Nonopioid Analgesics: The Selection and Use of Adjuvant Therapies

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Disclosures

- Clinical advisory board: Daiichi Sankyo
- The presentation will include “off-label” uses of some medications and indicated on the individual slide
Current Situation

- The opioid epidemic
  -$6 billion over the next 2 years\(^1\)
- Research and development\(^2\)
  - Peptides, kappa agonists, and gene-targeting
- Cannabidiols\(^3\)
  - Current clinical trials for chronic pain


Learning Objectives

- Describe where adjuvant analgesics act in the pain pathway and their differences in mechanism of action
- Compare risks and benefits for different adjuvant analgesics
- Choose an adjuvant analgesic based on current guidelines and/or evidence-based medicine as well as individual patient factors
Why Use Adjuvant Analgesics?

- An estimated 1 out of 5 patients with nonmalignant pain or pain-related diagnoses are prescribed opioids
- Almost 2 million Americans abused or were dependent on prescription opioids in 2014
- From 1999 to 2015, >180,000 people died from overdoses related to prescription opioids
- Since 1999, sales of prescription opioids in the United States have quadrupled

https://www.cdc.gov/drugoverdose/prescribing/guideline.html
accessed 2.9.2018

Risk Factors for Opioid Overdose or Addiction

**Overdose**
- Daily dose > 100 MEDD
- Long-acting (LA) or extended-release (ER) formulation
- Combination with benzodiazepines
- Long-term use (> 3 months)
- Period shortly after initiation of LA/ER formulation
- Age > 65 years
- Sleep-disordered breathing
- Renal/hepatic impairment
- Depression
- Substance use disorder
- History of overdose

**Addiction**
- Daily dose > 100 MEDD
- Long-term opioid use (> 3 months)
- Depression
- Substance use depression
- Adolescence

MEDD = morphine equivalent daily dose
Contraindications to Opioids

- Respiratory instability
- Acute psychiatric instability
- Uncontrolled suicide risk
- Active, untreated alcohol or substance use disorder
- True opioid allergy
- Concomitant medications with life-limiting drug interactions
- Prolonged QTc (≥500 msec) with methadone
- Active diversion
- Condition not likely to improve with opioids


Pharmacotherapy
(based on a new taxonomy)

<table>
<thead>
<tr>
<th>Drug Class / Mechanism of Action</th>
<th>IASP Pharmacology of Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>Antinociceptive</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Peripheral desensitization</td>
</tr>
<tr>
<td>TCAs</td>
<td>Descending modulator</td>
</tr>
<tr>
<td>SNRIs</td>
<td>Descending modulator</td>
</tr>
<tr>
<td>Local anesthetics</td>
<td>Peripheral desensitization</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Antinociceptive</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Antinociceptive</td>
</tr>
<tr>
<td>NMDA antagonists</td>
<td>Antihyperalgesic</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>Peripheral desensitization</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>Antinociceptive</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Peripheral desensitization</td>
</tr>
<tr>
<td>Skeletal muscle relaxants</td>
<td>Descending modulator</td>
</tr>
</tbody>
</table>

Where Do Adjuvants Work?

Pain Terminology

- Acute
- Acute on Chronic
- Chronic
- Nociceptive
- Neuropathic
Inflammatory Pain

**Diagnosis**
- Clinical setting
  - Postoperative
  - Trauma
  - Infection
  - Arthritis
- Distribution
  - Joints
  - Area of infection or trauma
  - Surgical incision
- Quality
  - Aching
  - Throbbing
  - Worse with movement
- Physical findings
  - Warm
  - Red
  - Swollen

**Drug Management**
- NSAID
  - Ibuprofen
  - Naproxen
  - Ketorolac (IV form)
  - Meloxicam
  - Celecoxib
  - Corticosteroids
    (short course)

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**Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)**
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)


NSAIDs—COX Selectivity and Associated Risk

Celecoxib & Cardiovascular (CV) Safety

- Clinical question: How does the CV safety of celecoxib, a COX-2 selective NSAID, compare to that of a nonselective NSAID, such as ibuprofen or naproxen?
- Primary composite outcome of CV death (including hemorrhagic death), nonfatal MI, or nonfatal stroke
- Mean treatment duration of 20.3±16.0 months and a mean follow-up period of 34.1±13.4 months
- In regards to the primary outcome, celecoxib was found to be non-inferior to both ibuprofen and naproxen
- Risk of GI events was significantly lower with celecoxib compared to both ibuprofen and naproxen
- Study funded by Pfizer

