Learning Objectives:

- Identify the role of nonopioid medications for managing pain
- Describe common adverse effects associated with available nonopioid medications
- Discuss counseling strategies that support the efficacy of nonopioid analgesics
Algorithm for Selecting Nonopioid Analgesics

Uncontrolled Pain

Suspected Etiology
Musculoskeletal, Inflammatory
Descriptors
Aching, stabbing, sharp, continuous, throbbing, pressure
Chronicity
Acute

Suspected Etiology
Neuropathic, Central
Descriptors
Shooting, burning, numb, pins and needles, deep, intermittent, radiating
Chronicity
Subacute, Chronic

Acetaminophen
NSAIDs
Skeletal Muscle Relaxants

Tricyclic Antidepressants
SNRIs/Atypical Antidepressants
Anticonvulsants
Topical Anesthetics

Current alcohol use, hepatic disease
Avoid Acetaminophen

Heart failure, renal disease, history of upper GI bleeding
Avoid NSAIDs or use with caution

History of falls, long QT-syndrome, serotonin syndrome
Avoid Skeletal Muscle Relaxants or use with caution

Primary insomnia
Consider Tricyclic Antidepressant

Co-occurring depression or GAD
Consider SNRI (depression) or Anticonvulsant (i.e., gabapentinoids)

Co-occurring bipolar disorder
Consider Anticonvulsants with mood stabilization data

Co-occurring seizure disorder
Consider Anticonvulsants: avoid or use antidepressants with caution
Acetaminophen and Ibuprofen for Acute Pain

Percent with 50% pain relief

- Ibuprofen 200 mg: 37%
- Acetaminophen 500 mg: 28%
- Ibuprofen 400 mg: 40%
- Oxycodone 15 mg: 21%
- Oxy 10 + acet 1000: 37%
- Ibu 200 + acet 500: 62%
NSAIDs

- Significant side effects include acute renal failure in hypovolemia or CKD, increased bleeding times, risk of upper and lower GI bleed, and CV toxicity.
- Topical NSAIDs may provide symptomatic relief without significant systemic exposure.

<table>
<thead>
<tr>
<th>Table 3. Comparative Cyclooxygenase Activity of Commercially Available Nonsteroidal Anti-inflammatory Drugs</th>
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</thead>
<tbody>
<tr>
<td>5- to 50-fold COX-2 Preferential</td>
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<tr>
<td>&lt;5-fold COX-2 Preferential</td>
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<tr>
<td>COX-1 Preferential</td>
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</tbody>
</table>

*Based on log IC₅₀ ratios of COX-1/COX-2. COX = cyclooxygenase; IC = inhibitory concentration.

<table>
<thead>
<tr>
<th>Table 4. Balancing the Risk of Cardiovascular and Gastrointestinal Toxicity of Nonsteroidal Anti-inflammatory Drugs</th>
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<tbody>
<tr>
<td>RISK CATEGORY</td>
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<td>----------------</td>
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<tr>
<td>Low CV risk</td>
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<tr>
<td>High CV risk (low-dose aspirin required)</td>
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</tbody>
</table>

COX = cyclooxygenase; CV = cardiovascular; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor.
Skeletal Muscle Relaxants

- All equally effective for short-term relief of low back pain
- Not more effective than NSAIDs for acute low back pain
- Not recommended for chronic pain
- All are sedating, while metaxalone is considered least sedating
- Tizanidine is structurally similar to clonidine (alpha agonist), which can result in reduced blood pressure and the risk of rebound hypertension upon abrupt discontinuation
- Carisoprodol is metabolized to meprobamate, a barbiturate, increasing its abuse potential
- Most possess serotonergic activity, consider prior to using concurrently with other serotonin active drugs
Pain is Complicated

Four Types of Pain
1. Nociceptive
2. Neuropathic
3. Central Sensitization
4. Opioid Withdrawal
Antidepressants

TCAs
- Secondary amines have less anticholinergic side effects, ie – sedation
- Use lowest dose possible for pain management and sleep
- Postural hypotension and QT prolongation are possible. Screen for known heart disease, syncope, palpitations, dyspnea or chest pain. Avoid in those with CV disease or established conduction abnormalities

SNRIs
- Exhibit efficacy in neuropathic pain, fibromyalgia, and chronic musculoskeletal pain
- Dose-dependent increases in blood pressure should be expected
- GI side effects (nausea, diarrhea) are common when initiated and may subside with time

<table>
<thead>
<tr>
<th>Tricyclic Antidepressants</th>
<th>SNRIs</th>
<th>Atypical Antidepressants</th>
<th>SSRIs</th>
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</thead>
<tbody>
<tr>
<td>3° amines</td>
<td>Venlafaxine</td>
<td>Bupropion</td>
<td>Paroxetine</td>
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<tr>
<td>Doxepin</td>
<td>Desvenlafaxine</td>
<td>Trazodone</td>
<td>Escitalopram</td>
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<td>Imipramine</td>
<td>Duloxetine</td>
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<td>Amitriptyline</td>
<td>Milnacipran</td>
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<td>Clomipramine</td>
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<td>Trimipramine</td>
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<tr>
<td>2° amines</td>
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<tr>
<td>Protriptyline</td>
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<td>Nortriptyline</td>
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<td>Desipramine</td>
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Anticonvulsants

- Gabapentin, Pregabalin: Start at lower doses and titrate slow for improved tolerability. Sedation, ataxia, weight gain, and edema are common side effects. May have efficacy for co-occurring anxiety disorder.
  - Gabapentin: 100mg QHS then 100mg TID, continue up to 1800mg per day depending on renal function

- Consider Valproic Acid or Topiramate for co-occurring migraine headaches

- Some anticonvulsants require therapeutic drug monitoring (carbamazepine, valproic acid). All anticonvulsants have risk for drug-induced rashes, increased suicidal ideation, and significant drug-drug interactions.
References

