Pharmacologic Management of Pain in Older Patients

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INTRODUCTION

• Pain management
  – What’s pain? ➔ etiology, acuity, pathophysiology
  – Physiologic changes in elderly patient
  – Methods
  – Route of administration
  – Balance between optimal analgesia and side effect
  – Monitor components
INTRODUCTION

- Physiologic changes in elderly patients
  - Changes in metabolism
    - more difficult to get optimal serum concentrations of medications
    - more difficult to clear medications from the system
  - Gastrointestinal (GI) motility is decreased and absorption by the GI system may be altered
  - An increased body mass index → fat-soluble medications to have longer half-lives
  - liver metabolism decreases
  - Glomerular filtration rate decreases
INTRODUCTION

- Methods
  - Nonpharmacologic methods
    - RICE - Rest, Ice, Compression, Elevation
    - superficial heat or ice
    - transcutaneous electrical nerve stimulation (TENS)
    - sustained stretching of the affected muscle and joints
    - low-level aerobic activity
    - Etc.
INTRODUCTION

- Methods
  - Pharmacologic methods
    - Administer medication ROUTINELY not PRN
    - Use the least invasive route of admin, First
    - Begin with a low dose. Titrate carefully until comfort.
    - Reassess and adjust dose frequently to optimize pain relief while monitoring and managing side effects.
INTRODUCTION

- Route of administration
  - If the oral route is being utilized for food entry, then medications for nonemergent treatment should be given orally as well.
  - Blood concentrations achieved via oral medications are more steady as compared to intravenous dosing, thus reducing the risk of adverse effects in the older population. \(^\text{12}\)
• Acute injuries or acute exacerbations of chronic conditions should be treated in a different way than persistent pain.
• Initial treatment of non-acute, non-emergent pain with acetaminophen products and non-steroidal analgesics is recommended.
• Acute pain - Unless contraindicated, should include 2-4 days of around-the-clock acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs)
**World Health Organisation (WHO) analgesic Ladder**

- **Step 1**: Non-opioid with/without adjuvant analgesic
- **Step 2**: Opioid for mild to moderate pain plus non-opioid with/without adjuvant analgesic
- **Step 3**: Opioid for moderate to severe pain plus non-opioid with adjuvant analgesic

**Guidelines**:
- Pain persisting, move up one step
- Signs of toxicity or severe side effects, reduce dose or move down one step

**Medication**
• Non-opioids
  – Acetaminophen
    • should be considered as initial and ongoing pharmacotherapy in the treatment of persistent pain, particularly musculoskeletal pain
    • effectiveness and good safety profile.
    • Maximum daily recommended dosages of 4 gm per 24 hrs
MEDICATION

• Non-opioids
  – Acetaminophen
    • Around-the-clock dosing for several days is effective as compared to waiting for the pain to be uncontrolled to take a dose. For a new injury or acute exacerbation of a chronic problem.
    • Absolute contraindications: liver failure
    • Relative contraindications and cautions: hepatic insufficiency, chronic alcohol abuse/dependence (reduce intake)
MEDICATION

• Non-opioids
  – Nonselective NSAIDs and COX-2 selective inhibitors
    • Older adults are at higher risk of adverse events
    • the lowest effective dose should be used for the shortest period
    • should not take more than one nonselective NSAIDs/COX-2 selective inhibitor for pain control.
    • Ibuprofen or naproxen are good first-line choices for patients with low GI risk
• Non-opioids
  – Nonselective NSAIDs and COX-2 selective inhibitors
    • Absolute contraindications: current active peptic ulcer disease, chronic kidney disease, heart failure
    • Relative contraindications and cautions: hypertension, H. pylori, history of peptic ulcer disease, concomitant use of corticosteroids or SSRIs
    • Significant GI bleeding, which is further increased with the co-administration of aspirin for cardiovascular disease (esp. Ibuprofen)
MEDICATION

• Non-opioids
  – Nonselective NSAIDs and COX-2 selective inhibitors
    • NSAIDs with caution, who are at risk for nephrotoxicity due to volume depletion and use of diuretics.
    • If the GI risk is higher, an NSAID can be co-administered with either misoprostol or a proton pump inhibitor.
    • Cyclooxygenase-2 (COX-2) selective inhibitor have fewer GI risks but have increased cardiovascular toxicity.
    • If a COX-2 inhibitor is chosen due to higher GI risk, co-administration of low-dose aspirin for cardioprotection should be considered.
MEDICATION

