Medical Marijuana for the PCP: Medical Evidence, State Regulations, & Public Health Implications

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3/4/15
Agenda

• Medical Evidence – current state of evidence for use of marijuana as medicine

• The Massachusetts law – “An Act for the Humanitarian Medical Use of Marijuana”

• Public health - what every PCP should know
Marijuana: pathophysiology

- Endocannabinoid system: functions alongside adrenergic, cholinergic, and dopaminergic systems; composed of receptors CB1 and CB2 and endogenous endocannabinoids
  - CB1: mainly central and peripheral neurons (but also in immune cells)
  - CB2: mainly immune system (but also in neurons)

Multiple Functions of Endocannabinoid Signaling in the Brain
Annual Review of Neuroscience
Vol. 35: 529-558 (Volume publication date July 2012)
Cannabinoid Receptors Are Located Throughout the Brain and Regulate:

- Brain Development
- Memory & Cognition
- Motivational Systems & Reward
- Appetite
- Immunological Function
- Reproduction
- Movement Coordination
- Pain Regulation & Analgesia
Marijuana: pathophysiology

• Exogenous cannabinoids (marijuana and synthetics) bind to receptors to cause a myriad of effects

• Psychotropic/Neurologic:
  – Euphoria, relaxation (paranoia for some)
  – Decrease short term memory, cognition
  – Intensify sensory perceptions, hallucinations
  – Motor function – increase function initially then decrease with decreased coordination, ataxia, dysarthria
  – Duration – can last 7+ days and longer in long term users

• Physiologic effects include: increased heart rate, vasodilation, cardiac output, and neurologic (ex: analgesia)
**Marijuana : pathophysiology**

*Cannabis sativa* (smoked marijuana = flowers and leaves of the female plant) contains >500 chemical constituents, with 60+ cannabinoids or biologically active compounds. THC and CBD are 2 of these.

<table>
<thead>
<tr>
<th><strong>Delta-9-Tetrahydocannabinol or THC:</strong></th>
<th><strong>Cannabidiol or CBD:</strong></th>
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<tbody>
<tr>
<td>Cognitive changes and mood modulation</td>
<td>Mitigates THC effects and reduces anxiety, paranoia</td>
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<tr>
<td>Ameliorates spasticity</td>
<td>Anti-inflammatory</td>
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<td>Analgesia</td>
<td>Neuro-protective properties</td>
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<td>Increase appetite</td>
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?abuse
Marijuana : pathophysiology

• Types of cannabinoids
  – Synthetics:
    • dronabinol (Marinol) – single synthetic THC; 6 hour duration: FDA approved for chemo induced N/V and anorexia in AIDS
    • nabilone (Cesamet) – single synthetic THC; 12 hours duration: FDA approved for chemo induced N/V
  – Plant extracts:
    • Sativex spray (nambiximols) – natural extract of delta9 THC, THC:cannabidiol ratio 1:1; available in Canada, UK/Europe
    • Cannador (pill extract) - natural extract of delta9 THC, THC:cannabidiol ratio 2:1; available in Europe, used in research
  – Botanical:
    • Smoking or eating marijuana plant products
Marijuana: pathophysiology

- **Vaporization**: heat 180°C to 200°C, to convert cannabinoids and other compounds found in herbal cannabis into a fine mist that can be inhaled
  - Avoids byproducts of combustion
  - Similar THC levels achieved compared to smoking

- **Smoking vs. ingesting**: easier to titrate and control levels with smoking
  - Smoking allows peak levels in 10 min and bioavailability relies on technique and cigarette vs pipe (latter most efficient)
  - Ingesting causes more intense outcome – conversion to different and more potent metabolite with greater blood brain penetration
  - 45-120 minutes until effect, and 4-6 hours duration (or more), and variable effect!
Vaporizer
Marijuana: pathophysiology

- **Pregnancy**: THC crosses the placenta and can be found in breast milk.
Evidence Review
Evidence Review: Pain