NSAIDs—Dosing

<table>
<thead>
<tr>
<th>Medication</th>
<th>Initial Dose</th>
<th>Maximum Dose (depending on indication)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>100 mg daily-BID</td>
<td>200-800 mg/day</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>IR: 50 mg TID-QID</td>
<td>DR: 150-200 mg/day in 2-4 doses ER: 100 mg/day</td>
</tr>
<tr>
<td>Etodolac</td>
<td>IR: 200-400 mg q6-8h</td>
<td>IR: 1000 mg/day</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>400-800 mg q4-6h</td>
<td>2.4-3.2 g</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>IR: 25-50 mg BID-TID</td>
<td>ER: 75 BID or 150 mg daily</td>
</tr>
</tbody>
</table>

Lexi-Comp, Inc. (Lexi-Drugs®). Lexi-Comp, Inc.; Hudson, OH; accessed 2.9.2018
NSAIDs—Dosing (cont’d)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Initial Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketorolac</td>
<td>PO: 20 mg initial then 10 mg q4-6h</td>
<td>PO: 40 mg/day</td>
</tr>
<tr>
<td></td>
<td>IV: 30 mg once or 15-30 mg q6h</td>
<td>IM/IV: 120 mg/day</td>
</tr>
<tr>
<td></td>
<td>IM: 60 mg once or 30 mg q6h</td>
<td>MAX: x5 DAYS</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>7.5 mg daily</td>
<td>15 mg/day</td>
</tr>
<tr>
<td>Naproxen</td>
<td>IR: 250 mg q6-8h, 500 mg q12h</td>
<td>IR: 1000-1500 mg/day</td>
</tr>
<tr>
<td></td>
<td>ER: 1000 mg daily</td>
<td>ER: 1000-1500 mg/day</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>20 mg daily</td>
<td>20 mg/day</td>
</tr>
<tr>
<td>Sulindac</td>
<td>150-200 mg BID</td>
<td>400 mg/day</td>
</tr>
</tbody>
</table>

Lexi-Comp, Inc. (Lexi-Drugs™). Lexi-Comp, Inc.; Hudson, OH; accessed 2.9.2018

NSAIDs and GI Adverse Effects

- Strategies to prevent gastric mucosal damage in chronic NSAID users:
  - Proton pump inhibitor (PPI)
  - Histamine-2 receptor antagonist (H2RA)
  - Use of COX-2 selective NSAID
- Risk factors for NSAID-related GI toxicity:
  - History of peptic ulcer disease or upper GI bleed
  - ≥65 years old
  - Presence of comorbidities such as rheumatoid arthritis
  - Concomitant use of anticoagulants, aspirin or corticosteroids

Topical NSAIDs

- **Diclofenac sodium 1% gel**
  - Dose:
    - Upper extremity (hands, elbows, wrists): 2g applied QID up to 8g on any one joint
    - Lower extremity (knees, ankles, and feet): 4g applied QID up to 16g on any one joint
  - Avoid showering/bathing for ≥1 hour after application
  - Wearing of clothing or gloves should be avoided for ≥10 minutes after application

- **Diclofenac epolamine 1.3% patch**
  - Dose: 1 patch applied BID to the most painful area

- Both products carry the same boxed warnings but are proposed to have a more favorable safety profile than oral NSAIDs

- Most common adverse effect: application site reactions

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Corticosteroids

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Corticosteroids

Prostaglandin inhibition  Cell membrane stabilization

Corticosteroid Mechanism of Action in Analgesia

Sodium channel blocker (neuropathic pain)  Osteoclast inhibition (bone pain)


Corticosteroids (cont’d)

- Intra-articular corticosteroid injection – knee and hip OA
- For RA: “Low-dose glucocorticoids should be considered as part of the initial treatment strategy (in combination with one or more conventional synthetic (cs)DMARDs) for up to 6 months, but should be tapered as rapidly as clinically feasible.”
  - “Low dose” defined as ≤ 7.5mg prednisone or equivalent per day
- May consider the addition of an oral corticosteroid as a temporary adjuvant for pain relief
  - In acute disc herniation, acute or persistent migraine, flares of rheumatic pain
  - Use the lowest effective dose for the shortest period of time necessary

