Pain Management: Pharmacological

Pain Resource Nurse Program
Module 3

The Resource Center of the Alliance of State Pain Initiatives
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Classes of Analgesics

- **Nonopioids** – acetaminophen and NSAIDs* (for mild to moderate pain)
- **Opioids** - morphine is the prototype (for moderate to severe pain)
- **Adjuvant Analgesics** (drugs with primary indications other than pain, e.g., antidepressants and antiepileptics for neuropathic pain)
- **Other Adjuvants** – although not analgesics, they are often critical to the effective management of pain in certain populations or for the treatment of related symptoms such as depression and anxiety

*nonsteroidal anti-inflammatory drugs
Principles of Pharmacologic Management

- Perform and record assessments regularly
- Obtain a thorough medication history
  - Drugs used, response, side effects
- Assess use of OTC drugs and herbal preparations
- Assess for drug-related fears because they may lead to poor adherence
Principles of Pharmacologic Management

- Base the initial drug choice on the type and intensity of pain
- Patients may have more than one site and type of pain
- Give adequate doses
- Give drugs at appropriate dosing intervals
- When treating persistent pain, it is important to give drugs an adequate trial
Principles of Pharmacologic Management

- Use multimodal therapy: Two or more analgesics with different mechanisms of action may provide pain relief with less side effects.
- Add non-pharmacologic therapies (physical and behavioral) to get better pain control, less side effects.
- Repeatedly assess response to treatment.
- Remember the goals: relieve pain, improve function; taper and discontinue drugs that don’t meet those goals.
- Whenever possible treat the cause.
Overview of Nonopioids
Acetaminophen and NSAIDs

- All are effective against mild to moderate nociceptive pain
- No evidence for effectiveness against neuropathic pain
- All have an analgesic ceiling
- To prevent liver damage, restrict the acetaminophen dose to 4 g in 24 hours; use a lower total dose in the elderly
- Use special caution with the NSAIDs
Acetaminophen

- Analgesic, antipyretic, not an anti-inflammatory
- Few if any side effects at therapeutic doses
- A dosage form for parenteral administration is now available
- Hepatotoxicity a serious concern
  - use caution with opioid combination drugs
  - alcoholics at special risk
  - use caution in persons who are not eating regularly
- Uncertainty about risk of “analgesic nephropathy” with long-term use, especially if used in combination with aspirin or other NSAIDs
Classes of NSAIDs

- **Nonselective (inhibit COX-1 and COX-2)**
  - Aspirin the prototype: irreversible inhibitor
  - Non-acetylated salicylates: choline magnesium trisalicylate
  - Non-salicylates
    - Propionic acid derivatives
    - Indoles
    - Acetic acid derivatives, one of which can be given parenterally
    - Others

- **Selective COX-2 inhibitors (the coxibs)**
  - Celecoxib (Celebrex): also inhibits COX-1
  - No parenteral form available
NSAIDs: Mechanism of Action

- Inhibit cyclooxygenase (COX), the enzyme that catalyzes the formation of prostaglandins (PGs) and thromboxane (TXA$_2$).
- PGs are important in maintaining the normal physiology of many organs and tissues.
- TXA$_2$ causes platelet aggregation.
- PGs are released whenever cells are damaged, e.g., in trauma and surgery.
- PGs sensitize peripheral pain receptors.
NSAIDs

- At least two forms of cyclooxygenase
  - COX-1 is constitutive: it catalyzes the formation of substances which protect the GI mucosa, maintain kidney function and cause platelet aggregation
  - COX-2 is induced in inflamed tissue; also present in kidney and CNS
- Leads to the two classes of NSAIDs
  - Non-selective (inhibit both COX-1 and COX-2)
  - “More” selective COX-2 inhibitors
Pharmacologic Effects

- Analgesic
- Antipyretic
- Anti-inflammatory

- Non-selective NSAIDs decrease platelet aggregation; selective COX-2 inhibitors should not because there is no COX-2 in platelets
- Affect uterine contractility
## Drug Dosages and Dosing Intervals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Average Dose (mg)</th>
<th>Interval (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>500-1000</td>
<td>4-6</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>400-600; oral and IV</td>
<td>4-6</td>
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<tr>
<td>Naproxen</td>
<td>500 initial, 250 after</td>
<td>12</td>
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<tr>
<td>Ketoprofen</td>
<td>25-50</td>
<td>6-8</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>30 or 60 mg parenteral</td>
<td>6</td>
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<tr>
<td>Diclofenac</td>
<td>50</td>
<td>8</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>1000 initial, 500-750 after</td>
<td>8-12</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>200-400</td>
<td>12-24</td>
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</table>
NSAIDs: therapeutic use

