**Pharmacology for Pain Management**

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**Disclosures:**

Most material for this lecture has been shamelessly stolen from others.

Inadequate credits have been given in my slides to all who have contributed to this lecture.

**Definition of Pain**

- "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (IASP, 1979)
- "Pains what the person says it is, existing when and where the person says it does." (McCaffery & Beebe, 1999)

**Paradigms Taxonomy (old)**

- **Category I**
  - Acute
  - Normal
  - Natural
  - Nociceptive
  - Peripheral
  - Physiological
  - Primary
  - Stimulus response

- **Category II**
  - Chronic (pain syndrome)
  - Abnormal
  - Presynaptic
  - Central
  - Neuropathic
  - Secondary
  - CNS remodeling

**Types of Pain**

- **Eudynia**
  - Expected pain, "good pain", warning pain, acute pain, category I pain
  - Common Complaint

- **Maldynia**
  - Abnormal pain, destructive pain, chronic pain, category II pain
  - Chronic Illness

- **Types of Pain**
  - Nociceptive
  - Visceral
  - Neuropathic
  - Inflammatory
Visceral Pain

- Pain we feel when our internal organs are damaged or injured
- The most common form of pain
- Poorly localized
- Not all internal organs are sensitive to pain
- Internal organs with nociceptors are mostly the hollow viscera

**Neuropathic pain**

- Is the result of damage to the peripheral nervous system and often appears to be without cause. Examples of neuropathic pain are diabetic neuropathy, postherpetic neuralgia, poststroke pain, and phantom limb pain. Chemotherapy and spinal cord injury may also be underlying factors.

**Inflammatory pain**

- Can also be protective, because this guarding of sensitive injured tissues or joints provides an opportunity for healing. One goal of treating inflammatory diseases, such as rheumatoid arthritis, is to control the inappropriate or excessive inflammatory actions of macrophages, mast cells, and granulocytes.

**Pharmacologic Agents Affect Pain Differently**

- **Descending Modulation**
  - Anticonvulsants
  - Opioids
  - NMDA-Receptor Antagonists
  - Tricyclic/SNRI Antidepressants

- **Central Sensitization**
  - Anticonvulsants
  - Opioids
  - NMDA-Receptor Antagonists
  - Tricyclic/SNRI Antidepressants

- **Peripheral Sensitization**
  - Local Anesthetics
  - Topical Analgesics
  - Tricyclic Antidepressants

**A Brief History of Medicine**

2000 BC- Here, eat this root
1000 AD- That root is heathen, here say this prayer
1800 AD- That prayer is superstition, here drink this potion
1900 AD- That potion is snake oil, here swallow this pill
1950 AD- That pill is ineffective, here take this antibiotic
2000 AD- That antibiotic is artificial, here eat this root
All Medications are not alike
The Right Tool for the Right Job

Pharmacology
- Opioids & Opioid Like Analgesics
- Non-opioid Analgesics
- Adjuvant Medications

Opiate Agonists
- Alfentanil
- Codeine
- Diacetylmorphine
- Fentanyl
- Hydrocodone
- Hydromorphone
- Levomethadyl Acetate
- Levorphanol
- Meperidine
- Methadone
- Morphine

Opiate Agonists
- Opium
- Oxycodone
- Oxymorphone
- Propoxyphene
- Remifentanil
- Sufentanil
- Tapentadol
- Tramadol
- Buprenorphine
- Butorphanol
- Nalbuphine
- Pentazocine
Opiate Agonists

- Codeine
- Fentanyl
- Hydrocodone
- Hydromorphone
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- Morphine
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- Oxymorphone
- Sufentanil
- Tapentadol
- Tramadol
- Buprenorphine
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- Nalbuphine
- Pentazocine

Mixed Agonist-Antagonists

- Buprenorphine
- Butorphanol
- Nalbuphine
- Pentazocine

Opiate Agonists

- Codeine
- Fentanyl
- Hydrocodone
- Hydromorphone
- Methadone
- Morphine
- Oxycodone
- Oxymorphone
- Sufentanil
- Tapentadol
- Tramadol

Opiate Agonists

- Tramadol
  - Weak \(\mu\) agonist
  - Releases serotonin
  - Mild norepinephrine reuptake inhibitor
  - Analgesic potency closer to codeine
- Tapentadol
  - \(\mu\) agonist
  - Norepinephrine reuptake inhibitor
  - Structurally similar to tramadol
  - Analgesia similar to hydrocodone & oxycodone
- Schedule II

