## The Spectrum of Opioid Use: Minimizing Harm

Charles Brackett, MD, MPH, FACP, FASAM September 29<sup>th</sup>, 2023



Opioid Response Network





#### Commercial Support/Sponsorship:

There is no commercial support for this training.

#### **Conflict of Interest**:

In accordance with continuing education guidelines, speakers and planning committee members are asked to disclose relationships with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

**Faculty:** Dr. Brackett has no relevant financial relationship(s) with ineligible companies to disclose. He will be discussing "off label" use of buprenorphine for pain.

**<u>Planning Committee Members</u>**: Have no relevant financial relationship(s) with ineligible companies to disclose.

#### **Mitigation Steps Implemented:**

There were no reported financial relationships to be mitigated.



## **Multidimensional Care for Chronic** Pain



Study duration on **all** treatments for **chronic pain** are ≤ 12 months, vast majority are < 12 weeks Tayeb BO, et al. Pain Med. 2016

Multimodal approaches are more cost-effective than single modality options Flor H. et al. Pain 1992 Roberts AH. et al. Clin J Pain. 1993

## Non-Opioid Pharmacologic

## Nociceptive Pain

- Acetaminophen (max dose 2g?3g?4g?)
- Non Steroidal Anti-inflammatory Drugs (NSAIDs) (GI, renal, cardiac SEs- low dose/brief)
  - Topical
  - Naproxen lowest cardiac? (?PPI)
  - COX-2
  - Non-acetylated salicylates

## Neuropathic/Nociplastic Pain

- Antidepressants
- Anticonvulsants
- Topical lidocaine or capsaicin

## Muscle Relaxants– avoid

## Antidepressants

- Duloxetine- SNRI (Serotonin-Norepinephrine Reuptake Inhibitor), safest, but fall risk
  - Can be effective in non-neuropathic pain, including non-radicular low back pain and osteoarthritis
  - Effective for co-morbid anxiety/depression
- TCAs (Tricyclic Antidepressants): Secondary amines: nortriptyline, desipramine



## Anticonvulsants



Pregabalin and gabapentin for pain

Gabapentin/Pregabalin

- Effective for neuropathic pain
  - Post-herpetic neuralgia
  - Painful diabetic neuropathy
- Fibromyalgia (just pregabalin, NNT 10)
- NOT effective for radicular pain/sciatica, non-neuropathic pain



## Non Systemic Approaches: Topicals and Injections

- Topical NSAIDs (diclofenac gel 1%)
- ♦ Capsaicin
- Lidocaine cream/gel/patches
  - PHN (Post Herpetic Neuralgia), PDN (Painful Diabetic Neuropathy), CRPS (Complex Regional Pain Syndrome)
- Steroid injections (epidural, joint)
- Trigger point injections
- Hyaluronic acid, PRP (Platelet-Rich Plasma) injections (knee)



# **Complementary/Alternative**

#### Annals of Internal Medicine

ORIGINAL RESEARCH

#### Effectiveness of *Curcuma longa* Extract for the Treatment of Symptoms and Effusion-Synovitis of Knee Osteoarthritis 12/1/20A Randomized Trial

Zhiqiang Wang, MPharm; Graeme Jones, PhD; Tania Winzenberg, PhD; Guogi Cai, MmedSci; Laura L. Laslett, PhD; Dawn Aitken, PhD; Ingrid Hopper, PhD; Ambrish Singh, MTech; Robert Jones, MD; Jurgen Fripp, PhD; Changhai Ding, PhD; and Benny Antony, PhD

#### JAMA | Original Investigation

Association of Pharmacological Treatments With Long-term Pain Control in Patients With Knee Osteoarthritis A Systematic Review and Meta-analysis

12/25/18





## Activation of µ-Opioid



- Turn on descending inhibitory systems
- Prevent ascending transmission of pain signal
- Inhibit terminals of C-fibers in the spinal cord
- Inhibit activation of peripheral nociceptors
- Activate opioid receptors in midbrain ("reward pathway")



