The Nature of Chronic Pain and the Role of Opioids in Pain Management
The Problem of Pain

- Pain costs the U.S. economy an estimated $560 billion a year
  - Health care costs
  - Welfare and disability payments
  - Lost tax revenues
  - Lost productivity (work absence)

- 40 million pain-related physician visits each year
  - The most common reason for medical visits

- Push toward opioid maintenance therapy for chronic nonmalignant pain
Prevalence of Recurrent and Persistent Pain in the United States\textsuperscript{2}

- One in four Americans suffers from recurrent pain (defined as a daylong bout of pain at least once each month).
  - One in 10 Americans reports having persistent pain of at least 1 year’s duration.
  - One in 5 persons over age 65 reports pain persisting for more than 24 hours in the preceding month (6 in 10 report pain persisting more than 1 year).
  - Two out of 3 veterans of the armed forces report having persistent pain attributable to their military service (1 in 10 take prescription medicines to manage pain).
What Is Pain?

- Pain has been defined as an unpleasant **sensory and emotional** experience associated with actual or potential tissue damage.³

- The experience of pain is **more than a simple sensory process**. It is a complex perception involving higher levels of the central nervous system, emotional states, and higher order mental processes.⁴
There Are Multiple Types of Pain

A. Nociceptive
   Noxious Peripheral Stimuli

B. Inflammatory
   Inflammation

C. Neuropathic
   Multiple Mechanisms
   Peripheral Nerve Damage

D. Noninflammatory/Nonneuropathic
   Abnormal Central Processing
   No Known Tissue or Nerve Damage

Examples

- Strains and sprains
- Bone fractures
- Postoperative
- Osteoarthritis
- Rheumatoid arthritis
- Tendonitis
- Diabetic peripheral neuropathy
- Postherpetic neuralgia
- HIV-related polyneuropathy
- Fibromyalgia
- Irritable bowel syndrome
Causes of Chronic Pain

- Chronic pain occurs if the body’s alarm system (pain) does not turn off when it should.

- The symptom of pain at that point becomes the disease of pain, or chronic pain.
Everyone experiences pain differently.

An individual’s response to pain depends on his or her physiology, genetics, and environment, and on how he or she has been acculturated to experience distress.
Components of Chronic Nonmalignant Pain

- Perception of pain as a 4-step model:

1. **Transduction**: Acute stimulation in the form of noxious thermal, mechanical, or chemical stimuli is detected by nociceptive neurons.

2. **Transmission**: Nerve impulses are transferred via axons of afferent neurons from the periphery to the spinal cord, to the medial and ventrobasal thalamus, to the cerebral cortex.
Components of Chronic Nonmalignant Pain continued

- Perception of pain as a 4-step model:

  3. **Perception**: Cortical and limbic structures in the brain are involved in the awareness and interpretation of pain.

  4. **Modulation**: Pain can be inhibited or facilitated by mechanisms affecting ascending as well as descending pathways.
Sources of Chronic Pain

- Osteoarthritis
- Low back pain
- Myofascial pain
- Fibromyalgia
- Headaches (e.g., migraine, tension-type, cluster)
- “Central pain” (e.g., spinal cord injury, stroke, MS)
Sources of Chronic Pain continued

- Chronic abdominal pain (e.g., chronic pancreatitis, chronic peptic ulcer disease, irritable bowel syndrome)
- Sickle cell disease
- Complex regional pain syndrome, Types I and II
- Phantom limb pain
- Peripheral neuropathy
- Neuralgia (e.g., postherpetic, trigeminal)
Treatment Goals in Managing Chronic Nonmalignant Pain

- Improve patient functioning.
- Identify, eliminate, or reduce pain reinforcers.
- Increase physical activity.