Dosing and Conversion Chart for Opioid Analgesics
### Equal Analgesic Opioid Dosing

<table>
<thead>
<tr>
<th>Opioid</th>
<th>IV</th>
<th>PO</th>
<th>Transdermal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>0.1</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>1.5</td>
<td>7.5</td>
<td>30</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>10</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Morphine</td>
<td>10</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>10</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Meperidine</td>
<td>20</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>120</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>0.4</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>150</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tapentadol</td>
<td>38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Opioid induced hypogonadism

- **Men**
  - Erectile dysfunction
  - Impotence
  - Loss of muscle mass
- **Women**
  - Irregular periods
  - Oligomenorrhea
  - Amenorrhea
- **In Both**
  - Flushing & sweating
  - Loss of libido
  - Infertility
  - Depression & Anxiety
  - Low energy levels
  - Osteoporosis & fractures

### Do We Use Too Much?

- USA 4.6 percent of the world’s population
- Use 80% of the global supply of opioids
- 99% of the global supply of hydrocodone
- 1.85 million in USA dependent or abusing prescription opioids
- Deaths from prescription drug overdoses
  - 2nd-leading cause of accidental deaths nationwide

### Non-opioid Analgesics

- **Acetaminophen**
- **NSAIDs**

### Acetaminophen

- Derived from coal tar
- Class of drugs known as “analgesics”
- Only such drug still in use today
- Acute overdose fatal liver damage
- In rare individuals, a normal dose can also
- Skin is heightened by alcoholism
- Toxicity is the foremost cause of acute liver failure in the Western world
NSAIDs

- Analgesic
- Antipyretic
- Anti-inflammatory
- Mechanism
  - Inhibit both peripheral and central cyclooxygenase, reducing prostaglandin formation
  - Multiple isoforms of COX
    - COX-1
    - COX-2
    - COX-3
### NSAIDs

<table>
<thead>
<tr>
<th>Chemical Class</th>
<th>Generic Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>COX-2 Selective Inhibitors</td>
<td>celecoxib</td>
</tr>
</tbody>
</table>

### NSAIDs

<table>
<thead>
<tr>
<th>Chemical Class</th>
<th>Generic Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-acidic</td>
<td>nabumetone</td>
</tr>
<tr>
<td>Acids</td>
<td>aspirin, diflunisal, choline magnesium trisalicylate, salsalate</td>
</tr>
<tr>
<td>Salicylates</td>
<td>ibuprofen, naproxen, fenoprofen, ketoprofen, flurbiprofen, oxaprozin</td>
</tr>
</tbody>
</table>

### NSAIDs

- Acetic acids
- COX-2 inhibitors
- Fenamates
- Naphthylalkanones
- Oxicams
- Proprionic acids
- Salicylates, acetylated
- Salicylates, non-acetylated

### NSAIDs: COX-2 Selectivity

- Properties - All NSAIDs
  - Nonspecific analgesics, but greater effectiveness likely in bone pain and inflammatory pains
  - Dose dependent effects, with ceiling dose
  - Marked individual variation in response to different drugs
  - Drug to drug variation in toxicities partly determined by COX-1/COX-2 selectivity
NSAIDs: GI Toxicity

- Increased risk of gastroduodenopathy: varied lesion
- Increased risk of both upper and lower GI bleeding
- Varied symptoms and no correlation between severity of symptoms and extent of lesions
- Toxicity related to drug, dose, duration, comorbidities, concurrent therapies

PUD: Relative Risk Current Use vs Nonuse

GI Risk: Coxibs

Cumulative incidence of gastroduodenal ulcers: A 12-week study in RA patients

- Gastrointestinal toxicity reduced by
  - proton pump inhibitors
  - misoprostol
  - (?) H2 blockers

NSAIDs: GI Risk

NSAID GI Risk: Probability of Recurrent GI Bleeding in 6 Months

All patients

- Celecoxib 4.5% (3.1-6.7)
- Diclofenac + Omeprazole 6.4% (4.3-8.4)

Without concomitant ASA

- Celecoxib 4.5% (2.7-6.3)
- Diclofenac + Omeprazole 5.6% (3.6-7.7)
NSAIDs
- Bleeding Diathesis
  - COX-2 inhibitors: Reduced effect on platelets
- Renal Toxicity
  - COX-2 inhibitors: no evidence of renal sparing

