and Alcohol Dependence. 2014;136:162–5
- IBD: improved pain and diarrheal symptoms
  - Inflamm Bowel Dis 2014;20:472–80
  - Inflamm Bowel Dis 2013;19:2809–14
- Pediatric treatment-resistant epilepsy: parents giving CBD-enriched cannabis shows decreased seizure frequency
  - Epilepsy Behav. 2013;29(3):574-7

Summary of Clinical Trials

- Cannabinoids may have a role for the treatment of refractory seizures and pain, especially neuropathic pain
- Appropriate and consistent dosing/concentrations difficult
- Study limitations: short duration, small numbers enrolled, varying THC and CBD content of plant material, difficult to blind pts
- Unfavorable side effect profile
- More research is needed

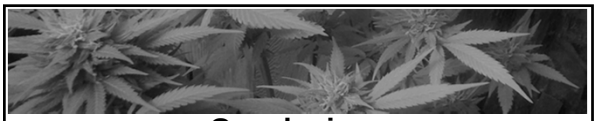
What about our Patient?

Hash
Hash oil
Buds
Edibles
Tinctures
Chews
Sodas/Teas
Topicals

http://www.tokeofthetown.com/2011/03/03/dispensary_image_la_dispensary_lottery.jpeg

Recommendations for Pharmacists

1. Ask about the use of marijuana
2. Discuss potential benefits and adverse effects
3. Check for drug interactions
4. Counsel about patient safety issues including keeping out of the reach of children and using proper packaging and labeling of marijuana
5. Follow clinic and/or hospital policies and procedures



Conclusions

- The endocannabinoid system, including CB1 and CB2 receptors, is the key target for exogenous cannabinoids.
- Psychoactive effects of marijuana related to THC, but other cannabinoids also involved with physiologic effects.
- Clinical studies indicate MMJ may have a role in patients with pain and seizures refractory to other treatments.
- Risk for potential adverse events may or may not outweigh benefit provided.
- Patient-provider relationship is an critical component of approaching the management of pain with cannabinoids.

Medical Use of Cannabinoids: Clinical Pearls

1

JAMES B RAY, PHARM.D., CPE
PHARMACY CLINICAL COORDINATOR – PAIN AND PALLIATIVE CARE
UNIVERSITY OF VIRGINIA HEALTH-SYSTEM
AMERICAN COLLEGE OF CLINICAL PHARMACY
OCTOBER 2104

Disclosures

2

- Dr. Ray reports the following relevant financial relationships:
  - Speakers Bureau
    - Millennium Health
    - Cadence Pharmaceuticals
    - Pain Weekend
  - Consultant
    - Mallinckrodt Pharmaceuticals
  - Other
    - Personal consulting company – Alchemy Consulting, P.C.

Objectives

3

- Describe the mechanism of action and dosing of cannabinoid agents utilized in pain and symptom management
- Explain pharmacokinetics and pharmacodynamics of the various cannabinoids utilized for pain and symptom management
- Recognized common or serious drug interactions and adverse effects associated with medical use of cannabinoids

M.O.A. in Pain Relief

4

- Antinociceptive effects mediated through mechanisms distinct from those responsible for other behavioral effects
  - Endogenous & exogenous cannabinoids exert influence on the following:
    - Opioid, $5HT_3$, NMDA and α3 glycine receptors
    - Homeostatic pain modulation
    - Activation of central noradrenergic pathway & peripheral adrenoreceptors
  - CB_2 receptors in DRG, spinal cord , microglia & brain
    - CB_2 agonists trigger release of β endorphin
  - Differential effects
    - Sensory (intensity; quality)
    - Affective (unpleasantness; suffering)

Pertwee RG, et al. Pharmacol Rev 2010;62:588-631.
Thiago RL, et al. Anesth Analg 2013;116:463-72.
Xiong W, et al. J Exp Med 2012;209:1121-34.

THC:CBD

5

- Recreational marijuana vs "medical marijuana"
  - THC levels increased from 4.56% to 11.75% and CBD levels decreased from 0.24% to 0.08%
    - Genetic engineering
- THC is responsible for the "high" of cannabis
  - Anxiety – lower doses reduce, higher doses increase – in most individuals
    - Common SEs – drowsiness, unsteady gait, dizziness, inability to focus thoughts, confusion, mood changes, delusions, and hallucinations
    - Same issues with synthetic THC
  - Memory – STM, LTM?
  - Psychosis, Addiction
- CBD attenuates the euphoric effects of THC
  - Research needs to focus on CBD for "medical marijuana" to have value

Burgdorf JR, et al Drug Alcohol Depend 2011;117:59-61., Moreire FA, et al. Curr Top Behav Neurosci 2010;2:429-50.
Crean RD, et al. J Addict Med 2011;5:1-8., Haney M, et al. Neuropsychopharmacology 2013;38:1557-1565.
Issa MA, et al. Clin J Pain 2014;30:472-478.

