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Opioid Therapy For Pain: *An Evidence Review*

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Educational Objectives

At the conclusion of this activity participants should be able to:

- Review evidence on use of opioid therapy for chronic pain
- Assess risks and benefits of long-term opioid therapy for chronic pain and factors associated with prescription opioid overdose and misuse

Note: Best practices to reduce risks related to prescription opioids are discussed in a different lecture

Case

- 53-year old female transferring care because her PCP is leaving practice
  - Shoulder and hip pain secondary to avascular necrosis, s/p shoulder replacements, hip decompression, hip replacement
  - Fibromyalgia, non-radicular low back pain, chronic headache
  - Depression, fatigue
  - Gastroparesis, irritable bowel syndrome
  - Morphine IR 30 mg 5 tabs (150 mg) every 8 hrs + oxycodone 5 mg 8 tabs (40 mg) every 6 hrs
    - Morphine equivalent dose/day: 690 mg
  - Modafinil 20 mg po daily
  - Pain 6/10 on average, with day to day fluctuation
  - Can carry out activities of daily living with pain, limited exercise, no aberrant behaviors

Background

- Chronic non-cancer pain highly prevalent, with substantial burdens
  - Estimates vary, up to 1/3 of adults report some CNCP
- Opioids are increasingly prescribed for chronic non-cancer pain
  - About 5% of U.S. adults report use of long-term opioid therapy (LOT)[a]
  - The U.S. is ~5% of the world's population, but accounts for 80% of the world's supply of opioids (99% of hydrocodone)
- Opioids are associated with potential harms, both to patients and to society
- Large practice variations in use of LOT

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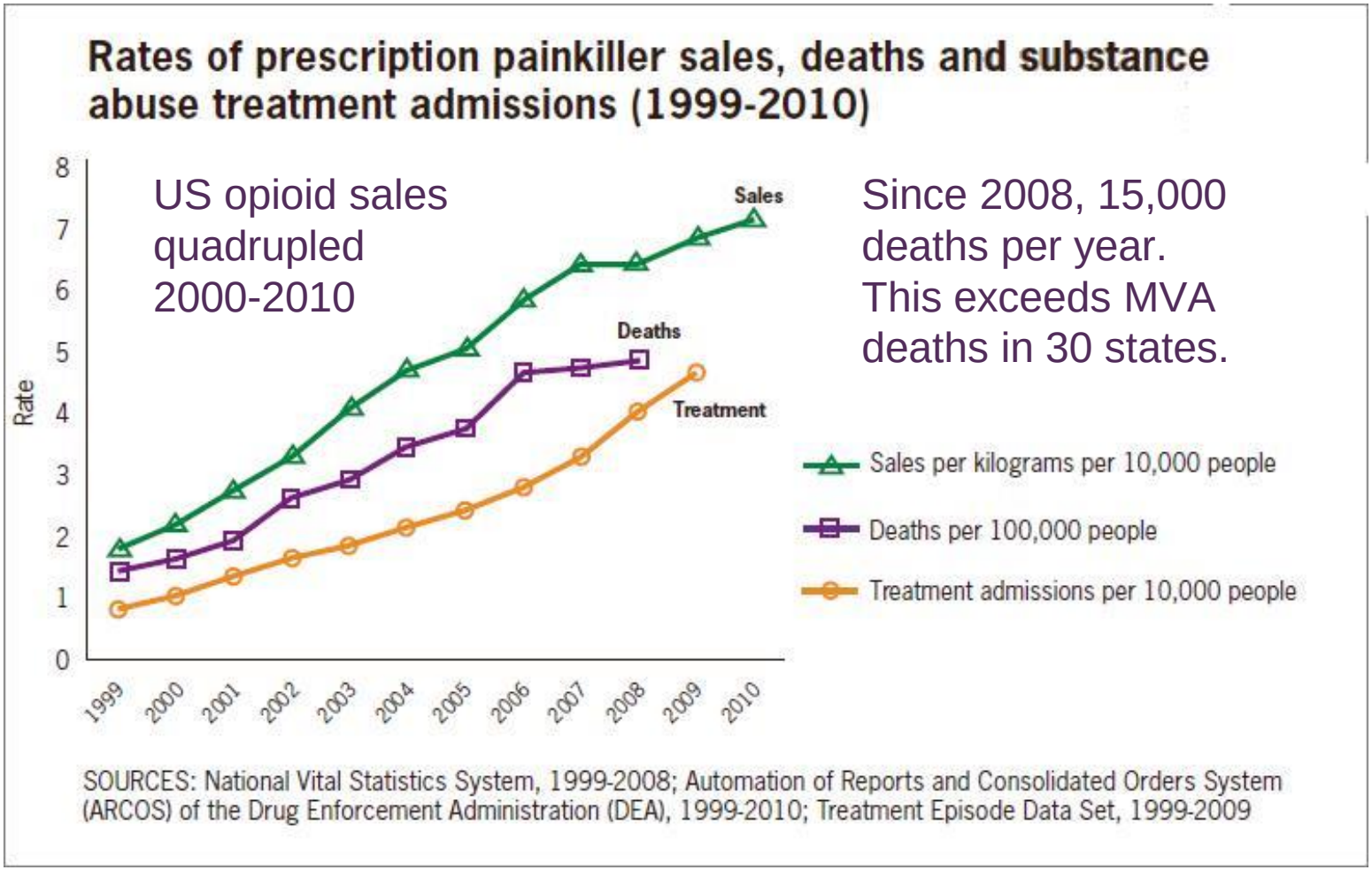
[a]Boudreau et al Pharmacoepidemiol Drug Saf 2009