4. Lexi-Comp, Inc. (Lexi-Drugs™). Lexi-Comp, Inc.; Hudson, OH; accessed 2.9.2018
Corticosteroids (cont’d)

- Dexamethasone:
  - Oral and IV: in divided doses q 6-12h
  - Intra-articular: 0.4 to 6 mg /day
- Prednisone: 5 mg to 60 mg PO daily
  - Discontinuation of long-term therapy requires gradual withdrawal by tapering the dose
- Adverse effects: weight gain, changes in mood and thinking, insomnia, elevated blood glucose, thin/fragile skin, increased bleeding risk, growth suppression, osteoporosis, bone fracture

4. Lexi-Comp, Inc. (Lexi-Drugs™). Lexi-Comp, Inc; Hudson, OH; accessed 2.9.2018

Neuropathic Pain

**Diagnosis**
- Clinical setting
  - Diabetes
  - MS
  - HIV
  - Spine surgery
- Distribution
  - Stocking/glove
  - Peripheral nerve
  - Nerve root/dermatome
- Quality & timing
  - Burning or shooting
  - Worse at night
- Physical findings
  - Allodynia
  - Cooler temps
  - Neurological deficit

**Drug Management**
- Anticonvulsants
  - Gabapentin
  - Pregabalin
  - Carbamazepine*/oxcarbazepine
  - Lamotrigine (off-label indication)
  - Topiramate (off-label indication)
- Antidepressants
  - TCAs (off-label indication)
  - SNRIs
- Local anesthetics
- Capsaicin

* Drug of choice for trigeminal neuralgia
Anticonvulsants

Anticonvulsants Gabapentin & Pregabalin

- Structurally related to GABA but it does not bind to GABA$_A$ or GABA$_B$ receptors or influence the degradation or uptake of GABA
- Binds to the $\alpha_2-\delta$ subunit of voltage-gated Ca$^{2+}$ channels in CNS and peripheral nerves
- Reduces the Ca$^{2+}$-dependent release of pro-nociceptive neurotransmitters, possibly by modulation of Ca$^{2+}$ channel function
- Pregabalin may also interact with descending noradrenergic and serotonergic pathways in the brainstem

1. Lexi-Comp, Inc. (Lexi-Drugs™). Lexi-Comp, Inc; Hudson, OH; accessed 2.9.2018
Anticonvulsants

**Gabapentin**
- Initial dose: 300 mg PO at bedtime
- Increase by 300-400 mg every 3-7 days, as tolerated, to lowest effective dose
- Maximum total daily dose: 3600 mg
- Renal dose adjustment required
- Baseline LFT and SCr and then monitor every 6-12 months thereafter
- Most common adverse effects:
  - Dizziness
  - Weight gain/edema
  - Sedation

**Pregabalin**
- Initial dose: 75 mg PO BID
- Titrate up to 150 mg PO BID or TID
  - Doses up to 600 mg have been evaluated with no significant additional benefit (increase in ADRs)
- Renal dose adjustment required
- Recommend baseline LFT and SCr and then monitor every 6-12 months thereafter
- Most common adverse effects:
  - Dizziness
  - Weight gain/edema
  - Sedation

Anticonvulsants (cont’d)

Gabapentin

▪ Renal dose adjustment:
  – CrCL >30-59 mL/min: 400-1400 mg/day
  – CrCL >15-29 mL/min: 200-700 mg administered as one daily dose
  – CrCL 15 mL/min: 100-300 mg administered as one daily dose
  – CrCL <15 mL/min: reduce daily dose in proportion to CrCL

▪ Hemodialysis patients:
  – Patients on hemodialysis should receive maintenance dose based on estimates of CrCL indicated above
  – Posthemodialysis supplemental dose should be administered after each 4 hours of hemodialysis


Anticonvulsants (cont’d)

Pregabalin

▪ Renal dose adjustment:

