Pain Management in the Elderly

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Continuing Education Credit

- Continuing Education Credit is available for:
  - Medicine (1.0 contact hour)
  - Nursing (1.0 contact hour)
  - Social Work (1.0 contact hour)

*Please complete the survey at the end of the presentation in order to receive continuing education credit. See special instructions for CE, CME and CPE credits at the end of this presentation.*
Objectives

• Review clinical pearls related to analgesic drug therapy selection, dosing, and monitoring in older adults
• Discuss pharmacokinetic and pharmacodynamics changes that may present in older adults and their relationship to medication use
• Explore strategies to prevent and manage adverse drug events that may occur in older adults taking analgesic medications
Pharmacologic Management: General Principles

- Determine cause of the pain
  - Recognize if multiple sites or types of pain are present
- Give adequate doses
- Allow adequate trial for each drug
- Reinforce goals of treatment
  - For chronic pain, this may not be a pain score = 0
- Utilize WHO ladder
  - A stepwise approach
- Implement a multimodal strategy
General Principles: WHO Analgesic Ladder

Step 1: Non-opioids ± Adjuvants

Step 2: Weak Opioids ± Non-opioids ± Adjuvants

Step 3: Strong Opioids ± Non-opioids ± Adjuvants
Opioids 
α₂-agonists 
NMDA antagonists 
Acetaminophen 
Anti-epileptics 
TCAs & similar

Local Anesthetics 
Opioids 
α₂-agonists

NSAIDs/COXIBs 
Local Anesthetics 
Anti-epileptics
General Principles, con’t

- Consider comorbidities
- Consider **contraindications** to medications
- Start with a **short** acting agent
- Use around-the-clock dosing for continuous pain
- Use **PO (oral) route** whenever possible
- Try to avoid painful routes of administration (IM)
- For chronic pain, the intention is to prevent pain, not to “chase” it.
- Use rescue doses for breakthrough pain
  - if rescue dose is used > 2-4 times/day, consider increasing the background dose.
Components of a Multimodal Approach

Non-Opioids to Consider:
- Acetaminophen
- NSAIDs
  - Ketorolac, ibuprofen, celecoxib, etodolac, others
- NMDA receptor antagonists
  - Ketamine, methadone
- Alpha2 agonists
  - Clonidine, dexmedetomidine
- Gabapentinoids
  - Gabapentin, pregabalin
- Local anesthetics
  - Bupivacaine, lidocaine, liposomol bupivacaine

Base multimodal regimen on:
- Efficacy
  - Consider neuropathic component
- Patient-specific factors
  - Age
  - Organ function
    - Renal, GI
  - Tolerability & Ease of Use
  - Cost
Benefits of Multimodal Analgesia

**EFFICACY**

- Reduced doses of analgesics in the treatment plan, especially opioids\(^1,2,3,4\)
  - Recent federal focus on limiting opioid use\(^14,15\)
- Superior pain relief, secondary to synergistic or additive effects of the various agents in the treatment plan\(^1,2,5,6,7\)
- Fewer “analgesic gaps” \(^1,2\)
- Reduce LOS \(^9\)
- Improved patient satisfaction \(^10\)

**SAFETY**

- Improved functional outcomes\(^1,2,8\)
- Reduced adverse events (including drug-related, and post-op related – i.e., fever, PONV,...)\(^11,12,13\)
- Decreased need for use of naloxone \(^11\)

Non-Opioids

NSAIDs and Acetaminophen
Acetaminophen

• Doesn’t show anti-inflammatory properties in vivo.
• Good analgesic, anti-pyretic
• Efficacy for nociceptive pain, $\varnothing$ neuropathic pain
• Prominent central activity
• Do not exceed $4 \text{g/day}$
  • Hepatotoxicity
  • Ceiling effect

Available in parenteral formulation
Aspirin

- Has anti-inflammatory, analgesic, antipyretic, and anti-platelet effects
- Different doses depending on the indication
  - Analgesic dose = 325-650 mg q 4-6 hr
  - Anti-inflammatory dose = 2.4 – 5.4 g/day in divided doses
  - Anti-platelet (MI prophylaxis) dose = 81-325 mg/day
NSAIDs

• How do select a specific drug?
  • What do you need the drug to do?
    • Fever
    • Pain (acute injury-related, menstrual-related, etc)
    • Inflammation
    • Anti-platelet
NSAIDs – clinical uses

