PAIN MANAGEMENT IN THE OLDER ADULT: QUALITY OF LIFE STILL MATTERS!

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MY TWO PERTINENT DISCLOSURES

1. I do not have a financial relationship or interest with any proprietary entity producing healthcare goods or services in conjunction with this presentation.
2. I will be discussing the off-label, adult use of FDA-approved pharmaceuticals. Such use requires a thorough review of the published literature in adults, especially in the older adult population.

MY LEARNER OBJECTIVES

- Characterize the epidemiology of pain in older adults
- Review geriatric pain and mood assessment methods
- Define health-related quality of life
- Describe the factors complicating and barriers to more effective pain management in the older adult
- Recognize importance of analgesic genetic polymorphism
- Apply multimodal pain management in older adults
- Justify the use of opioids in older adults
- Debate the American Geriatric Society Beers Criteria for potentially inappropriate medication use in older adults
THE AGING UNITED STATES POPULATION
“THE SILVER TSUNAMI”

Number of Americans > 65 years (millions)

<table>
<thead>
<tr>
<th>Year</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1900</td>
<td>3.1</td>
</tr>
<tr>
<td>1920</td>
<td>4.9</td>
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<tr>
<td>1940</td>
<td>9.0</td>
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<tr>
<td>1960</td>
<td>16.6</td>
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<td>1980</td>
<td>25.5</td>
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<td>2000</td>
<td>31.2</td>
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<tr>
<td>2010</td>
<td>40.3</td>
</tr>
<tr>
<td>2020</td>
<td>54.8</td>
</tr>
<tr>
<td>2030</td>
<td>72.1</td>
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PREVALENCE OF PAIN IN OLDER PERSONS

- Pain most common in older segments of the population
- Marked age-related increase in prevalence of persistent pain of 20%–80% until later middle age (50–65 years), then a plateau in "oldest" old (85+ years)
- Headache, abdominal pain, (new onset) back pain, and chest pain all peak during later middle age
- Exception is pain associated with degenerative joint disease (e.g., osteoarthritis) that shows an exponential increase until at least 90 years of age.

IMPACT OF PAIN IN OLDER PERSONS

“The remarkable increase in longevity is a triumph of modern medicine and improved public health; however, an increased lifespan is only a blessing if one can stay healthy, active, and engaged. Bothersome or unremitting pain represents a major threat to quality of life in all persons...”
HEALTH-RELATED QUALITY OF LIFE

**Health-related quality of life** (HRQoL) is a multi-dimensional concept that includes domains related to physical, mental, emotional and social functioning.

**Patient Reported Outcomes Measurement Information System (PROMIS) Global Health Measure** – 10-items: Assess global physical, mental and social HRQoL through questions on self-rated health, physical HRQoL, mental HRQoL, fatigue, **pain**, emotional distress, social activities, and roles.


SELF-REPORTED PAIN SCALES

- **Numerical Rating Scale (NRS)**
- **Verbal Descriptor Scale (VDS)**
- **Pain Thermometer (PT)**


ASSESSMENT OF PAIN IN OLDER PERSONS

- Identify assessment tool a patient can easily use
- Institutions should have several tool options available for use with older adults.
- "If the use of Numeric Rating Scale (NRS) is questionable, the **Verbal Descriptor Scale (VDS)** or **pain thermometer** have been shown to be the most preferred and easiest to understand tools and are recommended for literate patients."

ASSESSMENT OF MOOD

Screening for depression and anxiety very important
Patient Heath Questionnaire 9-Item Depressive Symptom Screener (PHQ-9)
Generalized Anxiety Disorder 7-Item Scale (GAD-7)
Well validated measures
Can be quickly completed
Thus measure at every visit


BARRIERS TO EFFECTIVE GERIATRIC PAIN MANAGEMENT: HEALTH CARE PROVIDERS

Fear that prescribing, dispensing and administering drug will lead to patient substance abuse or addiction
Risk of disciplinary action by federal or state regulators
Concern about multiple comorbidities and concomitant use of medications (polypharmacy)
Concerns about excessive side effects from opioids and other analgesic medications
Conventional belief that pain medication should be reserved for patient with only moderate-to-severe pain
Inadequate awareness and education about pain and patient-specific pain management therapies
Failure to re-evaluate patient’s pain status as underlying disease process progresses


BARRIERS TO EFFECTIVE GERIATRIC PAIN MANAGEMENT: PATIENTS AND/OR FAMILY

Ideology that pain builds character or is just part and parcel of “getting old”
Desire to be a “good patient” or to avoid additional testing – both resulting in underreporting of pain
Cognitive/memory impairments with difficulties in diagnosing pain and assessing treatment effectiveness
Lack of social capital, physical accessibility to pain treatment or cost of drugs and other interventions
Belief that narcotics will cause mental confusion, personality change, and drug-seeking behaviors
Fear that use of opioid analgesics will lead family and friends to view the patient as “druggie” (stigma)
Fear that a younger generation family member will divert (“steal”) the medication

Choosing an analgesic treatment will largely depend on the cause and intensity of pain and other individual patient factors, such as the presence of comorbidities, drug–drug interactions, drug–disease interactions, adherence to therapy, and cost.

