



Opioid Therapy for Chronic Pain



Erin E. Krebs, MD, MPH

February 6, 2015

Disclosure statement

- ▶ The members of the faculty and planning committee for this conference have indicated that they have no relevant financial relationships to disclose related to the content of the CME activity.
- ▶ **Speaker's disclosure**
 - ▶ I have research funding from VA, NIH, and FDA
 - ▶ Views expressed in this presentation are mine and do not reflect the position or policy of the VA or the US government



CME statement

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Objectives

- 1) Recognize potential benefits and harms of long-term opioid therapy for chronic pain.
- 2) Describe gaps in the evidence for long-term opioid treatment of common chronic pain conditions.
- 3) Identify risk factors for opioid-related harms



Focus of this talk

▶ Chronic pain

- ▶ Pain that persists and interferes with function
- ▶ Not associated with life-threatening/terminal illness
- ▶ Common conditions: chronic back pain & OA pain

▶ Opioids

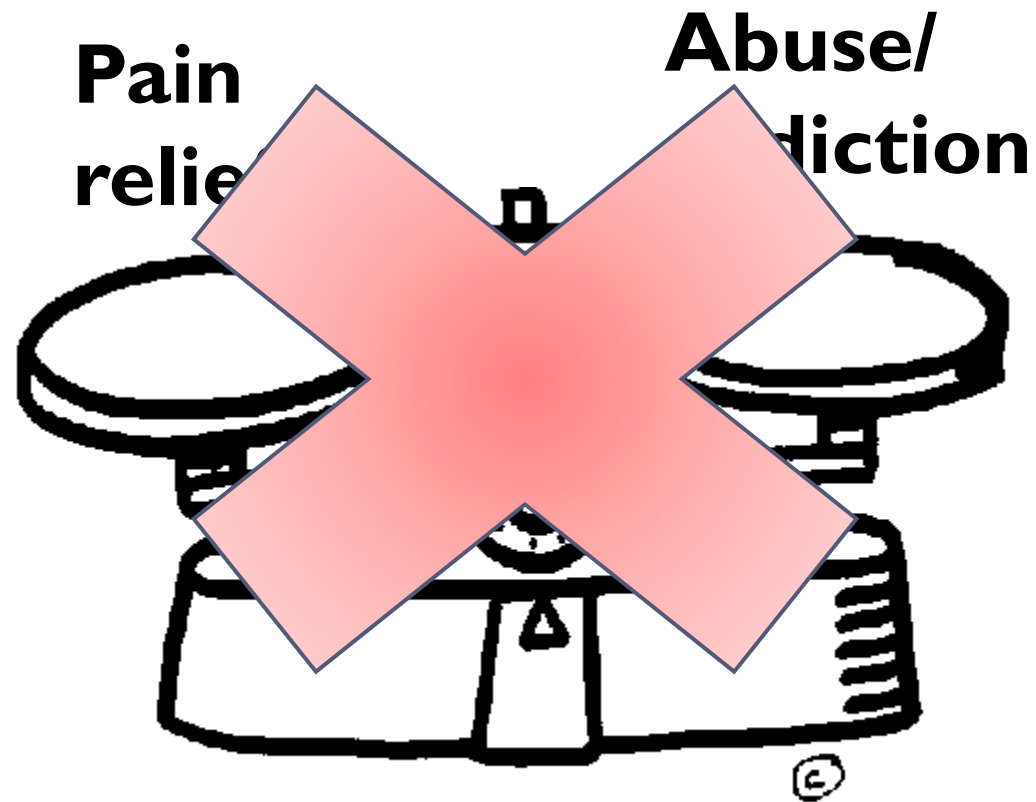
- ▶ Natural and synthetic relatives of morphine
- ▶ Tramadol is an atypical opioid