### 2022 CDC Guidelines on Prescribing Opioids for Pain



Nonopioid therapies are preferred for subacute and chronic pain. Clinicians should only consider initiating opioid therapy if expected benefits for pain and function are anticipated to outweigh risks to the patient. Before starting opioid therapy for subacute or chronic pain, clinicians should discuss with patients the known risks and realistic benefits of opioid therapy, should work with patients to establish treatment goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks (recommendation category: A, evidence type: 2).

https://www.cdc.gov/mmwr/volumes/71/rr/rr7103a1.htm



## **Opioids for Pain: How Well Do They Work?**

### **ACUTE pain treatment**

Percent of people getting 50% pain relief (from acute post-op pain) 1/NNT From Cochrane Review (Moore, Derry, Aldington, & Wiffen, 2015)

62.5





- 🔶 1-3 month
  - small improvement vs. placebo in pain and function, increased risk of harms
  - No benefit over non-opioid medications
- ♦ >3months
  - Evidence for effectiveness is very limited
  - Increased risk of serious harms that are dose-dependent



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

Erin E. Krebs, MD, MPH; Amy Gravely, MA; Sean Nugent, BA; Agnes C. Jensen, MPH; Beth DeRonne, PharmD; Elizabeth S. Goldsmith, MD, MS; Kurt Kroenke, MD; Matthew J. Bair; Siamak Noorbaloochi, PhD

#### RCT of 240 people

**CONCLUSIONS AND RELEVANCE** Treatment with opioids was not superior to treatment with nonopioid medications for improving pain-related function over 12 months. Results do not support initiation of opioid therapy for moderate to severe chronic back pain or hip or knee osteoarthritis pain.



## **Opioid Safety and Risks**



## Opioid Tolerance and Physical Dependence

Both tolerance and physical dependence are physiological adaptations to chronic opioid exposure

#### **Tolerance:**

- Increased dosage needed to produce specific effect
  - Develops readily for CNS (Central Nervous System) and respiratory depression
  - Less so for constipation
  - Unclear about analgesia

#### **Physical Dependence:**

• Signs and symptoms of withdrawal by abrupt opioid cessation, rapid dose reduction or exposure to an opioid antagonist (naloxone)



## Opioid Induced Hyperalgesia (OIH)

- Nociceptive sensitization that paradoxically increases pain with opioid exposure
- Mechanisms & incidence not fully understood
- 🔶 Pain
  - May become more generalized
  - May improve with reduced doses or taper off
- OIH must be distinguished from:
  - Tolerance: higher doses opioid required to achieve initial effects, pain improves with increased dosing at least temporarily
  - Withdrawal: clinical signs & symptoms related to opioid cessation, symptoms improve with opioid dosing
  - May limit clinical utility of long-term opioids in some patients

Wilson SH, Hellman KM, James D, Adler AC, Chandrakantan A. Mechanisms, diagnosis, prevention and management of perioperative opioid-induced hyperalgesia. Pain Manag. 2021 Apr;11(4):405-417 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8023328/



### **Potential Psycho-Social Harms of Opioids**

- Misuse: 21-29%
- Addiction: 8-12%
- Anxiety/Depression

Comprehensive Review



Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthemis

Kevin E. Vowles<sup>a,\*</sup>, Mindy L. McEntee<sup>a</sup>, Peter Siyahhan Julnes<sup>a</sup>, Tessa Frohe<sup>a</sup>, John P. Ney<sup>b</sup>, David N. van der Goes<sup>c</sup>

- Issues related to disruption of the endogenous opioid system
  - Reward deficiency 
    → low motivation, hyperkatifeia, social isolation



# **Higher Dose Opioids**

## Higher doses associated with:

- Hyperalgesia<sup>5,6</sup>
- Reduced function<sup>7,8</sup>
- Immunosuppression<sup>14</sup>
- Overdose<sup>9-13</sup>

#### Patient on high doses...

- Manage as higher risk
- Increase monitoring and support



Overdose risk approximately doubles at doses between 20 and 49 mg/day MED, and increases nine-fold at doses of 100 mg/day MED or more (Figure C)