• Several RCT have shown efficacy in reducing pain both as sole treatment or synergistically with opioids
  – ~30% pain reduction
  – Concurrent opioid studies - ability to reduce oxycodone, morphine dose

Grant, I et al. Medical marijuana: clearing away the smoke. Open Neurol. J. 2012; 6, 18–25
Evidence Review: Pain

• Type of pain?
  – Experimental or induced pain (intradermal injection of capsaicin) studies support efficacy
  – Best evidence in HIV neuropathic pain
  – Evidence for many types of pain – cancer, surgical, arthritic, etc

• Amount?
  – Mid strength marijuana cigarettes (4% THC) better than low dose (2%) or high dose (8%)
  – More is not better!!
Evidence Review: Pain

• How strong is marijuana compared to known prescription pain relievers?
  – Hard to find data
  – Netherlands Center for Human Drug Research found it was equivalent to pain relief of capsaicin, and lagged behind NSAIDS and opioids
  – ? Is it safer than prescription pain relievers
Evidence Review: Neurology

• Multiple Sclerosis:
  – Evidence for reduction of pain, stiffness, and spasticity

  • CAMS 2003: cannabis extract (CE) (n=197) vs. dronabinol (n=181) vs. placebo (n=198); Ashworth scale showed no significant difference but patient’s self report did show significant symptom improvement in spasticity, pain, mobility, sleep quality (THE LANCET • Vol 362 • November 8, 2003)
    2005 relook – lasting effects at 12 months (J Neurol Neurosurg Psychiatry 2005 Dec;76(12))
  • MUSEC 2012: cannabis extract (n=143) vs. placebo (n=134); self report of muscle stiffness relief 29.4% CE and 15.7% placebo (J Neurol Neurosurg Psychiatry 2012;83:1125–1132)

  – Some evidence for urinary symptom relief

  • Mult Scler 2010 November: no change in incontinence but improvement in # voids, nocturia, bladder symptom severity (Kavia RBC et al. Multiple Sclerosis 16(11) 1349–1359)
Evidence Review: Neurology

• Larger studies MS have looked at synthetic cannabinoids, cannabis extracts, and Sativex but not smoked marijuana

• Symptom relief – not disease modification!

• Precautions: Smoked cannabis affects cognition which may already be impaired in MS patients

(Pavisian et al, Neurology 2014)
Evidence Review: Neurology

- Other neurologic conditions:
  - No current evidence for tremor in Parkinson's, dyskinesia
  - More study is needed- many of the trials are too small
  - Comparative effectiveness with current treatments unknown
  - 1% severe adverse reactions

Evidence Review : GI

• Crohns: evidence for symptom improvement and disease modification in small studies...
  – 21 patients with intractable Crohns Disease already on treatment (Clinical Gastroenterology and Hepatology, Volume 11, Issue 10, 2013)
  – Patients were assigned randomly to groups given cannabis, twice daily, as cigarettes containing 115 mg of Δ9-tetrahydrocannabinol (THC) or placebo containing cannabis flowers from which the THC had been extracted
  – CDAI – Crohns Disease Activity Index
  – Precautions: this does not prove anti-inflammatory effect in Crohns– but does show improved quality of life - pain relief, weight gain, well being...
Figure 1 CDAI scores in study and placebo groups before and after treatment.