▶ Long-term

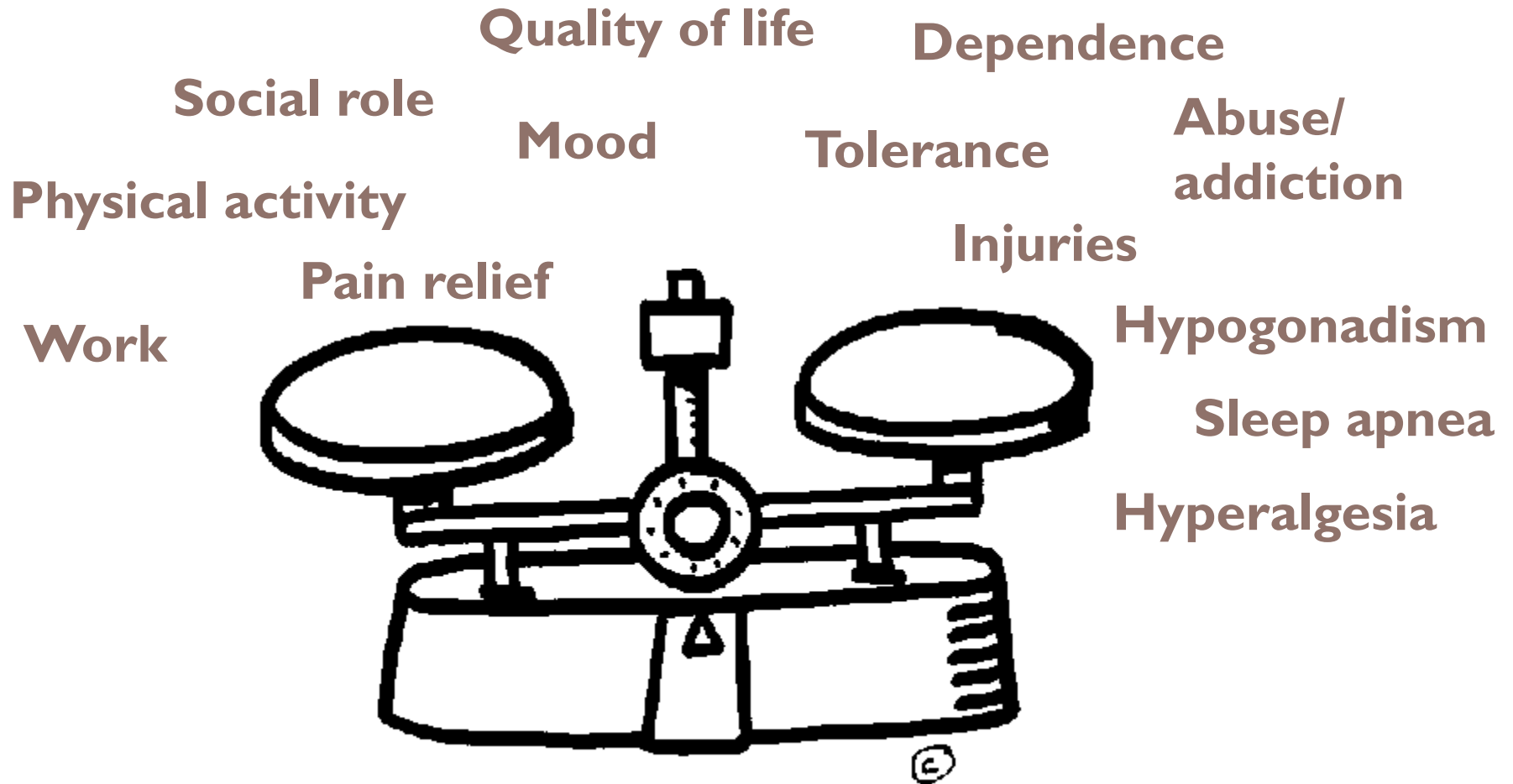
- ▶ Prescribed for pain that is not expected to resolve
- ▶ Duration = months → years → decades → lifetime?



Balancing benefits and harms



Balancing benefits and harms



True or false?

- ▶ Evidence from randomized controlled trials has demonstrated that opioids are...
 1. Better than placebo for chronic LBP and OA pain
 2. Better than acetaminophen for chronic LBP and OA pain
 3. Effective in providing relief from chronic pain for up to one year



Evidence for benefit

Trial evidence of short-term effects

Observational evidence of long-term effects

RCTs: Chronic low back pain

- ▶ **Cochrane review 2013**
 - ▶ RCTs \geq 4 weeks of opioid vs. placebo or active comparison
 - ▶ Excluded intravenous opioids/implantable pumps
- ▶ **Comparisons (n=15 trials)**
 - ▶ Strong opioids vs. placebo (n=7): morphine, oxycodone, hydromorphone, oxymorphone, tapentadol
 - ▶ Tramadol vs. placebo (n=5)
 - ▶ Misc: buprenorphine vs. placebo, tramadol vs. celecoxib, opioid vs. antidepressant
- ▶ **All short term (4-15 weeks)**
- ▶ **Dropout rates $>25\%$ in all studies (30-70% in most)**

RCTs: Chronic low back pain

▶ Results

- ▶ Strong opioids better than placebo for pain and function (moderate quality)
- ▶ Tramadol better than placebo for pain (low quality) and function (moderate quality)
- ▶ Evidence very low quality for other comparisons

▶ Conclusion:

- ▶ Opioids & tramadol are better than placebo in short-term
- ▶ No evidence that opioids are better than non-opioids
- ▶ No evidence that opioids are effective in long-term