- No NSAID is superior to the others as an analgesic/anti-inflammatory
- If one fails, try another
- Different potencies and durations of action
- Consider half-life, dosage regimen, toxicity, cost
- Aspirin, ibuprofen, naproxen and ketoprofen are available without a prescription
- Parenteral dosage forms of ketorolac and ibuprofen are available
Pain Management with NSAIDs

- Potential usefulness for the treatment of both acute and persistent (chronic) pain problems

- The risk of adverse effects has created considerable uncertainty about their use
Adverse Effects of NSAIDs

- GI tract – upper and lower gut: risk of GI bleed reduced 50% with a COX-2 inhibitor, but not if taking low dose aspirin
- Kidney – risk with both classes: fluid retention, increase in bp, renal failure
- “Hypersensitivity” reactions: aspirin-sensitive asthma with non-selective NSAIDs; skin rxs with coxibs
- Platelets – only COX-1 inhibitors
- CNS effects – changes may be subtle
- Cardiac effects
Cardiac Effects

- Coxibs may increase the risk of heart attack and stroke: data show an increase in mortality.
- Similar risks may be associated with the non-selective NSAIDs; only naproxen has not been implicated in an increased risk of cardiac events.
- The FDA strengthened warnings on all NSAIDs to include the risk of serious CV events in addition to GI bleeding.
- Patients with a previous MI should avoid celecoxib at any dose and non-selective drugs at high doses.
Current expert advice is to use the lowest dose of these drugs for the shortest period of time.

There is evidence that there has been a decrease in the incidence of adverse GI effects associated with NSAIDs.
Topical NSAIDs

- 1% diclofenac gel (Voltaren Gel®) – approved for treatment of OA pain
- Diclofenac patch (Flector®) – approved for treatment of acute pain due to minor strains, sprains and contusions
- Diclofenac topical solution (Pennsaid®): 1.5% diclofenac sodium solution in a carrier containing DMSO
- Myoflex® – 10% trolamine salicylate
Nonanalgesics for OA Pain

- Glucosamine and chondroitin sulfate: widely used despite lack of convincing evidence for efficacy
- Hyaluronic acid derivatives: FDA approved formulations for treatment of OA pain
Opioid Analgesics: Overview

- Drugs of choice for moderate to severe pain due to surgery, trauma and procedures; pain due to cancer
- Expert opinion supports their use for persistent pain problems in selected patients
- Effective for both nociceptive and neuropathic pain
- Available in many dosage forms; can be given by many routes of administration
Opioids: Definition of Terms

- **Opioid**: refers broadly to all compounds related to opium

- **Narcotic**: derived from the Greek word for stupor; once used for any drug that induced sleep; later associated with opioids; now used in a legal context to refer to drugs that are abused
Classes of Opioids

- Full agonists: morphine
- Partial agonists: buprenorphine
- Mixed agonist-antagonists: nalbuphine, butorphanol
- Antagonists: naloxone, naltrexone
- Dual action drugs: tramadol, tapentadol
  - opioid agonists
  - inhibit the reuptake of NE and 5-HT
Opioid Receptors

- μ, κ, and δ
- μ found in spinal cord, brain, the GI tract and to a lesser extent in the periphery
- μ mediates the analgesic and most side effects of morphine and other pure (full agonists)
- Partial agonist: agonist at μ receptors; antagonist at κ receptors
- Mixed agonist-antagonists: antagonists at μ receptors; agonists at κ receptors produce;
- Agonists at κ receptors produce dysphoric and psychotomimetic effects
- Endogenous opioid peptides have been isolated
Peripheral Receptors

- Opioid receptors are present on peripheral sensory nerves and are present in inflamed tissue

- Opioids may provide pain relief when administered directly into a painful site
Mechanism of Action

- Alter the sensory and affective aspects of pain
  - Inhibit the transmission of nociceptive information from the spinal cord dorsal horn
  - Activate descending pain inhibitory pathways
  - Alter limbic system activity

- Patients may report that pain is still present, but they feel more comfortable
Mechanism of Action

Spinal pain-transmission neuron

Primary afferent

(Presynaptic) \( \downarrow \text{Ca}^{2+} \text{ influx,} \downarrow \text{transmitter release} \)

(Postsynaptic) \( \uparrow \text{K}^+ \text{ conductance,} \rightarrow \text{IPSP} \)
Morphine

- The “gold standard,” the drug against which other opioid agonists are compared
- First isolated from opium in 1806
- Named after Morpheus, the Greek god of dreams
- Opium is derived from the dried juice of the poppy plant Papaver somniferum
- The poppy “juice” also contains codeine
- Morphine is a natural product – other opioid analgesics are partially or wholly synthetic
Opioid Agonists

“Short-acting”
- Morphine
- Hydromorphone
- Oxymorphone
- Codeine
- Hydrocodone
- Oxycodone
- Meperidine