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- 2. Ballantyne JC, Mao J. N Engl J Med. 2003
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- 7. Kidner CL, et al. J Bone Joint Surg Am. 2009
- 8. Townsend CO, et al. Pain. 2008
- 9. Dunn KM, et al. Ann Intern Med. 2010
- 10. Braden JB. Arch Intern Med. 2010
- 11. Bohnert AS, et al. JAMA. 2011
- 12. Gomes T, et al. Open Med. 2011
- 13. Paulozzi LJ. Pain Med. 2012
- 14. Edelman EJ, et al. JAMA Int Med. 2019



## **Opioid Use in the US**

Narcotic Analgesic Dispensed Volumes in Morphine Milligram Equivalents (MME) Bn





FIGURE 2. Rates\* of opioid pain reliever (OPR) overdose death, OPR treatment admissions, and kilograms of OPR sold — United States, 1999–2010

Opioid sales



Paulozzi et al, MMWR 2011;60:1487-92

#### FIGURE 1 Timeline of Opioid-related Overdose Deaths



Source: National Vital Statistics Systems Mortality File and the National Institute on Drug Abuse.

# **Opioid Use Disorder (OUD)**

OUD is a chronic, relapsing brain disorder characterized by compulsive use despite consequences, involving: Changes to brain involved in reward, stress, and self-control

Changes that persist after stopping drug use

Like other chronic diseases, OUD often involves cycles of relapse and remission

Without treatment, OUD is progressive and can result in disability or premature death



Volkow ND, Koob GF, McLellan AT. *N Eng J of Med.* 2016 Sordo L, et al. *BMJ.* 2017

## Opioid Use Disorder (OUD) – DSM 5

### Physiologic sequelae

- Tolerance
- Withdrawal
- Craving

### Loss of control

- Greater amounts of use or longer period of use than intended
- Persistent desire but unsuccessful efforts to cut down
- Inordinate amount of time obtaining, using, or recovering

### Adverse consequences of compulsive use

- Recurrent use resulting in failure to fulfill role obligations at work, school, or home
- Continued use despite persistent social or interpersonal problems
- Important social, occupational, or recreational activities given up
- Recurrent use in physically hazardous situations
- Use despite knowledge of persistent or recurrent physical or psychological problem likely caused or exacerbated by use



## **Reasons for Prescription Opioid Misuse**



SAMHSA. (2017). 2018 NSDUH



#### JAMA Psychiatry | Original Investigation

### Prescription Opioid Use and Risk for Major Depressive Disorder and Anxiety and Stress-Related Disorders A Multivariable Mendelian Randomization Analysis

Daniel B. Rosoff, AB, ScB; George Davey Smith, MD, DSc; Falk W. Lohoff, MD

### **Key Points**

**Question** Does prescription opioid medication have a potentially causal role in the risk for depression and anxiety disorder?

**Findings** In this 2-sample mendelian randomization study using genetic instruments for common pain medications, the genetic liability for prescription opioid use was associated with increased risk for major depression.

Meaning While further work is needed, this genetics-based study supports conventional observational literature suggesting prescription opioid use increases the risk for depression.



# PAIN



VIDEO

Jane C. Ballantyne<sup>a,\*</sup>, Mark D. Sullivan<sup>b</sup>, George F. Koob<sup>c</sup>

## Endogenous opioid system

- Reward processing
- Pain relief
- "Physical Withdrawal"
- "Emotional Withdrawal"
  - Hyperkatifeia/anhedonia/dysphoria/anxiety
  - Sleep disturbance, low energy, irritability
- Drug opposite effect: increased pain



#### REFLECTIONS

### When Physical and Social Pain Coexist: Insights Into Opioid Therapy

Mark D. Sullivan, MD, PbD<sup>1</sup> Jane C. Ballantyne, MD<sup>2</sup>

<sup>1</sup>Psychiatry and Behavioral Sciences, University of Washington, Seattle, Washington

<sup>2</sup>Anesthesiology and Pain Medicine, University of Washington, Seattle, Washington

#### ABSTRACT

The US opioid epidemic challenges us to rethink our understanding of the function of opioids and the nature of chronic pain. We have neatly separated opioid use and abuse as well as physical and social pain in ways that may not be consistent with the most recent neuroscientific and epidemiological research. Physical injury and social rejection activate similar brain centers. Many of the patients who use opioid medications long term for the treatment of chronic pain have both physical and social pain, but these medications may produce a state of persistent opioid dependence that suppresses the endogenous opioid system that is essential for human socialization and reward processing. Recognition of the social aspects of chronic pain and opioid action can improve our treatment of chronic pain and our use of opioid medications.