RCTs: Osteoarthritis pain

- ▶ **Opioids vs. placebo (n=10), duration 3-90 days**
 - ▶ Fentanyl, morphine, codeine (3), oxycodone (4), oxymorphone (tramadol excluded)
- ▶ **Results**
 - ▶ Opioids improved pain score 0.9 points more than placebo (i.e., 15% difference)
 - ▶ No effect of opioid strength or daily dose
- ▶ **Conclusion**
 - ▶ Opioids are better than placebo in short-term
 - ▶ No evidence that opioids are better than non-opioids or effective in long-term

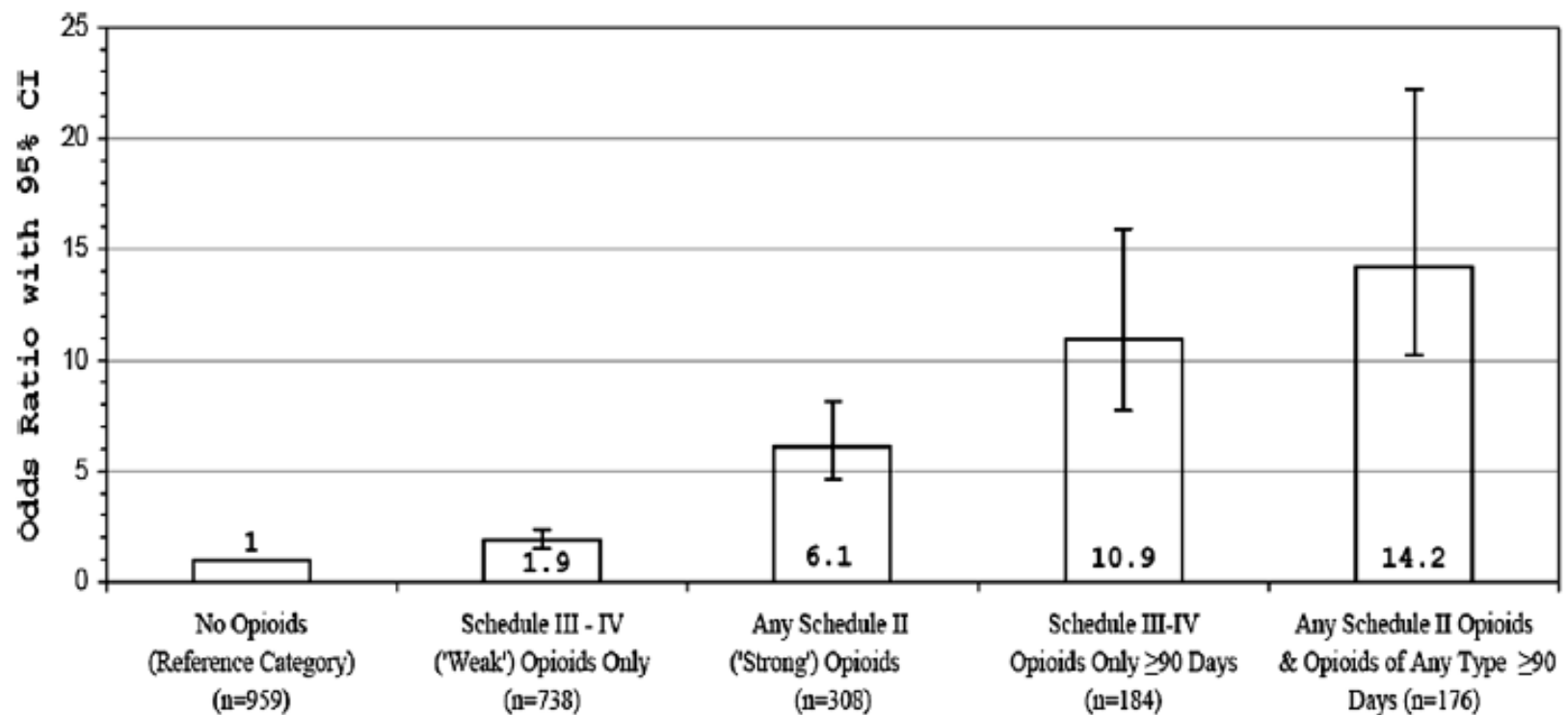
Observational evidence: quality of life

- ▶ Among patients with chronic pain...
 - ▶ Those on opioids have lower quality of life and worse function at follow-up compared with those on no opioids
- ▶ Among patients on opioids...
 - ▶ Those on moderate to high doses have worse quality of life and function compared to those on low doses

▶ Erickson, Pain 2006; Dillie J Am Board Fam Med 2008; Sjogren, Clin J Pain 2010;
Ashworth, Pain 2013

Observational evidence: disability

- ▶ Cohort of Utah workers with LBP
- ▶ Stronger opioids associated with worse outcomes



Summary of benefits data

▶ Trials

- ▶ Limited by highly selected participants, loss to follow-up
- ▶ Show opioids are better than placebo in short term
- ▶ Insufficient evidence for...
 - ▶ Opioid efficacy beyond 1-3 months
 - ▶ Opioids compared with other analgesics
 - ▶ “Strong” opioids compared with “weak” opioids
 - ▶ Long-acting opioids compared with short-acting opioids

▶ Observational studies

- ▶ Limited by selection bias, confounding
- ▶ Consistently show worse outcomes with greater opioid use



True or false?