“Ultra-short acting”
- Fentanyl IV, Oral TM

“Longer-acting”
- Extended release morphine
  - MS Contin®, Oramorph SR®, Kadian®, Avinza®, various generics
- Hydromorphone ER
  - Exago®
- Oxymorphone ER
  - Opana ER®
- Oxycodone ER
  - Oxycontin®
- Methadone
- Levorphanol
- Transdermal fentanyl
Pharmacokinetics

- Opioids agonists have very similar pharmacological effects, but significantly different pharmacokinetic properties.
- May be significant differences in absorption, distribution, metabolism and excretion.
- Most readily absorbed from the GI tract and many other sites.
- Fentanyl is absorbed through skin and mucous membrane.
- Many subject to extensive “first-pass” metabolism after an oral dose.
- Codeine, morphine and meperidine have active metabolites.
### Equianalgesic Dosing

<table>
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<th>Drug</th>
<th>Oral (mg)</th>
<th>IV (mg)</th>
<th>Duration (h)</th>
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<td>30</td>
<td>10</td>
<td>3 - 4</td>
</tr>
<tr>
<td>hydromorphone</td>
<td>7.5</td>
<td>1.5</td>
<td>3 - 4</td>
</tr>
<tr>
<td>oxymorphone</td>
<td>10</td>
<td>1</td>
<td>&gt; 4</td>
</tr>
<tr>
<td>methadone</td>
<td>2-5</td>
<td>2-5</td>
<td>6 – 8?</td>
</tr>
<tr>
<td>codeine</td>
<td>200</td>
<td>130</td>
<td>3 - 4</td>
</tr>
<tr>
<td>oxycodone</td>
<td>20-30</td>
<td>-</td>
<td>3 - 4</td>
</tr>
<tr>
<td>hydrocodone</td>
<td>30</td>
<td>-</td>
<td>3 - 4</td>
</tr>
<tr>
<td>meperidine</td>
<td>300</td>
<td>100</td>
<td>2 - 3</td>
</tr>
</tbody>
</table>
The Opioid Agonists

- Extremely effective analgesics
- Most have no dose ceiling
- Don’t produce end organ damage
- Differ in potency, ie, the dose needed to produce the same analgesic effect
- There is significant interpatient variability in response to different agonists probably due to genetically determined differences in \( \mu \)-receptors
Pharmacological Effects

- Analgesia
- Other CNS effects: drowsiness, mental clouding and others
- Cardiovascular system
- GI tract
- Pupillary size
- Smooth muscle
Desirable Effects of Opioids

- Effective analgesia
- Relief of anxiety
- Improved mood
Opioid Side Effects

- Constipation
- Sedation
- Psychomotor and cognitive impairment
- Nausea and vomiting
- Pruritus
- Respiratory depression
- Delirium
- At high dose, myoclonus and hallucinations
- Hormonal changes
Opioid Side Effects

- Predictable and controllable
- Time is your ally: tolerance develops to many side effects in 3-5 days, but not to constipation
- Multimodal therapy (non-drug therapies, addition of drugs that work by different mechanisms): lower dose requirement, lesser side effects with optimal analgesia
- Side effects may be less with one drug than another: opioid rotation
Constipation

- A common adverse effect of opioids to which tolerance does not develop

- Prophylactic bowel regimen
  - Osmotic agents: magnesium and sodium salts, lactulose, polyethylene glycol
  - Laxatives: docusate, bisacodyl, senna
  - Avoid bulk laxatives

- Peripherally acting \( \mu \)-antagonists: methylnaltrexone, alvimopan
Nausea and Vomiting

- Incidence 10-40%
- Very distressing to patients
- Several mechanisms
  - Stimulate CTZ
  - Increased vestibular sensitivity
  - Delayed gastric emptying
- May be triggered by constipation
- Treat with D₂-receptor or 5HT3-receptor antagonists
- EPS with D₂-receptor blockers
Sedation

- Seen with initiation of therapy or with dose increase
- Tolerance usually develops
- Prolonged sedation: look for comorbidities or use of other sedative drugs

Treatment
- Methylphenidate: 5 mg am and noon
- Modafinil (Provigil®): 100 mg (only anecdotal reports)
Pruritus

- Most common side effect with epidural or intrathecal opioids
- Mechanism not known: spinal opioid receptors involved
- Itch could be related to histamine release
- Treatment
  - second generation $H_1$-histamine receptor antagonists
  - IV nalbuphine
  - ondansetron
Respiratory Depression

- Feared and misunderstood
- Clinically significant respiratory depression is rare when patients in severe pain receive opioids
- Respiratory rate alone is not an indicator of respiratory status
- Sedation precedes respiratory depression
- Titrate carefully, methadone challenging
- Use naloxone very carefully
Delirium