Cannabis Induces a Clinical Response in Patients With Crohn’s Disease: A Prospective Placebo-Controlled Study

Clinical Gastroenterology and Hepatology, Volume 11, Issue 10, 2013, 1276 - 1280.e1

http://dx.doi.org/10.1016/j.cgh.2013.04.034
Evidence Review : GI

- **Hepatitis C - improving adherence to therapy?**

- **Cannabis use during hepatitis C treatment**
  - prospective cohort study
  - 71 patients with history of substance use being treated with interferon and ribavirin for hepatitis C infection were evaluated for cannabis use during treatment
  - 22 patients (31%) used cannabis
  - comparing cannabis use during treatment to no cannabis use
    - adherence to interferon and ribavirin therapy in 86% vs. 59% (p = 0.03, NNT 4)
    - early discontinuation of interferon and ribavirin therapy in 5% vs. 33% (p = 0.01, NNT 4)
    - sustained virologic response in 54% vs. 18% (p = 0.009, NNT 3)
    - posttreatment virologic relapse in 14% vs. 61% (p = 0.009, NNT 2)
    - end-of-treatment response in 64% vs. 47% (not significant)

  *(Eur J Gastroenterol Hepatol 2006 Oct;18(10):1057)*

- **Oral cannabinoids might improve anorexia and nausea in patients treated with ribavirin and interferon for chronic hepatitis C infection**
  - retrospective cohort study
  - 191 patients treated with interferon and ribavirin were assessed for use of oral cannabinoids
  - 25 patients (13%) used cannabinoids
  - compared with no cannabinoid use, cannabinoids associated with subjective anorexia and nausea improvement and higher rate of completion of full course of hepatitis C therapy

  *(Can J Gastroenterol 2008 Apr;22(4):376)*
Evidence Review : GI

• Hepatitis C - causing disease progression?

• Daily marijuana smoking associated with disease progression in patients with untreated chronic hepatitis C infection
  – based on 2 cohort studies
  – 270 treatment-naive patients with chronic hepatitis C infection were assessed for clinical demographics and frequency of marijuana use over span of hepatitis C infection
    • 33% reported daily marijuana smoking
    • daily marijuana smoking associated with
      – fibrosis progression rate > median value of cohort (OR 3.4, 95% CI 1.5-7.4)
      – rapid fibrosis progression rate (OR 3.6, 95% CI 1.5-7.5)
      – severe fibrosis (OR 2.5, 95% CI 1.1-5.6)
  – 315 treatment-naive patients with chronic hepatitis C infection were assessed for clinical demographics and frequency of marijuana use
    • 24.1% reported daily marijuana smoking
    • daily marijuana smoking associated with significant steatosis (OR 2.1, 95% CI 1.01-4.5)
Evidence Review : GI

• Hepatitis C – likely it is OK
  – Fibrosis/progression evidence is weak
  – No anticipated interactions with newer treatments
Evidence Review: HIV

• HIV related anorexia and wasting
  – Cochrane Review 2013 March has **mixed findings**
    • 7 studies, smoking or dronabinol, interventions and outcome measures variable on weight gain and appetite
    • Short duration of trials (up to 84 days) limits look at morbidity and mortality
  – # Small studies showing dronabinol and smoked marijuana increase appetite/weight
    
    - *J Pain Symptom Manag* 1995 Feb;10(2)89
    - *J Int Assoc Physicians AIDS Care* 2007 June
    - *Psychopharmacology Berlin* 2010 Dec;212(4);675

• HIV neuropathy
  – RCT and randomized trials support a **30 % pain reduction** with smoking
    • ≥ 30% reduction in pain scores in 46% cannabis vs. 18% placebo patients (p < 0.05, NNT 4), (Neuropsychopharmacology 2009 Feb;34(3):672)
    • > 30% reduction in pain score in 52% with cannabis vs. 24% with placebo (p = 0.04, NNT 4) (Neurology 2007 Feb 13;68(7):515)
Evidence Review: Cancer

• No evidence that it causes or cures cancer
  – Suggestion from *in vitro and animal studies* that cannabinoids may impair growth of various cancers (leukemia, colon, breast, hepatocellular)

• Helpful for antiemesis, appetite stimulant, antianxiety and sleep aid, antidepressant, analgesic
  – No comparative studies against current antiemetic therapies and marijuana not felt to be clearly superior
  – Anecdotal but sleep, pain, anxiety respond to MM
  – (MMS lecture J. Mark Sloan, MD Boston University)

• Concern: neutropenic patients and risk of inhaled fungal respiratory disease
  Anticancer Research October 2013 vol. 33 no. 10 4373-4380
Evidence Review: misc.

