Learning Objectives

After attending this presentation, learners will be able to:

▪ Describe the epidemiology of chronic pain in people with HIV infection
▪ Discuss evidence-based management approaches of chronic pain in people with HIV infection

Agenda

▪ Chronic pain in HIV: state of the science
▪ Evaluation
▪ Management
Agenda

• Chronic pain in HIV: state of the science
• Evaluation
• Management

Opioids

ARS Question 1

Which statement about chronic pain is true?
1. Chronic pain is very uncommon, occurring in < 1% of the US population.
2. The biological basis of chronic pain is controversial and not well-understood.
3. There are many highly efficacious, widely-available treatments for chronic pain.
4. Chronic pain is heavily influenced by psychological and social factors.
What is chronic pain?

- > 3 months, beyond normal tissue healing
- Examples:
  - chronic low back pain, other regional msk pain, chronic widespread pain, headaches, neuropathy
- Common in the general population
- Unique neurobiologic basis
- Heavily influenced by biological, psychological, and social factors


What is chronic pain?

- Associated with substantial disability
- Difficult to treat
- NAM/National Pain Strategy: key area of research focus, especially in populations most affected


Epidemiology of Chronic Pain in HIV

- Neuropathic pain is classically described
- Recent studies: predominance of msk pain
- Multisite pain common

Epidemiology

- Chronic pain is an important comorbidity in people living with HIV for two key reasons:
  - Prevalence (30-85%)
  - Impact on outcomes (limited by measurement)
    - Retention
    - Function
    - Healthcare utilization
    - Suboptimal ART adherence
    - Use of heroin
    - Poor patient-provider engagement

1. Merlin JS, J Acquire Immune Defic Syndrome, 2018
3. Jaio JM, Pain, 2015
4. Surratt HL, AIDS Pt Care STDs, 2015
5. Knowlton AR, J Palliat Care, 2015

What interventions have been studied in PLWH to date?

- Systematic review
  - 11 studies, mostly low or very low quality
  - 7 pharmacologic, 4 non-pharmacologic interventions (2 CBT, 1 hypnosis, 1 cannabis)
  - Controlled studies with positive results: capsaicin and cannabis, short term follow-up (≤ 12 weeks)
  - Of 7 pharmacologic interventions, 5 had substantial pharmaceutical industry sponsorship

To sum it up: there’s not much out there.

1. Merlin JS et al, AIDS Care, 2016

Agenda

- Chronic pain in HIV: state of the science
- Evaluation
- Management
ARS Question 2

I know my patient’s pain is real because:

1. The patient says so
2. The patient’s partner says so
3. The MRI says so
4. I have no idea, how should I know?

History and screening

- All that stuff you learned in school, plus:
- Impact of pain on function: PEG, how they spend their time
- Pain management history (get records!)
- Screen for:
  - Mood symptoms: PHQ-2, GAD-7
  - Etoh and substance use: NIDA quick screen
    https://www.drugabuse.gov/nmassist/
  - Sleep problems
    (and ask about history of these in the past)

Note coping and self-management
Diagnostic Testing

• Evidence-based judicious use is best
• You can’t always see pain on an image or a blood test
• This is a challenge for both the patient and the provider

Agenda

• Chronic pain in HIV: state of the science
• Evaluation
• Management

Treating chronic pain is challenging because:

• Communication about chronic pain can be difficult
– Patients and providers come with baggage, opioids rather than functional restoration become the focus
• Providers aren’t trained to do this
• Financial incentives to take a biomedical approach
• Commonly used medications have a limited evidence base and carry risk
• Patients may have mood disorders/addiction
• Best treatments are often inaccessible to patients

But...don’t despair. There are LOTS of things you can do.
General chronic pain treatment pearls

• Remember....first, do no harm!!
• Focus on evidence-based therapies, avoid unnecessary procedures, surgeries, medications
• Set concrete goals and timelines
• Be ready to discontinue therapies that don't work
  • If possible, treat psychiatric illness first