CDC: Parallel increases in opioid sales, deaths and substance abuse



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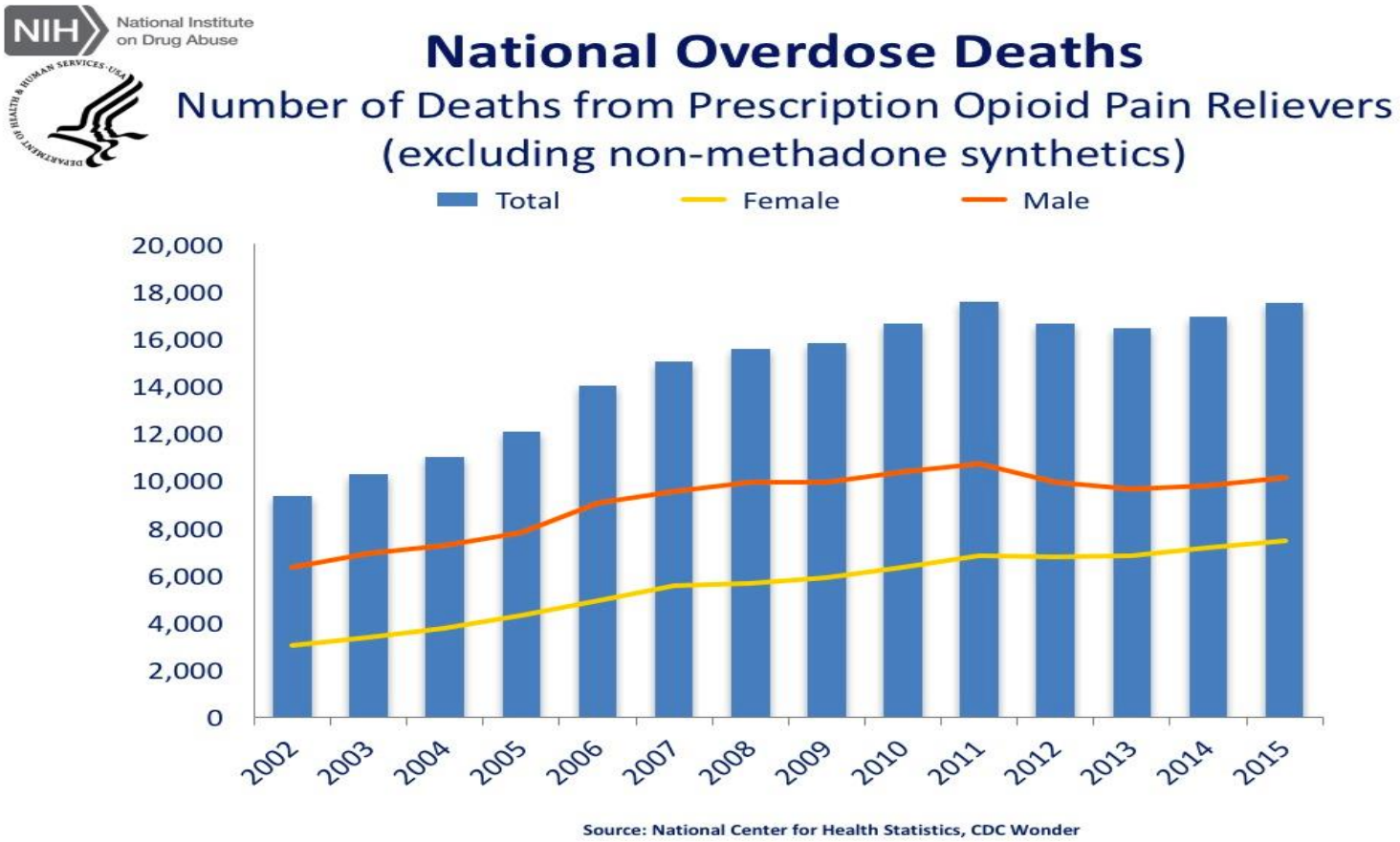
Slide courtesy Mark Sullivan

Prescription Opioid Overdose



Rates are per 100,000 population age-adjusted to 2008 U.S. standard population
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm

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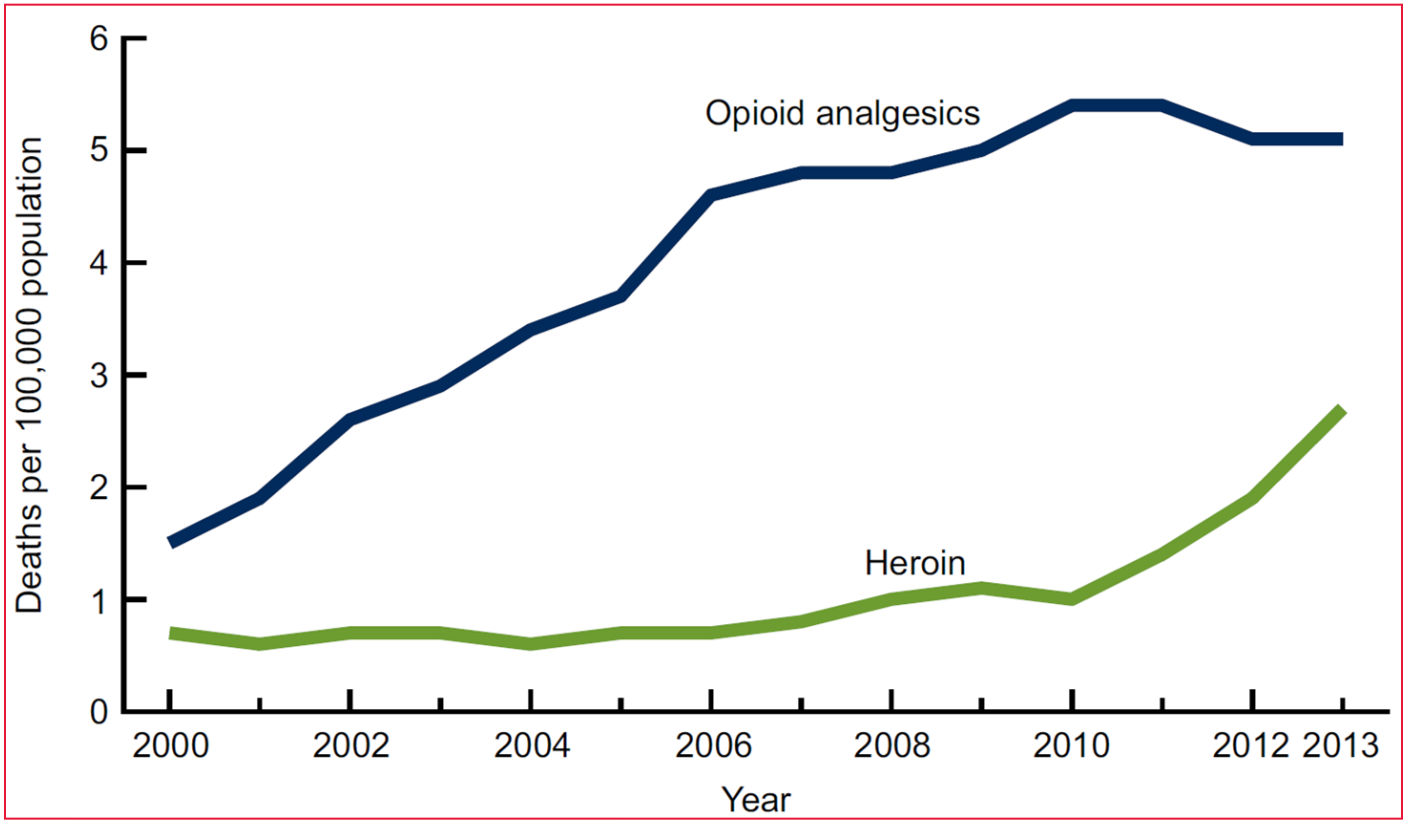
Opioid Overdose Trends, 2000-2013