Cannabidiol

6

- Anxiolysis - ↑ 5-HT transmission
- Attenuates memory impairing effect of THC
- Inhibits THC-elicited paranoia
- Anti-emetic
- Reduces/blocks CINP (animal data)
- Antiproliferative effects
  - Cytotoxic to leukemia cells
  - Inhibits lung cell invasion
  - Induces apoptosis
  - Synergistic with chemotherapy

Espejo-Porras F, et al. Neuropharmacology 2013;75:155-163., Morgan CJA, et al. Br J Psychiatry 2010;197:285-290.,
Englund A, et al. J Psychopharmacol 2013;27:19-27., Rock EM, et al. Br. J Pharmacol 2012;165:2620-2634., Ward
SJ, et al. Anesth Analg 2011;113:947-950., Ward SJ, et al. Br J Pharmacol 2014;17:636-645., Scott KA et al.
Anticancer Res 2013;33:4373-4380.,

Cannabidiol Safety Profile

7

- Not associated with:
  - Catalepsy
  - Changes in physiological parameters (HR, BP, Temperature)
  - GI transit changes
  - Psychomotor function
- Safe in:
  - Schizophrenic and Parkinson's patients

Bergamaschi MM, et al. Curr Drug Saf 2011;6:237-239.
Zuardi AW, et al. J Psychopharmacol 2005;20:683-686.
Zuardi AW, et al. J Psychopharmacol 2009;23:979-983.

Cannabinoid and NP Pain

8

NP Type	# Subjects	Cannabinoid type	Treatment Duration
HIV	50	3.56% THC, smoked	5 days
Chronic NP	34	THC+CBD 1:1, SL	12 weeks
Chronic NP	21	CT-3 (THC analog)	7 days
MS	630	THC extract – oral	15 wk with up to 52 wks
MS	24	Dronabinol	3 wk
MS	137	THC+CBD (Sativex)	10wk with up to 52 wks
MS	66	Sativex	4 week
Chronic NP	24	THC+CBD	2 week
Brachial plexus	48	Sativex vs THC vs P	Three 2 wk periods
Peripheral NP	125	Sativex	5 wk with up to 52 wks

Fine PG, et al. Curr Pain Headache Rep 2014;18:415 DOI 10.1007/s11916-014-0451-2

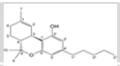
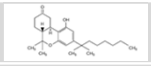
Medical marijuana in neurologic disorders

Neurologic Condition	Cannabinoid type	Recommendations
Multiple Sclerosis	Cannabis extract & THC	OCE effective for ↓ spasticity symptoms & pain THC probably effective OCE & THC ineffective for ↓ objective spasticity measures and tremors
	Oromucosal Spray	OSC effective for improving spasticity symptoms, pain & urinary frequency OSC ineffective for reducing objective spasticity measures or bladder incontinence or MS-tremor
	Smoked cannabis	Data inadequate regarding safety or efficacy for spasticity or pain relief
Huntington Disease	Nabilone	Underpowered studies, no conclusions can be made
Parkinson's Disease	Cannabis	Ineffective for levodopa-induced dyskinesias
Tourette Syndrome	Cannabis	Date insufficient to support or refute efficacy for THC for ↓ tic severity
Cervical Dystonia	Cannabis	Date insufficient to support or refute efficacy for THC for ↓ tic severity

Koppel BS, et al. Neurology 2014;82:1556-1563.