• Fibromyalgia - small studies
  – Reduced pain, anxiety, and self reported symptoms, nabilone vs placebo randomized study, n=40.  
    \[\text{(J Pain 2008 Feb;9(2):164)}\]
  – Improved quality of life QOL: smokers vs nonsmokers surveyed, n=56.  

• Rheumatoid Arthritis: one small study
  – Improved pain and sleep; Sativex vs placebo; n=58.  
    \[\text{(Rheumatology (Oxford) 2006;45:50–2.)}\]
Evidence Review: misc.

• Glaucoma – no evidence; lower pressures 60-65% for 3-4 hours; American Glaucoma Society does not recommend it

• Seizures – small studies (n=46 in all reported studies together) with CBD rich marijuana showed reduction/resolution of seizures; trial of CBD liquid for seizures is ongoing
Evidence Review: misc.

- **Schizophrenia** – Some studies have linked cannabis use and development of *psychosis*; genetics may play a role
- Cochrane review 2014 Schizophrenia and Cannabis - reviewed studies on treatment for cannabis use in schizophrenics and for therapeutic effects from cannabidiol; concluded that studies were small and inadequate to draw any conclusions
Evidence Review: adverse effects

- **Short term effects:**
  - Dizzy
  - Memory dysfunction
  - Sense of slowed time
  - Increase body awareness
  - Difficulty focusing
  - Incoordination
  - Sleepiness

- **Physiologic effects:**
  - Increased heart rate
  - Vasodilation and blood pressure drop

- **Physical effects:**
  - Vomiting
  - Cough/wheeze
  - Addiction & withdrawal
Evidence Review: adverse effects

- No overdose reported - THC spares brainstem so respiratory depression does not occur
- No clear COPD or cancer association known (but has not been studied)
- ? Risk for myocardial infarction - One study published on marijuana effect on heart rate variability & observational reports
Massachusetts Law:
“AN ACT FOR THE HUMANITARIAN MEDICAL USE OF MARIJUANA”
Massachusetts Law:

• Massachusetts voted 63% in favor of medical marijuana Nov 6 2012

• DPH regulations May 24 2013
  – Designed to avoid abuse of the system
  – Aimed at keeping marijuana away from children or non medical use as seen in other states
  – Process has been slow to start especially dispensary applications
Massachusetts Law:

- No requirement for insurance payers to cover
  - It will be out of pocket and expensive

- No requirement for physicians to participate
  - Doctor must register to be able to authorize patients

- No requirement for accommodation for marijuana use for workplace, schools, prisons, and public spaces
  - You cannot smoke in public!
Massachusetts Law:

• Physician role: you are not prescribing marijuana, you are recommending your patient to the state for a medical marijuana card to purchase marijuana and/or marijuana infused products
  – Your patient is responsible for dosing and administering
  – You are responsible for assessing the need for marijuana, conveying the risks and benefits to your patient, and having a treatment plan
Massachusetts Law:

- **Physician Role:** Registering yourself
- Have a Mass license, Mass Controlled Substance License, and practice in at least one office in the state
  - CME course – 2.0 credits - now available via MMS and the Answer Page CME course (enforced since 7/1/2014)
    - [http://www.theanswerpage.com](http://www.theanswerpage.com)
  - Must participate in PMP
  - Your authorization can be revoked for fraudulently authorizing a patient or not notifying state of changes in your status
  - DPH recommends you check with your own legal counsel or that of your employer before participating (Mass law protects you, federal does not)
Massachusetts Law:

• To Register: Massachusetts Department of Public Health’s Medical Use of Marijuana Online Registration System (the MMJ Online System
  – Virtual Gateway account to access
  – Program Support Center at 617-660-5370 between the hours of 9:00 am and 5:00 pm
Massachusetts Law:

• What are you recommending patient for?
  