<table>
<thead>
<tr>
<th>CrCL (mL/min)</th>
<th>Total Pregabalin Daily Dose (mg/day)</th>
<th>Dose Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60</td>
<td>150  300  450  600</td>
<td>BID or TID</td>
</tr>
<tr>
<td>30-60</td>
<td>75   150  225  300</td>
<td>BID or TID</td>
</tr>
<tr>
<td>15-30</td>
<td>25-50 75  100-150 150</td>
<td>QD or BID</td>
</tr>
<tr>
<td>&lt;15</td>
<td>25   25-50  50-75  75</td>
<td>QD</td>
</tr>
</tbody>
</table>

▪ Hemodialysis patients:
  – Patients on hemodialysis should receive maintenance dose based on estimates of CrCL indicated above
  – Posthemodialysis supplemental dose should be administered after each 4 hours of hemodialysis

Anticonvulsants (cont’d)

- **Gabapentin ER**
  - FDA-approved indication: postherpetic neuralgia
  - Do not use interchangeably with other gabapentin products
  - Max dose: Up to 1800 mg/day in single dose with evening meal
  - Titration recommendations:
    - Day 1: 300 mg
    - Day 2: 600 mg
    - Days 3-6: 900 mg
    - Days 7-10: 1200 mg
    - Days 11-14: 1500 mg
    - Day 15: 1800 mg
  - Renal dose adjustment:
    - CrCL 30-60 mL/min: 600-1800 mg
    - CrCL <30 mL/min: not recommended for use
    - Hemodialysis: not recommended for use


Anticonvulsants: Alternative Options

- **Carbamazepine**
  - Drug of choice for trigeminal neuralgia
  - May require titration of dose to maximum of 1200mg/day
  - Consider obtaining baseline CBC and LFTs; consider periodic monitoring of CBC and LFTs thereafter
  - Alternative agent: oxcarbazepine (similar efficacy but increased tolerability)

- **Oxcarbazepine**
  - Better tolerability compared to carbamazepine
  - Titration begins at 150 mg twice daily to a maximum dose of 1800 mg / day
  - Patients allergic to carbamazepine should also avoid oxcarbazepine, 25% allergic cross-reactivity

Anticonvulsants: Alternative Options

- **Lamotrigine** (off-label indication)
  - Data supports use in refractory trigeminal neuralgia, central post-stroke pain, SCI pain with incomplete cord lesion and brush-induced allodynia, HIV-associated neuropathy in patients on anti-retroviral therapy, and diabetic neuropathy
  - Most effective at doses between 200-400 mg/day
  - Note: follow strict titration schedule to reduce the risk of serious skin reactions
  - Hemophagocytic lymphohistocytosis

- **Topiramate** (off-label indication)
  - Data supports use in diabetic neuropathy, refractory trigeminal neuralgia, and for migraine prophylaxis
  - Dosing generally ranges from 50 - 100 mg / day
  - Dosing over 200 mg is generally side-effect limiting


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Anticonvulsants—Neurocognitive

- Psychomotor reaction time
- Learning, memory, and executive function
- Word finding
- Considerable variance based on:
  - Age
  - Multiple anticonvulsants
  - Serum drug concentrations
- All anticonvulsants appear to have some effect on neuropsych batteries

Antidepressants

Tricyclic Antidepressants (TCAs)

May initiate as follows:
- **Nortriptyline** 10 mg PO at bedtime (off-label indication)
- **Desipramine** 25 mg PO at bedtime (off-label indication)
- **Amitriptyline** 10-25 mg PO at bedtime (off-label indication)
  - Increase by 10-25mg PO every 7 days
  - Use doses <100 mg/day when possible
  - Use with caution in BPH, glaucoma, cardiac disease, and those at risk for suicide

*Lancet Neurol* 2015; 162–73.
TCAs

<table>
<thead>
<tr>
<th>Tertiary amines</th>
<th>Secondary amines (NE&gt;SHT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Nortriptyline</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Desipramine</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Protriptyline</td>
</tr>
<tr>
<td>Doxepin</td>
<td></td>
</tr>
<tr>
<td>Trimipramine</td>
<td></td>
</tr>
</tbody>
</table>

- Secondary amines tolerated better than tertiary amines
- Secondary amines equally effective in pain as tertiary amines
- Therapeutic drug monitoring of questionable utility
- Alzheimer's risk and anticholinergic activity

4. Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: a systematic review

TCAs—Anticholinergic & Sedation

- Muscarinic receptor antagonists
  - Blurred vision, constipation, dry mouth, urine retention, constipation, tachycardia, confusion, delirium, increased ocular pressure
  - Secondary amines < tertiary amines
- Antihistaminergic effects (sedation, delirium)
  - Maprotiline, amitriptyline, doxepin, and trimipramine
TCAs—Cardiovascular Risk

- Orthostatic/postural hypotension
  - Alpha adrenergic blockade (even at low doses)
- Slowed cardiac conduction, tachycardia, ventricular fibrillation, heart block, and ventricular premature complexes (similar to Class Ia AA)
- Sudden cardiac death (unclear association with QTc prolongation)
  - Avoid doses > 100 mg/day amitriptyline equivalents
- Avoid in those with cardiovascular disease or established conduction abnormalities
- Unclear increase in risk in those without pre-existing disease
- Screen for known heart disease, syncope, palpitations, dyspnea, or chest pain
- Baseline ECG recommended by some in those > 40 years of age
  ( > 50 years of age based on APA Depression Guidelines)
- Routine ECG monitoring not recommended unless CV symptoms arise

TCAs—Behavioral Health Risks

- Abrupt discontinuation
  - Withdrawal symptoms (GI, malaise, chills, rhinitis, and myalgias)
  - Rebound depression
- Increased suicidality vs overdose toxicity
  - Boxed warning for children, adolescents, young adults (18-24 years of age)
  - Cardiac (QTc) and anticholinergic toxicity at doses as little as 10 x prescribed
- Risk of “switching” to mania but small

SNRI

Venlafaxine

- Target dose (either IR or SA) is 225 mg/day
- Renal dose adjustment:
  - Mild (CrCL 60-89 mL/min) or moderate (CrCL 30-59 mL/min) impairment: total daily dose reduced by 25%-50%
  - Severe (CrCL <30 mL/min) impairment or hemodialysis: total daily dose reduced by 50% or more
- Hepatic dose adjustment:
  - Mild (Child-Pugh 5-6) to moderate (Child-Pugh 7-9) impairment: total daily dose reduced by 50%
  - Severe impairment (Child-Pugh 10-15) or hepatic cirrhosis: total daily dose reduced by 50% or more
- Use with caution in cardiovascular disease (can increase blood pressure and cause EKG changes)

Duloxetine

- Initiate at 30 mg PO daily x1 week, then increase to target dose of 60 mg PO daily
- In fibromyalgia and chronic MSK pain, no evidence that doses >60 mg/day provide additional benefit
- Not recommended for use in patients with ESRD or severe renal impairment
- Not recommended for use in hepatic insufficiency or impairment


SNRI (cont’d)

Milnacipran

- FDA-approved indication for fibromyalgia
- Initial dose: 12.5 mg PO once daily on Day 1
- Titration schedule:
  - 12.5 mg PO BID on Days 2-3
  - 25 mg PO BID daily on Days 4-7
  - 50 mg PO BID thereafter
- Target dose: 50 mg PO BID (100 mg/day)
- Maximum: 100 mg PO BID (200 mg/day)
- Dose adjustment required in renal impairment

Serotonin Syndrome

- Mental status changes
  - Anxiety, agitated delirium, restlessness, disorientation
- Autonomic hyperactivity
  - Diaphoresis, tachycardia, hyperthermia, HTN, vomiting, and diarrhea
- Neuromuscular changes
  - Tremor, muscle rigidity, myoclonus, hyperreflexia, and clonus
- Severity may range from benign to lethal
- Solely a clinical diagnosis
- Patient and caregiver education paramount


Diagnosis of SS—Hunter Criteria

- Serotonergic agent PLUS one of the following:
  - Spontaneous clonus
  - Inducible clonus and agitation or diaphoresis
  - Ocular clonus and agitation or diaphoresis
  - Tremor and hyperreflexia
  - Hypertonia
  - Temp above 38°C (100.4°F)
- Although clinical dx, consider CBC, BMP, INR, CPK, LFTs, UA, chest X-ray, head CT, to rule out differentials

SSRI/SNRI Bleeding Risk

- Blocked serotonin uptake into platelet
- De-amplification of platelet aggregation
- Controversial data suggests:
  - Minimal risk of upper GI bleed as monotherapy
  - Increased risk of upper GI bleed in combination with NSAIDs
  - Acid suppression therapy decreases risk


