Improving Pharmacologic Pain Management in Older Adults

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Conflict of Interest Disclosure

• Leigh M. Boehmer, Pharm.D., has no real or apparent conflicts of interest to report

Objectives

• Review how physiologic changes and altered pharmacology affect management of pain in the elderly
• Describe available tools for medication review for possible therapeutic duplication, inappropriate use, and drug interactions in the elderly
• Discuss special considerations for pharmacologic pain management in specific clinical settings in the elderly
Age-Related Physiologic Changes

• ↓ volume of distribution
  – ↓ lean body weight
• ↓ serum protein concentrations
• ↓ renal function
• ↓ liver mass and hepatic blood flow
• ↓ activity of drug-metabolizing enzymes
• ↓ pulmonary function

Age-Related Pharmacologic Changes

<table>
<thead>
<tr>
<th>Pharmacologic Concern</th>
<th>Changes with Aging</th>
<th>Common Disease Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal (GI) absorption or function</td>
<td>Slowing of GI transit time; may prolong effects of continuous release drugs; Opioid-related GI dysmotility may be enhanced</td>
<td>Disorders that alter gastric pH may ↓ select drug absorption; Surgically altered anatomy may ↓ select drug absorption</td>
</tr>
<tr>
<td>Transdermal absorption</td>
<td>Few changes in absorption under most circumstances</td>
<td>Temperature and other patch technology may affect absorption</td>
</tr>
<tr>
<td>Distribution</td>
<td>↑ fat to lean body weight ratio may ↑ Vd for fat-soluble drugs</td>
<td>Aging and obesity may result in ↓ drug half-life</td>
</tr>
</tbody>
</table>

Vd=volume of distribution

Achlorhydria and Drug Absorption

Which of the following agents has been associated with significantly increased GI absorption in the setting of achlorhydria?

a) morphine
b) oxycodone
c) hydromorphone
d) methadone
Age-Related Pharmacologic Changes

<table>
<thead>
<tr>
<th>Pharmacologic Concern</th>
<th>Changes with Aging</th>
<th>Common Disease Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver metabolism</td>
<td>• Oxidation may ↓ resulting in ↑ drug half-life&lt;br&gt;• Conjugation usually preserved&lt;br&gt;• First-pass effect usually unchanged&lt;br&gt;• Genetic polymorphisms may affect CYP450 enzymes</td>
<td>• Cirrhosis, hepatitis, or cancer may disrupt oxidation but usually not conjugation</td>
</tr>
<tr>
<td>Renal excretion</td>
<td>• GFR ↓ with age, which results in ↓ renal drug clearance</td>
<td>• CKD may further predispose to renal toxicity</td>
</tr>
<tr>
<td>Active metabolites</td>
<td>• renal clearance will prolong effects of metabolites</td>
<td>• Renal disease may result in ↑ drug half-life</td>
</tr>
</tbody>
</table>

CYP=cytochrome P, GFR=glomerular filtration rate, CKD=chronic kidney disease


Hepatic Changes in the Elderly

• ↓ liver mass by 1% per year after age 50
• 33% ↓ in flow and 21% ↓ in portal blood velocity over age 65
• ↓ serum albumin levels and quality<br>  – ↑ free fraction of protein bound drugs
• No significant change in liver function tests
• Decline in ability of liver to regenerate<br>  – Capacity, however, remains unchanged


Hepatic Changes in the Elderly

• 2 CYP enzymes most important to psychotropic prescribing ↓ with age (-1A2 and -3A)
• Bioavailability of high first-pass elimination drugs ↑ due to 30-40% ↓ in elimination of liver metabolized agents