• **Analgesic**
  - Acetaminophen
  - Ketorolac

• **Analgesic + anti-inflammatory**
  - Aspirin
  - Non-selective NSAIDs
    - Ibuprofen, ketoprofen, naproxen, indomethacin, etodolac
  - COX-2 selective NSAIDs
    - Celebrex (celecoxib)
  - Non-acetylated NSAIDs
    - Trilisate (choline magnesium trisalicylate), salsalate
NSAIDs – selection, con’t

- Can patient take meds orally?
  - Parenteral
    - Toradol (ketorolac), acetaminophen
  - Rectal suppositories
    - Aspirin, Acetaminophen

- Daily dosing (BID vs. TID or QID)

- Concern for organ systems
  - GI mucosa, kidneys, platelets, bone healing
  - Cardiovascular
    - Naproxen, ibuprofen, celecoxib safest
Special Considerations

- Anti-platelet effects
  - Aspirin: irreversible
  - Ibuprofen (& other NSAIDs): reversible

- Anti-inflammatory effects
  - Generally use higher doses than those for analgesia
    - Ex: Ibuprofen 400 mg TID – QID for inflammation

- NSAIDs marketed as COX-2 selective
  - Celebrex (celecoxib)
    - 100-200 mg BID
    - Warning if sulfa allergy

- “Non-selective” NSAIDs have different degrees of COX selectivity
COX-2 Selectivity

Log IC$_{80}$ ratio [Human whole blood assay COX-2/COX-1])

-3 -2 -1 0 1 2 3

-3 -2 -1 0 1 2 3

Rofecoxib
Etodolac
Meloxicam
Celecoxib
Diclofenac
Piroxicam
Diflunisal

> 50-fold COX-2 selectivity
5- to 50- fold COX-2 selectivity
<5-fold COX-2 selectivity

Adapted from Warner TD et al. Proc Natl Acad Sci USA 1999;96:7563-68.
NSAIDs – Adverse Reactions

- **GI ulcerations**
  - Male, age, PUD, alcohol use, smoking, corticosteroid use, anticoagulant use
  - Use of PPI or misoprostol to prevent/treat NSAID-related GI ulcerations

- **Bleeding**
  - COX-2 inhibitors and non-acetylated NSAIDs have lower bleeding risk

- **Sodium/water retention/↑ K⁺**
  - ↓ renal blood flow, GFR
  - CHF, cirrhosis w/ascites, chronic renal dz, hypovolemic

- **Interstitial nephritis**
- **Hypersensitivity reaction**
NSAIDs & Upper GI Complications
### Table 1. Summary of the numbers of studies and overall results.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Case-Control Studies</th>
<th>Number of Exposed Cases/Controls</th>
<th>Cohort Studies</th>
<th>Number of Studies</th>
<th>Number of Person-Years of Exposure</th>
<th>Total Number of Studies</th>
<th>Pooled RR (95% CI)</th>
<th>Cochran Q</th>
<th>p-Value</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen</td>
<td>24</td>
<td>3,103/24,468</td>
<td>17</td>
<td>159,824</td>
<td>41</td>
<td>1.09 (1.02, 1.16)</td>
<td>143.1</td>
<td>&lt;0.0001</td>
<td>70.70%</td>
<td></td>
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<tr>
<td>Ibuprofen</td>
<td>21</td>
<td>5,716/37,207</td>
<td>17</td>
<td>255,621</td>
<td>38</td>
<td>1.18 (1.11, 1.25)</td>
<td>226.7</td>
<td>&lt;0.0001</td>
<td>81.90%</td>
<td></td>
</tr>
<tr>
<td>Celecoxib</td>
<td>20</td>
<td>1,496/12,755</td>
<td>15</td>
<td>179,479</td>
<td>35</td>
<td>1.17 (1.08, 1.27)</td>
<td>236.9</td>
<td>&lt;0.0001</td>
<td>84.40%</td>
<td></td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>19</td>
<td>1,662/10,827</td>
<td>15</td>
<td>126,219</td>
<td>34</td>
<td>1.45 (1.33, 1.59)</td>
<td>227.8</td>
<td>&lt;0.0001</td>
<td>84.20%</td>
<td></td>
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<tr>
<td>Diclofenac</td>
<td>16</td>
<td>3,181/13,523</td>
<td>13</td>
<td>50,736</td>
<td>29</td>
<td>1.40 (1.27, 1.55)</td>
<td>224.4</td>
<td>&lt;0.0001</td>
<td>86.60%</td>
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<tr>
<td>Indomethacin</td>
<td>11</td>
<td>788/4,406</td>
<td>3</td>
<td>9,350</td>
<td>14</td>
<td>1.30 (1.19, 1.41)</td>
<td>20.8</td>
<td>0.1</td>
<td>32.60%</td>
<td></td>
</tr>
<tr>
<td>Piroxicam</td>
<td>7</td>
<td>288/1,216</td>
<td>1</td>
<td>0</td>
<td>8</td>
<td>1.08 (0.91, 1.30)</td>
<td>8.6</td>
<td>0.3</td>
<td>18.90%</td>
<td></td>
</tr>
<tr>
<td>Meloxicam</td>
<td>6</td>
<td>240/714</td>
<td>1</td>
<td>0</td>
<td>7</td>
<td>1.20 (1.07, 1.33)</td>
<td>2.8</td>
<td>0.7</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Etodolac</td>
<td>4</td>
<td>464/4,115</td>
<td>1</td>
<td>8,994</td>
<td>5</td>
<td>1.55 (1.28, 1.87)</td>
<td>18.9</td>
<td>0.01</td>
<td>57.70%</td>
<td></td>
</tr>
<tr>
<td>Etoricoxib</td>
<td>4</td>
<td>60/116</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>2.05 (1.45, 2.88)</td>
<td>0.7</td>
<td>0.9</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Valdecixib</td>
<td>1</td>
<td>2/2</td>
<td>4</td>
<td>5,629</td>
<td>5</td>
<td>1.05 (0.81, 1.36)</td>
<td>13.4</td>
<td>0.004</td>
<td>77.60%</td>
<td></td>
</tr>
</tbody>
</table>

