PAINWEEK

Nonopioid Analgesics:
The Selection and Use of Adjuvant Therapies

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Disclosures

- Nothing to disclose

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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

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Are opioids still a concern?

- Drug overdose fatalities involving opioids in the US from 1999 to 2017[1]
  - 399,230 (56.8% of all cases)
- Drug overdose fatalities involving opioids in the US in 2017 [1]
  - 47,600 (67.8% of all cases)
- Rate of overdose fatalities involving opioids in women age 30-64 from 1999 to 2017 increased by[2]
  - 492%

1. Scholl L, Seth P, Kariisa M, Wilson N, Baldwin G. Drug and Opioid-Involved Overdose Deaths — United States, 2013–2017. MMWR Morb Mortal Wkly Rep 2019;67:1419–1427.
2. VanHouten JP, Rudd RA, Ballesteros MF, Mack KA. Drug Overdose Deaths Among Women Aged 30–64 Years — United States, 1999–2017. MMWR Morb Mortal Wkly Rep 2019;68:1–5.

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Risk Factors for Opioid Overdose or Addiction

Risk factors for 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

Risk factors for addiction
- Age > 65 years
- Sleep disordered breathing
- Renal/hepatic impairment
- Depression
- Substance use disorder
- History of overdose

Volkow NJ et al. NEJM.2016;374:1253-1263.
MEDD = morphine equivalent daily dose

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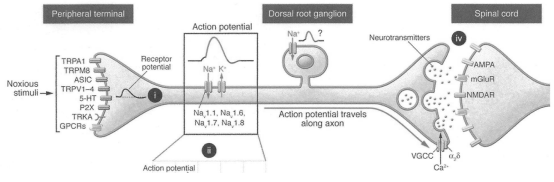
Where Do Adjuvants Work?



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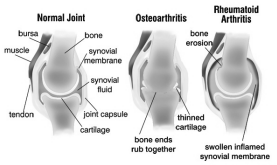
Inflammatory Pain

- NSAID
  - Ibuprofen
  - Naproxen
  - Ketorolac (IV form)
  - Meloxicam
  - Celecoxib
- Corticosteroids



https://www.practicalpainmanagement.com/pain/musculoskeletal/inflammatory-arthritis/pain-management-inflammatory-arthritis accessed 3.11.2019

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Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

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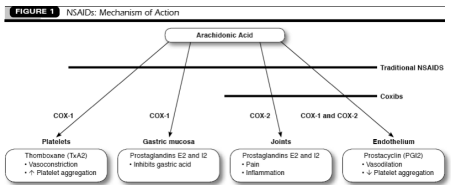
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)



JMCP. 2013;19(9):S3-S19.

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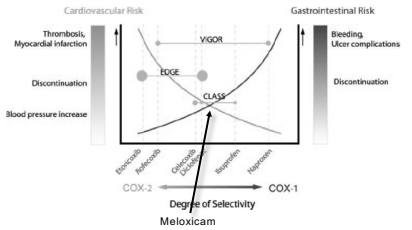
NSAIDs—COX Selectivity and Associated Risk



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Circulation. 2007;115:1634-1642.

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 ***noninferior*** to both ibuprofen and naproxen
- Risk of GI events was ***significantly lower*** with celecoxib compared to both ibuprofen and naproxen
- Study funded by Pfizer

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N Engl J Med 2016; :2519-2529.

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

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1. Am J Gastroenterol. 2009;104:728-738.
2. JMCP. 2013;19(9):S3-S19.
3. Circulation. 2007;115:1634-1642.

Topical NSAIDs

- Diclofenac sodium 1% gel
  - Dosing:
    - 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
- Diclofenac epolamine 1.3% patch
  - 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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1.Pain Medicine 2013; 14: S35–S39.
2.Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD007400.

Corticosteroids

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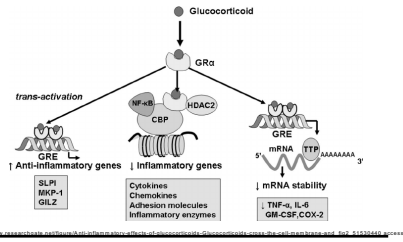
Corticosteroids



https://www.researchgate.net/figure/Anti-inflammatory-effects-of-glucocorticoids-Glucocorticoids-cross-the-cell-membrane-and_fig2_51326449 accessed 3.11.2019

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Glucocorticoids

- Mechanism of action leads to a decrease in production of heat shock proteins intracellularly leading to a decrease inflammation
- Multiple routes of administration
  - –Oral
  - –Parenteral
    - IV
    - IM depot
    - Intraarticular