• Non-opioids
  – Nonselective NSAIDs and COX-2 selective inhibitors
    • For patients with significant risk of both GI and cardiovascular toxicity, and for whom NSAIDs is considered the best therapeutic option, the combination of either naproxen or celecoxib with low-dose aspirin therapy should be considered.
    • Topical NSAIDs (eg, diclofenac) have been effective for short-term use in pain relief.
MEDICATION

• Non-opioids
  – Nonselective NSAIDs and COX-2 selective inhibitors
    • All patients taking non-selective NSAIDs and COX-2 selective inhibitors should be routinely assessed for gastrointestinal and renal toxicity, hypertension, heart failure, and other drug-drug and drug-disease interactions.
MEDICATION

• Non-opioids
  – Muscle relaxant
    • most often used for acute injury involving muscle pain.
    • directly affect neurotransmitters within the central nervous system (CNS), peripheral-acting agents at the level of the muscle itself.
    • generally thought to act as CNS depressants.
    • Most use for antispasticity.
    • There are three centrally-acting antispasticity medications: diazepam; baclofen; and tizanidine.
### Medications Affecting Muscle Tone

<table>
<thead>
<tr>
<th>Medication</th>
<th>Action</th>
<th>Starting Dose</th>
<th>Best Used For</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>GABA-A agonist</td>
<td>0.5-1 mg q 8 hr</td>
<td>Acute injury, few days only</td>
<td>Sedation, decreased muscle strength</td>
</tr>
<tr>
<td>Baclofen</td>
<td>GABA-B agonist</td>
<td>5 mg q 8 hr</td>
<td>Spinal cord origin spasticity</td>
<td>Weakness, lethargy</td>
</tr>
<tr>
<td>Tizanidine</td>
<td>Alpha-2 agonist</td>
<td>1 mg q 9 hr</td>
<td>CNS spasticity</td>
<td>↓ BP, pulse</td>
</tr>
<tr>
<td>Dantrolene</td>
<td>↓ calcium release and binding in muscles</td>
<td>25 mg bid</td>
<td></td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>Botulinum toxin</td>
<td>↓ ACh release at neuromuscular junction</td>
<td>Variable</td>
<td>Focal dystonia</td>
<td>Local weakness, serious adverse reaction from distant spread of the toxin</td>
</tr>
</tbody>
</table>

GABA = gamma-aminobutyric acid; ↓ = decreased; ACh = acetylcholine; q 8 hr = every 8 hours; bid = twice per day; CNS = central nervous system; BP = blood pressure.

* Dosage must be tapered off.
• Opioids
  – both acute and chronic pain that is moderate-to-severe in intensity, pain-related functional impairment or diminished quality of life due to pain.
  – in the geriatric patient → start at the lowest dose, titrate carefully, and assess the patient frequently for side effects.
  – common to use in combination with other drugs to treat pain, such as NSAIDS, anticonvulsants, and antidepressants.
  – Maximal safe doses of acetaminophen or NSAIDs should not be exceeded when using fixed-dose opioid combination agents as part of an analgesic regimen.
• Opioids
  – most commonly use:
    – Morphine (gold standard)
    – transdermal fentanyl (Duragesic®)
    – Hydromorphone (Dilaudid®)
    – oxycodone
    – Methadone
<table>
<thead>
<tr>
<th>Drug</th>
<th>Approximate Equipotency with Morphine (Drug : Morphine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydromorphone</td>
<td>5:1</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>1.5:1 to 2:1</td>
</tr>
<tr>
<td>Codeine</td>
<td>1:12</td>
</tr>
<tr>
<td>Methadone</td>
<td></td>
</tr>
<tr>
<td>Daily Morphine</td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td></td>
</tr>
<tr>
<td>30 – 90 mg</td>
<td>3.7:1</td>
</tr>
<tr>
<td>90 – 300 mg</td>
<td>7.75:1</td>
</tr>
<tr>
<td>&gt; 300 mg</td>
<td>12.75:1</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>80:1 to 100:1 (for subcutaneous dosing of each)</td>
</tr>
</tbody>
</table>