Even though older patients are generally at a heightened risk of adverse events, pharmacologic therapy can be safely initiated, and be effective, when all risk factors are taken into consideration.

CYP2D6 ISOENZYME

- One of the cytochrome (CYP) P450 isoenzymes
- CYP2D6 responsible for Phase I 0-demethylation
- Converts inactive pro-drug into active metabolite

<table>
<thead>
<tr>
<th>Pro-drug</th>
<th>Metabolite</th>
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</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>Morphine</td>
</tr>
<tr>
<td>Hydrocodeine</td>
<td>Hydromorphone</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Oxymorphone</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Oxymorphone</td>
</tr>
</tbody>
</table>

Oxycodone, hydromorphone & oxymorphone do not require metabolism to be active analgesics. Oxymorphone has 40X higher affinity for µ opioid receptor than oxycodone.

CYP2D6 GENETIC POLYMORPHISM

- CYP2D6 is critical for opioid effectiveness and toxicity.
- Patients are classified into the following four categories of CYP2D6 activity, from highest to lowest functioning:
  - Ultra-rapid metabolizer (UM)
  - Extensive or normal metabolizer (EM)
  - Intermediate metabolizer (IM)
  - Poor metabolizer (PM)
- 5-14% of Caucasians, 0-5% Africans, and 0-1% of Asians classified as PM
- 4-6% of Caucasians, 3-6% of African-Americans and 2% of Asian-Americans classified as UM
A PubMed search from 1980 to 2012 identified 42 cases of opioid-induced respiratory depression (OIRD) in chronic pain patients. Cases published pre-2000 mainly involved morphine in cancer patients, while post-2000 cases predominantly involved methadone or transdermal fentanyl in non-cancer pain patients. Specific OIRD factors also varied.

Cases published pre-2000 involved elevated opioid plasma levels due to renal impairment and sensory deafferentiation. Cases post-2000 involved elevated plasma levels due to CYP450 drug metabolism.

CYP2D6 also metabolizes TCAs, SSRIs, SNRIs, mexiletine, lidocaine, ondansetron, beta-blockers, and tamoxifen. Drugs that are weak inhibitors of cytochrome P-450 isozymes—such as citalopram, escitalopram, sertraline, and venlafaxine—would be expected to have fewer drug-drug interactions.

The basic pain treatment schema, or “rationale polypharmacy” for chronic pain, seeks to treat all four levels of the chronic pain process.
CLASSES OF CHRONIC MEDICATIONS FOR MULTIMODAL ANALGESIA

<table>
<thead>
<tr>
<th>Therapeutic Class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants (TCAs, SNRIs, SSRIs, NDRIs, TeCA/NaSSA)</td>
<td>Amitriptyline, nortriptyline, imipramine, desipramine; venlafaxine, duloxetine, milnacipran, citalopram, paroxetine, sertraline; buproprion; mirtazapine</td>
</tr>
<tr>
<td>Antiepileptics/Anticonvulsants</td>
<td>Carbamazepine, oxcarbazepine, phenytoin, topiramate, lamotrigine, levetiracetam, gabapentin, and pregabalin</td>
</tr>
<tr>
<td>Anti-arrhythmics</td>
<td>Lidocaine, meselicine</td>
</tr>
<tr>
<td>Topical formulations</td>
<td>Lidocaine, capsaicin, diclofenac</td>
</tr>
<tr>
<td>Analgesics</td>
<td>NASIDs, tramadol, opioids</td>
</tr>
<tr>
<td>NMDA antagonists</td>
<td>Ketamine, dextromethorphan, methadone</td>
</tr>
<tr>
<td>GABA-A and B antagonists</td>
<td>Clonazepam and baclofen</td>
</tr>
<tr>
<td>Alpha-2 agonists</td>
<td>Clonidine, tizanidine</td>
</tr>
<tr>
<td>Muscle relaxants</td>
<td>Baclofen, dantrolene, tizanidine, methocarbamol</td>
</tr>
</tbody>
</table>


PARADOX OF PAIN MANAGEMENT IN U.S.

- Institute of Medicine (IOM) concluded that pain is not optimally managed in the U.S. and that effective treatment of chronic pain will require a coordinated national effort to transform how the public, policy makers, and health care providers view the condition.

- Each day, 46 people die from an overdose of prescription opioids in the U.S.

- CDC Director Dr. Tom Frieden: “Prescription drug overdose is epidemic in the United States. All too often, and in far too many communities, the treatment is becoming the problem.”