- An acute confusional state
  - a common postop complication of particular importance for older patients
  - occurs in up to 80% of persons who are dying
- Most frequent medical complication of persons hospitalized with hip fracture
- Undertreated pain is a significant contributor
- Other risk factors
  - Metabolic abnormalities, alcohol abuse, physical function
  - Steroids, anticholinergics
Myoclonus

- May occur in the perioperative setting and in patients on chronic opioids
- Mild twitching to generalized spasms
- Dose related, but in unpredictable way
- May be due to accumulation of a toxic metabolite of morphine, e.g., M 3-G
- Rotate to a different opioid that doesn’t have a toxic metabolite
Concerns about chronic opioid therapy

- Effects on psychomotor function and cognition
- Changes in pain sensitivity
- Effects on neuroendocrine and immune systems
- Development of tolerance, physical dependence and addiction
Tolerance, Physical Dependence and Addiction

- **Addiction**
  - A primary, chronic, neurobiologic disease: impaired control over drug use, compulsive use, continued use despite harm, and craving.

- **Physical dependence**
  - Symptoms include yawning, sweating, lacrimation, rhinorrhea, anxiety, restlessness, insomnia, dilated pupils, piloerection, chills, tachycardia, hypertension, nausea and vomiting, crampy abdominal pains, diarrhea, muscle aches and pains.
  - Taper the dose to prevent withdrawal

- **Tolerance**
  - Effects diminish over time. Tolerance is not an inevitable consequence of chronic opioid therapy
Opioid Withdrawal
unpleasant, but not life threatening

- Regular withdrawal – immediately after stop treatment or are given an antagonist
  - Onset and duration depend on the half-life of the drug
  - Symptoms of withdrawal can be seen after as little as a week of therapy

- Protracted withdrawal
  - May last weeks or months
  - May account for relapse
## Schedules of Controlled Substances

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Drugs</th>
<th>Restrictions</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Heroin, marijuana, LSD</td>
<td>No currently accepted medical use in the US</td>
</tr>
<tr>
<td>II</td>
<td>Morphine, oxycodone, methadone, amphetamines</td>
<td>Written prescription order required except in an emergency; no refills</td>
</tr>
<tr>
<td>III</td>
<td>Hydrocodone, buprenorphine, THC in sesame oil</td>
<td>Oral prescription orders allowed; five refills allowed in 6 months</td>
</tr>
<tr>
<td>IV</td>
<td>Benzodiazepines, phenobarbital, butorphanol</td>
<td>Same as III</td>
</tr>
<tr>
<td>V</td>
<td>Pregabalin, antitussive and antidiarrheal preparation</td>
<td>Same as III</td>
</tr>
</tbody>
</table>
Principles of Opioid Therapy

- Successful use depends on individualization of therapy.
- Give the right drug at the right dose and the right dosing interval: essential to understand the pharmacokinetics of these drugs.
- Reducing/managing side effects is also key to providing adequate pain control.
- Confronting the myths about tolerance, dependence and addiction is critical.
Effective dosing requires knowledge of:
- onset of action, time to peak effect, duration of action, potential for accumulation with chronic dosing

Effective pain control with opioids requires titration of the dose:
- increase by % of current dose
  - mild pain: 25-50% increase
  - moderate to severe: 50-100% increase
Hydromorphone/ Oxymorphone

- Pharmacological effects essentially identical to those of morphine
- More potent; no active metabolites
- Both available in short-acting formulations
  - 2, 4, and 8 mg doses of hydromorphone
  - 5 and 10 mg doses of oxymorphone
- Extended release hydromorphone is available in 8, 12, and 16 mg tablets for once a day dosing
- Oxymorphone is available in an extended release form (Opana ER®) for twice daily dosing: 5, 10, 20 and 40 mg tablets
- Food and alcohol affect the absorption of oxymorphone from the extended release formulation
Codeine

- Codeine is a pro-drug and its conversion to morphine accounts for its analgesic effect
  - ~10% of codeine is metabolized to morphine by CYP 2D6
  - 7-10% of Caucasians are poor metabolizers,
  - Some individuals are ultrarapid metabolizers

- Codeine has a practical dose ceiling of 65-100 mg, above that, side effects become limiting

- Hydrocodone has a better side effect profile than codeine
Hydrocodone and oxycodone

- A variety of combination products are available,
- Hydrocodone is only marketed in combinations with nonopioids
- Hydrocodone is in Schedule III of the Controlled Substances Act which probably explains why it is the most prescribed opioid analgesic, in fact the most prescribed drug in the US.
- Oxycodone is available in combinations with nonopioids, in tablets, in a liquid formulation that contains 20mg/ml and in an extended release form (Oxycontin) in doses ranging from 20 to 160 mg.
- Diversion and abuse of hydrocodone and oxycodone combination products are significant; oxycodone ER has also been a “favorite”
Meperidine (Demerol®)

