Chronic Pain in People Living With HIV Infection: A Practical, Evidence-Based Approach

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IAS–USA

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 ot chronic pain in people with HIV infection

Slide 3 of 56

Agenda

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

Slide 4 of 56

Agenda

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

Opioids

Slide 5 of 56

Agenda

- Chronic pain in HIV: state of the science
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- Management

Slide 6 of 56

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.

Slide 7 of 56

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

IOM, Relieving Pain in America, 2011; Interagency Pain Research Coordinating Committee, National Pain Strategy, 2016.

Slide 8 of 56

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

IOM, Relieving Pain in America, 2011; Interagency Pain Research Coordinating Committee, National Pain Strategy, 2016.

Slide 9 of 56

Epidemiology of Chronic Pain in HIV

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

Ellis RJ, Arch Neurol, 2010; Jiao JM, Pain, 2015; Johnson A, J Opioid Manag, 2012; Perry B, *J Pallliat Med*, 2012; Miaskowski C, J Pain, 2011.

Slide 10 of 56

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[1]
      - No interaction between chronic pain and opioids for retention
    - Function[2]
    - Healthcare utilization[3]
    - Suboptimal ART adherence[4]
    - Use of heroin[5]
    - Poor patient-provider engagement[6]

1. Merlin JS, *J Acquire Immune Defic Syndrome,* 2018. 2. Merlin JS, *Pain Med,* 2013. 3. Jaio JM, *Pain,* 2015. 4. Surratt HL, *AIDS Pt Care STDs,* 2015. 5. Knowlton AR, *J Palliat Care,* 2015. 6. Mitchell MM, *AIDS Beh,* 2016.

What interventions have been studied in PLWH to date?

- Systematic review[1]
  - 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
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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?

Slide 14 of 56

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)

Slide 15 of 56

Note coping and self-management

Slide 16 of 56

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

Expert opinion.

Slide 17 of 56

Agenda

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

Slide 18 of 56

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.

Slide 19 of 56

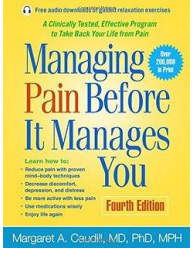
General chronic pain treatment pearls

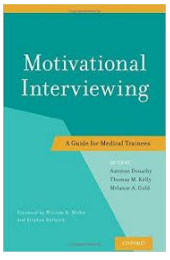
- Remember….first, do no harm!!
- Focus on evidence-based therapies, avoid unnecessary procedures, surgeries, medications
- Set concrete goals and timelines
- Be ready to discontinue therapies that don't work
- If possible, treat psychiatric illness first

Expert opinion.

Slide 20 of 56

Learn some MI and CBT tricks





Slide 21 of 56

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*

Slide 22 of 56

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

Slide 23 of 56

Gabapentinoids

PLOS MEDICINE

RESEARCH ARTICLE

Gabapentin, opioids, and the risk of opioid-related death: A population-based nested case–control study

Tara Gomes[1,2,3,4]*, David N. Juurlink[2,3,5,6], Tony Antoniou[1,2,7], Muhammad M. Mamdani[1,2,3,4,6,8], J. Michael Paterson[2,3,9], Wim van den Brink[10]

- Co-rx of opioids and gabapentin a/w increased odds of opioid-related death (OR 1.99, 95% CI1.61-2.47)
- Worse for moderate dose 900-1800mg (OR 2.05) and high dose >1800mg (OR 2.5)

Annals of Internal Medicine

OBSERVATIONS: BRIEF RESEARCH REPORTS

Pregabalin and the Risk for Opioid-Related Death: A Nested Case-Control Study

- Same findings

JAMA Internal Medicine | Special Communication | LESS IS MORE

A Clinical Overview of Off-label Use of Gabapentinoid Drugs

Christopher W. Goodman, MD; Allan S. Brett, MD

- Only approved for specific indications
- Lots of non-evidence based off label use carries risks

Slide 24 of 56

Non-pharmacologic approaches to chronic pain

PERSPECTIVE

A Research Agenda for Advancing Non-pharmacological Management of Chronic Musculoskeletal Pain: Findings from a VHA State-of-the-art Conference

William C. Becker, MD[1,2], Lynn E. Dellar, PhD[3], Alicia A. Heapy, PhD[1,2], Diana Higgins, PhD[4,5], Sarah L. Kiein, PhD, RN[6,7], Anthony Lisi, DC[1], Una E. Makris, MD, MSc[8,9], and Kelli D. Allen, PhD[10,11]

- The following are ready for implementation research:
  - Psych/behavioral: CBT, ACT, mindfulness
  - Exercise/movement: Tai Chi, Yoga, exercise therapy
  - Manual therapies: manipulation, acupuncture
  - Multimodal care: collaborative care, stepped care

Association Between Facility-Level Utilization of Non-pharmacologic Chronic Pain Treatment and Subsequent Initiation of Long-Term Opioid Therapy

Evan P. Carey, MS[1], Charlotte Nolan, MPA[1], Robert D. Kerns, PhD[2,3], P. Michael Ho, MD, PhD[2,4], and Joseph W. Frank, MD, MPH[2,3]

- VA study
- Availability a/w less LTOT imitation

Correlates of Use and Perceived Effectiveness of Non-pharmacologic Strategies for Chronic Pain Among Patients Prescribed Long-term Opioid Therapy