The goal is NOT total eradication of pain!
Nonopioid Pain Relievers

Can be an option—will review in detail in Module 9. Stay tuned.
Opioids

Natural (opiates) and semisynthetic

Synthetic
## Responses Mediated by Opioid Receptors

<table>
<thead>
<tr>
<th>G-Protein Coupled Receptor</th>
<th>Response of Activation</th>
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<tbody>
<tr>
<td>mu</td>
<td>Analgesia, respiratory depression, sedation, miosis, euphoria, reduced gastrointestinal motility</td>
</tr>
<tr>
<td>delta</td>
<td>Analgesia, euphoria</td>
</tr>
<tr>
<td>kappa</td>
<td>Analgesia, dysphoria, psychotomimetic effects, miosis, respiratory depression</td>
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Opioid Safety

- Side effects are common
  - Nausea, vomiting
  - Sedation, respiratory depression
  - Constipation, urinary retention
  - Sweating, insomnia, decreased sexual function
  - Cognitive impairment, psychomotor dysfunction
    - Opioid-induced delirium
Organ toxicity is rare
- Hypothalamic-pituitary-adrenal axis: decreased cortisol
- Hypothalamic-pituitary-gonadal axis: increased prolactin, decreased LH, FSH, testosterone, estrogen, progesterone

Overdose, especially when combined with other sedatives

Worsening pain (withdrawal or hyperalgesia)

Risk of addiction (opioid dependence)

Societal toxicity (diversion and trafficking)
FDA Warnings About Methadone

FDA Alert

- “Methadone doses for pain should be carefully selected and slowly titrated to analgesic effect even in patients who are opioid tolerant.”

- “Physicians should closely monitor patients when converting them from other opioids and changing the methadone dose, and thoroughly instruct patients on how to take methadone.”

- “Healthcare professionals should tell patients to take no more methadone than has been prescribed without first talking to their physician.”

- “Methadone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.”
Opioid Options

- Strong versus weak (ceiling effect)
- Duration and onset of action
  - “Rate hypothesis”—fast on, fast off—most addicting
- Patient’s prior experience
  - Mu polymorphisms—differences in opioid responsiveness
- Route of administration
- Side effects and cost

There are NO abuse-resistant opioids or opioid formulations!
Short-Acting Opioid Options

- Morphine
- Codeine
- Oxycodone
- Hydromorphone
- Hydrocodone
- Tramadol
- Incident pain
- Short episodes of activity
  - e.g., physical therapy
Short-Acting: Morphine

- OA: 15–60 minutes, PE: 30–60 minutes, DOA: 4–6 hours (SR preparation: 8–12 hours)
- Moderate to severe pain
- Morphine-6-glucuronide: active metabolite: renal excretion
- Morphine-3-glucuronide: metabolite with excitatory effects
- Medication crosses placenta and is in breast milk
Short-Acting: Codeine

- OA: 15–30 minutes, PE: 30–60 minutes, DOA: 3–6 hours
- Mild to moderate pain
- Hepatic and renal elimination
- Prodrug: 10 percent transformed to morphine
- Medication crosses placenta and is in breast milk
Short-Acting: Oxycodone

- OA: 10–15 minutes, PE: 30–60 minutes, DOA: 3–6 hours (SR preparation 8–12 hours)
- Moderate to severe pain
- Hepatic and renal elimination
- Medication crosses placenta and is in breast milk
Short-Acting: Hydromorphone

- Seven times more potent than morphine
- OA: 15–30 minutes, PE: 30–60 minutes, DOA: 4–6 hours
- Moderate to severe pain
- Hepatic elimination
- No active metabolites
- Medication crosses placenta and is in breast milk
Short-Acting: Hydrocodone

- OA: 15–30 minutes, PE: 30–60 minutes, DOA: 4–8 hours
- Mild to moderate pain
- Hepatic and renal elimination
- Medication crosses placenta and is in breast milk
Short-Acting: Tramadol

