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

- This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint providership of the Minnesota Medical Association and the University of Minnesota. The Minnesota Medical Association (MMA) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

- The Minnesota Medical Association designates this live activity for a maximum of 1 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.
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

Pain relief

Abuse/addiction
Balancing benefits and harms

- Quality of life
- Dependence
- Abuse/addiction
- Injuries
- Hypogonadism
- Sleep apnea
- Hyperalgesia

- Social role
- Physical activity
- Work
- Mood
- Tolerance
- Pain relief
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 ≥ 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)

Chaparro LE et al. Cochrane 2013
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

Chaparro LE et al. Cochrane 2013
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

Nuesch E et al. Cochrane 2009; Cepeda MS et al. Cochrane 2009
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

Volinn et al, Pain 2009
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* 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

<table>
<thead>
<tr>
<th>Dose (mg/day)</th>
<th>VA patients (fatal overdose)</th>
<th>HMO patients (any overdose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>20-49</td>
<td>1.9 (1.3, 2.7)</td>
<td>1.4 (0.6, 3.6)</td>
</tr>
<tr>
<td>50-99</td>
<td>4.6 (3.2, 6.7)</td>
<td>3.7 (1.5, 9.5)</td>
</tr>
<tr>
<td>≥100</td>
<td>7.2 (4.9, 10.7)</td>
<td>8.9 (4.0, 19.7)</td>
</tr>
</tbody>
</table>

Opioid overdose in patients

- One large case-control study

<table>
<thead>
<tr>
<th>Dose (mg/day)</th>
<th>Ontario patients (opioid-related deaths)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>1.0</td>
</tr>
<tr>
<td>20-49</td>
<td>1.3 (0.9, 1.8)</td>
</tr>
<tr>
<td>50-99</td>
<td>1.9 (1.3, 2.9)</td>
</tr>
<tr>
<td>100-199</td>
<td>2.0 (1.3, 3.2)</td>
</tr>
<tr>
<td>≥200</td>
<td>2.9 (1.8, 4.6)</td>
</tr>
</tbody>
</table>

Gomes T et al. Arch Intern Med 2011
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

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

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

## Risk factors for overdose and addiction

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Overdose</th>
<th>Opioid use disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substance use disorder (past or current)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Depression, anxiety, other mental health</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>High pain severity or impairment</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Younger age</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Family history of substance disorder</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Opioid dose &gt; 50 morphine-equiv mg/day</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Concurrent sedative-hypnotic rx</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
“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
“…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

- Patient alone
  - Severe opioid-induced nausea & constipation

- Shared equally
  - No clear benefit, low-risk regimen
  - No clear benefit, high-risk regimen

- Doctor alone
  - UDT positive for cocaine & negative for prescribed opioid

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!