### Effect of Reduced Hepatic Function on Opioid Pharmacokinetics

<table>
<thead>
<tr>
<th>Opioid</th>
<th>T&lt;sub&gt;1/2&lt;/sub&gt;</th>
<th>Metabolite [plasma]</th>
<th>Comment</th>
<th>Recommendation</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>↑</td>
<td>M6G ↓</td>
<td>Dose ↓</td>
<td>IIb</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>↑</td>
<td>↑</td>
<td>Dose ↓</td>
<td>IIb</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>↑</td>
<td>↑</td>
<td>No data</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>Fentanyl TD</td>
<td>↑</td>
<td>↑</td>
<td>Dose ↓</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>↑</td>
<td>↑</td>
<td>Low activity metabolite</td>
<td>Dose ↓</td>
<td>Iib</td>
</tr>
<tr>
<td>Methadone</td>
<td>↑</td>
<td>↑</td>
<td>No data</td>
<td>No dose change</td>
<td>Iib</td>
</tr>
</tbody>
</table>

T<sub>1/2</sub>=half-life, M6G=morphine-6-β-glucuronide, ↑=unknown, TD=transdermal

### Renal Changes in the Elderly

- ↓ size by 20-30% by age 70
- ↓ in renal blood flow by 10% per decade after age 20
  - GFR ↓ 10 mL/min per decade after age 20
  - Plasma filtration rate ↓ more than GFR
- ↓ free water absorption by 5% per decade after age 50
- ↓ length, #, and thickness of renal tubules
- ↑ interstitial tissue and tubular diverticula

### Effect of Impaired Renal Function on Opioid Pharmacokinetics

<table>
<thead>
<tr>
<th>Opioid</th>
<th>T&lt;sub&gt;1/2&lt;/sub&gt;</th>
<th>Metabolite [plasma]</th>
<th>Comment</th>
<th>Recommendation</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Ila</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>IIb</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>↑</td>
<td>↑</td>
<td>↓ clearance of parent compound and metabolite</td>
<td>Dose ↓</td>
<td>Iib</td>
</tr>
<tr>
<td>Fentanyl TD</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>III</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Iib</td>
</tr>
<tr>
<td>Methadone</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>IV</td>
</tr>
</tbody>
</table>

T<sub>1/2</sub>=half-life, M6G=morphine-6-β-glucuronide, M3G=morphine-3-glucuronide

References:
Narrowed Therapeutic Window

Drug Concentration

Therapeutic window

AGE

Adults

Elderly

Available at www.neurology.org. Accessed on 2.28.15.

Age-Related Pain Changes

- ↓ # and function of peripheral nociceptive neurons
- Thermal and vibratory stimuli sensory threshold increases with age
- 50% ↓ in Pacini’s corpuscles and 10-30% ↓ in Merkle’s disks (pain receptors)
- ↓ endogenous analgesic response via ↓ secretion of endorphins


Myelinated nerves:
- ↓ density
- ↑ abnormal/degenerating fibers
- Slower conduction velocity

Unmyelinated nerves:
- ↓ # large fibers
- No change in small fibers
- Substance P content ↓

Age-Related Pain Changes

- Central nervous system
  - Loss in # of dorsal horn, cortex, midbrain, and brainstem neurons
  - ↓ circulating catecholamines, acetylcholine, GABA, and serotonin
  - Altered cerebral evoked responses

GABA=gamma-aminobutyric acid

Factors Affecting Pain Perception

- Uncontrolled pain ↓ overall quality of life
- Loneliness ↓ pain threshold and is a risk factor for depression
  - Lack of intimate relationships, dependency and loss ↑ loneliness
- Depression and anxiety limit patients’ engagement in treatment and ↑ healthcare needs

Potentially Inappropriate Medication Use

Estimated annual US healthcare costs related to the use of potentially inappropriate medications (PIM) was which of the following?

