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Disclosure Statement

- I have no personal or financial conflicts to disclose.
- I will not discuss all adverse effects or contraindications.
First...a look at the world we live in.
For every FIVE new heroin users, FOUR of them got their start on prescription opioids.

On the street, heroin is generally cheaper than oxycodone.

Since 1999, the amount of prescription opioids sold in the U.S. has nearly tripled. In the same time period, deaths from prescription opioids have also tripled.

It’s affecting whole new demographics, which were not traditionally touched by heroin abuse.
Last year, the Surgeon General addressed primarily the patient end.

- Support, counseling, treatment

The provider end also must be addressed!

- We (medical professionals) helped create this problem.
- We need to help turn it around.
In Alaska, during 2009-2015 period:

- 774 drug overdose deaths
- 512 of them had prescription drugs as primary or contributing cause of death
- That’s 66%.

Highest overdose death rates are in Anchorage/Mat-Su.

Heroin use in AK has increased every year since 2010.

From 2009-2015, heroin-associated deaths have quadrupled.
Helpful Links:

- Alaska Division of Public Health
  - [https://dhss.alaska.gov/dph](https://dhss.alaska.gov/dph)
  - “Heroin and Opioid Information” (Tues, Aug 9 2016)

- Center for Disease Control & Prevention
  - [www.cdc.gov/drugoverdose/opioids](http://www.cdc.gov/drugoverdose/opioids)

- U.S. Dept. of Health & Human Services
  - [www.hhs.gov/opioids](http://www.hhs.gov/opioids)
Alaska State Legislation

- Introduced by Governor Walker, after declaration of opioid epidemic as public health disaster in Feb. 2017

- Highlights of HB159/SB79—"The Opioid Bill":
  - Mandated CME in pain management & opioid addiction for all providers
  - Patients may turn down opioids
  - Prescription dispensing limits for initial opioid prescriptions (7 days)
  - Changes to PDMP

-- Signed into law in July 2017! --
Questions to answer...

- What is opioid-induced hyperalgesia?
- What is multimodal analgesia?
- What does appropriate pain management look like?
- When should PCA’s be used?
- What tools can I use to optimize pain management?
- What drugs should I watch out for (e.g., Suboxone)?
Defining some terms...

- What is opioid-induced hyperalgesia (OIH)?
- What is multimodal analgesia?
Pain Processing Sites

- Peripheral receptors
- Spinal Cord
- Brain

The pain pathway is always changing!
Peripheral and central sensitization happen all the time.

Pain perception involves emotions.
Hyperalgesia: an exaggerated pain response to a normally painful stimulus

Allodynia: a painful response to a typically non-painful stimulus
Opioid-Induced Hyperalgesia (OIH)

- Disorder of central pain processing caused by acute or chronic opioid use
- Also known as “wind-up phenomenon”
- Can develop in days or months
- Not uncommon in patients with exclusive opioid use
- We see this every day.
The use of multiple drug classes (not just opioids) for pain management

Minimizes risk of adverse effects

Optimizes pain control

The best way to combat OIH
Drugs for Pain (*not all of them*)

- Opioids
- Acetaminophen
- Salicylates (aspirin)
- NSAIDS: naproxen, ibuprofen, ketorolac
- COX-2 Inhibitors: celecoxib
- Tricyclic antidepressants: amitriptyline, nortriptyline
- GABA-ergic drugs: gabapentin, pregabalin
- NMDA antagonists: ketamine, memantine, methadone
- Alpha-2 agonists: clonidine, dexmedetomidine
- Local anesthetics: local infiltration, nerve blocks, spinal/epidural, topical anesthetic (EMLA, Lidoderm)
NSAID’s

- Aspirin (salicylic acid)
- Ibuprofen, naproxen, ketorolac, diclofenac, indomethacin

- All above are reversible, non-selective COX inhibitors
- Decrease synthesis of prostaglandins (esp. PGE-2)
  - Decrease inflammation AND sensation of pain
  - Decrease fever
Celecoxib (Celebrex)

- An NSAID with COX-2 specificity

- This limits the adverse effects:
  - Lower risk of gastric irritation/ulceration
  - No effect on platelet function
  - (Same renal effects as other NSAIDS)
Acetaminophen

- No anti-inflammatory properties
- Effective analgesic and antipyretic
- Inhibits prostaglandin synthesis in CNS
  - very little effect on COX enzyme in peripheral tissues
- Oral, rectal, IV formulations
**IV Acetaminophen (Ofirmev)**

- Reaches peak plasma levels higher and faster (15min) than PO or PR
- Reaches much higher CNS concentration than can be achieved with PO or PR
- Reliable absorption and effect
- Opioid-sparing effect
- Higher patient and nurse satisfaction
- Expensive
Ketamine

- Synthesized in 1962
- NMDA-antagonist
- Potent analgesic
- Acts as a dissociative *anesthetic* at high doses.