Synthetic THC

10

	Dronabinol (Marinol®) Δ^9-THC (-)-*trans* isomer	Nabilone (Cesamet™)
		
ADME	A 10-20% D Total protein binding 90-99% Vd 10L/kg M Extensive – 11-OH-Δ-9-THC E Renal 10-15% Feces 35-=50%, TBC 0.2L/kg/hr $T_{½}$ 19-36 hrs (biphasic)	A 95.6-100%, Tmax 2hrs D 12.5l/kg M Extensive E Renal 20-25% as M Fecal 60-65 as M $T_{½}$ 2 hrs
Dosing	AIDS – Loss of appetite 2.5mg PO bid – max 20mg/day CINV – Prophylaxis 5mg/m² 1-3hrs prior to chemo, 5mg/m² q2-4hr for total of 4-6/day – max dose of 15mg/m²/dose	CINV – 1-2mg po bid, max dose 6mg/day
Interactions	Ritonavir - ↑ Dronabinol Topotecan - ↑ Topotecan	Weak I↓ CYP 2E1 & 3A4 Moderate I↓ CYP2C8 & 2C9

http://www.cesamet.com/pdf/Cesamet_PI_50_count.pdf
http://www.rxabbvie.com/pdf/marinol_PI.pdf

Nabiximols (Sativex™)

11

- Δ-9-tetrahydrocannabional 2.7mg and cannabidiol (CBD) 2.5mg/100 microlitre
  - THC and CBD appear in the plasma within 15 minutes after single oromucosal administration.
    - Cmax of about 4 ng/mL , 45-120 minutes after a single dose administration of a 10.8 mg THC dose
  - With food the mean Cmax and AUC for THC were 1.6- and 2.8-fold higher compared with fasting conditions. Corresponding parameters for CBD increased 3.3- and 5.1-fold.
  - There is a high degree of variability in pharmacokinetic parameters between patients.
- PK parameters for Sativex, vaporized THC extract and smoked cannabis

	C_{max} THC ng/mL	T_{max} THC minutes	AUC $_{(0-t)}$ THC ng/mL/min
Sativex (providing 21.6 mg THC)	5.40	60	1362
Inhaled vaporised THC extract (providing 8 mg THC)	118.6	17.0	5987.9
Smoked cannabis* (providing 33.8 mg THC)	162.2	9.0	No data

http://www.medicines.org.uk/emc/medicine/23262

Sativex

12

- Drug Interactions
  - The in vitro inhibitory effects of Sativex on the major CYP450 enzymes CYP3A4 and CYP2C19 occurs at concentrations substantially higher than the maximum observed in clinical trials. No interactions with regards to at risk-CYP3A4 substrates are expected.
  - Concomitant treatment with the CYP3A4 inhibitor ketoconazole produced an increase in Cmax and AUC of THC (1.2- and 1.8-fold, respectively), its primary metabolite (3- and 3.6-fold, respectively) and of CBD (2- and 2-fold, respectively).
  - Rifampicin caused reductions in Cmax and AUC of THC (40% and 20% reduction, respectively), its primary metabolite (85% and 87% reduction, respectively) & CBD (50% and 60% reduction, respectively)
    - If necessary, careful titration is recommended, notably within the two weeks following D/C of the inducer.
- Pharmacodynamic Interactions
  - Sedatives, anti-spasticity agents, EtOH

http://www.medicines.org.uk/emc/medicine/23262

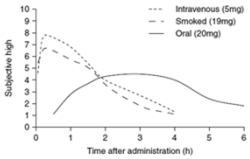
Sativex

13

- Clinical Efficacy
  - MS Spasticity Syed YY, et al. Drugs 2014;74:563-578.
  - Neuropathic pain Rahn EJ, et al. Neurotherapeutics 2009;6:713-737.
  - Cancer pain Johnson JR, et al. J Pain Symptom Manage 2013;46:207-218. Portenoy RK, et al. J Pain 2012;13:438-439.
- Adverse Effects Robson P. Expert Opin Drug Safe 2011;10:675-685. Wade D. Expert Rev Neurother 2012;12(4 Suppl):9-14.
  - No evidence of withdrawal or habituation
  - Dizziness, diarrhea, fatigue, nausea – (mild-moderate)
  - Low abuse potential

Avoid doing the Maureen Dowd! (Couchlock)

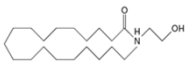
14



- Oral edibles have high first pass, 11-hydroxy-THC
  - More psychotropic and long lasting
  - Many products almost pure THC
  - Many doses of THC contained within one product

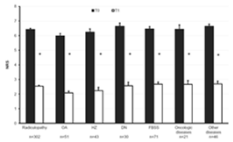
http://www.nytimes.com/2014/06/04/opinion/dowd-dont-harsh-our-mellow-dude.html?_r=0
Grotenhermen F. Clin Pharmacokinet 2003;42(4):327-360.