*Studies reporting adjusted risk estimates did not all report person-years of exposure.

doi:10.1371/journal.pmed.1001098.t001

Opioids
Opioid pharmacokinetics

• Duration of effect of “immediate-release” formulations
  • 3–4 hours po / pr
  • shorter with parenteral bolus
• Steady state after 3–5 half-lives
  • steady state after 1 day (24 hours)
Concentration vs. Time curves

- **IV**
- **Short-acting (PO)**
- **Long-acting (PO)**

**Adverse Effects**

**Pain**

*Analgesia*
Routine oral dosing
immediate-release preparations

• Codeine, hydrocodone, morphine, hydromorphone, oxycodone

• dose 3-4 h

• adjust dose daily
  • mild / moderate pain  ➲ 25%–50%
  • severe / uncontrolled pain ➲ 50%–100%

• adjust more quickly for severe uncontrolled pain
Tramadol (Ultram®)

- Synthetic opioid agonist
- Opioid-like properties
- Nonopioid properties from release of serotonin and inhibition of reuptake of serotonin and noradrenaline
- Do not administer to an opioid-tolerant patient
  - tramadol binds to the same receptor sites and may precipitate withdrawal
- Available in combination product with APAP
- Metabolized by CPY\textsubscript{450} 2B6, 2D6, 3A4 => drug interactions
  - Active metabolites
- Seizure risk
- Dosage adjustments for renal and hepatic impairment
- Became a CIV Controlled Substance in 2014
Tapentadol

• Acts on both ascending and descending pathways
• Little to no effect on serotonergic pathways; effect on norepinephrine reuptake
  • Nociceptive and neuropathic pain
• Metabolized by Phase 2 conjugation to glucuronides and sulfates
  • No active metabolites
• Dosing: Short Acting: 50, 75, or 100 mg q 4 to 6 hours
• Max 600 mg daily PO
  • Doses up to 700 mg on the first day of treatment may be used
• Short-acting: t1/2 of 4 hours
• Long-Acting form available: Dose 50 mg PO BID; may increase every 3 days up to 250 mg PO BID
Hydrocodone

• Many generic forms available
• High abuse potential
• Use limited due to NSAID/APAP concentration in combination products
  • FDA limited APAP concentration to 325 mg per tablet or capsule
• In 2014, hydrocodone was rescheduled to a CII controlled substance
Codeine

- Low incidence of physical dependence
- Weak opioid
- Little added analgesia with doses > 60 mg
  - 60 mg codeine ≈ 650 mg ASA
- Excellent antitussive
- 10% of codeine is demethylated to morphine, which accounts for the analgesic activity.
  - Avoid use if allergy to morphine
Buprenorphine

