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 years¹
- Research and development²
  – Peptides, kappa agonists, and gene-targeting
- Cannabidiols³
  – 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

2. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. Recommendations and Reports. 2016;65(1);149.

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

<table>
<thead>
<tr>
<th>Acute</th>
<th>Acute on Chronic</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nociceptive</td>
<td>Neuropathic</td>
<td></td>
</tr>
</tbody>
</table>
# 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>
</tbody>
</table>
| Diclofenac   | IR tablet: 50 mg TID-QID  
               | DR: 150-200 mg/day in 2-4 doses       
               | ER: 100 mg/day                        |
|              | IR: 150-200 mg/day    
               | DR: 200 mg/day                       
               | ER: 200 mg/day                        |
| Etodolac     | IR: 200-400 mg q6-8h  | IR: 1000 mg/day                         |
| Ibuprofen    | 400-800 mg q4-6h      | 2.4-3.2 g                               |
| Indomethacin | IR: 25-50 mg BID-TID  
               | ER: 75 BID or 150 mg daily            |
|              | IR: 200 mg/day        
               | ER: 150 mg/day                        |

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

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<thead>
<tr>
<th>Medication</th>
<th>Initial Dose</th>
<th>Maximum Dose (depending on indication)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketorolac</td>
<td>PO: 20 mg initial then 10 mg q4-6h IV: 30 mg once or 15-30 mg q6h IM: 60 mg once or 30 mg q6h</td>
<td>PO: 40 mg/day IM/IV: 120 mg/day 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 ER: 1000 mg daily</td>
<td>IR: 1000-1500 mg/day 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


Corticosteroids
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\textsubscript{A} or GABA\textsubscript{B} receptors or influence the degradation or uptake of GABA
- Binds to the $\alpha_2$-$\delta$ subunit of voltage-gated Ca\textsuperscript{2+} channels in CNS and peripheral nerves
- Reduces the Ca\textsuperscript{2+}-dependent release of pro-nociceptive neurotransmitters, possibly by modulation of Ca\textsuperscript{2+} channel function
- Pregabalin may also interact with descending noradrenergic and serotonergic pathways in the brainstem

1. Lexi-Comp, Inc. (Lexi-Drugs\textsuperscript{TM}). 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

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)

- Lamotrigine (off-label indication)
  - Data supports use in refractory trigeminal neuralgia, central poststroke 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

- Topiramate (off-label indication)
  - Data supports use in diabetic neuropathy, refractory trigeminal neuralgia, and for migraine prophylaxis
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 10-25 mg 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

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TCAs

<table>
<thead>
<tr>
<th>Tertiary amines</th>
<th>Secondary amines (NE&gt;5HT)</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

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3. Table adapted from Lexi-Drugs Online.
**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

References:

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)

**Baclofen**
- GABA analogue
- Selective GABA-B receptor agonist (↑ K+ conductance, ↓ Ca++ conductance)
- Muscle relaxant and analgesic (reduced substance P)
- 5 mg PO TID, may titrate every 3 days to effect
- Max dose: 80 mg/day
- Adverse effects: somnolence, increased seizure activity

**Tizanidine**
- Agonist of α2 receptors (presynaptic)
- Reduces adrenergic input to alpha motor neurons
- No effect on spinal cord reflex
- Less antihypertensive effect than clonidine
- 2 to 8 mg PO TID
- Max dose: 36 mg /day
- Side effects: hypotension, asthenia, elevated LFTs, hepatotoxicity

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