NB: Does not consider incomplete cross-tolerance
MEDICATION

• Opioids
  – When long-acting opioid preparations are prescribed, breakthrough pain should be anticipated, assessed, prevented and/or treated using short-acting, immediate-release opioid medications.
  – Methadone should be initiated and titrated cautiously only by clinicians well versed in its use and risks.
  – Patients taking opioid analgesics should be reassessed for ongoing attainment of therapeutic goals, adverse effects, and safe and responsible medication use.
MEDICATION

• Opioids
  – Side effects
    • Constipation – need proactive laxative use
    • Nausea/vomiting
    • Urinary retention
    • Neurotoxicity (OIN): delirium, myoclonus → seizures
    • Dry mouth
    • Respiratory depression
    • Drug interactions
    • Itch/rash

Most side effects are fairly mild and disappear with removal of the opiate therapy.
• Opioids
  – Morphine
    • easy to titrate and can be used in both acute and chronic pain.
    • elderly patients have a greater sensitivity to the potency of morphine and a decreased ability to clear morphine.
    • impair renally excreted ⇒ neurotoxic metabolites
    • Can be administered PO, IV, IT, PR, Epidural
    • It is 1/3 to 1/6 as potent when administered orally when compared to IV administration
MEDICATION

• Opioids
  – Morphine
    • significant side effects in the elderly, such as myoclonus, delirium, hallucinations, and significant sedation.
    • start at low doses and titrate slowly
    • check renal function prior to initiating morphine sulfate.
MEDICATION

• Opioids
  – Transdermal Fentanyl
    • provide analgesia for up to 72 hours
    • slow onset of action → difficult to use in the patient with acute pain, and titration becomes longer and more difficult.
    • less effective drug to use in the cachectic, frail patient.
    • The absorption of the drug can increase as body temperature increases.
    • Once the patch is removed, the time to drug elimination is significantly longer in the elderly patient.
MEDICATION

• Opioids
  – Methadone

  • potent, long-acting opiate analgesic, added benefits in neuropathic pain syndromes
  • should be used with extreme caution in the elderly patient.
  • extensively metabolized by the liver and GI mucosa.
  • Both the half-life and the elimination vary in individuals, especially the elderly.
MEDICATION

• Opioids
  – Methadone
    • Drug interactions occur with both inducers and inhibitors of the CYP450 isoenzyme 2D6 system.
    • use small doses and titrate slowly.
    • The practice of combining methadone with other long-acting opiates should be avoided in the elderly patient.
  – Meperidine and propoxyphene not be utilized by elderly patients.
MEDICATION

• Persistent neuropathic pain
  – Depression and anxiety commonly accompany persistent pain → should be screened for depression and its related symptoms.
  – treatments of choice:
    • Nonpharmacologic methods
    • Pharmacologic methods
      – Antidepressants
      – membrane stabilizer medications
      – opiates.
Persistent neuropathic pain
- treated only with opiates, have higher incidences of adverse events → development of opiate hyperalgesia
- The combined effects of two types of medications may lead to better analgesia with fewer side effects.
- Treatment of a coexisting anxiety disorder is a bit more problematic due to the potential drug-drug interactions of anxiolytics and pain medications.
MEDICATION

• Antidepressant
  – Improve mood, sleep, and, shown to have independent analgesic properties.
  – In older persons start at low doses, typically no more than half of the recommended dosage, then increased gradually over the first month of treatment.
  – Dosages for effective pain relief are usually less than those for depression.
  – Should not be combined MAOi
• Antidepressant
  – tricyclic antidepressants (TCAs).
    • inhibition of reuptake of the neurotransmitters serotonin and norepinephrine.
    • unwanted side effects due to the nonspecific inactivation of histamine, acetylcholine, and alpha-1 adrenergic receptors.
    • Common side effects include sedation, dry mouth, constipation, urinary retention, sinus tachycardia, memory impairment, orthostatic hypotension, blurred vision, and weight gain.
• Antidepressant
  – tricyclic antidepressants (TCAs).
    • EKG should be documented prior to any TCA therapy, as these medications can prolong the QT interval and worsen cardiac arrhythmias.
    • TCA selection is usually determined by the side-effect profile
      Ex. Nortriptyline is generally thought to have the lowest anticholinergic side-effect profile.
MEDICATION