- Partial µ-agonist
- High receptor affinity; slow dissociation
- Butrans = 7 day transdermal patch – SS in 3 days
- Buprenorphine incorporated into adhesive
- For pts taking up to 80 mg PO morphine equiv/day
- Dispensed with disposal unit, Schedule III
- 5, 10, 20 mcg/hr
- Risk for QTc prolongation
Morphine

• Reference standard for all potent opioids

• Metabolism:
  • glucuronidation by hepatic and extrahepatic sites (kidneys)
    • morphine - 3 - glucuronide
    • morphine - 6 - glucuronide
      • 4 times more potent than parent morphine
      • Metabolite is excreted renally ➜ caution in renal impairment
  • normorphine

• Duration upto 4 hours; available in long-acting

• Many dosage forms available
Hydromorphone (Dilaudid®)

- Pharmacologically similar to morphine
  - lasts upto 4 hours
- May have lower incidence of ADRs
  - respiratory depression
  - urinary retention
  - constipation
- Useful in renal impairment
  - no active metabolites
- More potent than morphine (7-8 times)
- Long-acting form: Exalgo – 24-hr formulation
  - 8, 12, 16 mg tablets
Oxycodone & Oxymorphone

- Good po bioavailability
- High abuse potential
- Use is limited because of NSAID/APAP concentration in combination preparations
- Metabolized to oxymorphone
- Schedule II Controlled Substance

- Highly metabolized; some active metabolites
- Dose on empty stomach
- No P450 interactions
- Nausea & pyrexia most commonly reported ADRs
- Available in short- and long-acting PO dosage formulations
Methadone

- Used for pain in late 1940’s
- Mainly used in opioid addiction treatment in 1960’s
  - Suppresses cravings, withdrawal symptoms, and euphoric effects for 24-36 hrs
- Increasing use as analgesic since late 1990’s
  - Some advantages as an analgesic
  - Cause for concern?
Methadone, con’t

• R-methadone = µ opioid agonist
• S-methadone = NMDA receptor antagonist; blocks reuptake of 5-HT & NE
• Long elimination t\(_{1/2}\)
• Toxicity seen days after dose
• Potential for QTc prolongation
  • Greatest with higher doses
  • Caution with antipsychotics & TCAs
• Metabolized by P\(_{450}\) 3A4, 2B6, 2D6
Methadone Monitoring: Recommendations from the American Pain Society and College on Problems of Drug Dependence in Collaboration with the Heart Rhythm Society

- Educate patient prior to the first methadone prescription
- Indications for treatment
- Goals of treatment
- Availability of alternative therapies
- Specific plans for monitoring, dose adjustments, potential ADRs

EKG Monitoring

• Prior to initiation of methadone with risk factors
  - Electrolyte abnormalities, impaired liver function, structural heart disease, genetic predisposition (prolonged QT syndrome), use of other drugs with QT prolonging properties

• Any prior EKG showing QTc > 450 ms

• “Consider” obtaining an EKG if patient not known to be at high risk, or EKG within past year showed QTc < 450 ms

Follow-Up Monitoring

- For patients with risk factors or any EKG with QTc ≥ 450, or history of syncope, repeat EKG at 2-4 weeks after initiation and any significant dose increase.
- When dose reaches 30-40 mg and again at 100 mg/d.
- Any time the patient develops new risk factors.
- If QTc > 500, switch to another opioid.
- If QTc 450 - 500, lower dose or switch opioid.

Methadone Drug Interactions

↑ Methadone Levels
• Quinolones
• Macrolides
• Azole antifungals
• SSRIs
• Ritonavir

↓ Methadone Levels
• Rifampin
• CBZ
• Phenytoin
• Efavirenz, Nelfinavir, Amprenavir, Darunavir
Fentanyl

- More potent than morphine
- Poor hypnotic activity
- Few cardiovascular effects
- **Metabolites are inactive**
  - good choice if renal impairment
- Limited itching/vomiting
- Poor po bioavailability (70% first pass metabolism)
Fentanyl Formulations

- Intravenous (IV)
- Transdermal
- Buccal
- Oral Transmucosal
- Sublingual
Fentanyl con’t.