- Only a 2-3 hour duration of action
- 300 mg PO = 10 mg IV morphine
- Metabolite, normeperidine, has a longer duration of action, is excreted by the kidney, is a CNS stimulant: tremors, twitches, seizures
- Restrict meperidine to short procedures
- No evidence that efficacy enhanced by Vistaril® or Phenergan®
- It does not have less effect on the sphincter of Oddi
Fentanyl

- Fentanyl is very lipid soluble, very potent, mcg rather than mg doses
- Available for IV, transmucosal and transdermal delivery
- IV fentanyl 100 times more potent than IV morphine
- Four transmucosal delivery systems approved for the treatment of breakthrough pain in cancer
- Transdermal patch delivery system: slow onset
  - 3 days to reach steady state blood levels
  - Slow rate of decline in blood levels after patch removed
- Conversion: divide 24 h morphine dose by 2 to get the approximate patch dose
Methadone

- Renewed interest in an old drug
  - Cheap
  - May be an NMDA receptor antagonist
- Long and unpredictable half-life
- High-dose: prolongation of the QT interval
- Use caution when converting to methadone; can’t rely on standard tables; conversion ratio depends on the dose
  - 30-90 mg: 4:1
  - 91-300 mg: 8:1
  - >300 mg: 12:1
- Methadone-related deaths increasing
Buprenorphine: A partial agonist

- Available since the 1980s for parenteral use in treatment of pain (Buprenex® others)
- Sublingual tablets, 2 and 8 mg, either alone (Subutex®) or with naloxone (Suboxone®) were approved in 2003
- Approved for office treatment of opioid dependence
- In high doses, acts as an antagonist, can precipitate withdrawal: can’t be substituted for other opioids
- Available as a transdermal patch for once weekly dosing
- In Schedule III of the Controlled Substances Act
Mixed Agonist-Antagonists

- Pentazocine, nalbuphine, butorphanol
- Why would they be used?
  - Claimed to be less addicting
  - Claimed to have less respiratory depressant effects
  - Not “scheduled” or in low schedule
- Significant limitations
  - Have an analgesic ceiling
  - Pentazocine with naloxone not an effective analgesic
  - Produce psychotomimetic effects
  - Will precipitate withdrawal in patients who are physically dependent on pure agonists
**Opioid Antagonists**

- **Naloxone (Narcan®)**: drug of choice for opioid overdose
  - Not effective orally
  - Administered IV to reverse the respiratory effects of opioid agonists
  - Short duration of action – shorter than that of pure agonists – so several doses or continuous infusion necessary to effectively treat opioid overdose

- **Naltrexone**
  - Orally effective
  - Longer duration of action – half-life 10 hours
  - FDA approved for treatment of alcohol abuse (does it decrease the craving?) and opioid abuse

- **Methylnaltrexone**
  - Peripherally acting
  - Approved for the treatment of opioid-induced constipation in patients with advanced illness
  - Administered subcutaneously
Tramadol and Tapentadol (Nucynta®)

- **Dual mechanism** - \(\mu\)-opioid agonists, block reuptake of NE and 5-HT (tapentadol much lesser effect on 5-HT reuptake)

- **Tramadol** approved for mild to moderate pain
  - has an analgesic ceiling
  - has an active metabolite
  - nausea, vomiting, confusion
  - can trigger seizures
  - available in combination with acetaminophen and in an extended release formulation for once daily dosing

- **Tapentadol** approved for moderate to severe acute pain
  - An extended release form is in clinical trials
  - Claimed to have better side effect profile that pure agonists, less nausea and vomiting reported in some studies
Opioids with Limited Efficacy

- **Opioid agonists**
  - Codeine – dose-limiting side effects
  - Hydrocodone – dose limited by toxicity of acetaminophen and aspirin with which it is combined
  - Meperidine - metabolite has CNS toxicity

- **Partial agonist: buprenorphine**

- **Mixed agonist-antagonists**

- **Dual action drugs**
  - Tramadol
  - Tapentadol
Adjuvant Medications

- Drugs with primary applications other than pain management
- Some are effective in certain painful conditions
- Drugs for neuropathic pain
  - Antidepressants
  - Anticonvulsants
  - Local Anesthetics
  - Alpha$_2$-adrenergic agonists
  - NMDA receptor antagonists
- Corticosteroids and others
- Muscle relaxants
- Hypnotics and anxiolytics
Drugs for Neuropathic Pain

- Antidepressants
- Antiepileptics
- Local Anesthetics
- Opioids
- Others
- No evidence for benefit from NSAIDs and acetaminophen
Pharmacologic Management

- Current practice: “trial and error”
- First-line treatments have been identified
- If patients do not respond adequately to one first-line drug, choose another, but one that works by a different mechanism
- Remember that the response may be limited
- There may be advantages to combining two drugs
First-line Drugs for Neuropathic Pain
not in order of preference