- a) $3 billion
- b) $5.5 billion
- c) $7.2 billion
- d) $9.3 billion
Screening Tool to Alert doctors to the Right Treatment (START)

- “Inappropriate” prescribing:
  - Acts of commission (giving unsuitable drugs)
  - Acts of omission (failure to give when indicated)
- N=600 elderly (≥65 yoa) patients admitted with acute illness to a teaching hospital
  - START used to assess errors of omission
  - ≥1 omissions found in 57.9% of patients

START Criteria (Select Examples)

- Cardiovascular system
- Respiratory system
- Central nervous system (CNS)
  - Antidepressant in the presence of clear-cut symptoms, lasting at least 3 months (N=10)
- GI system
- Locomotor system
  - Anti-rheumatic drug therapy with known, mod-severe disease lasting >12 weeks (N=13)
- Endocrine system

Likelihood of Omission

- 65-74 yoa: 55.2% (1 med omitted)
- 75-84 yoa: 54.8% (1 med omitted)
  - OR 1.05, CI 0.71-1.45; P=0.93
- ≥85 yoa: 72.2% (1 med omitted)
  - OR 2.08, CI 1.24-3.5; P<0.01
- Females vs. males (1 med omitted)
  - OR 2.29, CI 1.65-3.19; P<0.01
## 2012 Updated Beers Criteria: Pain

<table>
<thead>
<tr>
<th>Therapeutic Class/Drug(s)</th>
<th>Rationale</th>
<th>Recommendation</th>
<th>Quality of Evidence</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
</table>
| Meperidine                | - Neurotoxicity  
- Not effective in doses used | Avoid | High | Strong |
| Non-COX selective NSAIDs  | - ↑ risk GI bleeding and peptic ulcer dx | Avoid chronic use, unless other options are not available | Moderate | Strong |
| Indomethacin, Ketorolac   | - ↑ risk GI bleeding  
- Most AEs of all NSAIDs (indomethacin) | Avoid | Moderate/High | Strong |


## 2012 Select Updated Beers Criteria

<table>
<thead>
<tr>
<th>Therapeutic Class/Drug(s)*</th>
<th>Rationale</th>
<th>Recommendation</th>
<th>Quality of Evidence</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
</table>
| Antispasmodics             | - Highly anticholinergic  
- Uncertain effectiveness | Avoid, except in short term palliative settings (e.g., ↓ oral secretions) | Moderate | Strong |
| Tertiary TCAs              | - Highly anticholinergic  
- Sedating  
- Orthostatic hypotension | Avoid | High | Strong |

*Select examples only. TCA=tricyclic antidepressant


## 2012 Select Updated Beers Criteria

<table>
<thead>
<tr>
<th>Therapeutic Class/Drug(s)*</th>
<th>Rationale</th>
<th>Recommendation</th>
<th>Quality of Evidence</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
</table>
| Benzodiazepines            | - ↑ sensitivity to class  
- ↓ drug metabolism  
- ↑ risk of cognitive impairment | Avoid for treatment of insomnia, agitation, or delirium | High | Strong |
| Skeletal muscle relaxants  | - ↑ fracture risk, sedation  
- Efficacy at tolerable doses questionable | Avoid | Moderate | Strong |

*Select examples only

Screening Tool of Older Persons’ potentially inappropriate Prescriptions (STOPP)

Study population
715 consecutive admissions to a university teaching hospital in patients ≥65 yoa

Design
STOPP and Beers criteria applied to prospective review of diagnoses, reason for admission, and concurrent medications

Results
• Primary endpoint: identification of PIM via STOPP and Beers criteria
• Secondary endpoint: Proportion of PIM with causal connection to reason for admission


STOPP Results

• STOPP criteria:
  – 336 PIMs divided amongst 35% (N=247)
  - 25% one PIM, 7% two PIMs, 1% three PIMs, 1% four PIMs; 1 patient with five PIMs
  – 91% AEs responsible for admission “caught”
• Beers criteria:
  – 226 PIMs divided amongst 25% (N=177)
  - 19% one PIM, 5% two PIMs, 3% three PIMs; 1 patient with four PIMs
  – 48% AEs responsible for admission “caught”