Learn some MI and CBT tricks

Pain Education

• What is chronic pain
• Patience
• Partnership and collaboration
• Pharmacologic and non-pharmacologic management
• Role of multiple team members
• Mind-body connection
  • Functional goals
Non-opioid pharmacologic therapies

- Acetaminophen - OA, < 3g, consider relative contraindications
- NSAIDs - back pain, consider CV (naproxen), GI (cox-2/celecoxib), renal risk
- Muscle relaxants
- Benzodiazepines
- Anticonvulsants
- Antidepressants
- Topicals
  - Specific indications: e.g., lidocaine post-herpetic neuralgia, capsaicin post-herpetic/DSP, diclofenac-OA

Gabapentinoids

- Co-rx of opioids and gabapentin a/w increased odds of opioid-related death (OR 1.99, 95% CI 1.61-2.47)
- Worse for moderate dose 900-1800mg (OR 2.05) and high dose >1800mg (OR 2.5)
- Only approved for specific indications
- Lots of non-evidence based off labeled use carries risks

Non-pharmacologic approaches to chronic pain

- Psych/behavioral: CBT, ACT, mindfulness
- Exercise/movement: Tai Chi, Yoga, exercise therapy
- Manual therapies: manipulation, acupuncture
- Multimodal care: collaborative care, stepped care
- NPT: Tai chi, PT, TENS, heat, acupuncture, massage, CBT/psych, weight/strength, yoga, pool, herbals
- Felt to be helpful by participants
Medical Marijuana and CBD

• Medical marijuana:
  – Low quality evidence suggests very limited benefits for neuropathic pain
  – Evidence about harms is growing
  – (supplemental slides if there are questions)

• CBD:
  – No evidence base
  – No regulation

My best advice to you

• Develop a team in your office:
  – Physician, nurse, social worker, pharmacist

• Develop a team in your community:
  – Physical therapist/PM&R physician
  – Anesthesiologist/interventionist
  – Psychologist
  – Psychiatrist
  – Addiction physician that prescribes bup, naltrexone
  – Methadone program
  – Addiction treatment program

(Oppn’t forget schools / training programs)
My take on opioids

• They ARE NOT first-line therapy for chronic pain
• They work for some people
• However, evidence of benefit is limited
• What we know about their risk is growing

• The recent CDC Guideline for Prescribing Opioids for Chronic Pain is a good starting place:
  https://www.cdc.gov/drugoverdose/prescribing/guideline.html

Lack of evidence of benefit

• “No study of opioid therapy versus placebo, no opioid therapy, or nonopioid therapy evaluated long-term (>1 year) outcomes related to pain, function, or quality of life.…..Evidence is insufficient to determine the effectiveness of long-term opioid therapy for improving chronic pain and function.”

What are the role of opioids in chronic pain?

• Back, hip, knee OA; opioids not superior to acet/NSAID
• This analysis addresses limitations of prior analyses
• Updates prior analyses to April 1 2018
Lots of evidence of risks/harms

• “Evidence supports a dose-dependent risk for serious harms.”
  – Decreased function/return to work
  – Induced depression (duration > dose)
  – Motor vehicle accidents (OR 1.2-1.4 ≥ 20mg equivalents of morphine compared to < 20)
  – Falls (especially soon after initiation)
  – Addiction (~10%)
  – Overdose (worse with dose > 100 mg equivalents of morphine, co-rx benzos)

What to do when you have a patient sitting in front of you

Whether to start (less common case)

• “Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate (recommendation category: A, evidence type: 3).”
Whether to continue (more common case – “inheriting”)

• “Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids (recommendation category: A, evidence type: 4).”

CDC, MMWR, 2016.

How to “evaluate for harms”

• “Universal precautions” approach
  – Opioid Treatment Agreements
  – Urine Drug Testing
  – Practitioner Database Monitoring Programs

Limited evidence, but can be very useful, becoming standard of care. Know your state's requirements.