- ▶ Evidence from randomized controlled trials has demonstrated that opioids are...
 1. Better than placebo for chronic LBP and OA pain
TRUE (in short term)
 2. Better than acetaminophen for chronic LBP and OA pain
FALSE (no studies)
 3. Effective in providing relief from chronic pain for up to one year
FALSE (no studies)
-





Evidence for harms

True or false?

1. In patients receiving long-term opioid therapy, overdose risk increases with prescribed dose
2. Screening for & treating sleep apnea before starting long-term opioids reduces respiratory adverse events
3. Hyperalgesia often develops within one month of starting opioid therapy



Categories of harms

- ▶ **Harms to patients receiving opioid therapy**
 - ▶ Overdose & addiction
 - ▶ Medical adverse effects
 - ▶ Physiologic adverse effects
- ▶ **Collateral/public health harms**
 - ▶ Diversion
 - ▶ Accidental overdose



Opioid overdose in the population

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

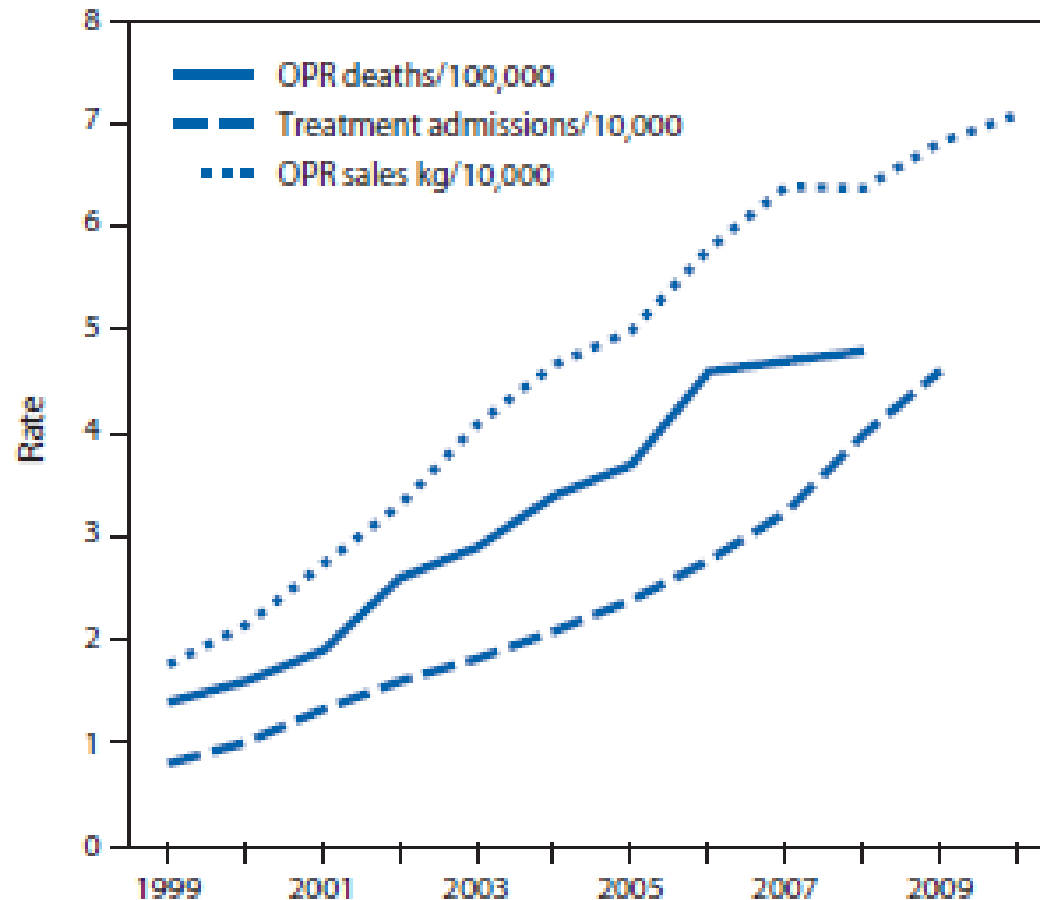


Figure from CDC, MMWR 2011;60:1487–92

Opioid overdose in patients

- ▶ Two large retrospective cohort studies

	VA patients (fatal overdose)	HMO patients (any overdose)
Dose (mg/day)	Hazard ratio (95% CI)	
<20	1.0	1.0
20-49	1.9 (1.3, 2.7)	1.4 (0.6, 3.6)
50-99	4.6 (3.2, 6.7)	3.7 (1.5, 9.5)
≥ 100	7.2 (4.9, 10.7)	8.9 (4.0, 19.7)