  – You can authorize for a patient for **up to year or LESS**
    • No less than 15 days and up to one year
  
  – You can specify the full amount or **LESS**   -
    • **Full amount= 10 ounces for 60 days supply**
    • 1 oz ~ 60 joints so this is enough for 10 joints a day or 600 joints for 2 months
  
  – **MIP = marijuana infused product**
    • ‘equivalent amount of 60 day supply may be dispensed as a MIP’
Massachusetts Law:

• To authorize a patient:
  – “bona fide patient physician relationship”:
    • Complete history, physical, therapeutic plan, & counsel on risks and benefits
    • You have an ongoing role in care
  – You are claiming that “the risks are outweighed by the benefits of medical marijuana ....” for your patient
Massachusetts Law:

- **Who can you authorize?**
  - *Any disease* – law lists several but includes “any other debilitating condition that physician determines…”
  - Defines *debilitating* as “weakness, cachexia, wasting syndrome, intractable pain, or nausea, or impairing strength or ability, and progressing to such an extent that *one or more of a patient’s major life activities is substantially limited.*
  - If the condition is no longer debilitating, i.e. their Crohns is in remission, you cannot authorize
Massachusetts Law:

• Who can you NOT authorize?
  – Yourself or any family member
  – You cannot work at nor have any direct or indirect financial interest in a dispensary, offer discounts of any kind, or have any financial gain from authorizing patients (other than your normal visit fee)
  – Nor can your direct family members, co-workers, employees
Massachusetts Law:

- **Pediatric** case exceptions:
  - require parent or guardian approval
  - certification by two physicians, one of whom must be a pediatrician or pediatric specialist.
  - life-limiting illness, likely to result in death within two years.
  - the two physicians may override the life-limiting restriction if they document the benefits of medical use of marijuana outweigh the risks.
Massachusetts Law:

- **Patient Role**: they apply to DPH for card after they have your authorization/certification; must have proof of Mass residence; they register on line (DPH website)
  - Age 18+
  - One year maximum
  - 60 day supply – 10 ounces
  - Card is $50/year
Massachusetts Law:

- **Personal Caregivers**: a designated, registered person over age 21 who can purchase, administer, and/or cultivate MM for a registered patient
  - Cannot be paid
  - Cannot work for more than one patient
  - Can be a hospice, nursing home, or medical facility worker if patient is in residence
  - Cannot be the authorizing doctor

- **Hardship Cultivation Status**: can grow at home if financially, physically, or logistically unable to access dispensary

- As a healthcare provider – you authorize your patient, DPH handles personal caregivers & hardship status
Massachusetts Law:

• What will dispensaries look like? Are they open?
  – **11 dispensaries** currently approved by DPH – none open yet (potentially winter 2014-5)
  – **Regulations** on security, appearance, products
    • No novelty items such as tee shirts
    • No ads including pricing, no medical or marijuana symbols
  – Regs on seed to sale inventory, security, disposal or product, and access – only card holders can enter!
  – “RMD must have a program to provide reduced cost or free marijuana to patients with documented verified financial hardship. “
Massachusetts Law:

- MIPS and marijuana products will be:
  - No nonorganic pesticides
  - Best practices to avoid fungus, mold
  - In opaque packaging
  - Labeled including THC content, dosing
  - Patient education materials will be available
  - “Keep away from children”
Public Health Implications
Burning questions...