• Be alert to concerning behaviors that can arise


Opioid Treatment Agreements

• NOT contracts
• Informed consent; you and your patient’s responsibilities
  – One prescriber, one pharmacy
  – Take as prescribed, no changes on one’s own
  – Urine drug testing
  – How medicines are refilled, replacement rxs
  – Conditions for stopping opioids
Urine Drug Testing

• Useful for checking for adherence to rx’d drugs and for presence of substances not rx’d
• "A tool not an oracle": lots of pitfalls
• Send screening immunoassay; discuss unexpected results; if still unclear, send confirmatory test (GCMS/LCMS); if still unclear, consider ddx
• Know your toxicologist
• Be mindful of cost
• Consider POC
• Decision support: Mytopcare.org

Prescription Drug Monitoring Programs (PDMP)

• State-by-state, lots of variability
• Tells you three things that predict OD:
  – Dose
  – Multiple rx’s
  – Opioid and benzo co-rx

Concerning Behaviors

• Examples include:
  – Unexpected urine results
  – Running out early/other rx problems
  – Multiple prescribers
  – Belligerent behavior
• All have a differential diagnosis
• Tips for evaluating these behaviors:
  – Detailed exploration with patient
  – Re-education
  – Closer monitoring, small prescriptions (is this a pattern? does the patient have an opioid use disorder?)
  – Involvement of psychiatry/addiction colleagues
Pearls about harms

- Try to decide whether the patient has an opioid use disorder (so you can refer to tx)
- This can be HARD
- Regardless: you may determine that the risks of opioid rx > benefits

Recognizing Opioid Use Disorder (1/2)

1. Opioids are often taken in longer amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
Recognizing Opioid Use Disorder (2/2)

6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.

7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.

8. Recurrent opioid use in situations in which it is physically hazardous.

9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

This is complicated!
Maybe I can just avoid it...

• The bad news: there aren’t enough pain specialists to see patients with chronic pain
• So:
  -- Whether you’re in primary care, psychiatry, neurology, palliative care, or another subspecialty....
  -- Whether you’re a doctor, NP, PA, RN, social worker, pharmacist....
• Patients will look to you for help. You will be their best chance of getting help
• It is so rewarding

How to make this as easy as possible

• Develop systems in your practice
• Utilize unique skills of team members
• Develop policies and agreed-upon approaches
• Utilize resources
  -- Those mentioned today
  -- CDC materials
  -- Conferences: AMERSA, ASAM, regional APS
  -- Providers’ Clinical Support System (PCSS)
  -- www.mytopcare.org
In sum

- Chronic pain is a major problem
- We have a lot more to offer than opioids
- If you do prescribe opioids (and you will), use a universal precautions approach
- Diagnose and facilitate addiction treatment
- Utilize available resources

My contact information: merlinjs@pitt.edu
Pathophysiology: pain sensitivity

Temporal Summation of Heat Pain 48 Celsius

HIV VL Detectable (N = 11)
HIV VL Undetectable (N = 35)
Controls (N = 50)

Temporal Summation of Mechanical Pain

HIV with CP (N = 46)
HIV without CP (N = 46)
### Pathophysiology: inflammation

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Chronic Widespread Pain</th>
<th>No Pain</th>
<th>Adjusted OR (95% CI)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>IL-1β</td>
<td>0.63 (0.05 - 1.77)</td>
<td>1.34 (1.04 - 1.72)</td>
<td>0.15 (0.05 - 0.64)</td>
<td>0.02</td>
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<tr>
<td>IL-6</td>
<td>0.72 (0.44 - 1.35)</td>
<td>1.13 (0.86 - 1.49)</td>
<td>0.65 (0.44 - 0.98)</td>
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<td>TNF-α</td>
<td>2.90 (2.12 - 3.74)</td>
<td>1.11 (0.85 - 1.47)</td>
<td>2.66 (2.13 - 3.49)</td>
<td>0.02</td>
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<tr>
<td>Eotaxin</td>
<td>134 (103 - 209)</td>
<td>126 (91 - 188)</td>
<td>1.16 (0.98 - 1.37)</td>
<td>0.09</td>
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<tr>
<td>IL-15</td>
<td>2.47 (1.92 - 3.25)</td>
<td>1.19 (0.83 - 1.71)</td>
<td>2.39 (1.92 - 2.92)</td>
<td>0.35</td>
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<tr>
<td>Leptin</td>
<td>20.0 (11.4 - 39.2)</td>
<td>1.19 (0.75 - 1.91)</td>
<td>18.2 (9.7 - 30.0)</td>
<td>0.02</td>
</tr>
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</table>

Adjusted model contains categorical age and sex.