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Glucocorticoids (cont'd)

- Caution should be exercised in patients with the following conditions
  - –Diabetes
  - –Psychiatric history
  - –Heart failure
  - –Adrenal suppression
    - Taper needed when therapy exceeds 10 to 14 days
  - –Immunocompromised

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Neuropathic Pain

- Anticonvulsants
  - –Gabapentin
  - –Pregabalin
  - –Carbamazepine/oxcarbazepine
  - –Lamotrigine (off-label indication)
  - –Topiramate (off-label indication)
- Antidepressants
  - –TCAs (off-label indication)
  - –SNRIs
- Local anesthetics

https://www.everydayhealth.com/neuropathy/guide/symptoms/ accessed 3.12.2019

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Anticonvulsants

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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 α_2-δ 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

J Clin Psychiatry. 2007 Mar;68(3):483-4.

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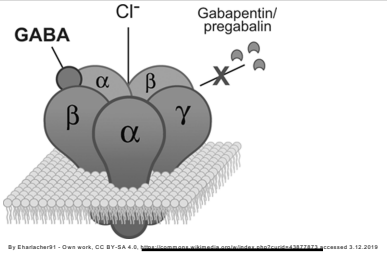
Mechanism of action α_2-δ ligands



By Ehanlacher91 - Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=43777477, accessed 3.12.2019

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Anticonvulsants

Gabapentin

- Initial dose: 100 mg to 300 mg by mouth up to 3 times daily
- Increase dose based on response and tolerability to a maximum total daily dose of 3600 mg
- Renal dose adjustment required
- NO hepatic adjustment needed
  - Gabapentin is not metabolized by hepatic enzymes
- Most common adverse effects:
  - Dizziness and drowsiness (approx. 20%)
  - Ataxia
  - Fatigue

https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6961 accessed 3.12.2019

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Anticonvulsants (cont'd)

Pregabalin

- Initial dose: 25 mg to 150 mg by mouth once or twice a day
- Increase dose in 1 week based on tolerability to a maximum daily dose of 450 mg
  - Doses up to 600 mg have been evaluated with no significant additional benefit
- Renal dose adjustment required
- NO hepatic adjustment needed
  - Pregabalin is minimally metabolized by hepatic enzymes
- Most common adverse effects:
  - Dizziness and somnolence
  - Peripheral edema

https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/152621 accessed 3.12.2019

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Anticonvulsants: Alternative Options

- **Carbamazepine**
  - Drug of choice for trigeminal neuralgia
  - May require titration of dose to maximum of 1200 mg/day
  - Consider obtaining baseline CBC and LFTs
    - Consider periodic monitoring of CBC and LFTs thereafter
- **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

1. Hooten M, et al. Institute for Clinical Systems Improvement. Pain: Assessment, Non-Opioid Treatment Approaches and Opioid Management. Updated September 2016.
2. Update on neuropathic pain treatment for trigeminal neuralgia. Neuroscience, 20.2.107-14 2015.

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Anticonvulsants: Alternative Options (cont'd)

- **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 antiretroviral 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
  - Immune response?
- **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

1. Neurol Sci (2006) 27:S183–S189.
2. R.H. Dworkin et al. / Pain 132 (2007) 237–251.

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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

1. Meador KJ. *Epilepsy Res.* 2006;68(1):63-67.
2. Pandina GJ, et al. *Pediatr Neurol.* 2010;42(3):187-195.
3. Koch MW, Polman SKL. Oxcarbazepine versus carbamazepine monotherapy for partial onset seizures. Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No.: CD006453. DOI: 10.1002/14651858.CD006453.pub2.
4. Hessen E, et al. *Acta Neurol Scand.* 2009;119(3):194-198.

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Antidepressants

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Tricyclic Antidepressants (TCAs)

Initial dosing of TCAs

- **Nortriptyline** 10 mg at bedtime (off-label indication)
- **Desipramine** 25 mg at bedtime (off-label indication)
- **Amitriptyline** 10-25 mg at bedtime (off-label indication)
  - Use with caution in BPH, glaucoma, cardiac disease, and those at risk for suicide

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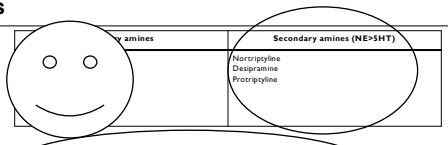
Lancet Neurol 2015; 162–73.