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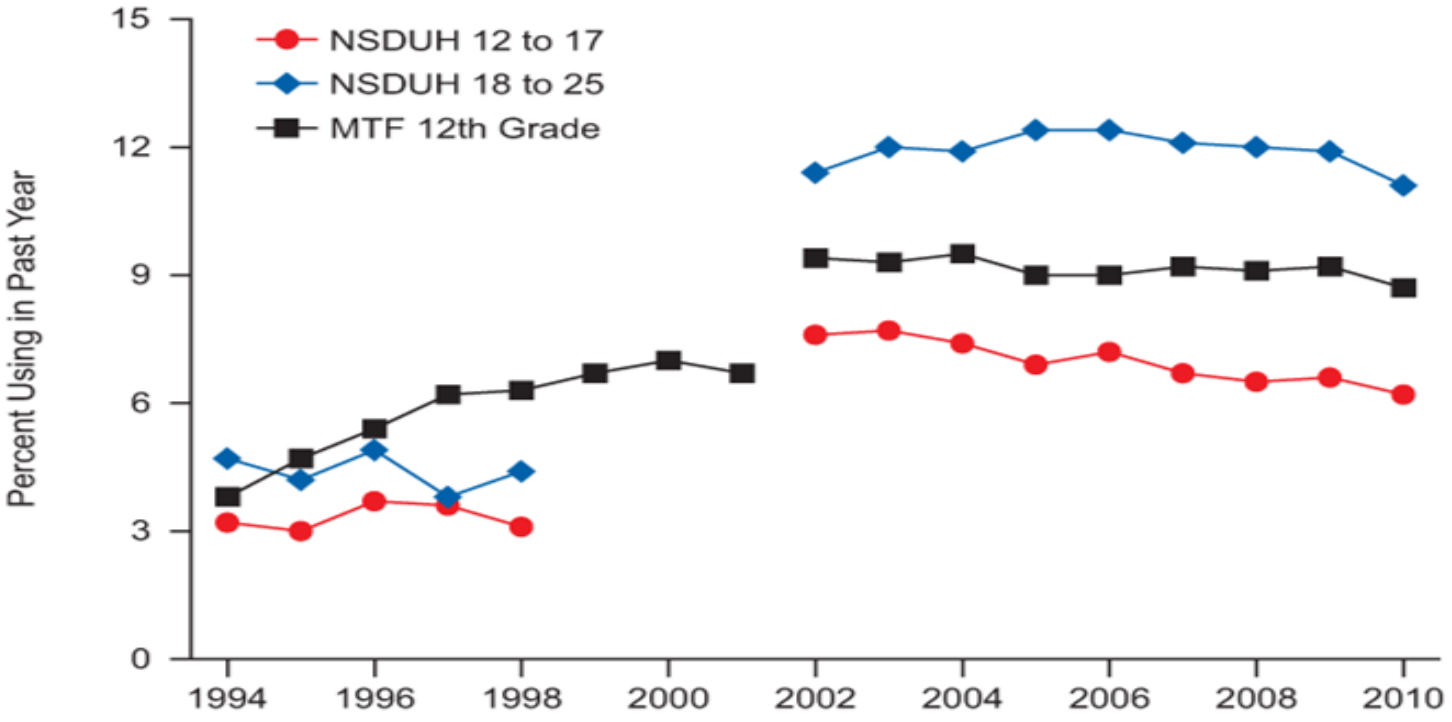
Source: CDC/NCHS National Vital Statistics System NCHS Data Brief, No. 190, March 2015

Nonmedical pain medication use among adolescents and young adults



SAMSHA 2010 National Survey on Drug Use and Health

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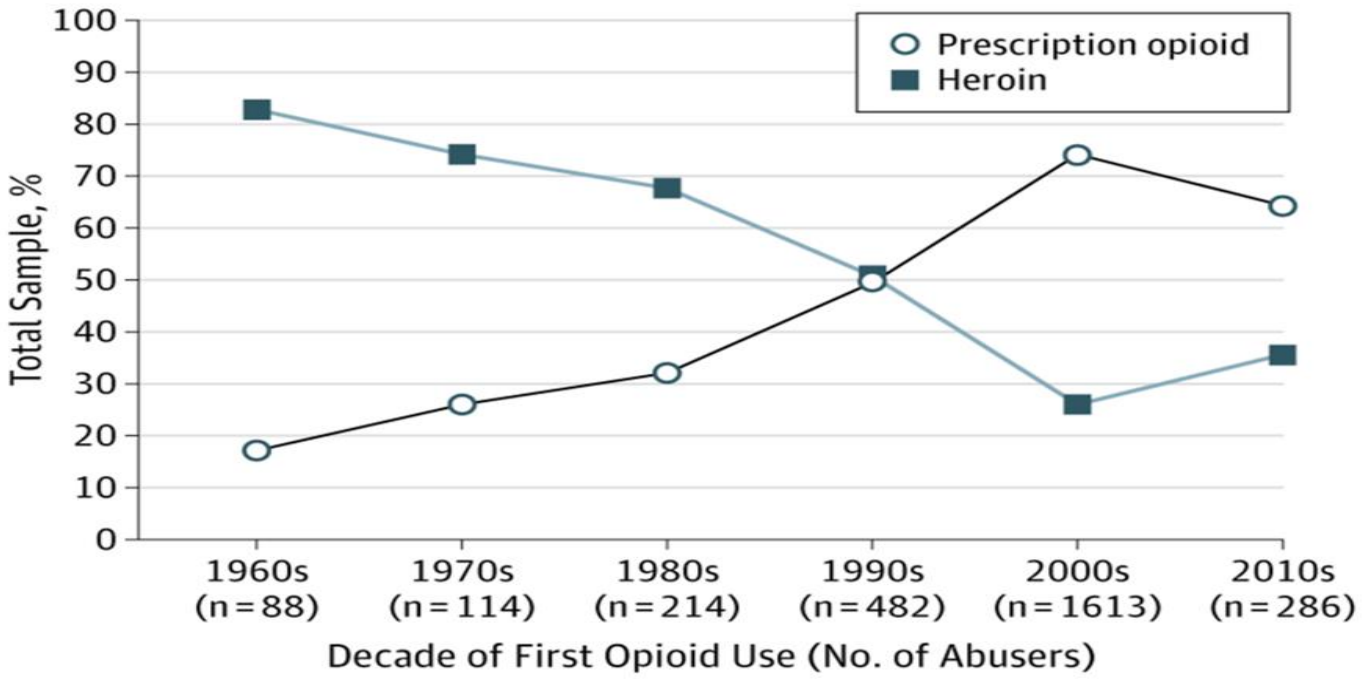
First Opioid of Abuse in Those Using Heroin



Cicero TJ et al. JAMA Psychiatry 2014

Prescribing Trends

- Since ~2010, opioid use for chronic pain increased from 8% to 16%
  - Use of more potent opioids increased from 2 to 9%
  - Increases observed across age groups and in men and women
  - Increased use of schedule II opioids; greatest increase in daily doses occurred in prescriptions of schedule II opioids

Caudill-Slosberg MA. Pain 2004;109:514; Boudreau D. Pharmacoepidemiol Drug Safety 2009;18:1166; Sulivan MD 2008;138:440; Campbell CI Am J Pub Health 2010;100:2541

How did we get here?

- Perceived undertreatment of chronic pain
  - Laws or regulations passed in >20 states to allow use of opioids for chronic pain
- Low risk of abuse observed with use of opioids in palliative care settings
  - "…patients rarely demonstrate euphoric responses to opioid drugs, and neither analgesic tolerance nor physical dependence is a significant clinical problem."