Ann Fam Med 2021;19:79-82. https://doi.org/10.1370/afm.2591.

#### Social exclusion and physical pain share brain circuitry

- Endogenous opioid system involved in socialization and group formation
- - Artificial dichotomy between physical pain and social pain



Those with social pain are at higher risk of both LTOT (Long Term Opioid Therapy) and OUD

PAIN 164(4):p 870-876, April 2023.

#### **Research Paper**

# PAIN

### Delphi study to explore a new diagnosis for "ineffective" long-term opioid therapy for chronic pain

Sara N. Edmond<sup>a,b,\*</sup>, Jennifer L. Snow<sup>a</sup>, Jamie Pomeranz<sup>c</sup>, Raymond Van Cleve<sup>d,e</sup>, Anne C. Black<sup>a,f</sup>, Peggy Compton<sup>g</sup>, William C. Becker<sup>a,f</sup>



PERSPECTIVES Complex Persistent Opioid Dependence with Long-term Opioids: a Gray Area That Needs Definition, Better Understanding, Treatment Guidance, and Policy Changes

Ajay Manhapra, MD<sup>1,2,3,4</sup>, Mark D. Sullivan, MD<sup>5</sup>, Jane C. Ballantyne, MD<sup>5</sup>, R. Ross MacLean, PhD<sup>2,3</sup>, and William C. Becker, MD<sup>3</sup>

- Harms>benefits, Unwilling/unable to taper, despite:
  - Poor pain control, declining function (usually blamed on pain)
  - Psychiatric or medical instability
- Don't meet criteria for OUD
- Negative Affect/Reward deficiency
- Hyperkatifeia- hypersensitivity to emotional distress
- Social isolation







## **Collateral Opioid Risk**

## Risks

- Young children's ingestion and overdose
- Adolescent experimentation leading to overdose and addiction

## Mitigating risk

- Safe storage and disposal (i.e., lock box)
- Educate family members
- Have poison control number handy
- Naloxone distribution (if available)\*



## **Initiating Opioids**

### ✤ Risk Assessment

- PDMP (Prescription Drug Monitoring Program)
- Urine drug testing (UDT)
- Opioid Risk Tool (ORT)
- Informed Consent and pain management agreement
- Establish goals- function, quality of life (baseline PEG)
- Start with IR (Immediate Release) forms and use lowest effective dosage; consider buprenorphine
- Carefully justify a decision to use >50 MME
- ♦ Bowel regimen
- Consider Naloxone (if >50 MME, or concurrent sedative)
- Opioid storage and disposal



### Re-evaluate risks/benefits in 1-4 weeks after dose change, then every 3-4 months

- Is the patient making progress toward functional goals?
  - PEG=pain, enjoyment of life, general activity
- Review side effects (including psychologic, OIH)
- Monitor adherence to treatment plan
- Monitor for aberrant behavior/SUD
  - PDMP- multiple prescribers
  - UDT (Urine Drug Test) illicit or meds
  - Early refill requests, lost prescriptions, dose escalation
  - Use to treat symptoms other than pain
  - Worsening social or behavioral problems

#### PAIN – 5 A's

- Analgesia
- Activity/Function
- Aberrant/Problematic behavior, not present
- Adverse events
- Affect





1. What number best describes your pain on average in the past week:											
0	1	2	3	4	5	6	7	8	9	10	
Nop	bain									Pain as bad as you can imagine	
2. What number best describes how, during the past week, pain has interfered with your <u>enjoyment of life</u> ?											
0	1	2	3	4	5	6	7	8	9	10	
Doe inter	s not fere									Completely interferes	
3. What number best describes how, during the past week, pain has interfered with your general activity?											
0	1	2	3	4	5	6	7	8	9	10	
Does not interfere										Completely interferes	



POMI (Presciption Opioid Misue Index): yes to 2+ means OUD likely Do you ever:

- Use your medication more often than prescribed?
- Use more of your medication (higher dose) than prescribed?
- Need early refills for your pain medication?
- Feel high or get a buzz after using your pain medication?
- Take your pain medication because you are upset, to relieve of cope with problems other than pain?
- Go to multiple physicians or EDs seeking more of your pain medication?