Crystal C. Lozier, PhD[1,2], Shannon M. Nugent, PhD[1,2], Ning X. Smith, PhD[1], Robin Jo Yarborough, PsyD[1], Steven K. Dobscha, MD[1,2], Richard A. Deyo, MD, MPH[1,2], and Benjamin J. Morasco, PhD[1,2]

- NPT associated with higher pain disability
- NPTs: Tai chi, PT, TENS, chiro, acupuncture, massage, CBT/psych, weight/strength, yoga, pool, herbals
- Felt to be helpful by participants

Use of Non-Pharmacological Pain Treatment Modalities Among Veterans with Chronic Pain: Results from a Cross-Sectional Survey

Sara N. Edmond, Ph.D.[1,2], William C. Becker, M.D.[1,2], Mary A. Driscoll, Ph.D.[1,2], Suzanne E. Decker, Ph.D.[1,2], Diana M. Higgins, Ph.D.[3,4], Kristin M. Mattocks, Ph.D., M.P.H.[1,4], Robert D. Kerns, Ph.D.[1,2,3], and Sally G. Haskell, M.D.[1,2]

- College education and mental illness a/w beh therapies
- Female gender and non-opioid pain meds a/w exercise/ movement

Slide 25 of 56

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

Slide 26 of 56

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

  (Don't forget schools / training programs)

Slide 27 of 56

Opioids

Slide courtesy of Erin Krebs.

Slide 28 of 56

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

Slide 29 of 56

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."**

Chou R, *Annals Intern Med*, 2015.

Slide 30 of 56

What are the role of opioids in chronic pain?

JAMA | Original Investigation

Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain
The SPACE Randomized Clinical Trial

- Back, hip, knee OA; opioids not superior to acet/NSAID

JAMA | Original Investigation

Opioids for Chronic Noncancer Pain
A Systematic Review and Meta-analysis

CONCLUSIONS AND RELEVANCE In this meta-analysis of RCTs of patients with chronic noncancer pain, evidence from high-quality studies showed that opioid use was associated with statistically significant but small improvements in pain and physical functioning, and increased risk of vomiting compared with placebo. Comparisons of opioids with nonopioid alternatives suggested that the benefit for pain and functioning may be similar, although the evidence was from studies of only low to moderate quality.

- This analysis addresses limitations of prior analyses
- Updates prior analyses to April 1 2018

Slide 31 of 56

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)

Webster BS et al, *Spine*, 2007; White KT et a, *Am J Phys Med Rehabil*, 2009; Volinn E et al, *Pain*, 2009; Franklin GM et al, *Spine*, 2008; Brede E et al, *Arch Phys Med Rehabil*, 2012; Degenhardt L, *Lancet Psychiatry*, 2015; Chou R, *Annals Intern Med*, 2015; CDC, *MMWR*, 2016; Brennan MJ, *Am J Med*, 2013; Scherrer JF, *JGIM*, 2013; Soderberg KC, *CNS Drugs*, 2013; Gomes T, *JAMA Int Med*, 2013.

Slide 32 of 56

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

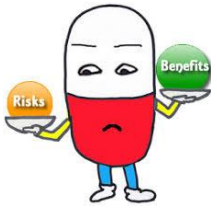


Image courtesy of: www.pilladvised.com

Slide 33 of 56

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)."

Slide 34 of 56

CDC, *MMWR*, 2016.

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

Gourlay D, *Pain Med*, 2005; Starrels JL, *Ann Int Med*, 2010.

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

Starrels JL, *Ann Int Med*, 2010.

Slide 38 of 56

Prescription Drug Monitoring Programs (PDMP)

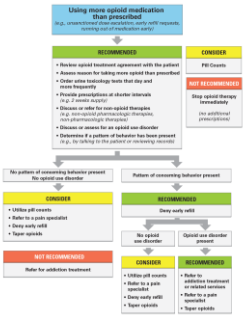
- State-by-state, lots of variability
- Tells you three things that predict OD:
  - –Dose
  - –multiple rx's
  - –opioid and benzo co-rx

Slide 39 of 56

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

Slide 40 of 56



www.mytopacare.org

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.

DSM-5.

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.

DSM-5.

Slide 44 of 56

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*

Slide 45 of 56

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
  - Panel management (Liebschutz et al, JAMA Int Med, 2017)
- Utilize resources
  - Those mentioned today
  - CDC materials
  - Conferences: AMERSA, ASAM, regional APS
  - Providers' Clinical Support System (PCSS)
  - www.mytopcare.org

Slide 46 of 56

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

Slide 47 of 56

Question-and-Answer

Slide 48 of 56

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Chronic Pain in People Living With HIV Infection: A Practical, Evidence-Based Approach

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Slide 49 of 56

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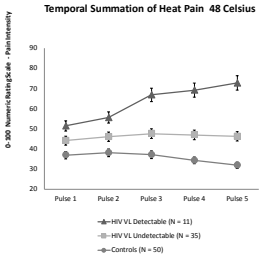
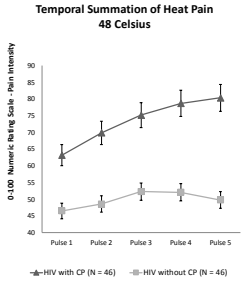
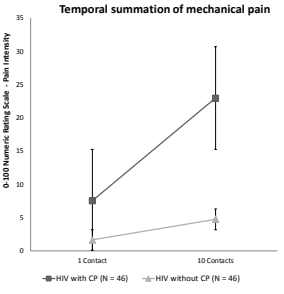
Bonus slides