    Portenoy RK. J Law Medicine Ethics 1996;24:296
- Case series describing benefits of long-term opioid therapy for chronic pain, with low rates of abuse, addiction, or other serious AE's
  - *Porter J, NEJM 1980; 302(2): 123.*
  - Most prescribed low doses (<20 mg MED/day)
- No ceiling dose used in palliative care settings
  - "Escalation of the opioid dose until either adequate analgesia occurs or intolerable and unmanageable side effects supervene is standard practice in cancer pain management."— *Portenoy RK. J Pain Symptom Management 1996;11:203*
- Emphasis on round-the-clock dosing using sustained-release formulations

  Portenoy RK 1986;25:171; Haythornthwaite JA 1998;15:185

Evidence on Effectiveness of Opioid Therapy for Chronic Non-cancer Pain

- Short-term follow-up:
  - Versus placebo
    - Pain intensity (71 trials): Mean difference -0.79 point (95% CI -0.93 to -0.67) on a 0 to 10 point pain scale
    - Pain response (44 trials): RR 1.35 (95% CI 1.24 to 1.48)
    - Function (44 trials): Standardized mean difference -0.22, (95% CI -0.28 to -0.16)
    - Little incremental benefit with increased doses
  - Versus nonopioids
    - No difference in pain intensity (14 trials), likelihood of pain response (12 trials), or function (11 trials)
- Intermediate and long-term follow-up:
  - No placebo-controlled trials
  - Versus non-opioids
    - One trial (SPACE) found no difference between stepped therapy with opioids vs. non-opioids in function, opioid therapy associated with higher (worse) pain intensity (4.0 vs. 3.5 on 0 to 10 scale)

Chou et al. Opioid Treatments for Chronic Pain Comparative Effectiveness Review AHRQ 2020

Limitations of Evidence on Effectiveness of LOT

- High loss to follow-up
- Trials typically excluded patients at higher risk for addiction or overdose, psychological comorbidities, and serious medical comorbidities
- Limited evidence on commonly treated conditions
  - Fibromyalgia, headache, others
- No trial compared LOT vs. cognitive behavioral-based exercise therapy or interdisciplinary rehabilitation

Opioids vs. Non-opioid Pharmacological Therapy

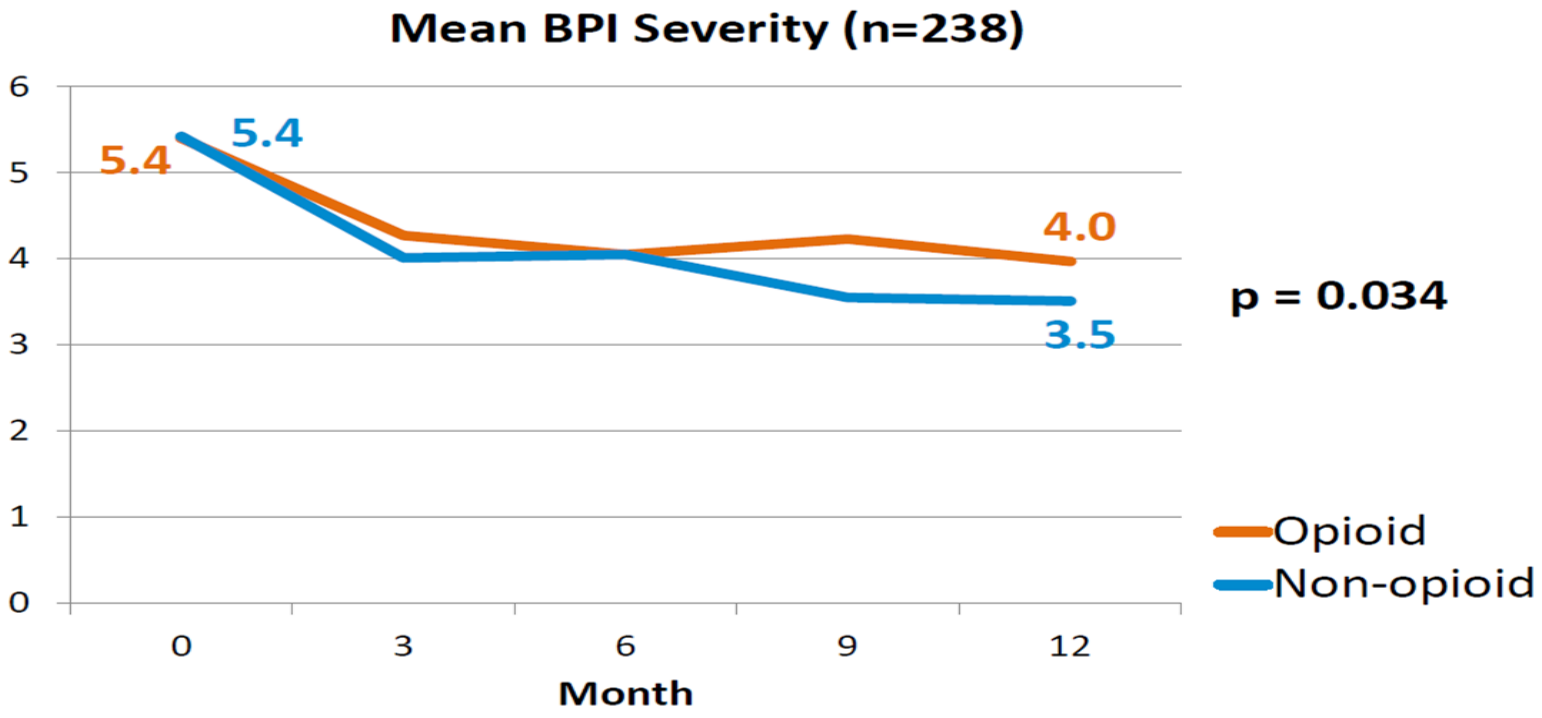
SPACE RCT of stepped therapy starting with opioid therapy vs. initial non-opioid therapy for chronic LBP and OA pain

- One year VA trial in primary care, n=240
- Open-label for patients and clinicians, assessment masked
- All patients received individualized medication management using collaborative telecare pain management model
- Average opioid dose 26 vs. 1 mg MED/day
- At 12 mos, no difference in function, pain slightly worse in opioid group
- Opioids associated with more adverse symptoms; no deaths or OUD

Krebs E. JAMA 2018;319:872-82

SPACE Trial

Pain intensity



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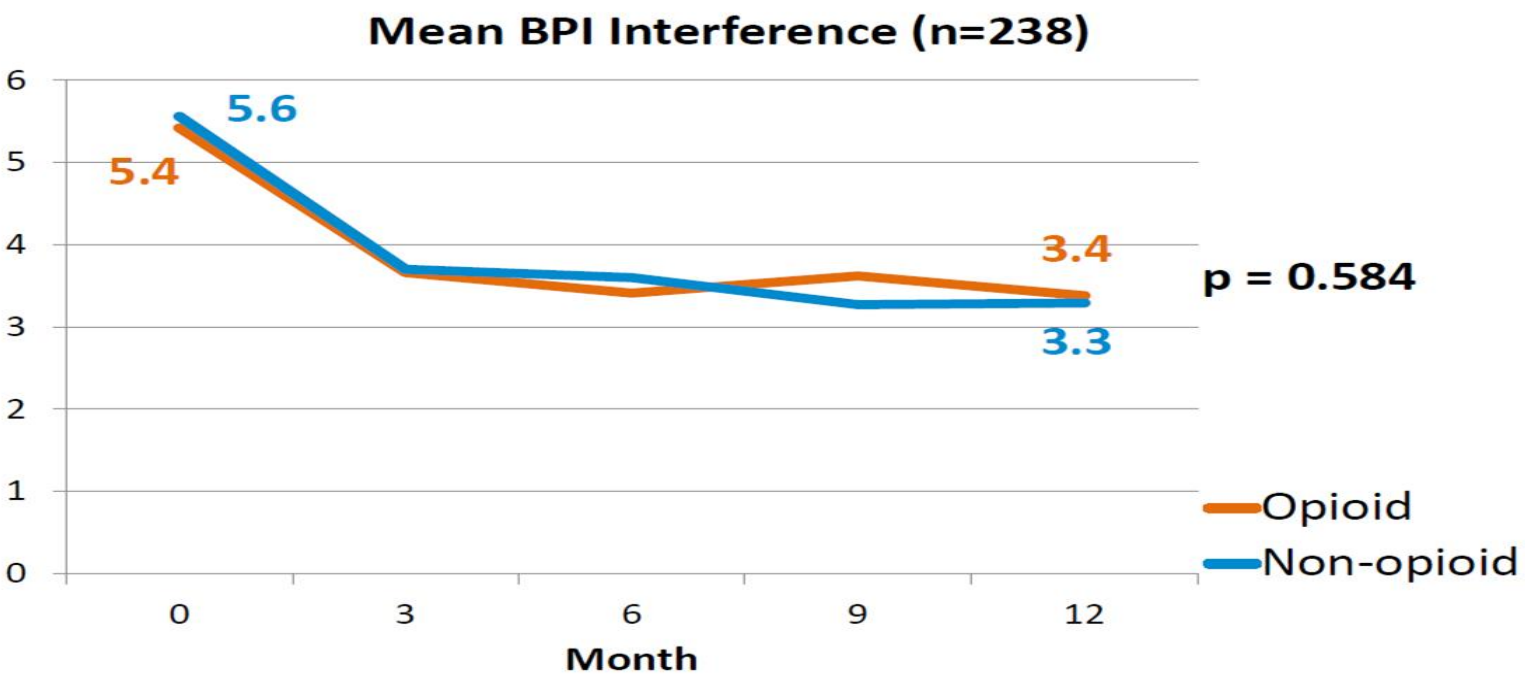
Krebs E. JAMA 2018;319:872-82