Management of Risky or Harmful Prescription Opioid Use

## JAMA Health Forum.

April 21, 2022 \_\_\_\_

#### JAMA Forum The False Dichotomy of Pain and Opioid Use Disorder

Katie Fitzgerald Jones, MSN, CARN-AP; Diana J. Mason, PhD, RN

## Pain with net harm from opioid use:

- Clear cut OUD with concurrent pain
- Patients on prescription opioids with likely OUD, but patient doesn't accept/recognize
- Complex Prescription Opioid Dependence
- Patients getting pain relief, but at the expense of significant side effects or risk



Inadequate pain relief on opioids

#### **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. Koenig, PhD; Lilian Hoffecker, PhD, MLS; Hannah R. Dischinger, BS; Steven K. Dobscha, MD; and Erin E. Krebs, MD, MPH

# Function, sleep, anxiety, pain, and quality of life often improve with dose reduction





June 13, 2022

#### Original Investigation | Pharmacy and Clinical Pharmacology Long-term Risk of Overdose or Mental Health Crisis After Opioid Dose Tapering

Joshua J. Fenton, MD, MPH; Elizabeth Magnan, MD, PhD; Irakis Erik Tseregounis, PhD; Guibo Xing, PhD; Alicia L. Agnoli, MD, MPH, MHS; Daniel J. Tancredi, PhD

**CONCLUSIONS AND RELEVANCE** These findings suggest that opioid tapering was associated with increased rates of overdose, withdrawal, and mental health crisis extending up to 2 years after taper initiation.



#### Original Investigation | Public Health

Association of Opioid Dose Reduction With Opioid Overdose and Opioid Use Disorder Among Patients Receiving High-Dose, Long-term Opioid Therapy in North Carolina

Bethany L. DiPrete, PhD, MSGH; Shabbar I. Ranapurwala, PhD, MPH; Courtney N. Maierhofer, MPH; Naoko Fulcher, MS; Paul R. Chelminski, MD, MPH; Christopher L. Ringwalt, DrPH; Timothy J. Ives, PharmD, MPH; Nabarun Dasgupta, PhD, MPH; Vivian F. Go, PhD; Brian W. Pence, PhD



### Talking Points From the 2022 VA Guideline

"Evidence shows that the best treatments for chronic pain are options such as behavioral interventions, rehabilitation therapies, and non-opioid medications."

"Science has demonstrated that long-term opioid use can lead to multiple problems including loss of pain-relieving effects, increased pain, unintentional death, OUD, and problems with sleep, mood, hormonal dysfunction, and immune dysfunction. I am concerned about your health and safety."

"While opioids were prescribed to you, we now understand in general that the risks outweigh the benefits when opioids are used long-term. Let's work on reducing your dosage of opioids and discuss other treatment options."



Further guidance for clinicians: Managing Difficult Conversations About Opioids (air.org)

HHS Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-Term Opioid Analgesics

9/19



			ġ.			<u>.</u>	
Collaborate with patient, get buy in	Reassure	Optimize treatment of pain and behavioral health issues	Get support of your team	Go slowly	Consider comfort meds	Warn that pain may worsen before improving	Warn that tolerance is lost rapidly → increased risk o OD
SDM, MI Offer choices, control	Control pain, don't let them feel abandoned	Healthy lifestyle, sleep, social connections	Frequent check-ins	10% per month Pause but don't go backward	Clonidine, tizanidine	Validate that this is hard	Prescribe or provide Narcan



#### **Annals of Internal Medicine**

**IDEAS AND OPINIONS** 

## Rethinking Opioid Dose Tapering, Prescription Opioid Dependence, and Indications for Buprenorphine

Roger Chou, MD; Jane Ballantyne, MD; and Anna Lembke, MD

Figure. Clinical pathway for consideration of tapering in patients using opioids for >90 d.