NSAIDs: Risk of CV Toxicity
- All NSAIDs seem to have a small risk for cardiovascular thromboembolic events, and probably heart failure

NSAIDs: Risk of CV Toxicity
- APPROVe (Adenomatous Polyp Prevention on Vioxx)
  - Rofecoxib 25 mg/d vs. placebo
  - Risk of CV events began to increase after 18 months
  - After about 2.5 yrs, CV events in
    - 46/1,287 patients taking rofecoxib (3.5%)
    - 26/1,299 patients taking a placebo (2%)
- Vioxx withdrawn from market on 9/30/04

NSAIDs: Risk of CV Toxicity
- Celecoxib
  - No increased risk in CLASS study
  - No increased risk in two other prevention studies
    - Prevention of Spontaneous Adenomatous Polyps Trials
    - Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT)

NSAIDs: Risk of CV Toxicity
- Parecoxib/Valdecoxib
  - Postop CABG (N = 1671)
  - Parecoxib + valdecoxib vs. valdecoxib vs. placebo
  - Relative risk (95% CI) of CV events 1.9 (1.1, 3.2) for each drug group compared with placebo

NSAIDs: Risk of CV Toxicity
- ADAPT
  - Celecoxib 200 mg bid vs. naproxen 220 mg bid vs. placebo
  - 50% increase in CV risk over 3 years in the naproxen group
- NIH closed the study
Drugs used for musculoskeletal pain

All nonselective NSAIDs and COX

Multipurpose analgesics

Drugs used for muscle spasm

Protective effects of ASA may be attenuated

Drugs used for neuropathic pain

Drugs used for bone pain

Inhibition of COX

There is no evidence that nonselective NSAIDs reduce CV risk, as ASA does

NSAIDs: Guidelines for Use

- Consider as nonspecific analgesics
- Risk: benefit calculation required in every case
- Significant CV history, CHF, renal insufficiency are strong relative contraindications
- Consider celecoxib for chronic use in the presence of GI risk factors
- For acute use: many possible
- Use lowest effective dose
- Rotate drug if ineffective
- Note instruction regarding ASA

Adjuvant Analgesics

- Traditional definition
  
  *Drugs with indications other than pain which may be analgesic in specific circumstances*

- Numerous drugs in diverse classes, some now specifically indicated for pain

Adjuvant Analgesics

- Multipurpose analgesics
- Drugs used for neuropathic pain
- Drugs used for musculoskeletal pain
- Drugs used for bone pain
- Drugs used for bowel obstruction
- Drugs used for muscle spasm
- Co-morbid mood disorders

### NSAIDs Risk of CV Toxicity: Summary

- There is no evidence that nonselective NSAIDs reduce CV risk, as ASA does
- Inhibition of COX-2 activity, whether or not COX-1 activity is also inhibited, increases risk
- Protective effects of ASA may be attenuated by NSAIDs and dosing order may be important
- All nonselective NSAIDs and COX-2 selective NSAIDs are now required to have a "box warning" for CV risk (as of 6/05)

### Inhibition of Platelet Aggregation on Ibuprofen Plus Aspirin

- Consider as nonspecific analgesics
- Risk: benefit calculation required in every case
- Significant CV history, CHF, renal insufficiency are strong relative contraindications
- Consider celecoxib for chronic use in the presence of GI risk factors
- For acute use: many possible
- Use lowest effective dose
- Rotate drug if ineffective
- Note instruction regarding ASA

### Adjuvant Analgesics

- Multipurpose analgesics
- Drugs used for neuropathic pain
- Drugs used for musculoskeletal pain
- Drugs used for bone pain
- Drugs used for bowel obstruction
- Drugs used for muscle spasm
- Co-morbid mood disorders
Adjuvant Analgesics

- Multipurpose analgesics
  - Corticosteroids
  - Antidepressants
  - Alpha-2 adrenergic agonists
  - Topical therapy: Lidocaine, capsaicin and others
- Drugs used for neuropathic pain
  - Anticonvulsants
  - Sodium channel blockers
  - NMDA receptor antagonists
  - Others: GABA agonist, cannabinoids

Corticosteroids

- Limited data, but widely accepted as analgesic in diverse disorders
- In advanced disease, low dose regimen continued indefinitely used for neuropathic pain
- Toxicity limits long-term use in diseases other than chronic inflammatory conditions