1. per 50 unit increase.
2. per 25 unit increase.

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### Hot Topics

#### Trends in opioid prescribing

- Opioid prescribing in the United States before and after the Centers for Disease Control and Prevention’s guidelines for opioid prescription.
- Rates were already declining, but guidelines released w/greater decline.
- Reductions in high-dose use, overlapping opioid/benzodiazepine use.
- Declining since 2012, now accelerating.
- MME per capita still much higher than 1999.
**Opioid risks**

*Original Research*
*Annals of Internal Medicine*

**Association of Tramadol With All-Cause Mortality Among Patients With Osteoarthritis**

- Found association between opioid misuse (overlapping prescriptions, multiple prescribers/pharmacies) and OD mortality in Medicare database
- Wider range of misuse behaviors defined by clinicians
- Developed management approaches based on consensus

**NIH HEAL: Area of Opportunity #3**

**Management of sub-syndromal and low-severity OUD:** OUD begins with opioid misuse, below the threshold OUD, or for which the use of existing medications for OUD is not indicated. This project will study sub-syndromal OUD (i.e. opioid misuse that does not meet any criteria for DSM-5 OUD diagnosis) and/or low-severity OUD (OUD that meets only one or two DSM-5 diagnostic criteria). Historically, such low-severity opioid misuse, especially in the context of co-occurring pain and psychiatric disorders, has been poorly identified in clinical settings. HEAL will recruit individuals with sub-syndromal and low-severity OUD in general medical settings such as primary or integrated care settings to define, identify, and intervene in the management of opioid misuse.

**Chronic pain risks**

*Original Research*
*Annals of Internal Medicine*

**Chronic Pain Among Suicide Decedents, 2003 to 2014: Findings From the National Violent Death Reporting System**

- Chronic pain is common among people who commit suicide (9%)
- 18% of suicides in these patients are from opioid overdose (nominal firearms)
- 65% of decedents with chronic pain who self-reported pain as a factor in their suicide
- Major limitation: could not determine pain vs. other factors as cause

*The New York Times*

**When the Cure Is Worse Than the Disease**

“Officials with the Centers for Disease Control admit that they do not specifically track suicides by patients who have lost medical access to pain relievers. ... But there is much anecdotal evidence that chronic pain drives patients to suicidal thoughts. Karen King, for example, says she has had four hospitalizations because of suicidal thoughts or attempts in the past year alone.”
Chronic pain and opioid risks

Tapering

• Pain clinic, patient education, voluntary tapers
• Slow tapers, starting at 5% twice in 1 mo, then 10%/week max
• 75% of those approached enrolled, 38% of those completed

Some people are asking, have we gone too far?
Cancer pain

- Cancer patients omitted from most LTOT studies
- CDC guideline causes confusion: 1) draws distinction between patients with cancer undergoing treatment and all others, differences between CDC and NCCN (e.g., w/r/t long-acting opioids, and
- 3) lack of evidence for non-pharm approaches in cancer

Adults receiving active cancer treatment
- Difficulty filling rx 22%, awkwardness communicating w providers 10%,
- taking less med than needed 20%

Manage panels (often large) of cancer survivors with chronic pain
- Only 4% reported not using opioid risk mitigation strategies
- 53% spend > 30 minutes per day managing opioid misuse behaviors
- Least confident in ability to manage addiction (5/10), 27% reported systems to manage addiction, 13% waivered

Adults receiving active cancer treatment
- Difficulty filling rx 22%, awkwardness communicating w providers 10%,
- taking less med than needed 20%