- Infusion 0.1-0.25 mg/kg/hr → fewer opioids, better pain control.
- Higher doses may cause hallucinations
  - Can be minimized with benzo pre-treatment
Methadone

- Synthesized in 1939

- Affects *multiple receptors*:
  - Opioid agonist (like morphine)
  - NMDA antagonist (like ketamine)
  - Serotonin/Norepinephrine reuptake inhibitor (like SNRI’s)

- PO form: highly variable duration of action.
- IV form: predictable and long-lasting
Opioids

- **Strong agonists**
  - Morphine, meperidine, methadone, fentanyl, sufentanil, alfentanil, remifentanil, heroin

- **Weak agonists**
  - Codeine, propoxyphene

- **Agonist-Antagonists**
  - Buprenorphine (Subutex)
  - Nalbuphine (Nubain)

- **Pure antagonists**
  - Naloxone (Narcan)
  - Naltrexone (Revia, Vivitrol)
Opioid Tolerance & Dependence

- **Tolerance:** Escalating doses needed to reach same effect

- **Physical Dependence:** Physiologic adaptation to the presence of the drug; abstinence causes withdrawal

- Dependence is *not* addiction
Opioid-Induced Hyperalgesia (OIH)

- Disorder of central pain processing caused by acute or chronic opioid use
- Also known as “wind-up phenomenon”
- Not uncommon in patients with exclusive opioid use
- *This can happen over hours/days—it doesn’t always take months.*
- We see this every day.
Minimizing OIH

- Preemptive analgesia
- Good baseline pain control—Avoid the ups and downs!
  - More reliance on longer-acting drugs
  - More orals, less IV
- MULTIMODAL ANALGESIA!
  - A little bit of everything, rather than a lot of one thing
  - Minimizes side effects of any one drug class
  - NMDA receptor has been directly linked with OIH
What is Multimodal Analgesia?

- **Opioids**
- **Acetaminophen**
- **Salicylates (aspirin)**
- **NSAID’s:** naproxen, ibuprofen, ketorolac
- **COX-2 Inhibitors:** celecoxib
- **Tricyclic antidepressants:** amitriptyline, nortriptyline
- **GABA-ergic drugs:** gabapentin, pregabalin
- **NMDA antagonists:** ketamine, memantine, methadone
- **Alpha-2 agonists:** clonidine, dexmedetomidine
- **Local anesthetics:** local infiltration, nerve blocks, spinal/epidural, topical (EMLA, Lidoderm), IV lidocaine
Benefits of Multimodal Analgesia

- Minimizes side effects of any one drug class
- Better pain control with less opioid!

- Minimizes opioid exposure:
  - Less opioid-induced hyperalgesia
  - Less respiratory depression
  - Less constipation
  - Less nausea/vomiting
  - Less itching
  - Less opioid tolerance & dependence
  - Earlier discharge
In conclusion...

- Multimodal analgesia is:
  - Better.
  - Safer.
  - Cheaper.
• **Opioids are not all bad!**
  • We still need them.

• Just don’t forget about the other tools in the toolbox!
  • Don’t be complacent; be creative.
Who Can Benefit from Multimodal Therapy?

Everyone.

(including us)
64 yo man with chronic low back pain.

Pain poorly managed on oxycodone and ibuprofen

Has baseline pain score of 6/10.

Can’t we do better than this?
Some Drug Choices...

- Opioids
- Acetaminophen
- Salicylates (aspirin)
- **NSAIDS**: naproxen, ibuprofen, ketorolac
- COX-2 Inhibitors: celecoxib
- **Tricyclic antidepressants**: amitriptyline, nortriptyline
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Try something longer acting?
Some Options for Neuropathic Pain

- TCA’s (amitriptyline, nortriptyline, desipramine)
- Gabapentinoids (gabapentin, pregabalin)
- NMDA antagonists (methadone, ketamine, memantine)
- Local anesthetics
- Capsaicin
- Anticonvulsants (lamotrigine, carbamazepine, topiramate)
- SNRI’s ( duloxetine, venlafaxine)
- Device-based therapies (TENS, spinal cord stimulator)
Questions?
Optimizing Pain Management

- Good baseline pain control—Avoid the ups and downs!
  - More orals, less IV
  - More reliance on longer-acting IV drugs (e.g., not fentanyl)
  - Do NOT assume that a PCA is always the best way to control acute pain.