- OA: Less than 1 hour, PE: 2–3 hours, DOA: 3–6 hours
- Hepatic and renal elimination
- Mild to moderate pain
- Medication provides analgesia via at least two mechanisms
  - 30 percent of effect: low binding to opioid receptors
  - 70 percent of effect: mild inh of NE and serotonin reuptake
- Adverse effects: N/V, constipation, sedation
- Medication may lower seizure threshold
- Clinical physical dependence, has abuse potential
- Medication crosses placenta and is in breast milk
Long-Acting Opioid Options

- Slow-release delivery system
  - Transdermal fentanyl
  - Extended-release morphine
  - Extended-release oxycodone

- Intrinsic pharmacokinetic property
  - Methadone

- Persistent moderate to severe pain

- Baseline analgesia
Long-Acting: Transdermal Fentanyl

- Medication requires predictable blood flow to dermal application site
- $25\mu g = \text{morphine }30-60\text{ mg po }= 6-9\text{ oxycodone}$
- Takes about 8–14 hours to achieve peak serum levels
- Removal of patch still leaves SQ reservoir with $t\frac{1}{2}$ of about 18 hours
- Absorption altered with fever, broken skin, edema, and decreased subcutaneous fat
- Medication crosses placenta and is in breast milk
Long-Acting: Methadone

- OA: 30–60 minutes, PE: 2–3 hours, DOA: 6–8 hours but t½ VARIABLE and UNPREDICTABLE
- NMDA receptor antagonist
- 5HT, NE uptake inhibition
- QTc prolongation, risk of torsades de pointes
Agonist-Antagonists

- OA: 15–30 minutes, PE: 1–3 hours, DOA: 3–6 hours
- Mild to moderate pain
- Hepatic and renal elimination
- Analgesia in opioid-naïve patients
- Precipitated withdrawal in physically dependent patients
- Psychotomimetic (psychosis) effects
Drugs That Interact With Opioids

- PDR lists 73 interactions, some of which are groups.
- Antiretrovirals have multiple and variable interactions—check before use.
- CNS depressants have an additive effect.
  - Opioids, anesthetics, sedatives, ethanol
  - Respiratory depression, hypotension, profound sedation, coma
- The potential exists for serotonin syndrome with SSRIs and tramadol.
- Grapefruit inhibits methadone metabolism.
- Smoking induces CYP1A2 and decreases methadone levels.
Drug Interactions

Levels reduced by 3A4 inducers:

- Self-induces its own metabolism
  - 3.5-fold increase in total clearance between first dose and steady state

- Anticonvulsants
  - Phenytoin, carbamazepine, phenobarbital

- Antiretrovirals
  - Amprenavir, efavirenz, lopinavir, nelfinavir, nevirapine, ritonavir, zidovudine

- Other
  - Rifadin, chronic alcohol use
Drug Interactions continued

Levels increased by 3A4 inhibitors:

- Psychotropics
  - Diazepam, fluvoxamine, fluoxetine, sertraline

- Antimicrobials
  - Erythromycin, ciprofloxacin, azole antifungals, clarithromycin, protease inhibitors

- Others
  - Diclofenac, doxycycline, nicardipine, propofol, quinidine, and verapamil, nifedipine, cimetidine, acute alcohol use
Pain Alters Opioid Responses

- Significantly less opioid reward or euphoria\textsuperscript{12}
- Less morphine analgesic tolerance in pain assays\textsuperscript{13}
- Fewer morphine physical withdrawal symptoms\textsuperscript{13}
- Patients on morphine with successful nerve block will develop respiratory and CNS depression\textsuperscript{14}
Can Opioids Worsen Pain?

- In animal studies, chronic opioid administration resulted in increased pain sensitivity versus placebo.15

- Patients on methadone maintenance show enhanced pain sensitivity versus controls.16

- Does release of peptides, “antiopioids,” increase levels of dynorphin?