Antidepressants

- Multipurpose analgesics
  - Numerous RCTs but few in medically ill populations
  - Classes
    - Tricyclic antidepressants
      - 3胺 antidepressants: amitriptyline, imipramine, doxepin
      - 2胺 antidepressants: desipramine, nortriptyline
    - SNRIs: duloxetine, venlafaxine, desvenlafaxine
    - SSRIs: paroxetine, citalopram, others
    - Others: bupropion
- Analgesic efficacy
  - Studies suggest TCAs > SNRIs > SSRIs
  - Of the tricyclics: 3胺 antidepressants (amitriptyline) > 2胺 antidepressants (imipramine)
  - But not all drugs have been studied
  - No comparative studies against duloxetine—now indicated for pain in diabetic neuropathy
  - Of the SSRIs, limited data in support of paroxetine and citalopram
- Side effects
  - 3胺 drug > 2胺 drug > SNRIs/SSRIs/bupropion
  - CNS, nausea, anticholinergic (TCAs), CV (TCAs), sexual (SSRIs, SNRIs)
- Based on safety and likelihood of efficacy, most reasonable choices would be 2胺 antidepressants or SNRIs
  - Desipramine
  - Nortriptyline
  - Duloxetine
  - Venlafaxine
  - Also consider bupropion
α-2 Adrenergic Agonists
- Multipurpose analgesics but little evidence
- Tizanidine usually better tolerated than clonidine
- In RCT, intrathecal clonidine worked for cancer-related pain (Ellenbogen JC, et al, Pain, 81:329; 1999)

Topical Adjuvant Analgesics
- Other topical compounds
  - Lidocaine/prilocaine cream (EMLA)
  - Ketamine
  - Other antidepressants
  - Other NSAIDs
  - Various anticonvulsants
  - Opioids

Topical Adjuvant Analgesics
- Drugs used for neuropathic pain
  - Anticonvulsants
  - Sodium channel blockers
  - NMDA receptor antagonists
  - Others: GABA agonist, cannabinoids

Adjuvant Analgesics
- Along with antidepressants, the major drug class for neuropathic pain
- Gabapentin most commonly used
  - Despite NNT less favorable than TCAs
  - Alpha-2-delta protein modulator (not gaba-ergic)
  - Positive RCT’s
    - Gabapentin in neuropathic cancer pain (Benedittis, Br J Clin Pharm, 50:574, 2000)
    - Usual effective dose: 600-3600 mg/day and sometimes higher

Anticonvulsants
- Gabapentin most commonly used
  - Not hepatically metabolized
  - No drug-drug interactions
  - Side effects usually tolerable
  - Usual effective dose: 600-3600 mg/day and sometimes higher

Topical Adjuvant Analgesics
- RCTs support benefit in neuropathic and arthropathic pain
  - Lidocaine 5% patch
  - Capsaicin
  - Doxepin
  - Lidocaine gel 5%
  - Aspirin

Adjuvant Analgesics
- Drugs used for neuropathic pain
  - Anticonvulsants
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Anticonvulsants
- Gabapentin most commonly used
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**Anticonvulsants**

- **Pregabalin**
  - Same analgesic mechanism as gabapentin
  - Positive RCTs in PHN/diabetic neuropathy/fibromyalgia (e.g., Gawehn RH et al, Neurol 90:274-283, 2003)
- **Commercially priced favorably relative to gabapentin**
- **Easier titration and faster onset of effect**
- **Same safety profile as gabapentin**
- **Positive effects on sleep and anxiety**
- **Effective at 150-600 mg/d**
- **Priced favorably relative to gabapentin**

- **Dextromethorphan**
  - Positive RCTs in diabetic neuropathy, HIV neuropathy, post-stroke pain, spinal cord injury pain (e.g., Vestergaard K et al, Neurol 873, 2004)
- **Be aware of hypersensitivity reactions**
- **Topiramate**
  - Positive RCTs in diabetic neuropathy and headache (e.g., Raskin P et al, Neurol 63:865, 2001)
  - Be aware of hypersensitivity reactions
- **Lamotrigine**
  - Positive RCTs in diabetic neuropathy, HIV neuropathy, post-stroke pain, spinal cord injury pain (e.g., Vestergaard K et al, Neurol 873, 2004)
  - Be aware of hypersensitivity reactions
- **Memantine**
  - Positive RCTs in diabetic neuropathy and headache (e.g., Raskin P et al, Neurol 63:865, 2001)
  - Be aware of hypersensitivity reactions
- **Ketamine**
  - Positive RCTs in diabetic neuropathy, HIV neuropathy, post-stroke pain, spinal cord injury pain (e.g., Vestergaard K et al, Neurol 873, 2004)
  - Be aware of hypersensitivity reactions