- **Antidepressants**
  - Tricyclics
  - SNRIs: duloxetine, venlafaxine,

- **Neuronal calcium channel modulators**
  - Gabapentin and pregabalin

- **Topical analgesics**: 5% lidocaine

- **Systemic analgesics**
  - Opioid agonists
  - Tramadol
Antidepressants

all effective antidepressants, not all effective for treatment of NP

- Tricyclics: differ in side effect profiles
- SNRIs: non-tricyclic dual reuptake inhibitors
  - duloxetine, venlafaxine, milnacipram (only for fibromyalgia)
- SSRIs
  - not proven effective against NP
  - effective antidepressants
- Others (sometimes called atypical drugs)
  - include bupropion, mirtazapine, nafazodone
  - limited evidence of efficacy
Tricyclic Antidepressants

- Most studied, particularly for diabetic neuropathy pain
- Least tolerated, especially in the elderly: start low, go slow
- Large number of drugs: amitryptyline (most significant side effects), imipramine, clomipramine, nortriptyline, desipramine (better side effect profiles), maprotiline
  - Titrate slowly to effect or limiting side effects
  - Risk of intentional overdose
  - Risk of conduction abnormalities; get baseline EKG
Tricyclic antidepressants*  
*prolong the QT interval, may need a baseline EKG

<table>
<thead>
<tr>
<th></th>
<th>Sedation</th>
<th>Orthostatic hypotension</th>
<th>Anticholinergic Effects</th>
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</thead>
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<tr>
<td>Amitriptyline</td>
<td>+++</td>
<td>++++++</td>
<td>+++</td>
</tr>
<tr>
<td>Desipramine</td>
<td>+</td>
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<tr>
<td>Metabolite of amitriptyline</td>
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SNRIs: Serotonin and Norepinephrine Reuptake Inhibitors

- Fewer side effects than TCAs
- duloxetine (Cymbalta®)
  - First drug released for both depression and NP
  - Start: 30 mg a day; max 60 mg twice daily
  - 4 week trial
- venlafaxine (Effexor®, Effexor XR®)
  - 37.5 mg once or twice daily; max 225 daily
  - 4-6 week trial
Antiepileptic Drugs

- First generation
  - Older drugs such as carbamazepine (Tegretol®) and phenytoin (Dilantin®)

- Second generation
  - A dozen have been released in the last fifteen years; gabapentin and now pregabalin most used
  - Greater tolerability, fewer drug-drug interactions, new mechanisms of action
Gabapentin (Neurontin®) and pregabalin (Lyrica®)

- These are the antiepileptics with the best evidence of efficacy
- Both are modulators of neuronal calcium channels
- Not metabolized, few drug interactions, monitor kidney function; dosage modification when kidney function impaired
- Sedation common; ataxia, peripheral edema, dizziness, diplopia, nausea
- Possible role in managing postop pain
- Significant antianxiety effects
Gabapentin and Pregabalin

- **Gabapentin**: start at 100 to 300 mg in a single dose at bedtime or 100-300 mg tid; increase every 1-7 days as tolerated; 1800 to 3600 mg/day in divided doses

- **Pregabalin**: start at 50-75 mg bid; increase the dose by 50-75 mg every other day. May see improvement in a week at 150 mg/day. Target dose is 300-600 mg/day. Can give as 200 mg tid or 300 mg bid

- Antianxiety effects
- Perioperative analgesia
Other Antiepileptics

- **Carbamazepine (Tegretol®):** 200 mg three times a day. Side effects include sedation, dizziness, nausea, unsteadiness, 2% leukopenia, thrombocytopenia.

- **Phenytoin (Dilantin®):** 100-200 mg three times a day; sedation, mental clouding, unsteadiness.

- **Valproic acid (Depakote®):** 200-400 mg twice or three times a day; sedation, nausea, tremor.

- **Clonazepam (Klonopin®):** 0.25-.05 mg three times a day; drowsiness, ataxia.

- **Lamotrigine (Lamictal®):** 200-400 mg per day; rash, Stevens-Johnson syndrome; strict titration regimen to reduce the risk of serious cutaneous rxs.
5% Lidocaine Patch (Lidoderm®)

- Apply up to 3 patches (4?) for up to 12 hours during a 24 hour period
- Patches may be cut to fit the lesions
- Little (3%) systemic absorption
- Titration not necessary; adequate trial: 2 weeks
- Adverse effects: redness or rash at the site of application
- Other topical drugs, e.g., capsaicin
Capsaicin (from chili peppers)