Palmitylethanolamide (PEA)



15

- Congener of the endocannabinoid anadamide
  - Peroxisome proliferator-activated receptor alpha (PPAR-α)
    - Inhibits release of pro-inflammatory mediators
  - Inhibits microglia activation
- Dietary food, nutraceutical
  - (Normast®, PeaPure®)
- Most research done in Europe
  - Chronic pelvic pain
  - Neuropathic pain



Calabro RS, et al. Pain Med 2010;11(5):781-4.
Gatti An, et al. Pain Med 2012;13:1121-1130.
Keppel Hesselink JM et al. J Pain Res 2012;5:437-442.

Conclusions

16

- Commercially available cannabinoids have poor efficacy and tolerability for treating pain
- Nabiximols appear promising – studies just getting underway
- Medical marijuana based on current science appears to have little value for pain, especially with high concentration of THC
- Palmitoylethanolamide deserves further investigation in well designed RTC for prevention and as an adjunct for pain management

2014 ACCP Annual Meeting

My doctor gave me marijuana… what's the big deal?

Jennifer M. Strickland, PharmD, BCPS

October 13, 2014

Conflict of Interests

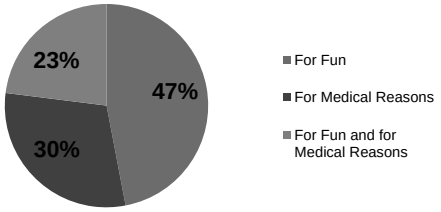
- None relevant

Learning Objectives

- 1. Relate the use of medical marijuana to possible effects on the associated provider-healthcare professional relationship.
- 2. Explore the psychosocial and societal aspects of medical use of cannabinoids.
- 3. Differentiate between medical and non-medical uses of cannabinoids in patients with pain or other distressing symptoms.

Why Do People Use Marijuana?

Among people who used marijuana in the past year:



SOURCE: Pew Charitable Trust, 2013 (reference list).

4

Cannabis / Marijuana

- Complex alkaloid mixture
  - more than 400 compounds derived from the Cannabis sativa plant
  - Up to 80 cannabinoids (Radwan 2009)
- Most abundant and active:
  - Delta-9 tetrahydrocannabinol (THC- most psychoactive)
  - Cannabidiol
  - Cannabinol
  - Cannabichromene CBC (second most abundant)

Marijuana

- Dry, shredded mix of leaves, flowers, stems, and seeds, usually from *Cannabis sativa* or *Cannabis indica* plant
- Hundreds of variants of plants
  - North American plant bred to exhibit high concentrations of THC
- Common names: grass, weed, pot, reefer, Mary Jane, ganja
- Smoked, inhaled, ingested

SOURCE: SAMHSA, 2012 (reference list).

6

Available "Preparations"

- Dried flowering tops/leaves of plant
  - THC concentration 0.5-5% in past, now 20-25%
- Hashish
  - Dried cannabis resin and flowers
  - THC concentration 2-8% or higher
- Hash Oil ("Wax")
  - Extraction of THC from hashish with an organic solvent
  - THC concentration 15-50%
- Synthetic Marijuana ("Spice", "K2")

SOURCES: NIDA 2012c; DEA 2013; Hallett, 2013 (reference list). 7

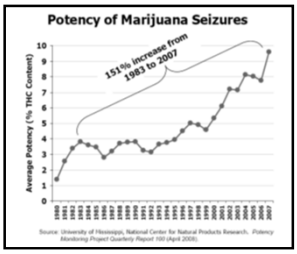
Delivery Systems

- Variable delivery systems
  - Joints
    - ~500 mg of marijuana inside of rolled papers
    - 0.5-1 gram cannabis typically
    - THC concentration: 5-150 mg (only need 2-3 mg for effect)
    - 20-70% of THC delivered in smoke
  - Blunts
    - 20% THC absorption
  - Pipes
    - 50% absorption
  - Water pipes
    - 90% absorption ("Bongs")
  - Ingestion

Delivery System: Smoked

- No rate control for dosing or potency
- No standardization
  - Variable strains
- Unpredictable
- Absorption dependent on
  - Technique
  - Delivery method
  - Time to exhale

"It's not your father's 'pot' anymore"



- Increased potency over time
- 1960s-70s average THC concentrations: 1-2%.
- Today: Concentrations up to 20%

SOURCES: Kleber, 2012; TRI, 2012 (reference list). 10

Medical Marijuana vs. THC Medications

- Medical Marijuana is **not** FDA approved
  - FDA approval assures that medications are effective, safe, and properly labeled
  - FDA cannot evaluate medical marijuana as a drug since it is a plant, not a standardized medical formulation
  - Medical marijuana is different everywhere, depending on how it is bred, under what conditions it is grown, etc.
  - No way to know if medical marijuana is pure. Can be contaminated by pesticides, mold, fungus.