- Transdermal formulation
  - depot develops
  - if converting from a short acting product, must continue to give short acting dose with initial application of patch (for 12 hours)
  - analgesic effect continues for about 12 hours after removal of patch

- Delivery over 72 hours - some patients require q 48 hours
- Caution in patients <50 kg
- Do not use for acute or post-op pain
- Do not use >25 mcg patch if patient is opioid-naive
Specific Long-Acting Formulations

• Morphine
  • MS Contin
  • Oramorph SR
  • Avinza
  • Kadian

• Methadone*

• Oxycodone
  • OxyContin
  • Xartemis (combination with APAP)

• Oxymorphone
  • Opana ER

Hydromorphone
  • Exalgo
Opioids - ADRs

- Respiratory depression
  - RR of 8
  - use naloxone 0.1 - 0.4 mg, titrate to respiratory rate
• Focus on accidental opioid overdoses

• Database from 2004 – 2011 on opioid-related ADEs
  
  • 47% wrong dose
  • 29% improper patient monitoring
  • 11% others (e.g. drug interactions, excessive doses)
Consider Risks for Respiratory Depression

- Sleep apnea
- Morbid obesity (BMI >30) with high risk of sleep apnea
- No recent opioid use
- Post-op; thoracic or upper abdominal
- Functional status
- Older age
- Longer length of time given anesthesia during surgery
- Receiving other sedating drugs: benzo’s, antihistamines, sedative, CNS depressants
- Pre-existing cardiac or pulmonary dz; major organ failure
- Smoker
Recommendations

• Full body skin assessment
  • E.g. look for fentanyl or buprenorphine patch; incisions from implanted pumps

• Assess respirations
  • set frequency
  • Consider when dose changes or addition of more opioids

• High-risk opioids identified
  • Methadone
  • Fentanyl
  • IV hydromorphone

• Use technology to reduce system errors
  • SmartPumps
  • CPOE
  • PCA to reduce risk of oversedation
Opioid Antagonists

• **Naloxone**: drug of choice for opioid overdose
  • Not effective orally
  • Administered IV to reverse the respiratory effects of opioid agonists; can also be administered intranasally
    • Naloxone dispensing programs nationwide
  • Short duration of action – shorter than that of pure agonists – so several doses or continuous infusion necessary to effectively treat opioid overdose
  • Will precipitate withdrawal in persons who are physically dependent

• **Naltrexone**
  • Orally effective
  • Longer duration of action – half-life 10 hours
  • FDA approved for treatment of alcohol abuse and opioid abuse
Table 2. Association Between Risk Factors and Treatment With Naloxone for Opioid-Associated Oversedation or Respiratory Depression

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal disease</td>
<td>6.034 (2.565–14.195)</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>5.829 (2.687–12.642)</td>
</tr>
<tr>
<td>Concurrent sedating medication</td>
<td>4.750 (1.949–11.578)</td>
</tr>
<tr>
<td>Smoking history</td>
<td>4.421 (2.114–9.245)</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>3.600 (1.742–7.441)</td>
</tr>
<tr>
<td>Hepatic disease</td>
<td>2.444 (0.798–7.486)</td>
</tr>
<tr>
<td>Age range, yr</td>
<td></td>
</tr>
<tr>
<td>61–70</td>
<td>1.739 (0.791–3.821)</td>
</tr>
<tr>
<td>71–80</td>
<td>1.876 (0.688–5.119)</td>
</tr>
<tr>
<td>&gt;80</td>
<td>1.227 (0.505–2.985)</td>
</tr>
<tr>
<td>BMI of ≥30 kg/m²</td>
<td>1.132 (0.568–2.257)</td>
</tr>
<tr>
<td>Opioid naive</td>
<td>0.317 (0.150–0.667)</td>
</tr>
</tbody>
</table>
Risk Factor Grouping Graph

- **Control Group**
- **Naloxone Group**
Opioid ADRs, con’t…

- Changes in level of consciousness
  - usually transient (few days)
  - can use stimulants:
    - methylphenidate - 2.5 to 5 mg q Am
  - for opioid-induced confusion/hallucinations, use haldol 0.5 to 1.0 mg po or 0.25 to 0.5 mg IM or IV

- Antitussive effect
• Pupil constriction
  • antagonized by atropine

• Nausea/Vomiting
  • opioids stimulate CTZ
  • prochlorperaizine, metoclopramide, meclizine, others

• Constipation
  • ↑ GI transit time
  • tolerance does NOT develop to constipation
  • bowel regimen needed
‘ Older’ Therapies for OIC: Laxatives