- An agonist at TRPV1 receptors on nociceptive nerve fibers of the skin.
- A 0.025% capsaicin cream in lidocaine-containing vehicle used for PDN or PHN
- An 8% patch (Quetenza®) approved in Nov 2009 for moderate to severe PHN pain
  - A single 60-minute application of up to 4 patches no more often than every 3 months
  - May be significant application-associated pain
Ketamine

“Literature suggests subanesthetic doses can provide short-term relief of refractory NP in some patients”

Subanesthetic doses may reduce morphine requirements in the first 24 hours after surgery

“Utility may be less as analgesic per se but more as an antihyperalgesic, antiallodynic, or tolerance-protective agent”

Bell RF. Pain 2009; 141: 210-214
“Evidence to guide its use at subanesthetic doses for pain control is limited and in part contradictory”

Ketamine: Does Life Begin at 40? Pain Clinical Updates 2007; XV: 1-6
Adam et al. Small-dose ketamine infusion improves postoperative analgesia and rehabilitation after TKA. Anaesth Analg 2005; 100: 475-480
Opioids

- Opioid agonists
  - Start with short-acting
  - Convert to long-acting if response

- Tramadol
  - Short acting – with or without acetaminophen
  - Ultram® ER
    - Allows once a day dosing
NMDA Receptor Antagonists: Dextromethorphan and Ketamine

- Clinical usefulness limited by side effects
- Subanesthetic doses of ketamine may reduce morphine requirements in the first 24 hours after surgery
- The NMDA receptor is one of the binding sites for glutamate
- The NMDA receptor appears to play a critical role in neuronal plasticity and sensitization
What About Marijuana?

- **Sativex®**: buccal spray contains THC and CBD
- Approved in Canada as adjunctive treatment for NP in adults with MS
- Few CB1 receptors in the cardiorespiratory area of the brainstem which increases safety in overdose
- Efforts in many states to “legalize” medical marijuana
Alpha$_2$-Adrenergic Agonists

- **Clonidine**
  - Helpful in some neuropathic pain problems, particularly CRPS/PHN; pain refractory to opioids
  - Oral and transdermal forms
  - Hypotension, rebound hypertension, dizziness

- **Tizanidine**
  - Analgesic dose range between 4 and 40 mg/day
  - Spasticity, neuropathic pain, fibromyalgia (?)
  - Sedation, dizziness, hepatotoxicity
  - Less hypotensive than clonidine
Baclofen: GABA\textsubscript{B} receptor agonist

- Binds to presynaptic receptors in dorsal horn, brainstem, etc
- Uses: spasticity, neuropathic pain
- Therapeutic dose: 30-200 mg/d
- Sedation, orthostasis
- Taper the dose as abrupt withdrawal has been associated with seizures
Corticosteroids

- For treating rheumatoid arthritis and other acute inflammatory disorders
- To treat metastatic bone pain
- Multiple routes of administration
- Intra-articular injection of triamcinolone (Aristospan and others) or methylprednisolone (Depo-Medrol and others) can relieve an acutely inflamed rheumatoid joint
- Systemic use: many potential adverse effects which may be especially significant in the elderly
- Suppress the HPA axis
Bisphosphonates
(Not analgesics, for osteoporosis)

- Alendronate (Fosamax®, Fosamax Plus D®),
  risedronate (Actonel®, Actonel with Calcium®),
  ibandronate (Boniva®),
  zolendronic acid (Reclast®) [latter once-yearly IV injection]

- Studies show a significant reduction in vertebral fractures, thus less pain.

- Oral bisphosphonates poorly absorbed; must take after overnight fast while in an upright position along with 8 ounces of water.

- Many potential adverse GI effects
Muscle Relaxants

- Proven efficacy
- Questionable efficacy
- Other so-called “centrally acting” muscle relaxants: very limited or inconsistent data relating to their efficacy
  - Methocarbamol (Robaxin®)
  - Chlorzoxazone (Panaflex®)
  - Metaxalone (Skelaxin®)
  - Cyclobenzaprine (Flexeril®)
  - Carisoprodol (Soma®) – is abused
Muscle Relaxants

- Carisoprodol (Soma)
  - Metabolized to meprobamate, abused, effect related to sedative effects
- Cyclobenzaprine (Flexeril)
  - Use for only up to 3 weeks, a tricyclic
- Chlorzoxazone (Parafon Forte)
  - An antihistamine?
- Methocarbamol (Robaxin)
  - Sedative
- Orphenadrine (Norflex)
  - Analgesic?, also marketed with aspirin and caffeine
- Metaxalone (Skelaxin)
  - Lack of abuse, less sedation.
Muscle Relaxants for LBP

- Widely used to treat musculoskeletal pain
- Account for 16% of prescriptions written for low back pain in the US despite very limited or inconsistent data about efficacy
- “Muscle relaxants have some limited use for acute LBP, but the effect is small and the risks of abuse are real. No studies support long term use.” Van Tulder et al. Cochrane Database Syst Rev 2007
Antispasmodics