SPACE Trial

Pain interference with function



Krebs E. JAMA 2018;319:872-82

Evidence on Short-term Harms of Opioid Therapy vs. Placebo for Chronic Non-cancer Pain

Outcome	Number of trials	RR (95% CI)	Absolute risk difference
Discontinuation due to adverse events	61	2.25 (1.86 to 2.73)	10%
Nausea	60	2.46 (2.17 to 2.80)	17%
Vomiting	49	3.57 (2.98 to 4.34)	7%
Constipation	58	3.38 (2.96 to 3.92)	14%
Somnolence	52	2.97 (2.44 to 3.66)	9%
Dizziness	53	2.66 (2.37 to 2.99)	8%
Pruritus	30	3.51 (2.47 to 5.16)	7%

Chou et al. Opioid Treatments for Chronic Pain Comparative Effectiveness Review AHRQ 2020

Addiction and Misuse

Trials not designed to assess risk of addiction and misuse

- In observational studies:
  - Rates of misuse averaged between 21% to 29%
  - Rates of addiction averaged between 8% to 12%
  - Definitions inconsistent across studies and behaviors vary in seriousness
  - Poorly standardized methods to detect these outcomes
- One study (n=801) based on detailed, standardized interviews[a]
  - 26% purposeful oversedation
  - 39% increased dose without prescription
  - 8% obtained extra opioids from other doctors
  - 18% used for purposes other than pain
  - 12% hoarded pain medications

[a]Fleming et al. J Pain 2007
Vowles et al. Pain 2015

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Factors associated with increased risk of overdose, or observed in high proportions of overdoses

- Misuse behaviors
  - Obtaining opioid prescriptions from multiple providers
  - Running out early, losing prescriptions
  - Unauthorized dose escalations
- Recent initiation of opioids
- Methadone
- Concomitant use of benzodiazepines
- Substance use
- Psychological comorbidities
- Higher doses of opioids

Overdose: Dose-response Relationship

- Observational studies consistently show an association between opioid dose and risk of overdose or death in patients with chronic pain
- Risk starts to increase at relatively low doses and continues to increase
- Studies matched or adjusted for potential confounders available in administrative databases
  - Potential for residual confounding by indication
- Difficult to determine whether patients had chronic pain and duration of therapy

Association Between Opioid Dose and Overdose Risk

- **Cohort study (n=9940, 51 opioid overdoses, 6 fatal)**
  - Risk of opioid overdose (vs. 1 to <20 mg/day)
    - ≥100 mg/d: HR 8.9 (4.0-20)
    - 50 -<100 mg/d: HR 3.7 (1.5-9.5)
    - 20-<50 mg/d: HR 1.4 (0.57-3.6)
- **Case-control study (VA, 750 cases)**
  - Risk of opioid overdose-related death (vs. 1 to <20 mg/day)
    - >=100 mg/d: HR 7.2 (4.8-11)
    - 50-<100 mg/d: HR 4.6 (3.2-6.7)
    - 20-<50 mg/d: HR 1.9 (1.3-2.7)
- **Nested case-control study (Ontario, 498 cases)**
  - Risk of opioid-related mortality (vs. 1 to <20 mg/day)
    - ≥200 mg/d: OR 2.9 (1.8-4.6)
    - 100-199 mg/d: OR 2.0 (1.3-3.2)
    - 50-99 mg/d: OR 1.9 (1.3-2.8)
    - 20-49 mg/d: OR 1.3 (0.94-1.8)

Ref: Dunn et al. Ann Intern Med 2010;152:85-92; Bohnert et al. JAMA 2011;305:1315-21; Gomes et al. Arch Intern Med 2011;171:686-91

Other Harms of Opioids

- Hyperalgesia
  - Paradoxical increased sensitivity to pain
  - Prevalence, risk factors and clinical significance not well understood
- Hypogonadism
  - Primarily based on cross-sectional studies
  - One study showing association with increased use of testosterone and ED meds
- Falls/fracture risk
- Myocardial infarction
- Poorer functional outcomes

Chou et al. Opioid Treatments for Chronic Pain Comparative Effectiveness Review AHRQ 2020
Deyo 2013; Franklin et al. Spine 2008

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Initiation and Titration of Opioids

- Opioids are not first-line therapy for chronic pain
- In appropriately selected patients who do not respond to non-opioid therapy, view an initial course of opioids as a short-term, therapeutic trial
  - Do not continue long-term opioid therapy in patients who are not benefitting
  - Re-assess within 1-4 weeks
- Start at low doses and titrate cautiously
- Insufficient evidence to recommend short- vs. long-acting opioids, round-the-clock versus PRN
  - Potential benefits of long-acting, round-the-clock dosing unproven
  - Potential harms of long-acting, round-the-clock dosing include increased risk of hyperalgesia, tolerance, endocrinologic adverse effects
  - Initiation with long-acting opioids associated with increased risk of overdose
  - Methadone and fentanyl not recommended as first line options due to less predictable/more complicated dosing/pharmacokinetics
  - Buprenorphine for chronic pain in higher risk patients; evidence lacking to show improved safety but theoretically lower respiratory risk
    - Higher dose buprenorphine formulations approved for treatment of opioid use disorder (off-label for pain)