SOURCE: Kleber, 2012 (reference list). 11

"Medical" marijuana

- Not homogenous material
  - Varies widely based on strain, cultivation, storage, harvesting and other factors (similar to opium)
- Various methods of delivery (smoked, vaporized, teas, etc) – no standardized or reproducible way of ensuring a specific reproducible dose
- No quality control mechanisms (no recalls)
  - Microbe contamination
    - Aflatoxins not destroyed by heat or smoking – may lead to aspergillosis
  - Heavy metal or pesticide contamination
    - Los Angeles dispensary: pesticide levels 170 times permitted for herbal products[1,2]
- Unmonitored supply chain, no labeling, advice given by unlicensed and untrained personnel in dispensaries

1 People v Hemp Factor V et al. No. BC 424881 (Cal Sup Ct. Oct 30, 2009)
2) In 2005, a cannabis advocate died from a neurological condition believed to have resulted from handling cannabis contaminated by pesticides, which was being distributed through cannabis dispensaries. Gardner F. "Jane Weirick: Death of an Organizer," CounterPunch (Oct. 2005) http://www.counterpunch.org/gardner10292005.html

Efficacy

- Numerous claims
  - Pain, including neuropathic pain
  - Nausea/vomiting
  - Cachexia/anorexia
  - MS
  - ALS
  - Glaucoma
  - Alzheimer's
- Few randomized trials
- Mostly small studies, case reports

State Laws

- Laws legalizing marijuana in some form exist in 23 states and the District of Columbia

http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx

Financial Impact

- $9 billion dollars spent annually on fight against marijuana
  - 33,000 state inmates, 10,000 federal inmates due to marijuana use / distribution
  - Estimated cost ~$1 billion / annually

Physician – patient relationship

- May negatively impact patient – physician relationship
  - May be due to inherent conflicts of interest within the healthcare system
  - Patient demands for medical marijuana
  - Patient reliance on single "magic bullet"
  - May be used as replacement for prescription medications by patient[1]
    - Over 50% may be utilizing medical marijuana rather than proven prescription medication
    - ~13% appear to be using to replace alcohol

Reinarman C et al. Who are medical marijuana patients? Population, characteristics from 9 California Assessment clinics. J Psychoactive Drugs 2011. 43(2):128-35.

Marijuana use and Opioid Use

- 25% fewer opioid-related deaths in states allowing medical marijuana
  - 24.8% lower annual opioid overdose mortality rate
  - Relationship stronger over time
    - 20% lower in first year after medical marijuana law enacted
    - 33.7% lower five years after implementation

Hayes MJ, Brown MS. Legalization of medical marijuana and incidence of opioid mortality. JAMA Intern Med 2014;

Physician – Patient Relationship

- Public acceptance rather than clinical data has driven approval of medical marijuana
  - Colorado:
    - 46% believe physicians should NOT recommend medical marijuana
    - 60% believe drug's risks outweigh benefits
- Federal status may discourage patients from self-reporting
- Risks of drug interactions
- Possible limitations to treatment (e.g., organ transplant)
- Perception of "aiding and abetting" drug use

Physician-Patient Relationship
State Requirements

- Varies due to state requirements
  - Minnesota – requires physicians ***who choose to participate*** to certify the patient has one of 9 eligible conditions, counsel patients appropriately, provide information about outcomes to registry
- Often places clinicians in difficult position
  - White papers and statements suggesting that providers should not advocate for a therapy with limited evidence

Medical Associations

- Conflicting positions regarding MM
  - VA – against
  - American Academy of Physicians – against except under medical supervision and for specific indications
  - American College of Physicians – support prescription cannabinoids over MM
- Many Medical Associations have called for further studies of medical marijuana
  - Many are not supportive of legislation that involves physicians certifying, authorizing, or otherwise directing patients in the area of medical marijuana outside of clinical trials (e.g., Minnesota)