Pathophysiology: pain sensitivity







Pathophysiology: inflammation

Cytokine	Absolute values (median, IQR) Chronic Widespread Pain	No Pain	Adjusted OR (95% CI)	p-value
IL-1β	0.63 (0.05-1.77)	0.15 (0.05-0.64)	1.34 (1.04-1.72)	0.02
IL-6	0.72 (0.44-1.35)	0.65 (0.44-0.98)	1.13 (0.87-1.46)	0.35
TNF-α	2.90 (2.12-3.74)	2.66 (2.13-3.49)	1.11 (0.85-1.47)	0.45
Eotaxin	134 (103-209)	126 (91-188)	1.16 (0.98-1.37)*	0.09
IL-15	2.47 (1.92-3.25)	2.39 (1.92-2.92)	1.19 (0.83-1.71)	0.35
Leptin	20.0 (11.4-39.2)	18.2 (9.7-30.0)	1.19 (0.75-1.91)**	0.46

Adjusted model contains categorical age and sex.
*per 50 unit increase.
**per 25 unit increase.

Merlin JS et al, under review.

Slide 53 of 56

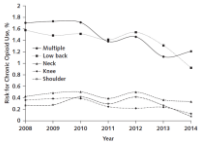
Hot Topics

Slide 54 of 56

Trends in opioid prescribing

OBSERVATIONS: BRIEF RESEARCH REPORT

Risk and Risk Factors for Chronic Opioid Use Among Opioid-Naive Patients With Newly Diagnosed Musculoskeletal Pain in the Neck, Shoulder, Knee, or Low Back



- Opioid rx among naïve patients is declining

Annals of Internal Medicine ORIGINAL RESEARCH

Opioid Prescribing in the United States Before and After the Centers for Disease Control and Prevention's 2016 Opioid Guideline

Amy S.B. Bohnert, PhD, MHS; Gary P. Guy Jr., PhD, MPH; and Jon L. Losby, PhD, MSW

- Rates were already declining, but guideline release a/w greater decline
- Reductions in high-dose rx, overlapping opioid/benzo, all opioid

JAMA Internal Medicine Published online February 11, 2019

RESEARCH LETTER

County-Level Opioid Prescribing in the United States, 2015 and 2017

- Declining since 2012, is now accelerating
- MME per capita still much higher than 1999

Slide 55 of 56

Opioid risks

ORIGINAL RESEARCH — Annals of Internal Medicine

Opioid Analgesic Use and Risk for Invasive Pneumococcal Diseases
A Nested Case-Control Study

JAMA | Original Investigation

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

Slide 56 of 56

Opioid misuse behaviors

Annals of Internal Medicine — ORIGINAL RESEARCH

Patterns of Potential Opioid Misuse and Subsequent Adverse Outcomes in Medicare, 2008 to 2012

- Found association between opioid misuse (overlapping prescriptions, multiple prescribers/pharmacies) and OD mortality in Medicare database

JGIM

Managing Concerning Behaviors in Patients Prescribed Opioids for Chronic Pain: A Delphi Study

- 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.

Slide 57 of 56

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%)
- 16% of suicides in these patients are from opioid overdose (remainder firearm)
- 60% of decedents with chronic pain who left a note 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."

Slide 58 of 56

Chronic pain and opioid risks

REVIEW ARTICLE

Understanding Links among Opioid Use, Overdose, and Suicide

Amy S.B. Bohnert, Ph.D., and Mark A. Ilgen, Ph.D.

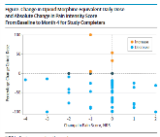
Slide 59 of 56

Tapering

RESEARCH LETTER

Patient-Centered Prescription Opioid Tapering In Community Outpatients With Chronic Pain

- 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



Annals of Internal Medicine REVIEW

Patient Outcomes in Dose Reduction or Discontinuation of Long-Term Opioid Therapy

A Systematic Review

Joseph W. Frank, MD, MPH; Travis I. Lovejoy, PhD, MPH; William C. Becker, MD; Benjamin J. Morasco, PhD; Christopher J. Kimmey, PhD; Lilian Hoffecker, PhD, MLS; Hannah N. Dischinger, BS; Steven K. DeBiasi, MD; and Eric D. Kirbas, MD, MPH

- Heterogeneous interventions, voluntary taperes
- Psychosocial support helps

Slide 60 of 56

Some people are asking, have we gone too far?

Health & Science

The Washington Post: Health-care providers say CDC's opioid guidelines are harming pain patients

STAT: Tapered to zero: In radical move, Oregon's Medicaid program weighs cutting off chronic pain patients from opioids

By Lev Facher @levfacher

The New York Times: *Good News: Opioid Prescribing Fell. The Bad? Pain Patients Suffer, Doctors Say.*

Doctors and insurers are using federal guidelines as cover to turn away patients, experts tell the C.D.C. and Congress.