- MULTIMODAL ANALGESIA!
  - A little bit of everything, rather than a lot of one thing
  - Minimizes side effects of any one drug class
  - For severe and/or chronic pain, block the NMDA receptor if you can!
Patients who can take PO meds

DO NOT NEED A PCA
PCA's: An institutional addiction

- Many PCA orders are inappropriate.

- **Most patients who can take oral meds SHOULD NOT HAVE A PCA!** They should take oral meds!
  - Cheaper
  - Easier
  - Safer
  - Better pain control (longer-lasting analgesia)
  - Better patient satisfaction
  - Faster discharge
  - Lower risk of OIH

- If you must use a PCA, morphine and Dilaudid are FAR more effective (and safer) than fentanyl.
A 86yo man with 8 broken ribs after fall off of tractor. Treated exclusively with fentanyl PCA since admission. Has been sleeping for 18 hours, but wakes up in agony.

Our typical plan:
- Stop PCA
- Scheduled Tylenol
- Scheduled Ibuprofen
- PRN oxycodone Q3hrs
- IV Dilaudid for breakthrough pain only
- Consider adding Lyrica/Neurontin for a few days
- Consider Lidoderm patches to site
Optimizing Pain Management

- Good baseline pain control—Avoid the ups and downs!
  - More orals, less IV
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Acute Pain Service consulted to see patient in the ICU

HPI: 23yo female, 33 weeks pregnant. Hospitalized 4 weeks prior with a cervical spinal cord injury.

Ventilator-dependent with tracheostomy—unable to wean

Complains of intractable neuropathic pain down both arms. No other pain.
Pain has been poorly controlled with current regimen of meds:

- Fentanyl patch 25 mcg/hr (600 mcg per day)
- IV fentanyl Q1hr PRN: 600-1000 mcg per day
- Oxycodone Q4hr PRN: 60-100 mg per day
- Acetaminophen Q4hr PRN: 2000-3000mg per day
- Gabapentin 600 mg TID
Case Report (cont.)

- Patient has exclusively neuropathic pain, but...
- Use of focused anti-neuropathic agents limited by risk to fetus:
  - No NSAID’s
  - No TCA’s
  - Minimal GABA-ergic drugs (gabapentin)
- Neuropathic pain treated almost exclusively with PRN opioids
  - Pain is poorly controlled (surprised?)
  - Patient may have developed OIH
    - Massive cumulative opioid exposure
    - No baseline pain control. Up and down all day.
Patient has real pain from her trauma.

Some of this may be OIH.

In any case, she is at high risk for OIH.
So what do you do?

- Control her pain
- Minimize OIH
My Plan:

- Start oral methadone 20 mg BID
  - Opioid agonism AND NMDA antagonism
- **Scheduled acetaminophen** to insure good baseline level
- Continue **scheduled gabapentin & fentanyl patch**
- Continue PRN oxycodone
- Start PRN IV **hydromorphone** for breakthrough pain
- **STOP** PRN Fentanyl
Day 1

- Pain dramatically better
- Able to tolerate T-piece for first time
- Oxycodone use in past day: 60 mg
- IV hydromorphone use in past day: 4 mg

**Plan:**
- Increase methadone to 30 mg BID
- Advise patient that oral opioids will provide better, longer-lasting baseline coverage than IV opioids
Day 2

- Pain better still
- Still tolerating T-piece
- Oxycodone use in past day: 60 mg
- IV hydromorphone use in past day: 3 mg

Plan:
- Further increase methadone to 30 mg TID
- Decrease frequency of PRN IV hydromorphone, to encourage more reliance on PO oxycodone
- STOP Fentanyl patch
Day 3

- Good pain control, with more steady baseline
- Still on T-piece
- Oxycodone use in past day: 75 mg
- IV hydromorphone use in past day: 0.4 mg

**Plan:**
- Continue current regimen
Day 4

- Much better pain control, now has been on stable methadone regimen for 2 days
- Has not needed ventilator for 3 days
- Oxycodone use in past day: NONE
- IV hydromorphone use in past day: NONE

Plan:
- Continue current regimen
Day 5

- Pain well-controlled. Patient very pleased with her pain control.
- Has been completely weaned from ventilator for 4 days
- Has not had ANY PRN opioids for 2 days
- Oxycodone use in past day: NONE
- IV hydromorphone use in past day: NONE
Conclusion: A little NMDA blockade goes a long way.
**The problem:**
- Neuropathic pain poorly controlled with massive doses of PRN opioids
  - Oxycodone 60-100 mg per day
  - Fentanyl 1200-1600 mcg per day (IV, patch)

**The solution:**
- Treat neuropathic pain with NMDA antagonist (methadone)
- Patient is getting LESS opioid, and feels BETTER!
Poor Pain Management

- We see this EVERY DAY. We don’t have to.