- Anticholinergics/antispasmodics used to relieve cramps or spasms of the stomach, intestines and bladder.
- Some used to prevent nausea, vomiting and motion sickness
- Often used in patients with IBS
- Dicyclomine (Bentyl®), hyoscyamine (Levsin®),
- Other drugs available in other parts of the world
Hypnotics/Anxiolytics

**Hypnotics**
- First generation antihistamines
- Benzodiazepine receptor agonists – e.g., zolpidem (Sonata®), zaleplon (Sonata®), eszopiclone (Lunesta®)
- Benzodiazepines
- Sedative antidepressants – e.g., trazodone, doxepin (Silenor)
- Melatonin receptor agonist – ramelteon (Rozerem®)

**Anxiolytics**
- Meprobamate
- Benzodiazepines
- SSRIs
- Others: buspirone (Buspar®)
Hypnotics

- Antihistamines: diphenhydramine, doxylamine, FDA approved as OTC “sleep-aids”
- Benzodiazepines: all decrease the time to onset of sleep; prolong the first two stages; six are marketed for use as hypnotics
- Bz receptor agonists: zaleplon (Sonata), zolpidem (Ambien, Ambien CR) and eszopiclone (Lunesta); decrease sleep latency, little effect on sleep stages; rapid onset; most short-acting
- Melatonin receptor agonist: ramelteon (Rozerem); for insomnia characterized by difficulty falling asleep
- Sedative antidepressants: trazodone, doxepin
Treatment of Anxiety

- Immediate onset of action
  - Benzodiazepines

- Slow onset of action
  - Buspirone (Buspar)
  - SSRIs

- Can use a combination of drugs
Address all pain-related issues

- Depression
- Anxiety
- Psychosocial issues
Case Study

Osteoarthritis and Diabetes

- Alice Larsen is an 82-year-old former army nurse; she served for 4 years in Vietnam.
- She has had osteoarthritis for at least 20 years and now has multifocal pain involving her hips, knees, ankles and shoulders.
- Twelve years ago she was diagnosed with Type II diabetes; she has had trouble controlling her blood sugar. Recently she began to experience numbness and tingling in her legs. She also is experiencing burning on the bottoms of her feet.
- She lives alone in a small 3-bedroom house
Case continued

Analgesic History

- At one time ibuprofen relieved her OA pain, but she experienced dyspepsia and was advised to stop the drug. Rofecoxib helped for awhile, but it was taken off the market.
- She has been taking acetaminophen, but it really doesn’t help. She reports constant aching in her joints that she rates as 3-5/10 and up to 7/10 with activity. She is having trouble sleeping and says she can’t stand those feelings in her legs and she can’t wear shoes anymore.
- She is doing a better job of controlling her blood sugar and even managed to lose a little weight. But she says she probably lost the weight because cooking has become such a chore.
Mrs. Larsen was treated with 500 mg of naproxen twice a day and nonpharmacologic therapies, but her OA pain persists and has in fact increased in intensity.

Consideration might now be given to opioid therapy.

With what drug would you initiate therapy and how would you titrate to effect?

- Possibilities include tramadol, hydrocodone/acetaminophene, morphine, oxycodone, methadone.
Mrs. Larsen’s response to short-acting combination opioids is carefully explored. A dose of 20 mg of extended release oxycodone twice a day provides relief of her joint pain.

She still is experiencing numbness and tingling in her legs and burning on the bottoms of her feet.

What drugs would you recommend to treat that type of pain?
Neuropathic pain treatment

Therapies included

- Lidocaine patch applied to the bottom of her feet
- Pregabalin (Lyrica®) at a dose of 50 mg three times a day titrated to 200 mg tid
- Duloxetine (Cymbalta®) at 30 mg per day, increased to 60 mg per day after one week

Unacceptable sedation with pregabalin; pain relief after one week at 60mg/day of duloxetine

VA coverage challenges continue
Case continued
A Role for Nonopioids?

- Is there a role for nonopioids in the treatment of Mrs. Larsen’s OA pain?
- If so, which drug would you choose and which route of administration and why?
- If not, why not?
- Are there alternatives to APAP and NSAIDs?
Summary

- Analgesics play a major role in the management of pain.
- Use multimodal therapy to achieve optimal pain relief with minimal side effects.
- The three major classes of analgesics include:
  - Nonopioids for mild to moderate pain.
  - Opioids for moderate to severe pain.
  - Adjuvants many of which are used in the treatment of neuropathic pain.
- Base the choice of analgesic (or analgesics) on the intensity and type of pain.
Summary

- Analgesics play a major role in the management of pain
- Use multimodal therapy to achieve optimal pain relief with minimal side effects
- Base the choice from the three major classes on the intensity and type of pain
- Use adjuvants to address other problems