Pain in patients with serious illness

Use of Palliative Care Earlier in the Disease Course in the Context of the Opioid Epidemic
Educational, Research, and Policy Issues

Pain and Symptom Management for People with Serious Illness in the Context of the Opioid Epidemic
A Workshop
Medical marijuana for pain

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<th>Therapeutics</th>
<th>Review: In chronic noncancer pain, cannabinoids reduce pain (NNT 24) but increase adverse events (MMH 6)</th>
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</thead>
<tbody>
<tr>
<td>Outcome:</td>
<td>Mean difference of 3 on VAS</td>
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</tbody>
</table>

- Mean difference of 3 on VAS
- Medical MJ
- Should Physicians Recommend Replacing Opioids With Cannabis?
- Association of Medical and Adult-Use Marijuana Laws With Opioid Prescribing for Medicaid Enrollees
- Another ecological study
HIV as a qualifying condition

- 30 states\(^1\) including PA
- Unclear why. Some thoughts:
  - marijuana use is common in PLWH\(^2\)
  - dronabinol (THC analog) was FDA approved for AIDS wasting in 1991\(^3\)
  - other chronic symptoms common in PLWH appear on most states' lists (e.g., pain, nausea, fatigue)
  - advocacy\(^4\)


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Potential Uses in PLWH

- HIV itself
- Chronic pain
- AIDS Wasting
- Nausea/vomiting
- Fatigue
- Opioid tapering
- Opioid use disorder

Keep these in mind....

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To assess the evidence, what do you want to know?

- Number of studies and n
- Formulation
- Statistical significance of finding
- Quality of studies (randomization, blinding of outcome assessments, appropriate statistical methods, drop-out, etc)
- Start with evidence from general population, move to HIV
My approach to reading this literature

• Separate the notes from the noise:
  – Place most importance on systematic reviews/meta-analyses
  – Watch for editorials from trusted sources with evidence-based viewpoints

• Looked for studies about: nausea/vomiting due to chemo, appetite stimulation for HIV/AIDS, (chronic pain), spasticity due to MS or paraplegia, depression, anxiety, sleep, psychosis, glaucoma, Tourette’s

• 79 studies

• Studies grouped by indication, cannabinoid, and outcome
  – if more than 2 studies in 1 grouping, conducted meta-analysis

Whiting, JAMA, 2015.
<table>
<thead>
<tr>
<th>Method</th>
<th>% of White (in White)</th>
<th>% of Black (in Black)</th>
<th>% of Both (in Both)</th>
<th>% of Other (in Other)</th>
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**Statistically Significant**

**Not statistically significant**
Apoptotic stimulation in HIV/AIDS infection

Apoptotic stimulation in HIV/AIDS was assessed in 4 studies (4 reports, 29 participants). All studies assessed dexamethasone, 1 compared with placebo (1), and 1 compared with apergulate acetate. All studies were at high risk of bias. There was some evidence that dexamethasone was associated with an increase in weight when compared with placebo. More limited evidence suggested that it may also be associated with increased appetite, greater percentage of body fat, reducedannes, and improved functional status. However, these outcomes were rarely assessed in single studies and associations failed to reach statistical significance. The trial that evaluated dexamethasone and dexamethasone and apergulate acetate found significantly greater weight gain with both forms of combination than compared with placebo. The active comparison trial found that increased acetate was associated with increased weight gain than dexamethasone and that combining dexamethasone with apergulate acetate did not lead to additional weight gain.\(^{22}\)
• Mean difference of 3 on VAS

Therapeutics

Review: In chronic noncancer pain, cannabinoids reduce pain (NNT 24) but increase adverse events (NNH 46)

Clinical impact rating: ++

Cannabinoids to relieve chronic noncancer pain

Effectiveness

- Relieve pain
- NNT 24
- NNH 46
- Mean difference 3 on VAS

- Side effects
- Dizziness
- Dry mouth
- Transient increases in blood pressure

- Use with caution
- In patients with a history of cardiac disease

- Use with caution in elderly patients

- Use with caution in patients with a history of respiratory disease

- Use with caution in patients with a history of liver disease

- Use with caution in patients with a history of kidney disease
Long-term adverse health consequences