Opioid overdose in patients

▶ One large case-control study

	Ontario patients (opioid-related deaths)
Dose (mg/day)	Adjusted OR (95% CI)
<20	1.0
20-49	1.3 (0.9, 1.8)
50-99	1.9 (1.3, 2.9)
100-199	2.0 (1.3, 3.2)
≥200	2.9 (1.8, 4.6)

Addiction in prescription opioid use

- ▶ **AAPM,APS,ASAM (2001):**Addiction is a chronic neurobiological disease characterized by...
 - ▶ Loss of control
 - ▶ Compulsive use
 - ▶ Continued use despite harm
 - ▶ Craving
- ▶ **DSM-V (2013):** Opioid use disorder
 - ▶ Replaced “abuse” and “dependence”
 - ▶ Removed tolerance and withdrawal as criteria when opioids are prescribed



Addiction in prescription opioid use

- ▶ **Systematic review (2012): 0-31%**
 - ▶ Included RCTs, retrospective EMR studies, case series
 - ▶ Included wide range of outcomes
 - ▶ Chart diagnoses (ICD-9)
 - ▶ “Opioid misuse” behaviors
 - ▶ DSM-IV criteria
- ▶ **Cross-sectional diagnostic interview studies**
 - ▶ Fleming et al (2007): 801 patients treated with daily opioids in primary care: 3%
 - ▶ Boscarino et al (2010): 705 patients who received 4+ opioid prescriptions from an integrated health system: 26%

Incident opioid addiction in patients

- ▶ One large cohort study of new opioid use disorder diagnosis in patients prescribed opioids

	Short-term (1-90 d)	Long-term (>90 d)
Dose (mg/day)	AOR (95% CI)	AOR (95% CI)
0	1.0	1.0
1-36	3.0 (2.3, 4.0)	14.9 (10.4, 21.5)
36-120	2.8 (2.1, 3.7)	28.7 (20.0, 41.1)
>120	3.1 (1.7, 5.8)	122.5 (72.8, 206.0)

*Unadjusted rate in highest risk group: 6.1% (NNH 16.7)

Risk factors for overdose and addiction

	Overdose	Opioid use disorder
Substance use disorder (past or current)	X	X
Depression, anxiety, other mental health	X	X
Smoking		X
High pain severity or impairment		X
Younger age		X
Family history of substance disorder		X
Opioid dose > 50 morphine-equiv mg/day	X	X
Concurrent sedative-hypnotic rx	X	X



“Adverse selection” for opioid therapy

- ▶ Highest risk patients most likely to receive opioids
 - ▶ Depression and anxiety disorders
 - ▶ Alcohol and drug use disorders
 - ▶ Smoking
 - ▶ Multiple co-existing pain conditions or sites
- ▶ Among patients using long-term opioids, highest risk patients receive highest risk regimens
 - ▶ Higher doses
 - ▶ Concurrent benzodiazepines

Medical harms of opioids

- ▶ Perception of medical safety
 - ▶ American Geriatrics Society guidelines, 2009
 - ▶ NSAIDs: “rarely, and with extreme caution, in highly selected individuals”
 - ▶ Opioids: “all patients with moderate to severe pain, pain-related functional impairment, or diminished quality of life due to pain”
- ▶ Minimal data compared with other drugs
 - ▶ Estimated person-years observed in RCTs (M. von Korff)
 - ▶ NSAIDs: ~117,000
 - ▶ Opioids: ~1500

Opioids and sleep disordered breathing

- ▶ Endogenous opioid receptors involved in control of sleep and respiration
- ▶ Review of 18 human studies 1966-2005
 - ▶ 78% included ≤ 10 patients; total n=192
 - ▶ Central sleep apnea, periodic breathing, and ataxic breathing reported in patients on long-term opioids