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Drug</th>
<th>Typical Dose</th>
<th>Onset of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool Softener</td>
<td>Docusate sodium</td>
<td>100 mg PO daily</td>
<td>12 hr to 3 days</td>
</tr>
<tr>
<td>Osmotic agents</td>
<td>polyethylene glycol (Miralax)</td>
<td>17g pwdr in 4-8 oz of beverage</td>
<td>1-4 days</td>
</tr>
<tr>
<td></td>
<td>Magnesium salts</td>
<td>MgOH 400-800mg PO daily; Mg citrate 195-300mL PO daily</td>
<td>0.5 – 6 hr</td>
</tr>
<tr>
<td></td>
<td>Lactulose</td>
<td>10-20g PO daily</td>
<td>1-2 days</td>
</tr>
<tr>
<td></td>
<td>Glycerin suppository</td>
<td>1 supp PR daily PRN</td>
<td>15-30 min,</td>
</tr>
<tr>
<td>Stimulants</td>
<td>Bisacodyl</td>
<td>10-20mg PO daily; also PR</td>
<td>6-12 hr (PO); 20 min to 3 hr (PR)</td>
</tr>
<tr>
<td></td>
<td>Senna</td>
<td>17.2mg PO daily</td>
<td>6-12 hr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2-15 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2-5 min</td>
</tr>
<tr>
<td>Enema</td>
<td>Mineral oil</td>
<td>5-45 mL as single dose</td>
<td>2-15 min</td>
</tr>
<tr>
<td></td>
<td>Sodium phosphate</td>
<td>4.5 oz as single dose</td>
<td>2-5 min</td>
</tr>
</tbody>
</table>
Methylnaltrexone (Relistor®)

- A peripherally-acting opioid antagonist
- Inhibits opioid-induced decreases in GI motility
- Dosing for advanced illness is weight-based:
  - 38-61 kg; give 8 mg/dose
  - 62-114 kg; give 12 mg/dose
  - If <38 kg or >114 kg; give 0.15 mg/kg/dose
- Dosing for CNCP is 12 mg SC once daily
- Dose once, SQ, every other day PRN
- If Clcr<30, dose must be decreased by 50%
- Recently, a PO form was approved: 450 mg PO daily for CNCP
Naloxegol (Movantik™)

- A peripherally-acting opioid antagonist
- Inhibits opioid-induced decreases in GI motility
- Dose = 25 mg PO once daily in the morning
- Decrease dose to 12.5 mg when used concomitantly with moderate CYP3A4 inhibitors (e.g. diltiazem, verapamil)
- Contraindicated with concomitant use of strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin)
- Decrease dose to 12.5 mg in patients with Clcr < 60 ml/min
- Contraindicated with known / suspected GI obstruction
• Itching
  • appears not to be related to histamine release, as not all opioids cause release of histamine
  • antihistamines provide sedation, not relief of itching

• Biliary Tract
  • ↑ biliary tract pressure at 10mg morphine SC
  • ↓ biliary and pancreatic secretions

• Cardiovascular effects
  • except for meperidine, other opioids don’t produce substantial cardiovascular effects
  • opioids produce general bradycardia (vagal effect)
    • blocked by atropine
• Myoclonus
  • all opioids produce this effect; mostly meperidine
  • treat with benzodiazepine or barbiturate

• Urinary Retention
  • usually from intraspinal opioids
  • usually tolerance develops

• ↓ Uterine contractions & prolong labor

• Peripheral vasodilatory effect
  • through release of histamine
Tolerance, Addiction, and Physical Dependence

- Tolerance: an effect of a drug disappears over time as the subject is continuously exposed to the drug
  - tolerance develops to all opioids
  - tolerance to analgesic vs. nonanalgesic effects
    - ↓
      - sedation
      - respiratory depression
      - N/V
Addiction

• A compulsion or overpowering drive to obtain a drug to experience its psychologic effect

• Risk of addiction appears to be very small

• Addiction vs. pseudoaddiction
Physical Dependence

- Characterized by a **withdrawal syndrome** upon discontinuation of the drug. For opioids:
  - diaphoresis
  - lacrimation
  - tachycardia
  - abdominal cramps
  - N/V after 72 hours
Adjuvants
Pharmacotherapy for Neuropathic Pain

- Antidepressants
- Anticonvulsants
- Antiarrhythmics

Capsaicin
- Qutenza: TRPV1 agonist
- High potency
- Applied in MD office after topical anesthetic
- Applied for 1 hour then removed
- Provides relief from post-herpetic neuralgia for up to 3 months
Tricyclic Antidepressants

- Doses are 1/3 to 1/2 of the antidepressant doses
- Analgesic effect takes about 1/3 to 1/2 of the time required for antidepressant activity
- Analgesic effect is similar among all TCAs