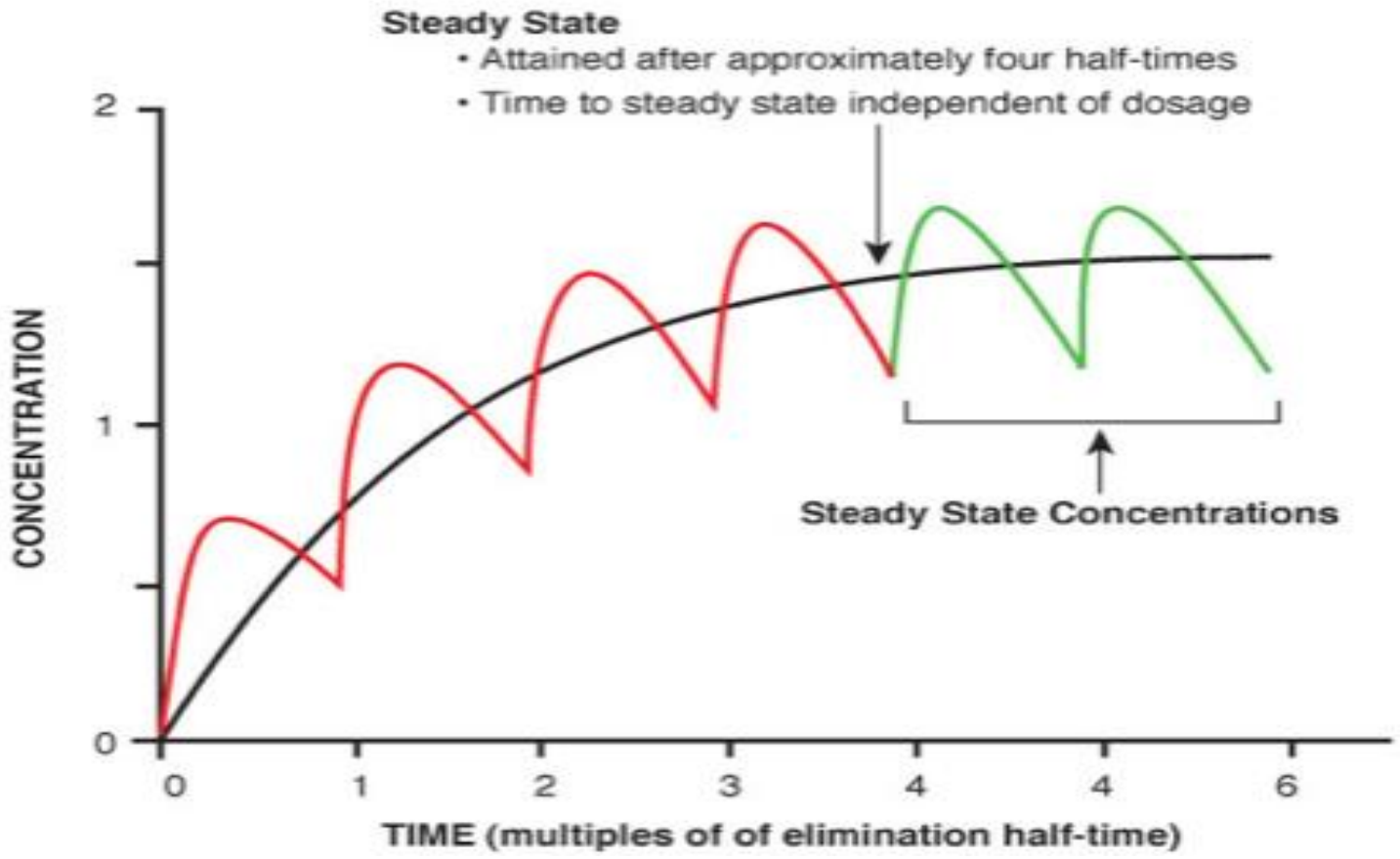
Dowell D et al. JAMA 2016 315(15):1624–1645

Methadone

- Synthetic opioid used for treatment of addiction and pain
- Increased methadone deaths nationwide
  - 1999: 800 deaths; 2008: 4900 deaths
  - Methadone accounted for 1.7% of opioid rx's in 2009 and 9.0% of morphine equivalents in 2010[a]
  - Involved in 31% of opioid-related deaths, and 40% of single-drug deaths[a]
- Half-life 15 to 60 hours, up to 120 hours
  - 60 hour half-life=12 days to steady-state
  - Start at 2.5 mg q8 hrs, increase slowly
- Higher doses of methadone associated with greater QTc interval prolongation
  - High proportion of reported cases of torsades de pointes occurred in patients prescribed >200 mg/day
  - ECG monitoring at baseline and at higher doses[b]
- Morphine to methadone conversion ratio increases at higher doses
  - Incomplete cross-tolerance

[a]MMWR 2012;61:493-7
[b]Chou R J Pain 2014;15:321-37

Time to Reach Steady State



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http://www.rxkinetics.com/pktutorial/1_6.html

Prolonged QTc and Torsades de Pointes

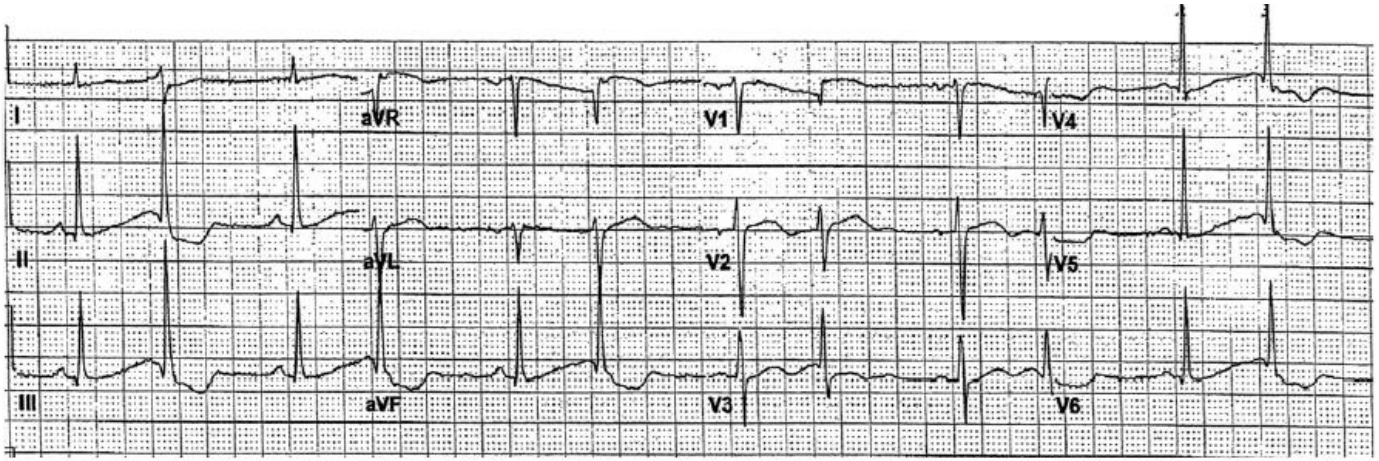

Figure 1 – Admitting ECG shows normal sinus rhythm with atrial bigeminy, nonspecific T-wave abnormality, and QTc prolongation (626 msec).

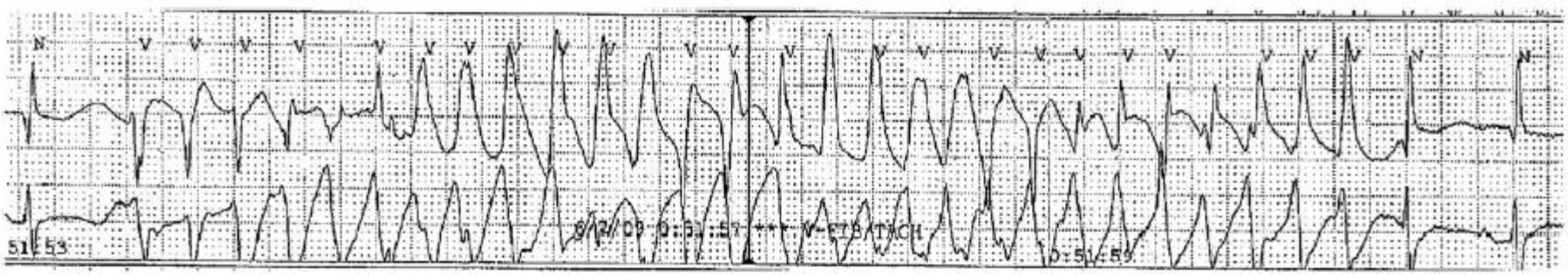

Figure 2 – Rhythm strip shows TdP.