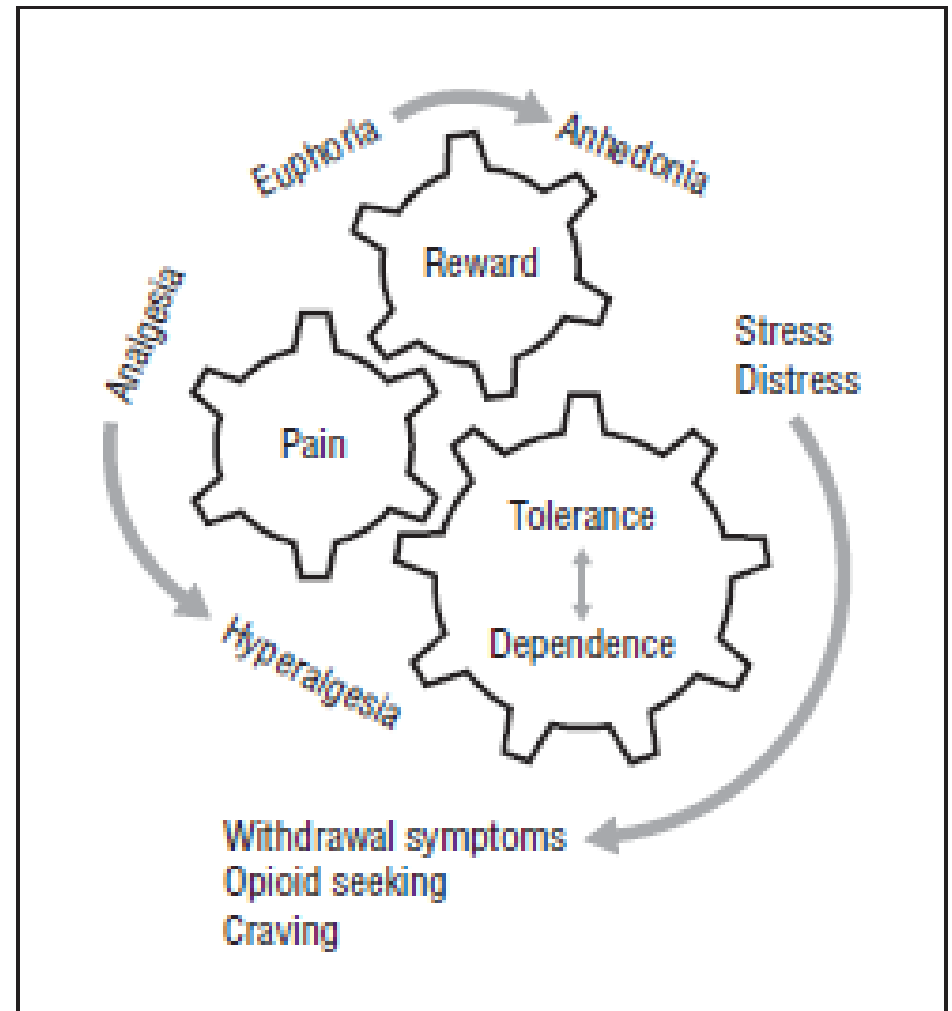


Opioids and sleep disordered breathing

- ▶ Case series of patients referred to sleep center for suspected sleep apnea (n=120)
 - ▶ Opioid use associated with...
 - ▶ More central apnea (13 vs. 2/hr)
 - ▶ More ataxic breathing (70% vs. 5%)
 - ▶ Lower SpO₂ during wakefulness and NREM
- ▶ Consecutive patients on stable round-the-clock opioids from one pain clinic (n=392)
 - ▶ 24% met criteria for central sleep apnea
 - ▶ Apnea rate associated with higher opioid dose and concurrent benzodiazepine use

Physiological adverse effects

- ▶ “Positive” unintended effects
- ▶ Physical dependence, tolerance, withdrawal
 - ▶ Increase with higher doses & longer duration
- ▶ Opioid-induced behavior



Tolerance and hyperalgesia

- ▶ Tolerance = desensitized *anti*-nociceptive pathways
- ▶ Opioid-induced hyperalgesia (OIH) = sensitized *pro*-nociceptive pathways
 - ▶ Potential manifestations:
 - ▶ Pain more severe than pre-opioid baseline
 - ▶ Pain increasingly diffuse and non-specific
 - ▶ Excessive, difficult to control post-operative or acute pain
- ▶ OIH observed in heroin addiction; data in chronic pain limited
- ▶ Mechanisms not fully established
- ▶ Relevance in practice is controversial

Tolerance and hyperalgesia

- ▶ **One RCT testing tolerance & hyperalgesia**
 - ▶ Morphine SR vs. placebo in LBP (n=139)
 - ▶ Morphine dose: mean 78.3 ± 37.5 mg /d
- ▶ **Experimental pain protocol at baseline and 1 month**
- ▶ **Measures**
 - ▶ Tolerance: increase in opioid infusion dose required for pain relief response
 - ▶ Hyperalgesia: reduction of pain threshold and pain tolerance (without opioid infusion)
- ▶ **Results: Significant tolerance, no hyperalgesia in morphine group compared with placebo**

Summary of harms data

- ▶ Prescribed opioids cause overdose deaths in patients
 - ▶ Risk increases with dose and sedative co-prescribing
- ▶ Addiction is common among patients with pain
 - ▶ Risk of iatrogenic addiction may increase with dose/duration
- ▶ Medical adverse effects are insufficiently understood
- ▶ Physiologic adverse effects are clinically relevant
 - ▶ Tolerance and physical dependence are expected
 - ▶ Role of hyperalgesia is unclear
- ▶ Risk for many harms is dose-related (unlike benefits)



True or false?