Organizational Viewpoints

- American Medical Association
- Institute of Medicine
  - Called for further research
- American Society of Addiction Medicine (ASAM)
  - White Paper
    - "All cannabis based therapy should be subjected to the rigorous scrutiny of the FDA regulatory process"
    - "lacks quality control and standardization"
    - "Physicians should carefully consider their ethical and professional responsibilities…should not advise a patient to seek treatment…about which the physician has inadequate knowledge regarding the composition, dose, side effects or appropriate therapeutic targets…"

Pharmacist-Patient Relationship

- Some states have suggested pharmacists should be responsible for dispensing medical marijuana
- Due to federal laws, pharmacists should be careful in recommending specific use, sources of medical marijuana or obtaining the drug for patient's use.
- ASHP Policy
  - Calls for making "cannabis available as a legal medicine where shown to be safe and effective and to immediately allow access to therapeutic cannabis through investigational new drug program."

?Gaming the System?

- 2011 survey of medical cannabis users
  - Critics have suggested that some users "game the system" to obtain medical cannabis "legitimately" for treatment of a condition, but then use it for nonmedical purposes

Reinarman C et al. Who are medical marijuana patients? Population, characteristics from 9 California Assessment clinics. J Psychoactive Drugs 2011. 43(2):128-35.

Health Impact of Marijuana Use

- Carcinogenic
  - Possibly more carcinogenic than tobacco smoke
    - due to carcinogenic hydrocarbins
    - Inhaled more deeply and held longer
    - Maertens et al 2009 found marijuana smoke caused more DNA and cellular damage than tobacco smoke
- Respiratory illness
  - One marijuana cigarette = pulmonary problems from 4-10 tobacco cigarettes
  - Increased risk for various pulmonary diseases (bronchitis, emphysema, lung cancer)

Maertens et al. The Genotoxicity of Mainstream and Sidestream Marijuana and Tobacco Smoke Condensates. *Chemical Research in Toxicology*. Online July 17, 2009.

24

Health Impact (continued)

- Cardiovascular illness
  - Increases blood pressure & heart rate 20-100% [1]
  - Up to 4.8 times risk of heart attack in hour after use
- Cerebrovascular risks
  - Frequent use associated with reduced blood flow to posterior cerebellum
    - Impacts memory, attention, overall cognition
    - 50% reduction in information processing speed in MS patients
    - Associaton with depression and anxiety

1. O'Leary DS et al. Neuropsychopharmacology 2002. 26(6).

Psychosocial and Cognitive Impact

- Frequent use associated with altered memory-related brain function[1]
  - Decreased blood flow in prefrontal cortex
- Neuropsychological decline[2]
  - Across numerous domains of functioning
  - Increased cognitive difficulty over time
  - Discontinuation of cannabis did not fully reverse neuropsychological dysfunction in adolescent-onset cannabis users

1. Block et al. Effects of frequent marijuana use on memory-related regional cerebral blood flow. Pharmacol Biochem and Behavior 2002; 72: 237-50. 2. Meier MH et al. Persistent cannabis users show neurospchyological decline from childhood to midlife. Proc Natl Acad Sci USA 2012; 109(40): E2657-64.

Depression / Anxiety

- Significant increase in Depression/Anxiety in frequent users
  - N=1600
  - 7 years
  - Frequent users (every day)
    - 5 times more likely to suffer from depression and anxiety compared to non-users
  - Less frequent use (at least once per week)
    - 2X as likely to develop depression than non-users
- Increased risk of schizophrenic symptoms
  - Correlated with early onset prior to age 15

Arseneault et al. BMJ 2002;325:1212

Social Impact: Colorado

- **100%** Traffic fatalities testing positive for marijuana (2007 – 2012)
- **57%** Marijuana-related emergency room visits (2011-2013)
- **268%** Marijuana-related exposures for children age 0-5 (2006 – 2013)
- **~4%** Potency of THC (1995-2013)

Legalization of Marijuana in Colorado: The Impact. Rocky Mountain High Intensity Drug Trafficking Area. Volume 2. August 2014

Other Botanicals *Required FDA approval*

- Digitalis purpurea – fox glove - CHF
- Papaver somniferum – opium poppy
- Atropa belladonna – nightshade -IBS
- Ephedra sinica – ephedrine - hypotension
- Salix alba – willow tree - ASA
- Taxis brevifolia – Pacific Yew tree – breast cancer

Summary

- Growing use of medical marijuana
- Potential for significant impact on physician-patient or pharmacist-patient relationship
  - Conflicts of interest
  - State or professional organization point of view
  - Federal laws
- Significant medical, psychosocial, and social impact to patients and communities