STOPP (Select) Criteria

<table>
<thead>
<tr>
<th>Criterion</th>
<th>N</th>
<th>PIM AE as a causal factor to admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long term, long-acting benzodiazepine</td>
<td>65</td>
<td>26 (fall 9; fall + fracture 8; fall + head injury 1; overdose 1; cognitive decline 7)</td>
</tr>
<tr>
<td>NSAID with h/o PUD or GI bleeding</td>
<td>3</td>
<td>1 (PUD)</td>
</tr>
<tr>
<td>NSAID with h/o mod-severe HTN</td>
<td>20</td>
<td>3 (GI bleed 2; PUD 1)</td>
</tr>
<tr>
<td>Long-term NSAID for joint pain</td>
<td>9</td>
<td>1 (PUD)</td>
</tr>
<tr>
<td>NSAID with chronic renal failure</td>
<td>9</td>
<td>1 (acute renal failure)</td>
</tr>
<tr>
<td>Long-term opiates in those with recurrent falls</td>
<td>1</td>
<td>1 (fall + femur fracture)</td>
</tr>
<tr>
<td>Long-term opiates as first-line therapy for mild-mod pain</td>
<td>13</td>
<td>3 (fall + femur fracture)</td>
</tr>
<tr>
<td>Long-term opiates in those with dementia, unless mod-severe pain</td>
<td>2</td>
<td>2 (delirium 1; fall + femur fracture 1)</td>
</tr>
</tbody>
</table>

h/o=history of, PUD=peptic ulcer disease, HTN=hypertension

Dietary Supplements

- Herbals
- Megavitamins
- Minerals
- Amino acids
- Folk remedies
- Lifestyle diets


Conditions for which CAM is Most Frequently Used

CAM=complementary and alternative medicine


Spectrum of Clinical Risk

Opioid Pharmacokinetic Interactions

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Primary Metabolism</th>
<th>Drug-Drug Interactions</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>UGT 2B7</td>
<td>Ranitidine, rifampin, valspodar</td>
<td>IIb</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>CYP 2D6</td>
<td>Unlikely to cause effects</td>
<td>IV</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>UGT 1A3, UGT 1A2</td>
<td>Very little data on effects</td>
<td>IV</td>
</tr>
<tr>
<td>Fentanyl TD</td>
<td>CYP 3A4</td>
<td>Potent inhibitors may ↑ fentanyl (ex., ritonavir, ketoconazole)</td>
<td>Ib</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>CYP 3A4</td>
<td>Only minor effects</td>
<td>IV</td>
</tr>
<tr>
<td>Methadone</td>
<td>CYP 2B6, CYP 3A4, 2C19</td>
<td>Inducers and inhibitors of respective CYP enzymes</td>
<td>IV</td>
</tr>
</tbody>
</table>

UGT=UDP-glucuronosyltransferase


Reasons for De-Prescribing in Geriatric Patients

- ↓ potential adverse effects
- ↓ associated drug(s) costs
- ↓ polypharmacy
- Improved quality of life
- Improved medication adherence


Approach to Safe De-Prescribing: A Geriatric Model

Establish Life Expectancy
Identify Treatment & Patient Goals
Assess Time to Benefit
Treatment Targets

Approach to Safe De-Prescribing: A Geriatric Model

- Accurate Med List
- Assess
- Adjust
- Follow Up and Repeat

Use Caution when De-Prescribing

<table>
<thead>
<tr>
<th>Drug/Class</th>
<th>Adverse withdrawal effect(s)</th>
<th>Suggested action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-blockers</td>
<td>Rebound HTN, agitation</td>
<td>Wean gradually</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Rebound tachycardia, palpitations, angina re-emergence</td>
<td>Wean gradually</td>
</tr>
<tr>
<td>Nitrates</td>
<td>Angina re-emergence</td>
<td>Gradual tapering</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Re-emergence of heart failure</td>
<td>Caution if H/o heart failure</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Delirium, insomnia, seizures</td>
<td>Wean gradually</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Anxiety, nausea, vomiting, dizziness</td>
<td>Wean gradually</td>
</tr>
<tr>
<td>Steroids</td>
<td>HPA suppression if long-term use</td>
<td>Wean gradually if long-term</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Dyskinesia, nausea, agitation</td>
<td>Wean gradually</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Dysphoric mood, agitation</td>
<td>Wean gradually</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Re-emergence of A. fib</td>
<td>Caution if H/o rapid A. fib</td>
</tr>
</tbody>
</table>

HTN=hypertension, HPA=hypothalamic-pituitary axis, A. fib=atrial fibrillation

Acetaminophen Trivia

Used as an analgesic and antipyretic, acetaminophen is available in more than ____ pharmaceutical products in the US?