- Does neuroadaptation to chronic opioid administration occur?17
Opioid-Induced Hyperalgesia

Pain Relief

Pain

Analgesic

Hyperalgesia

Analgesic
Evidence for the Efficacy of Opioids in Treating Chronic Pain\textsuperscript{19, 20, 21, 22}

- Mostly literature surveys and uncontrolled case series
- RCTs of short duration (less than 8 months) with small samples (fewer than 300 patients)
- Mostly pharmaceutical company sponsored
- Pain relief modest
  - Better analgesia with opioids versus control in all studies (statistically significant)
- Mixed reports on function
- Addiction not assessed
Evidence for **Overall Efficacy of Opioids in Treating Chronic Pain**

**Short-term efficacy:**

- Sixty-two RCTs in a recent meta-analysis, duration less than 16 weeks in 61 of the RCTs\(^{23}\)

- Opioids more effective than placebo for nociceptive and neuropathic pain (effect sizes 0.55–0.60)\(^{24}\)
Evidence for **Overall Efficacy of Opioids in Treating Chronic Pain** continued

**Long-term efficacy:**

- The Cochrane Review included 26 studies longer than 6 months.
- Twenty-five studies were case series or uncontrolled long-term trial continuations.
- Many patients discontinued due to adverse effects (23 percent) or insufficient pain relief (10 percent), but some evidence suggested that patients who continued on opioids experienced long-term pain relief.
Evidence for the Efficacy of Specific Opioids in Treating Chronic Pain

- Trials generally found no difference between opioids in efficacy, based on short-term trials.

- There was no clear difference in efficacy between long- and short-acting opioids, but the trials were designed to evaluate equivalence using efficacy designs.\textsuperscript{26}
There was no evidence to assess the benefits/harm of scheduled, round-the-clock versus as-needed dosing.\textsuperscript{27}

Long-acting, round-the-clock opioids may induce tolerance, leading to dose escalations.\textsuperscript{28}

For chronic pain, methadone was evaluated in a single, small, poor-quality trial of neuropathic pain.\textsuperscript{28}
Evidence of the **Risks** of Opioids in Treating Chronic Pain\textsuperscript{29}

- **High rates of adverse events**
  - Constipation, nausea, sedation, etc.

- **Hyperalgesia**
  - Paradoxical increased sensitivity to pain
  - Prevalence, risk factors, and clinical significance not well understood

- **Hypogonadism**
  - Primarily based on cross-sectional studies
  - Clinical significance not well understood
Evidence of the **Risks** of Opioids in Treating Chronic Pain continued

- Risk of falls and/or fractures
- Some studies show an increased risk of poor functional outcomes:
  - One study of patients in the Washington State Workers’ Compensation system with low back injury found increased risk of disability at 1 year in patients who received opioids within 6 weeks of injury (adjusted OR 2.2, 95 percent 1.5 to 3.1).
Evidence of the **Risks** of Opioids in Treating Chronic Pain continued

- The strongest risk factor for opioid abuse was personal or family history of substance abuse.³¹

- Other risk factors in some studies were depression, younger age, and preadolescent sexual abuse in women.
Evidence of the **Risks** of Opioids in Treating Chronic Pain continued

- Risk assessment instruments are available, but none has been well validated.

- There is no evidence regarding effects on clinical outcomes of using risk assessment instruments to guide patient selection.
Available evidence suggests that potential benefits of opioids are at best finely balanced with harms.

- Risk should be assessed as a standard practice.
- Risk mitigation strategies should be matched with level of assessed risk and used routinely.
- Readily available and effective nonopioid treatments for chronic pain, including those addressing psychosocial factors, are urgently needed.
Summary

- Opioids are good but not perfect analgesics.
- Opioids differ.
- Risks include side effects, overdose, and addiction, but organ toxicity is low.
- Slow onset and slow offset are less rewarding.
- Some chronic pain may worsen with chronic opioids.
- Optimal dose is determined by careful titration and monitoring.
- Exploit synergies with nonpharmacologic therapies through a comprehensive treatment plan.


References continued


27Ibid


30Ibid