- **Other anticonvulsants have limited data and are selected by trial and error**
- **Newer drugs have better safety profiles**
  - Lamotrigine, carbamazepine, phenytoin, valproate
  - Tiagabine, levetiracetam, zonisamide
- **No comparative trials**

**Sodium Channel Blockers**

- Oral mexiletine, tocainide, flecainide are analgesic in neuropathic pain (e.g., Dahanaran PN et al, Diabetes Care, 31:1094-1107, 2008)
- Efficacy of IV lidocaine supported by RCTs (Dahanaran PN et al, Current Medical Research and Opinion 25:1229, 2009)
- Side effects of oral drugs common and usually considered after other drugs fail
- IV lidocaine is an option for severe neuropathic pain

**NMDA-Receptor Antagonists**

- NMDA receptor involved in neuropathic pain and opioid tolerance
- Commercially-available drugs
  - Ketamine
  - Memantine
  - Dextromethorphan
  - Amantadine
NMDA-Receptor Antagonists

- Ketamine
  - 37 RCTs of ketamine plus opioids by single bolus or infusion show mixed but generally favorable results
  - 4 RCTs of co-administration to opioids in cancer pain: no conclusion possible
- Dextromethorphan
  - RCT of positive in DPN and negative in PHN
- Memantine and amantadine
  - Very limited positive data
  - several negative RCTs of memantine

Conclusion: Limited data, conflicting findings

Ketamine is useful in refractory pain

Cannabinoids

- Strong preclinical support for analgesic efficacy of both CB1 and CB2 agonists
- RCTs of THC in central pain (Svendsen et al, BMJ, 329:253, 2004)
- Recent positive RCTs of new formulation (THC plus cannabidiol in cancer pain) in central pain and in cancer pain (Berman et al, Pain, 112:299-306, 2004)

Other Drugs for Neuropathic Pain

- Baclofen
  - RCT in trigeminal neuralgia (Fromm et al, Ann Neurol, 15:240-44, 1984)
  - Intrathecal baclofen may relieve neuropathic pain apart from spasticity
- Calcitonin
  - RCT's in RSD and phantom pain (e.g., Jørgen and Nørre, Pain, 41:21-27, 1990)
  - limited experience

Strategies for Neuropathic Pain

- Initial Strategy
  - Treat etiology
  - Consider opioid if pain severe
  - Add gabapentin or pregabalin, if needed, unless comorbid depression is present
  - If comorbid depression is present, consider trial of desipramine, nortriptyline, duloxetine, or venlafaxine
  - Consider co-administered topical drug
- If first-line drug unsatisfactory, consider sequential trials of adjuvant analgesics, starting with other antidepressants or anticonvulsants
- Combination therapy is appropriate as long as each drug is demonstrably effective and tolerated
Adjuvant Analgesics for Musculoskeletal Pain

“Muscle relaxants”
- Numerous drugs, e.g., cyclobenzaprine, carisoprodol, orphenadrine, methocarbamol, chlorzoxazone, metaxalone
- Centrally acting analgesics
- Do not relax skeletal muscle

Adjuvant Analgesics for Cancer Pain

- For bone pain
  - Bisphosphonates (e.g., pamidronate, zoledronic acid, ibandronate)
  - Calcitonin
  - Radiopharmaceuticals (e.g., Sr89, Sm153)
- For bowel obstruction pain
  - Anticholinergics
  - Octreotide

Polypharmacy in the Elderly Is Common and Increases With Age

The Elderly Commonly Take Medications That Can Cause Dizziness/Somnolence*

- **Indicated in yellow.** Defined as drowsiness, dizziness, or somnolence listed as a common adverse effect in package insert.

CNS Drug Use Is Common in the General Elderly Population and Is Associated With Higher Risk of Mobility Limitation

**Effective Medication Prescribing GOALS**

- Reduction of pain
- Improve function / level of activity
- Minimize medication side effects
- Return to work
- Decreased health care utilization

Always ask
- # pain pills/day
- # other meds/day

Always Think
- Do No Harm
- K.I.S.S.
- Rule of 1