- a) 200
- b) 400
- c) 600
- d) 800
Acetaminophen (APAP) MOA

- Centrally acting analgesic, increases pain threshold
- MOA not well understood...
  - Nitric oxide pathway interaction
  - COX-2 inhibition
  - Interaction with serotonergic, opioidergic, or endocannabinoid systems
- Antipyretic due to action in hypothalamus
  - Vasodilation; ↑ peripheral blood circulation


APAP Highlights

- Treatment of choice for osteoarthritis
- Maximum daily dose usually 4 Gm
  - ↓ 50-75% in those with hepatic dysfunction or h/o alcohol abuse
- As of 3/2014, all products with >325 mg per dose have discontinued marketing


IV Acetaminophen (Ofirmev®)

- Approved for mild-to-mod pain and mod-to-severe pain in combination with opioids
- 3 active comparator studies found no significant difference in efficacy or AEs; 1 showed numerical ↓ in opioid consumption
- 2 meta-analyses showed ~20% reduced morphine requirements on post-op day 1
- Markedly more expensive than alternatives: oral or rectal acetaminophen and IV ketorolac

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

- 23.5% of elderly adverse drug event-related hospitalizations due to NSAIDs
- Non-acetylated forms (ex., salsalate) may have lower GI toxicity than aspirin
- COX-2 selective agents (ex., celecoxib) have fewer significant GI adverse events
- Concomitant administration of H2RAs or PPIs may ↓ the risk of GI ulceration
- Eradication of *H. pylori* ↓ NSAID-associated peptic ulceration

COX=cyclooxygenase, H2RA=H2 receptor antagonists, PPI=proton pump inhibitor


### NSAID COX-1/-2 Selectivity

![Diagram showing COX-1 and COX-2 selectivity](Image)


### Select NSAIDs for Persistent Pain in Older Adults

<table>
<thead>
<tr>
<th>Analgesic</th>
<th>Recommended Starting Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choline magnesium trisalicylate</td>
<td>500-750 mg PO every 8h</td>
<td>Long half-life may allow daily or BID dosing; minimal antiplatelet effect</td>
</tr>
<tr>
<td>Salsalate</td>
<td>500-750 mg PO every 12h</td>
<td>May need to check salicylate levels; minimal antiplatelet effect</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>100 mg PO daily</td>
<td>Higher doses linked to ↑ rates of GI and cardiovascular AEs</td>
</tr>
<tr>
<td>Naproxen sodium</td>
<td>220 mg PO twice daily</td>
<td>Less cardiovascular AEs</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>200 mg PO TID</td>
<td>May inhibit aspirin's antiplatelet effect</td>
</tr>
<tr>
<td>Diclofenac sodium</td>
<td>50 mg PO BID or 75 mg ER PO daily</td>
<td>May see higher cardiovascular risk profile</td>
</tr>
</tbody>
</table>

ER=extended release

### Common NSAID Adverse Events

<table>
<thead>
<tr>
<th>System</th>
<th>Adverse Event(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI</td>
<td>Dyspepsia, abdominal pain, gastric ulcers, bleeding, perforation</td>
</tr>
<tr>
<td></td>
<td>↑ risk with non-selective NSAIDs</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>↑ blood pressure, myocardial infarction, congestive heart failure, cerebrovascular accident</td>
</tr>
<tr>
<td></td>
<td>↑ risk with COX-2 selective NSAIDs</td>
</tr>
<tr>
<td>Hematologic</td>
<td>↑ risk for bleeding and anemia</td>
</tr>
<tr>
<td>Renal</td>
<td>Water and sodium retention, ↓ renal blood flow, electrolyte imbalances, prerenal azotemia, hyporeninemic hypoaldosteronism</td>
</tr>
<tr>
<td>Hepatic</td>
<td>↑ transaminases, hepatitis</td>
</tr>
</tbody>
</table>