Thanavaro, K, et al, (2011), Heart and Lung.

Morphine to Methadone Conversion

24 hour total oral morphine	Oral morphine to methadone conversion ratio
<30 mg	2:1
31-99 mg	4:1
100-299 mg	8:1
300-499 mg	12:1
500-999 mg	15:1
>1000 mg	20:1

Note: Proposed morphine to methadone conversion ratios vary

Managing Cancer Pain in Skeel ed. Handbook of Cancer Chemotherapy. 6th ed., Phil, Lippincott, 2003, p 663

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Fentanyl

- Absorption and pharmacodynamics of transdermal fentanyl are complex
- Gradually increasing serum concentration during the first part of the 72-hour dosing interval
- Variable absorption based on factors such as external heat
- Dosing in mcg/hr instead of mg
- Should be prescribed with clinicians familiar with its use and complexities

Dosing

- **No theoretical ceiling with opioids**
  - But, little evidence to guide prescribing at higher doses
  - Additional risks (hyperalgesia, endocrine), unclear benefit, and can be a marker for abuse, addiction, or diversion
  - Higher doses associated with increased risk of overdose
  - Unclear if persons who don't respond at relatively low doses will respond at higher doses (may be opioid non-responders)

- **Definitions of "higher dose" have varied and continue to evolve; trend towards lower dose thresholds based on new evidence on dose-dependent overdose risks**
  - 2009 APS/AAPM guideline defined >200 MME/day of as "higher dose"
  - 2016 CDC guideline recommends caution at 50-90 MME/day and to avoid doses >90 MME/day

- **Mitigating risks of higher doses**
  - Counsel patients on risks and provide opportunity to taper
  - More frequent or intense monitoring
  - Consider tapering off medication if not achieving therapeutic goals
  - Provide naloxone in conjunction with overdose education
  - Avoid co-prescribing of benzodiazepines and other medications (e.g., other sedatives, gabapentinoids) that may increase risk

High-dose Opioid Therapy Prescribing Patterns

- Small proportion of patients account for the majority of opioids prescribed
  - In one study, 5% of opioid users accounted for 48% to 70% of total use
- Factors associated with high dose therapy include:
  - Presence of substance use disorders
  - Presence of mental health disorders
  - Use of sedative-hypnotics and multiple opioids
  - Higher health service utilization
  - Multiple pain problems and high levels of medical and psychiatric comorbidity
- **“Adverse selection”— persons at highest risk are more likely to receive high dose opioids**
  - Address psychosocial risk factors or high distress when possible, rather than increasing dose

Weisner CM. Pain 2009;145:287; Edlund MJ. J Pain Symptom Manage 2010;40:279; Morasco BJ 2010;151:625; Kobus AM. J Pain 2012;13:1131; Braden JB 2009;31:564

Mitigating Risks Associated with Opioids

- Avoid higher doses
- Monitoring, including urine drug testing
  - Reassess at least every 3 months, more frequently for higher-risk persons, after initiation and dose increases
- Review prescription drug monitoring data
- Avoid sedative-hypnotics (particularly benzodiazepines)
- More frequent follow-up
- Addiction, pain, or psychiatric consultation
- More frequent refills with smaller quantities
- Naloxone co-prescription
- Abuse-deterrent formulations

Urine Drug Tests

Recommended to help identify risky behaviors that would otherwise be undisclosed:

- Non-invasive, objective documentation of compliance with treatment plan, including use or absence of prescribed drugs, non-prescribed drugs, and illicit substances
- Longer window or detection compared to blood

When to perform urine drug testing:

- At baseline and periodically, interval may be guided in part by assessed risk
  - Test if suspected aberrant behaviors and after major changes in treatment
- Optimal frequency and usefulness of individualized or random vs. routine testing uncertain
  - 1-2 times/year may be appropriate for low-risk patients; 3-4 or more times per year for higher risk
  - Individualized or random testing may miss some abnormal tests, but higher yield and reduced costs
  - Patients may have more opportunity to tamper or alter behavior if testing expected

Cannabis Use and Opioids

- High prevalence of cannabis use in patients with chronic pain, with or without opioids
  - 6.2% to 39% (Reisfield et al. Pain Med 2009;10:1431; Nugent et al. Ann Intern Med 2017;167:319)
- Some evidence that states with medical cannabis laws experience slower rates of increase in opioid analgesic overdose death rates compared to states without such laws. (Bachhuber, 2014)
  - But, other evidence that states with medical cannabis laws experienced an opioid overdose death rate 22.7% higher than expected (Shover, 2019)
- Evidence limited, but cannabis may have analgesic effects, particularly for neuropathic pain
  - Effects of cannabis vary depending on THC vs. cannabidiol (CBD) content
    - THC associated with psychoactive/intoxicating effects
    - CBD associated with medicinal effects
- Little evidence on psychomotor and other effects in patients using cannabis and opioids. (Nugent, 2017).
- Association between cannabis use and opioid and other substance misuse uncertain
- Increased risk of MVA with cannabis use
- Caution in patients unable to decrease cannabis use
  - May indicate cannabis use disorder

Opioid-deterrent Formulations

- Opioid-deterrent formulations recently approved by FDA or undergoing FDA approval process
  - Designed to be tamper-resistant or co-formulated with medications that reverse opioid effects or produce noxious side effects when tampered with
  - Effectiveness for reducing misuse/substance abuse and improving clinical outcomes difficult to study
  - Likely to be primarily effective in patients who crush or inject opioids
  - Some patients switched to opioid-deterrent formulations may seek other prescription or illicit opioids[a]

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[a]Cicero et al. NEJM 2012

High-risk Patients

- High-risk patients are more vulnerable to opioid abuse, misuse, addiction
- Clinicians prescribing opioids in high-risk patients must be able to implement additional measures to manage these risks
  - More frequent monitoring
  - Limited prescription fills
  - Consultation with addiction specialists and mental health professionals
    - Medications for opioid use disorder (methadone, buprenorphine, or naltrexone in conjunction with psychological therapies) recommended for most patients with opioid use disorder
  - If opioids utilized for pain, opioid-deterrent formulations may be helpful
  - Provide naloxone

Evaluation of Aberrant Drug-related Behaviors

- Aberrant drug-related behaviors must be evaluated
  - Behaviors vary in seriousness
  - Need to judge seriousness, the cause or causes, likelihood of recurrence, and clinical context
    - Predictors of high likelihood of future aberrant behaviors include 3 or more episodes of aberrant behaviors and sense of “losing control”
    - Serious behaviors include diversion, injecting oral drugs
  - Responses range from patient education and enhanced monitoring to referral to addiction specialist and discontinuation of therapy