- Exclusive opioids for pain—NEVER a good idea.
Other examples...

- **SP**: 69yo w/ chronic back/neck pain, stuck in bed with poor pain control for 3-4 weeks after major abdominal surgery. Admitted for failure to thrive and intractable pain.

- **BD**: 94yo with 4 broken ribs after ground level fall. Returns to ER after 3 days of refractory pain while on hydrocodone elixir.
SP: 69yo w/ chronic back/neck pain, stuck in bed with poor pain control for 3-4 weeks after major abdominal surgery. Admitted for failure to thrive and intractable pain.

BD: 94yo with 4 broken ribs after ground level fall. Returns to ER after 3 days of refractory pain while on hydrocodone elixir.
Appropriate pain management
- Employ multimodal analgesia (opioids should not be first choice)
- Rely more on oral meds
- PCA usually only for patients unable to take oral meds

Inappropriate Pain Management: An Epidemic!
- Overreliance on opioids leads to:
  - Poor pain control
  - Opioid-induced hyperalgesia
  - Opioid overuse/abuse → dependence/addiction
  - Adverse outcomes, including death

- The national opioid crisis—we created it. We need to help fix it.
How can we help?

- Educate providers on appropriate pain management
- Develop useful tools to ensure optimal outcomes and maximize patient safety
PAMC Pain Management Council

- Created in Spring 2015.

- Provider education has been a primary underlying initiative.

- Developed multimodal ordersets in summer/fall 2015.
  - Dec 2015: Fast-tracked at system level, in context of national PCA shortage
  - March 2016: Ordersets released
  - Oct 2016: Ordersets embedded into every post-op orderset in Providence system

- Ongoing projects include OSA task force and single-team pain management
PCA Orders 2015-17, Ortho Floor

PCA Shortage
# Orthopedics: Top Five PCA Prescribers (First Quarter) 2015 vs. 2016

<table>
<thead>
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<th>ORTHO PROVIDER</th>
<th>Q1 2015</th>
<th>Q1 2016</th>
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<td>Dr. A</td>
<td>35</td>
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<td>Dr. B</td>
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<td>Dr. C</td>
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<tr>
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<td>3</td>
</tr>
<tr>
<td>Dr. E</td>
<td>15</td>
<td>0</td>
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<td><strong>TOTAL BY QUARTER</strong></td>
<td><strong>118</strong></td>
<td><strong>10</strong></td>
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Knowledge + Tools = Better Patient Care!
PCA Use at PAMC 2015-2017: The Impact of Education

# of PCA orders

PCA Shortage
Good baseline pain control—Avoid the ups and downs!

- More orals, less IV
- More reliance on longer-acting IV drugs (e.g., not fentanyl)
- Do NOT assume that a PCA is always the best way to control acute pain.

MULTIMODAL ANALGESIA!

- A little bit of everything, rather than a lot of one thing
- Minimizes side effects of any one drug class
Shifting gears...
Opioid Blockade!
Drugs to watch out for...

- Opioid Agonist-Antagonists
  - Buprenorphine (Subutex)

- Pure opioid antagonists
  - Naloxone (Narcan): short-acting
  - Naltrexone (Revia, Vivitrol): long-acting
Subutex = buprenorphine
Suboxone = buprenorphine + naloxone (deterrent only)

Extremely high affinity for mu-opioid receptor. Almost nothing displaces it.

Takes several days to clear. TRANSITION to another opioid 5-7 days prior to any procedure/surgery with significant post-op pain.

If a patient is on buprenorphine, other opioids will be much less effective. Only options are:
- More buprenorphine
- Very high dose opioids
- Non-opioid drugs
Naloxone (Narcan)

- Short-acting opioid antagonist
- Half-life = 60-90 minutes
- Rapidly displaces all other opioids from the mu-opioid receptor. Completely blocks receptor.
Naltrexone

- Long-acting opioid antagonist (like Narcan, but lasts much longer)

- Clearance depends on formulation

- As long as naltrexone is on board, opioids will have almost no effect.

- Only option is non-opioid drugs
Naltrexone (cont.)

- **Revia** = naltrexone (PO)
- **Vivitrol** = naltrexone injection (dosed monthly IM)
- **Contrave** = naltrexone + wellbutrin (PO)

- Oral (**Revia**, **Contrave**): Takes 24-48 hours to clear
- IM injection (**Vivitrol**): Takes one month to clear

- As long as naltrexone is on board, *opioids will have almost no effect.*

- *Only* option is non-opioid drugs!
Questions?