### Patient Case Question

PD is a 60 yo female with OA of her right knee and a PMH of mod liver dysfunction and controlled HTN. She has been taking ibuprofen (IBU) 600 mg PO TID for 4 weeks with good relief, but her BP today is 187/92 mmHg. The best option for continued treatment of her OA is…?  

- a) APAP 1 Gm PO QID  
- b) Continue with current IBU schedule  
- c) Celecoxib 200 mg PO daily  
- d) Diclofenac gel 4 Gm TOP QID

### Short-Acting Opioid Highlights

- μ-opioid receptor agonism (primary)  
- No ceiling effect and have been shown to relieve all types of pain  
- Every patient should be prescribed a bowel regimen to prevent constipation  
- Long-term therapy associated with hormonal suppression  
- Scheduled administration before anticipated pain episode(s) may be appropriate in patients with cognitive impairment

Arnstein P. Pain Management Nursing. 2010;11(2); S11-22.
Pertinent LA Opioid Prescribing Information for Elderly Patients

Morphine sulfate ER: 30-, 45-, 60-, 75-, 90-, and 120 mg capsules (Avinza®)

Dosing interval
- Once a day

Dosing highlights
- Titrate using a minimum of 3-day intervals
- May open capsule and sprinkle pellets on applesauce; do not chew; use immediately
- Maximum dose: 1600 mg due to renal toxicity risk of fumaric acid

Drug interactions
- Alcohol may result in rapid release of a potentially fatal dose
- PGP inhibitors may ↑ absorption by about two-fold


Dosing interval
- Once a day

Dosing highlights
- Initial dose in mild to moderate hepatic dysfunction: 5 mcg/hr
- Maximum dose of 20 mcg/hr due to risk of QTc prolongation

Drug interactions
- CYP3A4 inhibitors may ↑ levels; CYP3A4 inducers may ↓ levels
- Class la and III antiarrhythmics may ↑ risk of QTc prolongation


Methadone: 5- and 10 mg tablets (Dolophine®)

Dosing interval
- Every 8-12 hours

Dosing highlights
- High inter-patient variability in absorption and metabolism
- Use low doses according to the table in the package insert

Drug interactions
- CYP450 inducers may ↑ levels; CYP450 inhibitors may ↓ levels
- Potentially arrhythmogenic agents may ↑ risk of QTc prolongation


Dosing interval
- One transdermal system every 3 days

Dosing highlights
- Use 50% of dose in mild or moderate hepatic or renal dysfunction
- Avoid use in severe hepatic or renal impairment
- Contraindicated in postoperative or mild pain management

Drug interactions
- CYP3A4 inhibitors may ↑ fentanyl exposure
- CYP3A4 inducers may ↓ fentanyl exposure


Hydromorphone ER: 8-, 12-, and 16 mg tablets (Exalgo®)

Dosing interval
- Once a day

Dosing highlights
- Moderate hepatic dysfunction: start with 25% of usual dose
- Moderate renal dysfunction: start with 50% of usual dose
- Must be able to swallow tablets whole

Drug interactions
- Do not use in patients with a sulfa allergy (sodium metabisulfite)


Morphine sulfate ER: 10-, 20-, 30-, 40-, 50-, 60-, 80-, 100-, 200 mg (Kadian®)

Dosing interval
- Once a day or every 12 hours

Dosing highlights
- Titrate using a minimum of 2-day intervals
- May open capsules and sprinkle pellets on applesauce; do not chew; use immediately
- May open capsule and mix into ~10 mL of water, then flush through a 16-French gastrostomy tube