TCAs



- 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

1. Watson, Neurology 1998;51:1166-1171.
2. McQuay Pain. 1996;68:217-227.
3. Table adapted from Lexi-Drugs Online. www.uptodate.com. Accessed 2.9.2018.
4. Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: a systematic review

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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

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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
- 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

1. Ray WA, et al. *Clin Pharmacol Ther.* 2004;75:234-241.
2. Gelenberg AJ, et al. Practice guideline for the treatment of patients with Major Depressive Disorder, 3rd Edition. www.psychiatryonline.org. Accessed 2.9.2018

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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

1. Labbate, LA, Fava, M, Rosenbaum, JF, et al. Drugs for the treatment of depression. In: Handbook of Psychiatric Drug Therapy, 6th ed, Lippincott Williams & Wilkins, Philadelphia 2010.
2. Dalal A, et al. *J Clin Psychopharmacology.* 1998;18:343-344.
3. Frye, MA, et al. *Am J Psychiatry.* 2009;166:164-172.
4. Van Scheyen JD, et al. *Arch Gen Psychiatry.* 1979;36:560-565.

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SNRI

Venlafaxine (off label)

- Initial dose: 37.5 mg to 75 mg ER by mouth once a day
- Increase dose by 37.5 mg to 75 mg ER daily every week
  - Target dose of 225 mg ER once daily
- Renal and hepatic dosing adjustments necessary
- Discontinuing therapy should be done over 2 to 4 weeks
- Most common adverse effects
  - Suicidal ideations [Black box warning]
    - Children and up to 24 years of age
  - Anxiety, insomnia

Duloxetine

- Initial dose: 30 mg by mouth once a day
- Increase dose to 60 mg ER every week
  - Maximum daily dose 120 mg
- Avoid use with severe renal or hepatic impairment
- Discontinuing therapy should be done over 2 to 4 weeks
- Most common adverse effects
  - Suicidal ideations [Black box warning]
    - Children and up to 24 years of age
  - Cognitive impairment

https://online.lexi.com/lco/action/home accessed 3.13.2019

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SNRI (cont'd)

- Milnacipran 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

https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/518 accessed 3.13.2019

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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

1. Boyer EW, et al. *N Engl J Med.* 2005;352(11):1112-1120.
2. Mackay FJ, et al. *Br J Gen Pract.* 1999;49(448):871-874.

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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

Dunkley EJ, et al. *QJM.* 2003;96(9):635-642.

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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

1. Dalton SO, et al. *Arch Intern Med.* 2003;163(1):59-64.
2. Loke YK, et al. Ailment *Pharmacol Ther.* 2008;27(1):31-40.
3. McCloskey DJ, et al. *Transl Res.* 2008;151(3):168-172.
4. de Abajo FJ, et al. *Arch Gen Psychiatry.* 2008;65(7):795-803.

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Local Anesthetics

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Lidocaine

- May be used topically or by injection
- Topical patch available in 0.5% to 5%
- 5% patch applied directly to area of postherpetic neuralgia[1]
  - No more than 3 patches concurrently
  - 12 hours on, 12 hours off
- Trigger point injections[2]
  - Lidocaine or procaine
  - Caution in patients on anticoagulants and local anesthetic allergy history

1. Kaliq W, et al. Topical lidocaine for the treatment of postherpetic neuralgia. Cochrane Database Syst Rev 2007;18:CD004846.
2. Alvarez DJ, et. al. Trigger Points: Diagnosis and management. American Family Physician 2002 65 (4): 653-61.

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Antispasticity and Antispasmodic Agents

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Muscle Spasms

- Baclofen
- Tizanidine
- Other agents
  - –Cyclobenzaprine, the TCA ?

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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

1. Chou R, et al. J Pain Symptom Manage. 2004;28:140-75.
2. Van Tulder MW, et al. Cochrane Database Syst Rev. 2003;(2):CD004252.
3. Pharmacotherapy 2008;28(2):207–213.
4. Ann Intern Med. 2007 Oct 2;147(7):478-91.
5. Skeletal Muscle Relaxants Quick Reference. Compiled by Nolan MJ and Fudin J.
6. Lexi-Comp, Inc. (Lexi-Drugs™). Lexi-Comp, Inc.; Hudson, OH; 1 May 2015.

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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

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1. Pharmacotherapy 2008;28(2):207–213.
2. Skeletal Muscle Relaxants Quick Reference. Compiled by Nolan MJ and Fudin J.

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

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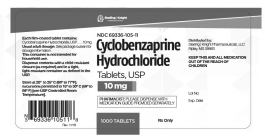
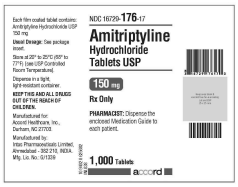
Cyclobenzaprine, or Something Else?





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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

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