Discontinuation of Opioid Therapy

- Taper or wean patients off of long-term opioid therapy when they:
  - Engage in intractable aberrant drug-related behaviors or drug misuse/diversion
  - Experience no progress towards meeting therapeutic goals
  - Experience intolerable adverse effects
- Continue to manage pain using non-opioid therapies
- Have an exit strategy when initiating a trial of long-term opioid therapy
  - Indications for stopping opioid therapy
  - Plans for tapering or discontinuing
    - Slow tapers over months or years may be required
  - Provide psychosocial support
  - Know resources for managing addiction and mental health issues

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Dowell D, et al. JAMA 2019; 322(19):1855

Driving and Work Safety

- Opioids may cause somnolence, incoordination, clouded mentation, or slower reflexes
- Counsel patients not to drive or perform dangerous activities when impaired
  - Impairment more likely when starting therapy, when increasing doses, and when using other drugs with psychoactive effects
  - No evidence that patients on opioids should be restricted from driving in the absence of signs of impairment
  - State laws vary on reporting requirements

Use of Opioids for Acute Pain

- Opioids generally considered the most effective medication for acute pain
  - But, recent data indicates that opioids may be no more effective than an NSAID alone for some types of acute pain
    - In LBP adding oxycodone/acetaminophen to an NSAID did not improve pain or function at 1 week (Friedman BW. JAMA 2015;314:1572)
    - Opioids no more effective than NSAIDs for third molar extraction
- Use of opioids for “minor” pain associated with increased risk of long-term use
  - Versus no opioid use, opioid within 7 days of minor surgery associated with 44% increased risk of use at 1 year (Alam A. Arch Intern Med 2012;172:425)
- Prescribing excessive quantities of opioids for acute pain results in leftover opioids
  - Source of diversion and unprescribed use
- More judicious use of opioids for acute pain
  - If used, usually limit opioids to a 3-5 day supply for most acute pain
    (Chou et al. Treatments for Acute Pain, Comparative Effectiveness Review AHRQ 2020)

Conclusions: What is the evidence?

- Opioids associated with modest short-term benefits and increased risk of various opioid-related side effects
- Evidence on long-term benefits limited but indicates no clear benefit versus non-opioid therapy
- Accumulating evidence on serious harms of long-term opioid therapy (including overdose) that appear to be dose-dependent
- Altogether, evidence suggests at best a close balance of benefits to harm
- For chronic pain, reserve opioids for appropriately selected patients with persistent pain despite non-opioid therapies
- If long-term opioid therapy prescribed, monitor patients and utilize risk mitigation strategies
- Patients on high doses warrant re-evaluation, additional monitoring, and follow-up
- Decrease dose or discontinue opioids in patients who are not improving or in whom benefits do not outweigh harms
- Judicious, time-limited use of opioids for acute pain with re-evaluation for persistent pain

Case

- Unclear if benefitting from very high doses of long-term opioid therapy, ?worsening of GI symptoms
- No signs of aberrant behaviors
- Slow taper initiated, over ~2 years
  - Morphine 450 mg/day reduced to 120 mg/day
  - Oxycodone 160 mg/day reduced to 5 mg bid prn
    - 690 mg/MED/day reduced to 135 mg/day
- Added non-opioid medications
  - Duloxetine 30 mg qD
  - Buspirone 30 mg bid
- Pain and function no worse than when on high doses, no serious withdrawal
  - Some periods of acute pain with temporary increases in opioids
  - Goal is to get down to <100 to 120 mg MED/day

Evidence-informed Approach to Appropriate Use of Opioids

- Preference for non-opioid therapies
  - Opioids alone do not address the psychosocial contributors to chronic pain
- Not all patients are appropriate for opioid therapy
- Use risk assessment to inform decisions
- Initiate at low doses and titrate slowly
- View initial treatment as a therapeutic trial
- Routine monitoring and risk mitigation
- Titration should be based on responsiveness of patients to initial, low doses
  - Patients who do not respond to low doses probably will not respond to higher doses—"opioid non-responders"
  - Taper in patients not responding or experiencing adverse effects
- Caution when reaching threshold doses
  - Little incremental benefit with dose escalation but increased harms
  - Much easier to titrate up doses than to titrate down

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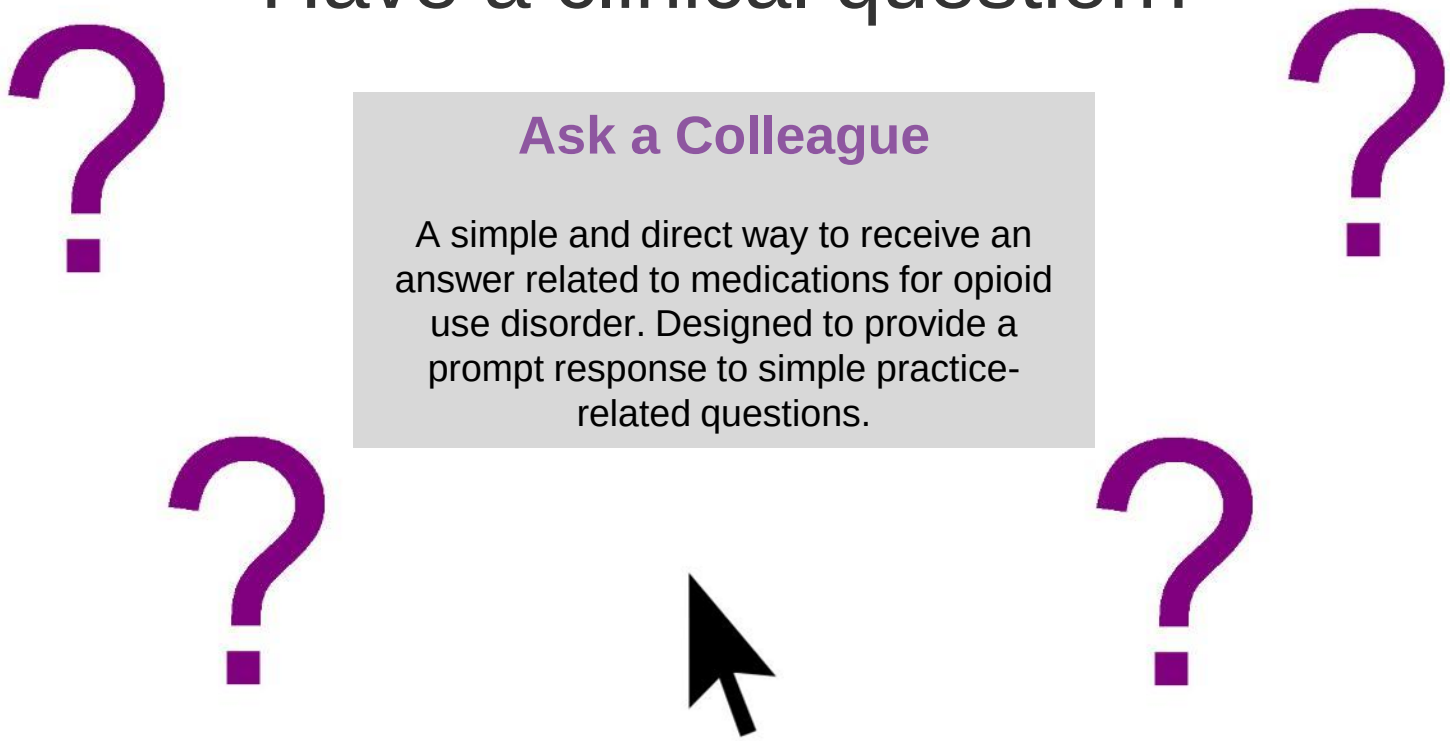

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