• Is it addictive?
• Is it safe for my patient?
• Will it affect public safety?
  – Motor vehicle accidents?
• What about children and brain development?
Public Health Implications

- Marijuana use increases in states with medical marijuana laws
- Youth perception of harm influences use of marijuana
- Youth rates increase with medical or legalized marijuana laws
Figure 6.2 Perceived Great Risk of Marijuana Use among Youths Aged 12 to 17: 2002-2013

- Smoke Marijuana Once or Twice a Week
- Smoke Marijuana Once a Month

* Difference between this estimate and the 2013 estimate is statistically significant at the .05 level.
12th Graders’ Past Year Marijuana Use vs. Perceived Risk of **REGULAR** Marijuana Use

Source: The Monitoring the Future study,

Source: University of Michigan, 2013 Monitoring the Future Study
US Youth Marijuana Rates-SAMHSA data

Figure 2.15 Daily or Almost Daily Marijuana Use in the Past Year and Past Month among Persons Aged 12 or Older: 2002-2013

Numbers in Millions

- Used Marijuana on 300 or More Days in the Past Year
- Used Marijuana on 20 or More Days in the Past Month

* Difference between this estimate and the 2013 estimate is statistically significant at the .05 level.
Figure 8.4 Past Month Marijuana Use among Youths in NSDUH, MTF, and YRBS: 1971-2013

MTF = Monitoring the Future; NSDUH = National Survey on Drug Use and Health; YRBS = Youth Risk Behavior Survey.
Marijuana Potency today

• THC concentration has increased substantially since you were in high school (<4% to 12%+)
  – Balance of THC to cannabidiol has been manipulated
    • THC has the psychotropic effects
    • Cannabidiol has the anti-inflammatory and anti-psychotropic effects (ex: seizure treatment)

• MIPS – medically infused products can be confusing to consumers as a “dose” can vary from one product to the next
Increases over Time in the Potency of Tetrahydrocannabinol (THC) in Marijuana and the Number of Emergency Department Visits Involving Marijuana, Cocaine, or Heroin
Adverse Effects of Marijuana

• NEJM June 2014 Volkow et al (Director, National Institute of Drug Abuse) – excellent review

• Heated debate on adverse and long term effects continues including:
  – Addiction and withdrawal
  – Brain development: cognitive and mental health effects for youth – anxiety, psychosis
  – Public Safety - driving impairment
Long Term Effects of Marijuana

Addiction: About 9% of users may become dependent, 1 in 6 who start use in adolescence, 25-50% of daily users

Estimated Prevalence of Dependence Among Users

* Nonmedical Use

Source: Anthony JC et al., 1994
<table>
<thead>
<tr>
<th>Effect</th>
<th>Overall Level of Confidence*</th>
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<tbody>
<tr>
<td>Addiction to marijuana and other substances</td>
<td>High</td>
</tr>
<tr>
<td>Abnormal brain development</td>
<td>Medium</td>
</tr>
<tr>
<td>Progression to use of other drugs</td>
<td>Medium</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Medium</td>
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<tr>
<td>Depression or anxiety</td>
<td>Medium</td>
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<tr>
<td>Diminished lifetime achievement</td>
<td>High</td>
</tr>
<tr>
<td>Motor vehicle accidents</td>
<td>High</td>
</tr>
<tr>
<td>Symptoms of chronic bronchitis</td>
<td>High</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Low</td>
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Public Safety

- Public Safety: meta-analysis of 9 studies with pooled analysis demonstrating increase risk of crash by 2.66 with marijuana
  - Dose dependent
  - Colorado recent rates of fatal MVA show increasing association or presence of marijuana

_Marijuana use and motor vehicle crashes_. Li MC, Brady JE, DiMaggio CJ, Lusardi AR, Tzong KY, Li G, - Epidemiol Rev - ; 34 (1); 65-72 MEDLINE is the source for the citation and abstract for this record
Medical Marijuana – good or bad?

• There is **reasonable evidence** for therapeutic use

• **More research is needed** - especially larger RCT

• **Mass law** has reasonable regulations attempt to avoid public harm but we don’t know how it will turn out....

• **Counsel your patients on youth access** just like you would for a narcotic - lock it!

• Understand **the adverse effects** including addiction and do a substance abuse assessment on your patient if you are authorizing

• **Take your role as an authorizing physician seriously and stay informed!!**
Questions?