By Jan Hoffman and Abby Goodnough

March 6, 2019

Slide 61 of 56

Cancer pain

VIEWPOINT

Bridging the Critical Divide in Pain Management Guidelines From the CDC, NCCN, and ASCO for Cancer Survivors

- 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

Opinion

AMERICAN MEDICAL ASSOCIATION HOUSE OF DELEGATES

RESOLVED: That our American Medical Association policy, D-120.947, A More Uniform Approach to Assessing and Treating Patients with Controlled Substances for Pain Relief, be amended by addition as follows:

3. Our AMA will work diligently with the Centers for Disease Control and Prevention and other regulatory agencies to provide increased leeway in the interpretation of the new guidelines for appropriate prescription of opioid medications in long-term care facilities and in the care of patients with cancer and cancer survivors, in much the same way as is being done for hospice and palliative care. (Modify Current HOD Policy)

Brief Report

Cancer and Opioids: Patient Experiences With Stigma (COPES)—A Pilot Study

Hailey W. Bulls, PhD, Aasha I. Hoogland, PhD, David Craig, PharmD, Judith Paice, PhD, RN, Young Doo Chang, MD, Ritika Oberoi-Jawal, MD, Sahana Rajasekhara, MD, Meghan Haas, DO, Margarita Bobonis, MD, Brian D. Gonzalez, PhD, Diane Portman, MD, FAAHPM, and Heather S.L. Jim, PhD
Moffitt Cancer Center (H.W.B., A.I.H., D.C., Y.D.C., R.O.-J., S.R., M.H., M.B., B.D.G., D.P., H.S.L.J.), Tampa, Florida; and Northwestern University (J.P.), Chicago, Illinois, USA

- Adults receiving active cancer treatment
- Difficulty filling rx 22%, awkwardness communicating w providers 15%, taking less med than needed 20%

Slide 62 of 56

Cancer pain

Journal of Pain and Symptom Management

Original Article

Managing Chronic Pain in Cancer Survivors Prescribed Long-Term Opioid Therapy: A National Survey of Ambulatory Palliative Care Providers

Jessica S. Merlin, MD, PhD, MBA, Kanan Patel, MBBS, MPH, Nicole Thompson, BA, Jennifer Kapo, MD, Frank Keefe, PhD, Jane Liebschutz, MD, MPH, Judith Paice, PhD, RN, Tamara Somers, PhD, Joanna Starrels, MD, MS, Julie Childers, MD, MS, Yael Schenker, MD, MAS, and Christine S. Ritchie, MD, MSPH

- 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

Brief Report

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- Adults receiving active cancer treatment
- Difficulty filling rx 22%, awkwardness communicating w providers 15%, taking less med than needed 20%

Slide 63 of 56

Pain in patients with serious illness

JAMA September 4, 2018 Volume 320, Number 9

VIEWPOINT

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

The National Academies of SCIENCES ENGINEERING MEDICINE

ROUNDTABLE ON QUALITY CARE FOR PEOPLE WITH SERIOUS ILLNESS

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

Slide 64 of 56

Non-pharm cont'd

JAMA Network Open.

Original Investigation | Health Policy

Coverage of Nonpharmacologic Treatments for Low Back Pain Among US Public and Private Insurers

- variable

Slide 65 of 56

Medical marijuana for pain

Therapeutics

Review: In chronic noncancer pain, cannabinoids reduce pain (NNT 24) but increase adverse events (NNH 6)

Stockings E, Campbell G, Hall WD, et al. ***Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies.*** *Pain.* 2018;159:1932-54.

Clinical impact ratings:

Cannabinoids vs placebo in chronic noncancer pain?

Outcomes	Number of comparisons (n)	Weighted event rates		ARR/RRI (95% CI)	ANNT/NNH (CI)
		Cannabinoid	Placebo		
≥ 30% pain reduction	9 (1734)	34%	26%	RRI 30% (11 to 51)	NNT 24 (15 to 67)
≥ 50% pain reduction	5 (752)	19%	14%	RRI 35% (−3 to 82)	Not significant
AEs‡	10 (1959)	82%	66%	RRI 24% (19 to 28)	NNH 6 (5 to 8)
Withdrawals for AEs	19 (3265)	14%	4.4%	RRI 212% (145 to 292)	NNH 40 (35 to 49)
		Mean difference (CI)§			
Change in pain intensity (100 mm VAS)	34 (3869)			−2.9 (−4.6 to −1.6)‖	

- Mean difference of 3 on VAS

VIEWPOINT

Should Physicians Recommend Replacing Opioids With Cannabis? JAMA. February 19, 2019 Volume 321, Number 7

JAMA Internal Medicine | Original Investigation | HEALTH CARE POLICY AND LAW

Association of Medical and Adult-Use Marijuana Laws With Opioid Prescribing for Medicaid Enrollees

Hefei Wen, PhD, Jason M. Hockenberry, PhD

- Another ecological study

Slide 66 of 56

Medical MJ

Slide 67 of 56

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]

1. https://www.leafly.com/news/health/qualifying-conditions-for-medical-marijuana-by-state
2. add
3. https://aidsinfo.nih.gov/news/12/fda-approves-new-indication-for-dronabinol
4. https://www.leafly.com/news/cannabis-101/most-common-qualifying-conditions-for-medical-cannabis

Slide 68 of 56

Potential Uses in PLWH

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

Keep these in mind…..

Slide 69 of 56

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

Slide 70 of 56

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

Slide 71 of 56

Original Investigation

Cannabinoids for Medical Use

A Systematic Review and Meta-analysis

Penny F. Whiting, PhD; Robert F. Wolff, MD; Sohan Deshpande, MSc; Marcello Di Nisio, PhD; Steven Duffy, PgD; Adrian V. Hernandez, MD, PhD; J. Christiaan Keurentjes, MD, PhD; Shona Lang, PhD; Kate Misso, MSc; Steve Ryder, MSc; Simone Schmidlkofer, MSc; Marie Westwood, PhD; Jos Kleijnen, MD, PhD

- 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.