- Imipramine
  - ↓
  - Desipramine

- Amitriptyline
  - ↓
  - Nortriptyline
Tricyclic Antidepressants

• Starting dose:
  • 25 mg qhs; ↑ q 3 days by 25 mg to 75 or 100 mg
  • May start lower if elderly or sensitive to anticholinergic effects:
    • 10 mg qhs; ↑ q 3 days by 10 mg
  • May need to titrate up to full antidepressant doses

• ADRs
  • Cardiac rhythm disturbances, dry mouth, sedation, urinary retention
Cautions & Contraindications

• Narrow-angle glaucoma
• Benign prostatic hypertrophy
• Urinary retention
• Constipation
• Arrhythmias/cardiac conduction disturbances
Duloxetine (Cymbalta ®)

- Approved August 2004 for diabetic peripheral neuropathy
- MOA similar to drugs like venlafaxine (Effexor) – causes dual reuptake inhibition of serotonin and norepinephrine
- Labeled dose for this indication is 60 mg QD
- Not recommended for patients with ESRD or Clcr <30. ADRs are similar to Effexor (insomnia or somnolence, dizziness, HA, fatigue)
Anticonvulsants

- Particularly useful for lancinating neuropathic pain
- Variability in pain response
- Monitoring of serum levels is generally not necessary
- Slow titration and weaning is recommended, especially in patients with a seizure history
Carbamazepine & Oxcarbazepine

**Carbamazepine (CBZ)**
- Most commonly used agent for trigeminal neuralgia
- 200 mg qhs; ↑ to 800mg daily in BID-TID doses
- Adverse effects include blurred or double vision, nystagmus, ataxia, dizziness, headache, hematologic effects (pancytopenia, aplastic anemia), SIADH
- Mild anticholinergic effects
- 3A4 substrate; inducer of 1A2, 2C8, 2C9, 2C19, 3A4

**Oxcarbazepine (Trileptal)**
- Unlabeled for neuropathic pain & bipolar
- 25-30% cross sensitivity if rxn to CBZ
- 3A4 inducer (interactions)
- Dosing 300 mg BID (upto 2400 mg/day)
- Use ½ dose if Clcr <30
- Side effect profile similar to CBZ
Gabapentin

• Data support its use in diabetic neuropathy, post-stroke pain, and neuropathic cancer pain

• Many clinicians choose gabapentin as first-line agent due to side effect profile and interactions

• Dose 100-300 mg QD, ↑ to TID dosing to a max dose of 3600 mg QD
Pregabalin (Lyrica®)

- Schedule V
- For diabetic peripheral neuropathy and postherpetic neuralgia
- Gamma-aminobutyric acid analog with similar pharmacology and side effects as gabapentin
- Binds to alpha$_2$-delta protein on voltage-gated calcium channels
- Studied doses range from 150-600 mg/d in 3 divided doses. Adjust dose for renal insufficiency (Clcr <60)
- Side effects: dizziness, somnolence, dry mouth, peripheral edema, blurred vision, weight gain, difficulty concentrating
- May increase CPK – monitor for rhabdo
- Monitor for ↓ platelets or ↑PR
Topiramate (Topamax®)

- 50 mg qhs, ↑ to BID, upto 400 mg per day
- Doses of 25-800 mg QD have been studied for neuropathic pain & migraine prophylaxis (off-labeled use for pain and cluster HA)
- Decrease dose by 50% if Clcr <70
- Can cause acidosis (↓ serum bicarb up to 67%)
- ↑ Risk of kidney stones; reduced by increasing fluid intake
- Cognitive dysfunction, mood disorders, sedation may occur
- Phenytoin and CBZ can decrease topiramate levels; topiramate can decrease digoxin or ethinyl estradiol levels
- Ammonia levels may be increased by topiramate
Antiarrhythmics

**Mexilitine**

- 150-200 mg QD or BID up to 1200 mg QD
- Previously, a lidocaine “test dose” was used to predict if patient will respond to oral mexilitine
- If patient has cardiac abnormalities, refer to cardiologist before starting mexilitine

**Lidocaine (patch)**

- Indicated for post-herpetic neuralgia
- Small amount of lidocaine is absorbed from patch
- May apply up to 3 patches, or cut patch to fit a smaller area
- Recent studies have applied up to 4 patches
- Penetration of lidocaine into intact skin is sufficient to produce analgesia, but less than needed to produce a complete sensory block
Summary of General approaches