1. In patients receiving long-term opioid therapy, overdose risk increases with prescribed dose

TRUE

2. Screening for & treating sleep apnea before starting long-term opioids reduces respiratory adverse events

FALSE (no studies)

2. Hyperalgesia often develops within one month of starting opioid therapy

FALSE



National Institutes of Health Pathways to Prevention Workshop: The Role of Opioids in the Treatment of Chronic Pain

David B. Reuben, MD; Anika A.H. Alvanzo, MD, MS; Takamaru Ashikaga, PhD; G. Anne Bogat, PhD; Christopher M. Callahan, MD; Victoria Ruffing, RN, CCRC; and David C. Steffens, MD, MHS

- ▶ “...evidence is insufficient for every clinical decision that a provider needs to make about the use of opioids for chronic pain, leaving the provider to rely on his or her own clinical experience.”

Role of opioids in chronic pain*

- ▶ Opioids should be considered only when potential benefits are likely to outweigh potential harms
 - ▶ Opioids should not be a default when other treatments fail
 - ▶ All factors contributing to pain-related distress should be addressed first
- ▶ Opioids should be prescribed at the lowest effective dose for the shortest possible duration
 - ▶ Dose seems to drive risk for major harms
 - ▶ Initial benefit may be lost due to tolerance
- ▶ Opioids should be discontinued when benefits are not evident or potential harms outweigh benefits



*my opinion



Practicing with insufficient evidence

Structured therapeutic trials

Shared decision-making

Case

- ▶ 45 year old woman with chronic low back pain, obesity, diabetes, depression, and tobacco dependence
 - ▶ Current meds: morphine SR 30 TID, hydrocodone/APAP PRN (6 tablets/day), zolpidem 10 QHS



Therapeutic trials

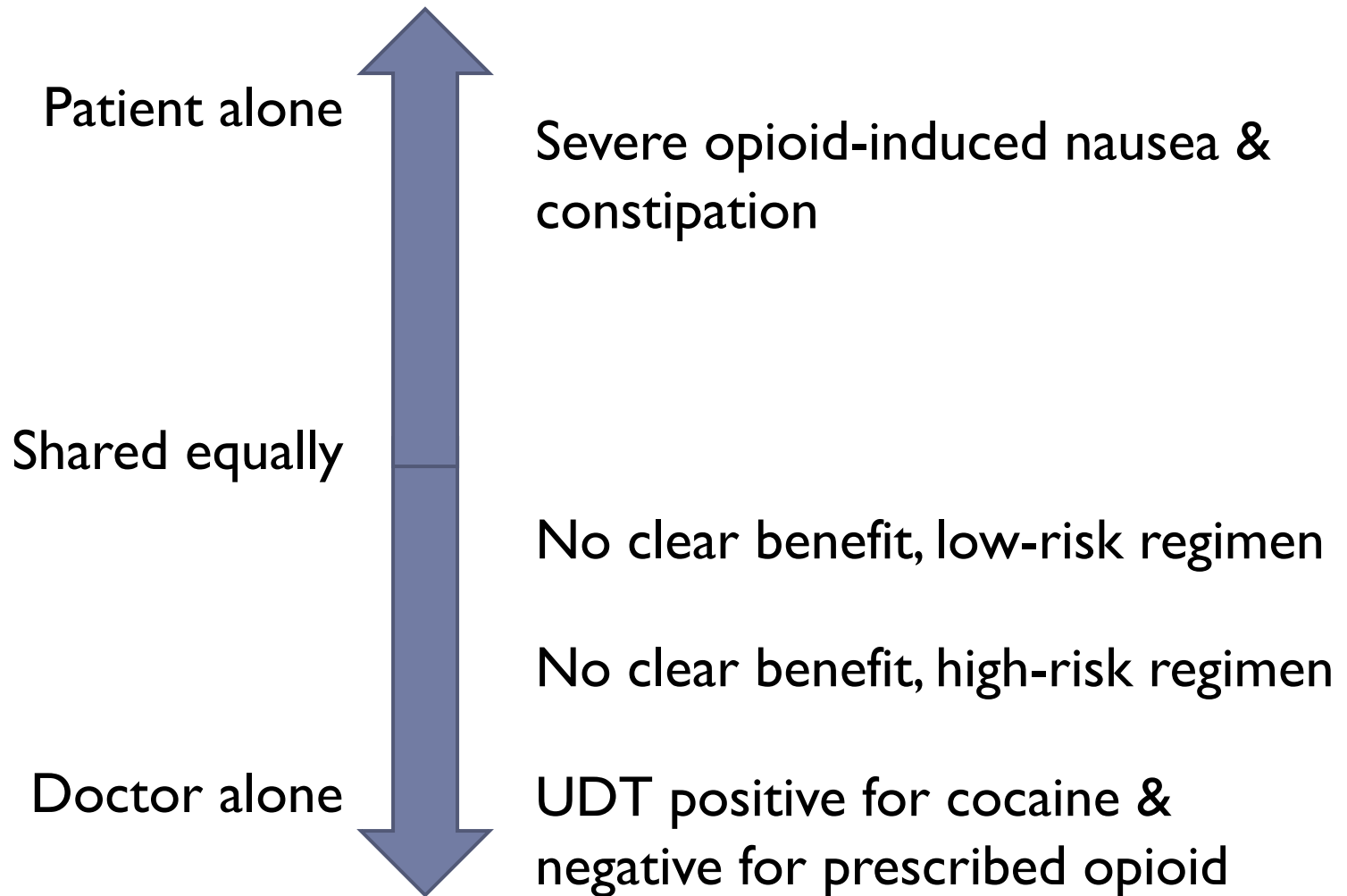
- ▶ Structured approach to evaluating changes in therapy
- ▶ Establishes expectation that therapy will be reconsidered if goals are not met
- ▶ Key steps
 1. Establish goals—how will we know if trial is successful?
 - ▶ Initiation: allow to walk for 20 minutes/day and attend weight loss meetings without feeling sedated
 - ▶ Taper: maintain current activities without withdrawal symptoms or long-term increase in pain
 2. Determine schedule of changes and timing of re-evaluation
 3. Develop contingency plans