Institute of Medicine (2011) : Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education and Research.

www.cdc.gov/vitalsigns/opioid-prescribing/

“This color-coded U.S. map shows the number of painkiller prescriptions per person in each of the fifty states plus the District of Columbia in 2012.”

www.nih.gov/sodium/potassium/potassium.html
### OPIOIDS FOR CHRONIC PAIN IN THE OLDER PATIENT

- **Hydrocodone** – Requires CYP2D6 → hydromorphone
  - 2.5 mg, 5 mg, 7.5 mg or 10 mg + 325 mg APAP
  - 2.5 mg + 167 mg APAP/5 mL elixir for a “start low/go slow” effort

- **Oxycodone** – Active parent prodrug
  - 2.5 mg, 5 mg, 7.5 mg or 10 mg + 325 mg APAP or without APAP
  - 5 mg/5 mL solution for start low/go slow

- **Hydromorphone** – Active parent prodrug
  - 2 mg hydromorphone = 5 mg of oxycodone
  - 2, 4, 8 mg tablets or 1 mg/1 ml liquid

- **Oxymorphone** – Fewer drug interactions (“cleaner”) + less active metabolites
  - 5 mg, 10 mg without APAP

- **Fentanyl** – Transdermal route has lower diversion risk
  - Rapid tolerance and hence frequent escalating dose
  - Difficult to convert back to oral equivalent opioid once on higher daily dose

- **Meperidine** – Excellent oral bioavailability
  - High protein bound with sustained clinical/side effects
  - Prolonged QTc possible at surprisingly low doses of 30 mg/day

### OXYMORPHONE IN GERIATRIC PATIENTS: THE OPTIMAL OPIOID?

- **Oxymorphone** extensively metabolized in the liver → primarily by UGT-2B7 to oxymorphone-3-glucuronide
- Does not significantly induce or inhibit CYP-2C9 or CYP-3A4 activity in healthy adults
- Based on available clinical trials, oxymorphone is a safe and effective opioid analgesic with similar dose-dependent side effects as other opioids.
- Because it is metabolized predominantly by non-CYP-450 mechanisms, oxymorphone should have fewer drug–drug interactions with agents that are metabolized by those common pathways.

### TRAMADOL: NEW 1ST LINE PRIOR TO USE OF PURE MU AGONIST OPIOID?

- **SNRI with weak mu-receptor agonist properties**
- **Musculoskeletal pain but also a “global analgesic”**
- Use endorsed by the American Geriatric Society
- Schedule IV per DEA as of August 18, 2014
- High side effect profile: dizziness/vertigo, nausea/vomiting, constipation, headache, somnolence
- Follow liver function tests with long-term, chronic use because reversible elevation can occur
- Avoid using (at least at higher doses) with all TCAs, probably all the SSRIs, and hydrocodone to avoid tramadol accumulation and attendant risk of grand mal seizure
- 0.5 to 1 mg/kg PO q 6 to 8 hours PRN
- 50 mg scored immediate release tablet at a sliding dose of 25 mg, 50 mg, 75 mg or 100 mg
TOPOCAL VERSUS ORAL NSAIDS FOR CHRONIC PAIN

- Cochrane: 7688 participants in 34 studies from 32 publications
- Randomized, double blind studies where at least one treatment was a topical NSAID product (cream, gel, patch, solution)
- Direct comparison of topical NSAID with an oral NSAID did not show any difference in efficacy
- Topical NSAIDs can provide good levels of pain relief
- Topical diclofenac solution is equivalent to that of oral NSAIDs in knee and hand osteoarthritis, but there is no evidence for other chronic painful conditions.
- Incidence of gastrointestinal adverse events is reduced with topical NSAIDs compared with oral NSAIDs.
- Dilcofenac: Flector® patch q 12 hours or Voltaren® gel QID

ANTIDEPRESSANTS AS ANALGESICS

- Tricyclic antidepressants
  - 2° amines: nortriptyline and desipramine preferable
  - Nortriptyline 5 mg/5 ml solution for gradual titration
  - Initial low-dose (5 to 10 mg) and monitor side effects
  - ECG to r/o WPW and prolonged QTc
  - Blood level at 0.5 mg/kg to r/o being “slow metabolizer”
- Serotonin norepinephrine reuptake inhibitors
  - Less α₁-adrenergic blockade/anticholinergic effects than TCAs
  - Venlafaxine: Dose of > 200 mg/day needed for analgesia
  - Duloxetine: Generic available in U.S. as of December 2013
- Selective serotonin reuptake inhibitors
  - Paroxetine and citalopram may have analgesic properties when used in combination with other medications (e.g., an opioid)