Slide 72 of 56

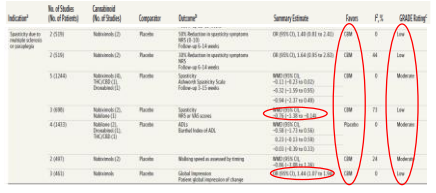
79	RCTs were included (No. or reports [No. of patients])[b]
28	Nausea and vomiting due to chemotherapy (37 [1772])
28	Chronic pain (63 [2454])
14	Spasticity due to multiple sclerosis or paraplegia (33 [2280])
4	HIV/AIDS (4 [255])
2	Sleep disorder (5 [54])
2	Psychosis (9 [71])
2	Tourette syndrome (7 [36])
1	Anxiety disorder (1 [24])
1	Glaucoma (1 [6])
0	Depression

Slide 73 of 56

Indication[a]	No. of Studies (No. of Patients)	Cannabinoid (No. of Studies)	Comparator	Outcome[a]	Summary Estimate	Favors	I^2, %	GRADE Rating[c]
Nausea and vomiting due to chemotherapy	3 (332)	Dronabinol (2), Nabinimols (1)	Placebo	Nausea and vomiting Complete response	OR (95% CI), 3.82 (1.55 to 9.42)	CBM	0	Low

Statistically significant

Slide 74 of 56



Indication[a]	No. of Studies (No. of Patients)	Cannabinoid (No. of Studies)	Comparator	Outcome[a]	Summary Estimate	Favors	I^2, %	GRADE Rating[c]
Spasticity due to multiple sclerosis or paraplegia	2 (539)	Nabinimols (2)	Placebo	30% Reduction in spasticity symptoms NRS (0–10) Follow-up 5–14 weeks	OR (95% CI), 1.48 (0.81 to 2.41)	CBM	0	Low
	2 (539)	Nabinimols (2)	Placebo	30% Reduction in spasticity symptoms NRS Follow-up 6–14 weeks	OR (95% CI), 1.64 (0.95 to 2.82)	CBM	44	Low
	5 (1,344)	Nabinimols (4), THC:CBD (1), Dronabinol (1)	Placebo	Spasticity Ashworth Spasticity Scale Follow-up 2–15 weeks	WMD (95% CI), −0.11 (−0.23 to 0.02) −0.32 (−1.39 to 0.95) −0.566 (−2.37 to 0.49)	CBM	0	Moderate
	3 (698)	Nabinimols (2), Nabilone (1)	Placebo	Spasticity NRS or VAS scores	WMD (95% CI), −1.76 (−2.38 to −1.14)	CBM	73	Low
	4 (1413)	Nabilone (2), Dronabinol (1), THC:CBD (1)	Placebo	ADLs Barthel Index of ADL	WMD (95% CI), −0.38 (−1.71 to 0.56) 0.23 (−0.13 to 0.59) −0.03 (−0.36 to 0.32)	Placebo	0	Moderate
	2 (497)	Nabinimols (2)	Placebo	Walking speed as assessed by timing	WMD (95% CI), −0.46 (−1.09 to 1.66)	CBM	24	Moderate
	3 (461)	Nabinimols	Placebo	Global impression Patient global impression of change	OR (95% CI), 1.44 (1.07 to 1.94)	CBM	0	Low

Slide 75 of 56

Indication[a]	No. of Studies (No. of Patients)	Cannabinoid (No. of Studies)	Comparator	Outcome[a]	Summary Estimate	Favors	I^2, %	GRADE Rating[c]
ANOREXIA	1 (88)	Dronabinol	Placebo	Weight gain No. of patients who gained ≥2 kg within 6 weeks	OR (95% CI), 2.2 (0.68 to 7.27)	CBM	NA	Low

Not statistically significant

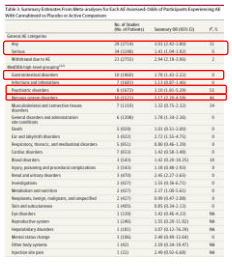
Slide 76 of 56

Appetite Stimulation in HIV/AIDS Infection

Appetite stimulation in HIV/AIDS was assessed in 4 studies (4 reports; 255 participants).[59-62] All studies assessed dronabinol, 3 compared with placebo (1 of which also assessed marijuana), and 1 compared with megastrol acetate. All studies were at high risk of bias. There was some evidence that dronabinol is 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, reduced nausea, and improved functional status. However, these outcomes were mostly assessed in single studies and associations failed to reach statistical significance. The trial that evaluated marijuana and dronabinol found significantly greater weight gain with both forms of cannabinoid when compared with placebo.[59] The active comparison trial found that megastrol acetate was associated with greater weight gain than dronabinol and that combining dronabinol with megastrol acetate did not lead to additional weight gain.[60]

Slide 77 of 56

Slide 78 of 56



Slide 79 of 56

Individual AEs			
Dizziness	41 (4243)	5.09 (4.10-6.32)	18
Dry mouth	36 (4181)	3.50 (2.58-4.75)	28
Nausea	30 (3579)	2.08 (1.63-2.65)	0
Fatigue	20 (2717)	2.00 (1.54-2.62)	0
Somnolence	26 (3168)	2.83 (2.05-3.91)	27
Euphoria	27 (2420)	4.08 (2.18-7.64)	49
Depression	15 (2353)	1.32 (0.87-2.01)	0
Vomiting	17 (2191)	1.67 (1.13-2.47)	0
Diarrhea	17 (2077)	1.65 (1.04-2.62)	15
Disorientation	12 (1736)	5.41 (2.61-11.19)	0
Asthenia	15 (1717)	2.03 (1.35-3.06)	0
Drowsiness	18 (1272)	3.68 (2.24-6.01)	44
Anxiety	12 (1242)	1.98 (0.73-5.35)	54
Confusion	13 (1160)	4.03 (2.05-7.97)	0
Balance	6 (920)	2.62 (1.12-6.13)	0
Hallucination	10 (898)	2.19 (1.02-4.68)	0
Dyspnea	4 (375)	0.83 (0.26-2.63)	0
Paranoia	4 (492)	2.05 (0.42-10.10)	0
Psychosis	2 (37)	1.09 (0.07-16.35)	25
Seizures	2 (42)	0.91 (0.05-15.66)	0