• Antidepressant
  – tricyclic antidepressants (TCAs).
    • Other medications that affect the CYP450 system in the liver may alter serum concentrations of TCAs.
    • Abrupt discontinuation of TCAs can result in a withdrawal syndrome including fever, sweating, nausea, or dizziness.
    • Careful, an amount three to five times the usual dose can be toxic → seizures, coma, and cardiac arrhythmias.
• **Antidepressant**
  – Selective serotonin reuptake inhibitors (SSRIs)
    • most likely due to their efficacy and low side-effect profile.
    • role for SSRIs in pain management separate from depression has not been proven effective.
  – serotonin-norepinephrine reuptake inhibitors (SNRIs)
    • have the analgesic efficacy of TCAs with a better side-effect profile (lack of alpha-1, cholinergic, or histaminergic receptor activation)
MEDICATION

• Antidepressant
  – Duloxetine and venlafaxine are both FDA-approved for depression.
    • Duloxetine has indications for the treatment of pain related to diabetic peripheral polyneuropathy and fibromyalgia
    • Both drugs can lower seizure thresholds and have a “black box” warning for increased suicidality in children, adolescents, and young adults.
# MEDICATION

## Antidepressants Used for Pain Management

<table>
<thead>
<tr>
<th>Medication and Action</th>
<th>Approved Use</th>
<th>Starting Dose</th>
<th>Maximum Dose</th>
<th>Contraindications</th>
<th>Metabolized by CYP450</th>
<th>Renal Dose Adjustment</th>
<th>Hepatic Dose Adjustment</th>
<th>Taper Off</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nortriptyline</strong> († SER, NEP)</td>
<td>Depression</td>
<td>10 mg qd</td>
<td>100 mg qd</td>
<td>Arrhythmias, urinary retention</td>
<td>Yes</td>
<td>N/A</td>
<td>?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Duloxetine</strong> († SER, NEP)</td>
<td>Depression, diabetic peripheral neuropathy, FM, anxiety</td>
<td>30 mg qd</td>
<td>60 mg qd</td>
<td>Suicidal ideation, history of seizure disorder</td>
<td>Yes</td>
<td>CrCl &lt; 70 mL/min/1.73m²</td>
<td>↓ 50%</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Venlafaxine</strong> († SER, NEP)</td>
<td>Depression</td>
<td>25 mg bid</td>
<td>75 mg tid</td>
<td>History of seizure disorder, hypertension, suicidal ideation</td>
<td>Yes</td>
<td>CrCl &lt; 30 mL/min/1.73m²</td>
<td>Contraindicated</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Bupropion</strong> († NEP; Dop)</td>
<td>Depression, ADHD</td>
<td>75 mg bid</td>
<td>450 mg qd</td>
<td>Suicidal ideation, history of seizure disorder, alcohol use</td>
<td>Yes</td>
<td>↓</td>
<td>Max 75 mg/day</td>
<td>No</td>
</tr>
<tr>
<td><strong>Trazodone</strong> († SER)</td>
<td>Depression, Insomnia</td>
<td>25 mg qhs</td>
<td>100 mg qhs</td>
<td>Orthostatic hypotension, priapism</td>
<td>Yes</td>
<td>?</td>
<td>Caution</td>
<td>Yes</td>
</tr>
</tbody>
</table>

† = increased; SER = serotonin; NEP = norepinephrine; Dop = dopamine; FM = fibromyalgia; ADHD = attention-deficit/hyperactivity disorder; qd = every day; bid = twice per day; qhs = every evening or bedtime; tid = three times per day; N/A = not applicable; CrCl = creatinine clearance; ↓ = decreased.
MEDICATION

• Anticonvulsants
  – the medications referred to as *membrane stabilizers*, usually considered for patients who cannot achieve adequate analgesia with other medications or combination of medications.
# Anticonvulsants Used for Pain Management