SSRI/SNRI—Cardiac Conduction

- Previously not associated with QTc prolongation or Torsades de Pointes
- Venlafaxine
- Citalopram > escitalopram
- Dose limits
  - Citalopram 40 mg adults, 20 mg ≥65 years
  - Escitalopram 20 mg adults, 10 mg ≥65 years
- Consider baseline ECG in those with cardiac disease history

Topical Products

Lidocaine

- Topical anesthetic and Class 1b anti-arrhythmic
- Available via OTC (0.5 % and 4 %) and prescription (5 %)
- Lidocaine 5 % patch applied directly to area of PHN
  - No more than 3 patches concurrently
  - 12 hours on, 12 hours off

Capsaicin 8 % Patch

Dose is a single, 60-minute application of up to 4 patches

| May be repeated every 3 months or as warranted by the return of pain | Only physicians or healthcare professionals under supervision of a physician are to administer capsaicin 8% patch | Consider monitoring BP during or shortly after patch application. Patients may require short-term pain medication postapplication |


Muscular Pain

Diagnosis
- Clinical setting
  - Muscular injury
- Distribution
  - Muscle group
- Quality & timing
  - Aggravated by certain movement or position
  - Better at rest
  - Pulling, ripping, aching, spasm, cramping
- Physical findings
  - Limited ROM
  - Trigger points
  - Muscle tightness
  - Taut bands or knots

Drug Management
- Baclofen
- Tizanidine
- Other agents
Muscle Relaxants

- Antispasticity agents
  - Spasticity: upper motor neuron disorder characterized by muscle hypertonicity and involuntary jerks
  - Multiple sclerosis, cerebral palsy, spinal cord injury
    - Tizanidine
    - Baclofen
    - Diazepam


Muscle Relaxants (cont’d)

- Antispasmodics
  - Primarily used for treatment of musculoskeletal conditions, such as back pain, sciatica, herniated discs, spinal stenosis, myofascial pain
    - Cyclobenzaprine
    - Metaxalone
    - Methocarbamol
    - Orphenadrine citrate
    - Carisoprodol

Indicated for **acute** use in low back pain!
- Less than 4 weeks use to treat an episode
- May be effective for an acute-on-chronic pain episode
III. Centrally-acting agents (spasmolytic drugs)

Muscle Relaxants (cont’d)

<table>
<thead>
<tr>
<th>Baclofen</th>
<th>Tizanidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>• GABA analogue</td>
<td>• Agonist of α2 receptors (presynaptic)</td>
</tr>
<tr>
<td>• Selective GABA-B receptor agonist (↑ K⁺ conductance, ↓ Ca²⁺ conductance)</td>
<td>• Reduces adrenergic input to alpha motor neurons</td>
</tr>
<tr>
<td>• Muscle relaxant and analgesic (reduced substance P)</td>
<td>• No effect on spinal cord reflex</td>
</tr>
<tr>
<td>• 5 mg PO TID, may titrate every 3 days to effect</td>
<td>• Less antihypertensive effect than clonidine</td>
</tr>
<tr>
<td>• Max dose: 80 mg/day</td>
<td>• 2 to 8 mg PO TID</td>
</tr>
<tr>
<td>• Adverse effects: somnolence, increased seizure activity</td>
<td>• Max dose: 36 mg/day</td>
</tr>
<tr>
<td></td>
<td>• Side effects: hypotension, asthenia, elevated LFTs, hepatotoxicity</td>
</tr>
</tbody>
</table>


Skeletal Muscle Relaxants

• Cyclobenzaprine—sedation, structurally a TCA
• Tizanidine—sedating, hypotension, best data
• Methocarbamol—less sedating, limiting evidence
• Orphenadrine—sedating, sodium channel blockade
• Carisoprodol—sedating, high abuse potential
• Diazepam—sedating, high abuse potential
• Metaxalone—less sedating, expensive
• Baclofen—data primarily intrathecal
• Dantrolene—hepatotoxicity
Conclusions

- Adjuvant and coanalgesics require judicious monitoring for safe use
- Extensive patient education regarding potential adverse effects is paramount
- Comorbid disease processes and concurrent medications may obscure adverse effects