Slide 80 of 56

Annals of Internal Medicine — REVIEW

The Effects of Cannabis Among Adults With Chronic Pain and an Overview of General Harms

A Systematic Review

Table 2. Summary of Evidence of the Benefits of Cannabis in Populations With Chronic Pain

Pain Type	Studies	Findings	Strength of Evidence*	Comments
Neuropathic	11 low-ROB studies; combined N = 593: 4 of smoked THC (28, 31, 33, 39); combined N = 150; 3 of vaporized THC (36, 40, 47); combined N = 97; 3 of nabiximols (24, 27, 42); combined N = 312; 1 of oromucosal spray delivering THC or THC+CBD (43); N = 34; 1 unclear-ROB study of nabiximols (26); N = 30; 1 high-ROB trial (35); N = 125	Studies did not find a clinically significant between-group difference on continuous pain scales, but a higher proportion of intervention patients had clinically significant pain relief up to several months later. In a meta-analysis of 9 studies, intervention patients were more likely to report ≥30% improvement in pain (combined RR, 1.43 [95% CI, 1.16–1.88]; I^2 = 38.6%; P = 0.111)	Low	Few patients enrolled in most low-ROB studies; inconsistent results; marked differences among studies in dosing and delivery mechanism; brevity of study duration; low applicability to formulations available in dispensaries

Slide 81 of 56

MS	3 low-ROB trials; combined N = 369; 24–279 per study: 1 of THC/CBD capsules (29); 1 of nabiximols (42); 1 of sublingual spray delivering THC, CBD, or THC+CBD (44); 5 unclear-ROB trials; combined N = 897; 24–339 per study: 3 of nabiximols (22, 38, 41); 1 of smoked THC (37); 1 of orally ingested THC (EPC002A) (45); 1 high-ROB trial of THC/CBD capsules (32); N = 657	No consistent clinically significant effects on pain	Insufficient	Few methodologically rigorous studies; inconsistent results; little long-term data; inclusion of pain as a secondary outcome; low applicability to formulations available in dispensaries
Cancer	2 unclear-ROB trials; combined N = 596; 177–360 per study: 1 of nabiximols (25); 1 of nabiximols and THC oromucosal spray in separate groups (23); 1 high-ROB trial of THC capsules (34); N = 10	No consistent clinically significant effects on pain	Insufficient	Small number of studies; methodological flaws, including high attrition, lack of clarity about randomization and blinding procedures, and use of nonstandard outcome measures
Other/mixed	1 unclear-ROB trial of nabiximols for rheumatoid arthritis (21); N = 58; 1 high-ROB trial of EPC002A (orally ingested 99% THC) for abdominal pain (46); N = 65; 3 cohort studies of mixed forms of cannabis (smoked, orally ingested, vaporized) for fibromyalgia (48), inflammatory bowel disease/Crohn disease (49), and nociceptive and/or neuropathic pain (50)	Small improvements in pain	Insufficient	Larger observational study had high attrition

Slide 82 of 56

Table 3. Summary of Evidence for the Harms of Cannabis in Chronic Pain and General Adult Populations

Outcome	Studies	Findings	Strength of Evidence*	Comments
General AEs	2 systematic reviews (10, 11) and 1 observational study of chronic pain (50)	Cannabis-based treatments associated with higher overall risk for short-term, nonserious AEs	–	Consistent findings except for serious AE
Motor vehicle accidents	Meta-analysis (51) of 21 observational studies; combined N = 239 739	Increase in collision risk (OR, 1.35 [95% CI, 1.15–1.61])	Moderate	Small but significant increase in risk seen consistently across numerous sensitivity analyses and after adjustment in meta-regression analyses
Medical AEs				
Pulmonary function	2 low-ROB prospective cohort studies (52, 53) with 20–32 y follow-up; combined N = 5885; 1 systematic review (54) of 5 observational studies (3 cohort, 2 cross-sectional); combined N = 351	In young adults, low levels of cannabis smoking did not adversely affect lung function over about 20 y. A previous meta-analysis of 5 studies found no increased risk for pulmonary adverse effects (OR, 0.80 [95% CI, 0.46–1.39])	Young adults: moderate; Older adults: no evidence	2 well-done prospective cohort studies, but limited information about effects of heavy use and no information in older or multimorbid populations
Cardiovascular effects	2 high-ROB observational studies: 1 case-crossover (55), N = 3882; 1 cohort (56), N = 2097	Cannabis use at time of MI not associated with mortality after mean 12.7-y follow-up, but longitudinal use not assessed. Risk of MI within 1 h of cannabis use significantly elevated compared with periods of nonuse, but finding may be inflated by recall bias (OR, 4.8 [95% CI, 2.9–9.5])	Insufficient	Recall bias; inadequate controlling for confounders; lack of longitudinal exposure data
Lung cancer	1 patient-level meta-analysis (57) of 6 case-control studies; combined N = 2150; 1 high-ROB cohort study (58); N = 49 231	Meta-analysis found no association between light cannabis use and lung cancer	Low	Recall bias; mostly light users, few heavy users; large cohort study had no information about exposure over time
Head/neck/oral cancer	Meta-analysis (59) of 9 case-control studies; combined N = 5732	No association between cannabis use and cancer (OR, 1.02 [95% CI, 0.91–1.14]); generally consistent across studies and no evidence of dose response	Low	Imprecise exposure measurement with potential recall bias; ever-use among studies ranged from 1%–83%
Testicular cancer	Meta-analysis (60) of 3 high-ROB case-control studies; combined N = 719	Increased cancer risk for weekly users compared with never-users seen with nonseminoma cancer but not seminoma cancer (OR, 1.92 [95% CI, 1.35–2.72])	Insufficient	Potential confounding from recall bias and tobacco use
Transitional cell cancer	1 high-ROB VA case-control study (61); N = 52	Risk of cancer with >40 joint-years cannabis use vs. none (OR, 3.4; unadjusted P = 0.012)	Insufficient	1 very small case-control study with several methodological flaws