- Addiction: 9% in individuals with any cannabis use, half of cases within 5 years; 17% in individuals who start as teens
  - Withdrawal syndrome: irritability, sleep problems, dysphoria, craving, anxiety
- Anxiety/depression, although causality difficult to determine
  - Psychosis
- Motor vehicle accidents; risk doubles after use, and is dose-related
- Nausea/vomiting
  - Pregnancy: low birth weight, children born with attention and problem-solving deficits
- These issues are all common in PLWH!

References:

Impact of legalization

- Lots of speculation (e.g., availability could lead to initiation)
- From CO and WA:
  - Increase in ED/inpatient admissions, calls to poison centers, motor vehicle and other fatalities
  - ED: edibles and intoxication, CV and psych; inpatient: inhaled, hyperemesis

References:
Opioid tapering, OUD treatment

- Ecological studies showing associations between mj legalization and decreased opioid use / overdose
- Largest prospective study¹:
  - Cohort study 1500 participants with chronic pain on long-term opioid therapy
  - Cannabis associated with:
    - Increased pain
    - Lower pain self-efficacy
    - No reductions in prescribed opioids

Opioid Tapering

- Limited evidence in general\(^1\)
- Conflicting evidence in PLWH\(^2\-4\)

Marijuana and HIV Outcomes

- Associated with
  - Suboptimal HIV primary care retention
  - Cognitive impairment
- Not with:
  - ART adherence
  - Virologic suppression
  - Mortality

Note that this is not counterbalanced by benefits in terms of pain or reduction in opioid prescribing

Add refs.
Potential Uses

- HIV itself
  - NO!!!!!! ART!!!
- Chronic pain
  - Little evidence in general, only one study in HIV with significant limitations
- AIDS wasting
  - Overweight/obesity much more common1; AIDS wasting → ART!
- Nausea/vomiting
  - Little evidence in general, none in HIV
- Fatigue
  - Little evidence in general, none in HIV
- Opioid tapering
  - Evidence is insufficient
- Opioid use disorder
  - NO!!!!!! Evidence-based treatments! (buprenorphine, methadone)

Synthesis

- Limited low-quality evidence for neuropathic pain, chemo-induced nausea, and MS spasticity
- No literature on formulation or dose
- What we know about risk is growing
- Does this sound familiar?

One author’s synthesis

- “In conclusion, if the states’ initiative to legalize medical marijuana is merely a veiled step toward allowing access to recreational marijuana, then the medical community should be left out of the process, and instead marijuana should be decriminalized. Conversely, if the goal is to make marijuana available for medical purposes, then it is unclear why the approval process should be different from that used for other medications. Evidence justifying marijuana use for various medical conditions will require the conduct of adequately powered, double-blind, randomized, placebo/active controlled clinical trials to test its short- and long-term efficacy and safety. The federal government and states should support medical marijuana research. Since medical marijuana is not a life-saving intervention, it may be prudent to wait before widely adopting its use until high-quality evidence is available to guide the development of a rational approval process. Perhaps it is time to place the horse back in front of the cart.”

D’Souza DC, JAMA, 2015.
Practical approach: how to prescribe

• Note: no real consensus from people who are actually prescribing!
• One author’s suggestion:
  – Discuss marijuana risks and benefits
  – Ideally prescribed by physician who knows patient; if not, communication key
  – Consider contraindications: anxiety, mood, psychotic, substance use disorders
  – Monthly follow-up for 3 months, then case-by-case

Hill KP, JAMA, 2015.

Clinical pearls from my practice

• Medical marijuana can be expensive
• Dispensaries are not medical environments
  – Recommendations made by non-medical personnel
  – No required monitoring
• Most patients just want someone to evaluate and treat their pain and symptoms
  – Other approaches may not have been tried!