Shared decision-making

- ▶ Patient-centered approach to managing clinical uncertainty
- ▶ Involves both patient and physician sharing information and expressing preferences
- ▶ Does not require physician to give up prescribing decision authority
 - ▶ Decisions that can/should be shared
 - ▶ Definition of treatment success
 - ▶ Rate of opioid taper/titration
 - ▶ Timing of follow-up (within reasonable range)
 - ▶ Degree of sharing depends on urgency of safety issues

Degree of decision sharing in opioid d/c



▶ Figure adapted from Makoul and Clayman. *Patient Educ Couns.* 2006;60(3):301-12.

Case

- ▶ 45 year old woman with chronic low back pain, obesity, diabetes, depression, and tobacco dependence
 - ▶ Current meds: morphine SR 30 TID, hydrocodone/APAP PRN (6 tablets/day), zolpidem 10 QHS
- ▶ **History**
 - ▶ Unemployed, on disability
 - ▶ Single parent, can't attend kids' soccer games
 - ▶ No good friends, no hobbies other than watching TV
 - ▶ Opioids “take the edge off” pain
 - ▶ Reports no alcohol or drug use
 - ▶ Regular UDT & PDMP checks appropriate, refills on time



45 year old woman with chronic LBP

- ▶ **Assessment: Chronic LBP with severe pain and functional limitations**
 - ▶ Benefit of opioids: unclear
 - ▶ Poor occupational, social, physical function
 - ▶ Ineffective pain self-management
 - ▶ Risk factors for harms: high opioid dose, concurrent sedative, depression, smoking



45 year old woman with chronic LBP

- ▶ **Plan: Discuss assessment and taper trial [doctor-led decision with patient input]**
 - ▶ *Your risk is higher than average because...*
 - ▶ *I want to start making some changes to improve the safety of your medications*
 - ▶ **Decisions to negotiate with patient**
 - ▶ **First step: reduce morphine, hydrocodone, or zolpidem?**
 - Start with morphine SR
 - ▶ **Rate of taper: weekly or monthly dose decrease?**
 - Decrease by 15 mg per month
 - ▶ **Follow up timing?**



45 year old woman with chronic LBP

- ▶ One year later...
 - ▶ Medication regimen
 - ▶ Morphine SR discontinued (from 30 mg tid)
 - ▶ Hydrocodone 4 tablets/day (from 6/day)
 - ▶ Zolpidem 5 mg QHS (from 10 mg)
 - ▶ Pain and function not substantially changed
 - ▶ Focusing visits on self-management goals
 - ▶ Walk around apartment complex 5 days/week
 - ▶ Attend all kids' games





Thank you!