ANTICONVULSANT ANALGESICS I

- Central calcium channel (α2δ) blockers
  - Gabapentin (Neurontin®)
    - 100 mg, 300 mg, or 400 mg capsule: 600 mg or 800 mg tablet
    - 250 mg per 5 ml solution → geriatric option to start low/go slow
    - Initially 50 to 100 mg tid, increased gradually to 300 mg tid, then as needed and tolerated to 600 to 900 mg tid
    - GFR 30-59 (BID), 15-29 (QD), <15 (1 dose post-dialysis)
  - Pregabalin (Lyrica®)
    - 25, 50, 75, 100, 150, 200, 225, and 300 mg hard-shell capsules
    - 20 mg per 1 ml solution → geriatric option for start low/go slow
    - FDA-approved only for fibromyalgia, diabetic neuropathy, and PHN
    - Initially 25 to 50 mg bid increased gradually to 150 mg bid and as needed to maximum of 300 mg bid
- May require 2 to 3 weeks for onset of efficacy
- Need to be taken on scheduled basis — not PRN
THE GABAPENTANOIDS

- Gabapentin
  - Exhibits saturable gastric absorption
  - Less predictable nonlinear (zero-order) pharmacokinetics
  - Blood levels can be monitored
  - Therapeutic range: 2-10-20 μg/mL

- Pregabalin
  - Plasma levels proportionately increase with increasing dose
  - Linear (first order) pharmacokinetics
  - Blood levels are not available
  - 95+% excreted unchanged renally
  - Periodically in patients at risk for CKD

- Dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and “thinking abnormal” (primarily difficulty with concentration/attention)

ANTICONVULSANT ANALGESICS II

- Carbamazepine (Tegretol®)
- Topiramate (Topamax®)
- Lamotrigine (Lamictal®)
- Oxcarbazepine (Trileptal®)
  - Peripheral and central Na channel blocker
  - 150 mg, 300 mg and 600 mg tablets
  - 300 mg per 5 ml oral suspension
  - Adults: 300 mg bid → target dose of 900 mg bid
  - 3% incidence of hyponatremia (< 125) in adults
  - Sedation common at higher doses – especially in the older population, so start with liquid @ low dose

AMERICAN GERIATRIC SOCIETY BEERS CRITERIA FOR POTENTIALLY INAPPROPRIATE MEDICATION USE IN OLDER ADULTS

- Dr. Mark Beers recognized more than 2 decades ago that the prevention of adverse drug events in older adults is crucial to the public health of this vulnerable population.

- Although not without limitations, the Beers Criteria have done more than any other tool in the past decade to improve the awareness of and clinical outcomes for older adults with polypharmacy and for the most vulnerable older adults at risk of adverse drug events.

- Accomplished this because of their explicit nature, simple application for non-pharmacy experts, and wide dissemination.

- The Beers Criteria remain simultaneously one of the most used and most controversial sets of medication criteria in the world.
<table>
<thead>
<tr>
<th>Therapeutic Category or Drug</th>
<th>Rationale</th>
<th>Recommendation</th>
<th>Quality of Evidence</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tertiary TCAs</td>
<td>Amitriptyline, Imipramine&lt;br&gt;Highly anticholinergic, sedating, and cause orthostatic hypotension</td>
<td>Avoid</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>Alpha agonists, central&lt;br&gt;Cholinergic&lt;br&gt;But: Tramadol is not listed</td>
<td>Clonidine&lt;br&gt;High risk of adverse D6 effects; may cause hypotension and anticholinergic hypotension</td>
<td>Avoid</td>
<td>Low</td>
<td>Strong</td>
</tr>
<tr>
<td>Skeletal muscle relaxants&lt;br&gt;Diceporol, Cyclobenzaprine, Methocarbamol</td>
<td>Tizanidine&lt;br&gt;Increase risk of cognitive impairment, delirium, falls, fractures, and motor vehicle accidents</td>
<td>Avoid</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>Non-selective NSAIDs&lt;br&gt;Etodolac, Meloxicam, Nabumetone</td>
<td>Clonazepam&lt;br&gt;Increase risk of cognitive impairment, delirium, falls, fractures, and motor vehicle accidents</td>
<td>Avoid</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>Opioids&lt;br&gt;Hydromorphone, Oxycontin</td>
<td>Carisoprodol, Cyclobenzaprine, Methocarbamol&lt;br&gt;Most muscle relaxants are poorly tolerated by older adults because of anticholinergic adverse effects, sedation, risk of fracture, effectiveness at dosages tolerated by older adults is questionable</td>
<td>Avoid</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td>Antiepileptic drugs&lt;br&gt;Gabapentin, Pregabalin</td>
<td>Hydrocodone, Oxycodone&lt;br&gt;Not included on 2012 AGS Beers Criteria</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
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</table>

2012 AMERICAN GERIATRIC SOCIETY BEERS CRITERIA: PAIN MEDICINES