Mental health AEs				
Suicidal behaviors	1 meta-analysis (62) of 4 observational studies	Significantly increased odds of suicide with any cannabis use (OR, 2.56 [95% CI, 1.25–5.27])	Insufficient	Inconsistent results; inadequate exposure ascertainment and adjustment for confounding
Mania	1 meta analysis (63) of 2 prospective studies	Increased incidence of new-onset mania symptoms among populations without diagnosis of bipolar disorder (OR, 2.97 [95% CI, 1.80–4.90])	Low	Small number of studies; exposure not well-characterized in 1 study, but other was large community-based cohort study also showing dose–response effect
Psychosis	1 systematic review (64); 8 studies (65–71, 74) including patients without psychotic symptoms at baseline: 3 low ROB, 3 medium ROB, 2 high ROB	History of cannabis use associated with increased risk for psychotic symptoms	Low	Consistent evidence from large observational studies and some evidence of increased risk with higher levels of use; consistent with data from small experimental studies suggesting risk of acute psychosis in some patients; magnitude of risk unclear and not specifically studied in chronic pain populations
Cognitive effects	2 systematic reviews (72, 73)	Active long-term cannabis use associated with small negative effects on all aspects of cognition. Mixed, inconsistent findings on long-term effects in past users.	Moderate; Insufficient (past use)	Consistent data from large number of studies on effects of active long-term use, but inconsistent findings from smaller number of studies regarding effects in those who abstained and no data available specifically in chronic pain populations

Therapeutics

Review: In chronic noncancer pain, cannabinoids reduce pain (NNT 24) but increase adverse events (NNH 6)

Stockings E, Campbell G, Hall WD, et al. ***Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies.*** *Pain. 2018;159:1932-54.*

Clinical impact ratings: ★★★★★★★ ★★★★★☆☆ ★★★★★☆☆

Cannabinoids vs placebo in chronic noncancer pain†

Outcomes	Number of comparisons (n)	Weighted event rates: Cannabinoid	Weighted event rates: Placebo	RBI/RRI (95% CI)	NNT/NNH (CI)
≥ 30% pain reduction	9 (1734)	34%	26%	RBI 30% (11 to 51)	NNT 24 (15 to 61)
≥ 50% pain reduction	5 (753)	19%	14%	RBI 35% (−3 to 82)	Not significant
AEs‡	10 (1959)	82%	66%	RRI 24% (19 to 28)	NNH 6 (5 to 8)
Withdrawals for AEs	19 (3265)	14%	4.6%	RRI 212% (145 to 292)	NNH 40 (35 to 49)
				Mean difference (CI)§	
Change in pain intensity (100-mm VAS)	34 (3869)			−2.9 (−4.6 to −1.5)‖	

- Mean difference of 3 on VAS

Review Article

The therapeutic effects of *Cannabis* and cannabinoids: An update from the National Academies of Sciences, Engineering and Medicine report

Donald I. Abrams

1.1.1. Chronic pain

Chronic pain is one of the most often cited reasons that patients are accessing medicinal *Cannabis* in states where it is available [3]. There were five fair-to-good quality systematic reviews that contributed to the conclusion that there is substantial evidence that *Cannabis* is an effective treatment for chronic pain in adults. The comprehensive review by Whiting et al. published in 2015 provided the basis for many of the conclusions reached in the NASEM report and included 28 randomized controlled trials in patients with chronic pain involving 2454 patients [4]. Neuropathic pain was the condition studied in 17 of the trials. Only five of the trials evaluated smoked or vaporized *Cannabis* plant material with most [13] investigating the whole plant extract oromucosal spray, nabiximols. An analysis that included seven trials of nabiximols and one of smoked *Cannabis* found that the plant-derived cannabinoids were 40% more likely to reduce pain than the control agent (OR 1.41, 95% confidence interval = 0.99–2.00). The effect size for the reduction of neuropathic pain with inhaled *Cannabis* compared to placebo was estimated at 3.22 (95% CI = 1.59–7.24) from a Bayesian pooled effect analysis of five published trials [5]. Of note, a more recent study from US Veteran's Administration investigators analyzing essentially the same cluster of published clinical trials of *Cannabis* plant-based medicines concluded with less conviction that pain was effectively treated [6].