• Use an individualized, **multimodal** treatment plan to manage pain, which includes:
  - Nonpharmacologic approaches
  - Non-opioid medications

• The best approach may be to start with a **non-narcotic**

• Take extra precautions with **opioid-naïve** patients
  - Short-term trial with sufficient time to assess response before increasing the dosage

• Recognize that opioid-tolerant patients often have more complex needs
Altered Pharmacokinetics

- **Absorption**
  - ↑ Gastric pH, ↓ Motility

- **Distribution**
  - ↓ lean body mass
  - ↑ body fat
  - ↓ muscle tissue mass
  - ↓ soft tissue mass
  - ↓ total body $H_2O$
  - ↓ albumin production
Altered Pharmacokinetics

• Metabolism
  • ↓ hepatic function
  • ↓ hepatic blood flow

• Elimination
  • ↓ renal mass
  • ↓ renal blood flow
  • ↓ GFR
  • ↓ tubular reabsorption
Hepatic Metabolism

• Phase I: Oxidation
  • Hydroxylation
  • Dealkylation
• Phase I: Reduction
  • Nitroreduction

• Phase II
  • Conjugation
  • Acetylation
  • Methylation

• Alprazolam, triazolam, diazepam

• Nitrazepam

• Oxazepam, lorazepam, temazepam, clonazepam
AGS: NSAIDs

- NSAIDs should be used with caution
- If used chronically, use prn, not ATC
- Short-acting NSAIDs may be preferred to avoid accumulation
- Avoid if history of PUD
- Avoid if abnormal renal function
- Avoid if bleeding problems
- Avoid use of more than one NSAID at the same time (QD ASA ok)
- Expect ceiling limitations

NSAIDs

• In the U.S., about 41,000 hospitalizations and 3,300 deaths occur each year in the elderly due to NSAID use.

• ↓ incidence of upper GI complications with addition of:
  • Misoprostol
  • PPIs
  • H₂-antagonists
Opioids

• Chronic use of opioids for persistent pain has fewer life-threatening risks than long-term daily use of high-dose non-selective NSAIDs

• Patients are likely to have opinions about opioids that may not be based on fact

• The older patient may contribute to undertreatment of pain due to exaggerated fears about addiction to pain medications

• Polypharmacy
AGS: Opioids

- Opioids for episodic or breakthrough pain should be used prn, not ATC
- Use long-acting opioids for continuous pain
- Titrate based on need
- Prevent constipation
  - Use bulking agents cautiously, ↑ physical activity, ↑ fluid intake, use osmotic, stimulant, or motility agent

AGS: Opioids

- Expect mild sedation or impaired cognitive performance
- Monitor for profound sedation and respiratory depression
- Mild nausea should resolve
- Persistent nausea may require an anti-emetic
- Monitor for pruritis or myoclonus

AGS: Opioids

- Re-evaluate frequently for efficacy and side effects
- Ask about prescriptions from other providers
- Requests for early refills should include evaluation for tolerance, progressive disease, or inappropriate behavioral factors

Review

- Obtain complete medical history with attention to:
  - Concurrent medications
  - Prior adverse reactions
  - Comorbid illnesses
- Resist prescribing without a diagnosis
- Begin with low doses and \( \uparrow \) slowly
- Continually review medications (incl. OTC)
- \( \downarrow \) or remove meds when appropriate
Additional Helpful References


Reminders

- After you close out of this webinar, you will receive a survey.
- Please complete this survey to receive continuing education credits.
- For Pharmacy (CPE) information, please email Faith Helm at flees@uri.edu for the CPE approval status, code and instructions for completing a separate program evaluation and reporting CPE data in the URI CPD evaluation system for pharmacists.
- RIGEC will email nursing and social work certificates on Mondays. Healthcentric Advisors will email CME certificates on Mondays.
- For questions about CME certificates, please email Susan Midwood at smidwood@healthcentricadvisors.org

Thank you!!
Geriatric Education Series

Series aims to enhance geriatric competencies of healthcare providers and professionals serving older populations, particularly those with complex care needs, and includes a total five, topic-focused courses offered annually.

1. **Palliative Care and Hospice** – Course 1 (currently being offered online)

2. **Stand Up and Stop Falls! Working Together to Prevent Falls in Older Adults** – Course 2 (March 2017)

3. **Optimal Pharmacotherapy** – Course 3 (April 2017)

4. **Cognitive Dysfunction** – Course 4 (June 2017)

5. **Mental, Social and Behavioral Health** – Course 5 (August 2017)

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