Published Online 8/27/19

# **Buprenorphine is an Analgesic**

#### Buprenorphine for Chronic Pain Management





Figure 1. The history of buprenorphine. Buprenorphine was originally developed as an analgesic and was subsequently used for OUD before novel delivery systems allowed for approval in chronic pain management [8,9,12,13]. FDA=Food and Drug Administration; OUD=opioid use disorder.



## Buprenorphine Acts Mostly in Lower CNS/Spinal Cord





## **Buprenorphine Works on Four Receptors**



- Reduced immunosuppression and impact on the HPA axis
- Reduction in suicidal thoughts, anxiety, and depression
- · Limited dysphoria



## **Buprenorphine: KEY characteristics**





#### **High Affinity**

**Partial Agonist** 



Volpe, *Regul Toxicol Pharmacol* 2011 SAMHSA, *TIP* 63, 2020 #ASAMAnnual2022



## **Transitioning to Buprenorphine**

1 mg bup ~20-30 MME

If <100-160 MME - consider Belbuca

If poor po (by mouth) and <80/day - consider Butrans

If on >100-160 MME or money issues - consider sl (sublingual) buprenorphine

- For \$, <100-160- hold opioid >8 hours and start 1-2 mg BID (for 60-120 MME)
- If>100-160MME- microinduction/overlapping low dose initiation (1/4 film=.5mg BID...)

If OUD - use buprenorphine/naloxone





### Dartmouth Knowledge Map

Management of Chronic Pain in Primary Care With a Focus on Risky or Harmful Prescription Opioid Use Clinician Guide

#### **Contact for Clinical Content** Charles Brackett, MD, MPH Email: knowledge.map@hitchcock.org

#### **D-H Review and Adoption Committee:**

Kathleen Broglio, DNP- Palliative Care Seddon Savage, MD- Pain and Addiction Musa Aner, MD- Pain Management **Release Date: April 2023** 

Hyunouk Hong, MD, MPH- GIM, Manchester Minda Gowarty, MD- GIM, Lebanon James Stahl, MD- GIM, Lebanon

#### Clinician Resources

#### Chronic Pain smartset in eDH

#### Pain- Non-pharmacologic/self-management approaches

- Oregon Health Authority : OPMC Pain Education Course : Oregon Pain Management Commission : State of Oregon 1.5 hour course
- Curable Health app for patients-sign up as a clinician, and give free 6 week trials to your ٠ patients; once signed up, this page has patient resources: https://www.curablehealth.com/connect
- ASAM free CME course: ASAM eLearning: The ASAM Pain & Addiction Essentials Online -Module 5: Treatment - Nonpharmacological Approaches

#### **Opioids and Pain**

- Primary Care Grand Rounds 4/20/23 https://dh.cloud-cme.com/ ٠
- Medicine Grand Rounds 7/8/22- Treatment of Complex Chronic Pain: Are Opioids Helping or Hurting? (CME available)
- Medicine Grand Rounds 11/13/20- Opioids and Pain Management: Preventing Harm and ٠ Maximizing Benefit (CME available through 11/13/23)
- ASAM eLearning: Pain Management and Opioids: Balancing Risks and Benefits 2023 (free CME)
- Boston University's free curriculum on Safer/Competent Opioid Prescribing: https://www.scopeofpain.org/
- Distinguishing Between Opioid Misuse and Opioid Use Disorder (air.org)
- Managing Difficult Conversations About Opioids (air.org)





- Non-pharmacologic approaches and non-opioid medications are first line for chronic pain
- Opioids have a limited role
  - Avoid in patients with nociplastic pain
  - Opioids can have negative effects on emotion, motivation, and socialization with/without OUD
  - Consider buprenorphine instead of other opioids
  - If opioids are not providing clear net benefit, taper or transition to buprenorphine