<table>
<thead>
<tr>
<th>Medication</th>
<th>Approved Use</th>
<th>Starting Dose</th>
<th>Maximum Dose</th>
<th>Risk</th>
<th>Renal Dose Adjustment</th>
<th>Hepatic Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>Neuropathic pain, PHN</td>
<td>100 mg qhs</td>
<td>3800 mg/day</td>
<td>Slow titration</td>
<td>CrCl &lt; 60 mL/min/1.73m²</td>
<td>N/A</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Neuropathic pain, PHN, FM</td>
<td>25 mg bid</td>
<td>300 mg/day</td>
<td>Dizziness, platelets</td>
<td>CrCl &lt; 60 mL/min/1.73m²</td>
<td>N/A</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Seizure, migraine</td>
<td>25 mg qhs</td>
<td>50 mg bid</td>
<td>Cognition</td>
<td>CrCl &lt; 70 mL/min/1.73m²</td>
<td>Caution</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Seizure</td>
<td>300 mg bid</td>
<td>1200 mg bid</td>
<td>Na</td>
<td>CrCl &lt; 50 mL/min/1.73m²</td>
<td>?</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Seizure, TN</td>
<td>100 mg bid</td>
<td>1200 mg bid</td>
<td>+HLA-B*1502, agranulocytosis or aplastic anemia</td>
<td>CrCl &lt; 10 mL/min/1.73m²</td>
<td>Caution</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Seizure</td>
<td>25 mg bid</td>
<td>250 mg bid</td>
<td>Rash</td>
<td></td>
<td>25-50%</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Seizure, migraine</td>
<td>250 mg qd</td>
<td>500 mg bid</td>
<td>Preg Cat D</td>
<td>N/A</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

PHN = postherpetic neuralgia; FM = fibromyalgia; TN = trigeminal neuralgia; qhs = every evening or bedtime; bid = twice per day; qd = every day; ↑ = increased; ↓ = decreased; Na = serum sodium concentration; Preg Cat D = positive evidence for fatal risk; CrCl = creatinine clearance; N/A = not applicable.

* Must be tapered off

* Age increases risk of serious dermatologic rash such as toxic epidermal necrolysis.

* +HLA-B*1502 allele carries significant risk for Stevens-Johnson syndrome.
• Others
  – Topical lidocaine in a 5% patch
    • approved for postherpetic neuralgia (persistent allodynia at the site of a herpes zoster rash, or shingles.)
    • Lidocaine inhibits sodium ion channels, stabilizing the neuronal membrane and impeding conduction of the action potential.
    • Up to three patches can be applied simultaneously for a total of 12 out of 24 hours.
    • All patches need to be removed for a period of 12 hours to avoid toxicity.
MEDICATION

• Others

  – Topical lidocaine in a 5% patch
    • Should not be applied to areas of inflamed or broken skin → affect their absorption and risk for toxicity.
    • Patients with elevated body temperatures will also have increased absorption of the medication
    • monitored for toxicity including tinnitus and ataxia.
    • should not be used with superficial heat such as heating pads

For postherpetic neuralgia, a better choice may be prevention with a high-potency single dose vaccine that has been shown to reduce the incidence of postherpetic neuralgia by 67%
INTERVENTIONAL PAIN MANAGEMENT

• Facet Joint Intervention
  (1) intra-articular joint injection with anesthetics and/or corticosteroids
  (2) blockade of the medial branch of the dorsal ramus
  (3) ablation of the medial branch

• Epidural Injections
  – caudal block
  – interlaminar approach
  – transforaminal approach,
INTERVENTIONAL PAIN MANAGEMENT

• Spinal Cord Stimulators
• Intrathecal Drug Delivery
  – chronic, refractory, malignant, or nonmalignant pain
  – dosing is significantly lower than via the oral route, sparing the patient from many of the systemic side effects of the medication.
  – morphine, hydromorphone, or fentanyl for analgesia, baclofen for spasticity, clonidine for neuropathic pain, and several others.
  – Medications may also be used in combination to achieve multiple goals.
TAKE HOME MESSAGE

- Prescribing decisions based on What’s pain?
  → etiology, acuity, pathophysiology
- Physiologic changes in elderly patient
- Non-pharmacological + pharmacological methods
- Oral route preferred.
- START LOW AND GO SLOW.
- Need frequent re-assessment
  • Monitor
  • effectiveness of analgesia
  • ADLs/functional status
  • adverse effect
REFERENCES

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