Drug interactions
- Alcohol may result in rapid release of a potentially fatal dose
- PGP inhibitors may ↑ absorption by about two-fold


16
Pertinent LA Opioid Prescribing Information for Elderly Patients

Tapentadol ER: 50-, 100-, 150-, 200-, and 250 mg tablets (Nucynta ER®)

Dosing interval: Every 12 hours

Dosing highlights:
- Dose once daily in moderate hepatic dysfunction with 100 mg per day maximum
- Avoid use in severe hepatic and renal dysfunction
- Serotonin syndrome has been described

Drug interactions:
- Alcohol may result in rapid release of a potentially fatal dose
- Contraindicated in patients taking MAOIs

Dosing interval: Every 12 hours

Dosing highlights:
- Use 5 mg every 12 hours as initial dose in patients with mild hepatic and/or renal dysfunction and patients >65 yoa
- Contraindicated in moderate and severe hepatic dysfunction

Drug interactions:
- Alcohol may result in rapid release of a potentially fatal dose

Pertinent LA Opioid Prescribing Information for Elderly Patients

Oxycodone CR: 10-, 15-, 20-, 30-, 40-, 60-, and 80 mg tablets (OxyContin®)

Dosing interval: Every 12 hours

Dosing highlights:
- Hepatic dysfunction: start with 30-50% of usual dose
- Renal dysfunction (CrCl <60 mL/min): start with 20% of usual dose
- Consider using other analgesics in patients with GI disorders that may predispose them to obstruction

Drug interactions:
- CYP3A4 inhibitors may ↑ oxycodone exposure
- CYP3A4 inducers may ↓ oxycodone exposure

Healthcare System Opioid Barriers

- Lack of a neighborhood pharmacy
- Transportation issues
- Absence of high dose opioid at pharmacy
- No caregiver to help with drug preparation and/or administration
- Negative attitudes toward patients needing opioid therapy

### Select Adjuvant Pain Agents

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Recommended Starting Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desipramine, nortriptyline, amitriptyline</td>
<td>10 mg PO at bedtime</td>
<td>Significant risk of AEs (anticholinergic and cardiovascular) in older patients</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>20 mg PO daily</td>
<td>Monitor BP, dizziness, and cognitive effects</td>
</tr>
<tr>
<td>Milnacipran</td>
<td>12.5 mg PO daily, titrate to 50 mg PO BID</td>
<td>↓dose 50% if CrCl &lt;30 mL/min; do not use with narrow angle glaucoma</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>100 mg PO at bedtime</td>
<td>Monitor sedation, ataxia, edema</td>
</tr>
<tr>
<td>Baclofen</td>
<td>6 mg PO up to TID</td>
<td>Monitor urinary function, cognitive effects, sedation; avoid abrupt discontinuation</td>
</tr>
<tr>
<td>Tramadol</td>
<td>12.5-25 mg PO every 4-6h</td>
<td>Mixed opioid, serotonin- and norepinephrine-reuptake inhibitor; monitor opioid AEs, seizures, serotonin syndrome</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>50 mg PO every 4-6h</td>
<td>Trials suggest ; GI AEs relative to opioids</td>
</tr>
</tbody>
</table>


### Future of Pain Management

- Non-traditional analgesics
  - Targeted gene therapy
    - Vectors deliver enkephalins to sensory nerves
  - Spicamycin derivative
    - Non-opioid acetylcholinesterase inhibitor
  - Tetrodotoxin derivative
    - Non-peptide, non-opioid neurotoxin
  - Cytokine and nerve growth factor inhibitors


### Parting Pearls

- Identify applicable age-related pharmacologic changes
- Conduct a prospective review for drug-drug/-herbal interactions before a prescription is written
- Remember PIMs to avoid and errors of omission
- Prescribe non-opioids, where appropriate
- Begin therapy with the lowest possible dose and increase slowly
- Consider the need for preventive, concurrent medications
- Discuss role of non-pharmacologic management