Slide 86 of 56

Long-term adverse health consequences[1]

- Addiction: 9% in individuals with any cannabis use, half of cases within 5 years; 17% in individuals who start as teens[2]
  - Withdrawal syndrome: irritability, sleep problems, dysphoria, craving, anxiety
- Anxiety/depression, although causality difficult to determine[3]
- Psychosis[4]
- Motor vehicle accidents; risk doubles after use[5], and is dose-related[6]
- Nausea/vomiting[7]
- Pregnancy: low birth weight, children born with attention and problem-solving deficits[8]

- These issues are all common in PLWH!

1. Volkow ND, NEJM, 2014. 2. Lopez-Quintero C, Drug Alcohol Depend, 2011. 3. add. 4. Radhakrishnan R, Font Psychiatry, 2014. 5. Hartman RL, Clin Chem, 2013. 6. Ramaekers JG, Drug Alcohol Dep, 2004. 7.add. 8. Volkow ND, JAMA, 2017.

Slide 87 of 56

Impact of legalization

- Lots of speculation (e.g., availability could lead to initiation)[1]
- From CO and WA:
  - increase in ED/inpatient admissions, calls to poison centers, motor vehicle and other fatalities[2]
  - ED: edibles and intoxication, CV, and psych; inpatient: inhaled, hyperemesis[3]

1. Budney AJ, Prev Med, 2017. 2. Maxwell JC, J Addict Med, 2016. 3. Monte AA, Ann Int Med, 2019.

Slide 88 of 56

Annals of Internal Medicine

EDITORIAL

Emergency Department Visits From Edible Versus Inhalable Cannabis

We must recognize that the full range of potential adverse health consequences from cannabis consumption are not fully understood. Research is needed not only to rigorously ascertain evidence about potential beneficial effects of cannabis but also to carefully characterize its potential negative effect

Slide 89 of 56

Opioid tapering, OUD treatment

- Ecological studies showing associations between mj legalization and decreased opioid use / overdose
- Largest prospective study[1]:
  - –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

1. Campbell G, Lancet Public Health, 2018.

Slide 90 of 56

VIEWPOINT

Should Physicians Recommend Replacing Opioids With Cannabis?

The suggestion that patients should self-substitute a drug (ie, cannabis) that has not been subjected to a single clinical trial for opioid addiction is irresponsible and should be reconsidered.

These approaches reflect the stigmatized nature of people with opioid addiction that cannabis therapy might be considered reasonable with no clinical trials when no comparable provision has been made for other chronic diseases for which claims of cannabis' benefits have been made (eg, no regulations have suggested that patients with diabetes stop taking insulin and take cannabis instead).

Slide 91 of 56

Cannabis in painful HIV-associated sensory neuropathy

A randomized placebo-controlled trial

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Abstract—*Objective:* To determine the effect of smoked cannabis on the neuropathic pain of HIV-associated sensory neuropathy and an experimental pain model. *Methods:* Prospective randomized placebo-controlled trial conducted in the inpatient General Clinical Research Center between May 2003 and May 2005 involving adults with painful HIV-associated sensory neuropathy. Patients were randomly assigned to smoke either cannabis (3.56% tetrahydrocannabinol) or identical placebo cigarettes with the cannabinoids extracted three times daily for 5 days. Primary outcome measures included ratings of chronic pain and the percentage achieving >30% reduction in pain intensity. Acute analgesic and anti-hyperalgesic effects of smoked cannabis were assessed using a cutaneous heat stimulation procedure and the heat/capsaicin sensitization model. *Results:* Fifty patients completed the entire trial. Smoked cannabis reduced daily pain 34% (median reduction; IQR = −71, −16) vs 17% (IQR = −29, 8) with placebo ($p = 0.03$). Greater than 30% reduction in pain was reported by 52% in the cannabis group and by 24% in the placebo group ($p = 0.04$). The first cannabis cigarette reduced chronic pain by a median of 72% vs 15% with placebo ($p < 0.001$). Cannabis reduced experimentally induced hyperalgesia to both brush and von Frey hair stimuli ($p \leq 0.05$) but appeared to have little effect on the painfulness of noxious heat stimulation. No serious adverse events were reported. *Conclusion:* Smoked cannabis was well tolerated and effectively relieved chronic neuropathic pain from HIV-associated sensory neuropathy. The findings are comparable to oral drugs used for chronic neuropathic pain.

NEUROLOGY 2007;68:515–521

Slide 92 of 56

Opioid Tapering

- Limited evidence in general[1]
- Conflicting evidence in PLWH[2-4]

1. Add Saitz JAMA. 2-4. add my JAIDS paper plus refs in comments below

Slide 93 of 56

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.

Slide 94 of 56

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 common[1]; 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)

Slide 95 of 56

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?

Slide 96 of 56

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.

Slide 97 of 56

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.

Slide 98 of 56

Practical approach: how to prescribe

Box. Practical Considerations for Medical Marijuana

An appropriate medical marijuana candidate should have:

1. A debilitating medical condition that data from randomized clinical trials suggest would respond to medical marijuana pharmacotherapy, such as nausea and vomiting associated with cancer chemotherapy, anorexia from wasting illnesses like AIDS, chronic pain, neuropathic pain, or spasticity associated with multiple sclerosis
2. Multiple failed trials of first- and second-line pharmacotherapies for these conditions
3. A failed trial of an US Food and Drug Administration–approved cannabinoid (dronabinol or nabilone)
4. No active substance use disorder or psychotic disorder or no unstable mood disorder or anxiety disorder
5. Residence in a state with medical marijuana laws and meets requirements of these laws

Hill KP, JAMA, 2015.

Slide 99 of 56

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!

Slide 100 of 56