Nonopioid Analgesics: The Selection and Use of Adjuvant Therapies
Courtney Kominek, PharmD, BCPS, CPE

Disclosures
- Consultant: Axial Healthcare
- Honoraria: Daiichi Sankyo
- This presentation was not a part of the presenter’s official duties at the VA and does not represent the opinion of the VA
- The presentation will include “off-label” uses of some medications, for example gabapentin and tricyclic antidepressants (TCAs)
Learning Objectives

- Describe where adjuvant analgesics act in the pain pathway and the differences in mechanism of action (MOA)
- Compare risks and benefits of different adjuvant analgesics for a given patient
- Choose an adjuvant analgesic based on current guidelines and/or evidence-based medicine as well as individual patient factors

Nonopioid Options

<table>
<thead>
<tr>
<th>NSAIDs</th>
<th>Tricyclic antidepressants (TCAs)</th>
<th>Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsants</td>
<td>Topicals</td>
<td>Skeletal muscle relaxants</td>
</tr>
</tbody>
</table>
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

**Mechanism of Action**

- **Gastric mucosa (COX-1)**
  - Prostaglandins E2 and I2
- **Joints (COX-2)**
  - Prostaglandins E2 and I2
- **Platelets (COX-1)**
  - Thromboxane
- **Endothelium (COX-1 and COX-2)**
  - Prostacyclin

Arachidonic acid

JMCP. 2013;19(9):S3-S19
NSAIDs—
COX Selectivity and Associated Risk


COX-1 and COX-2 Selectivity
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


NSAID Boxed Warnings

Cardiovascular Risk
- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, MI, and stroke which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at a greater risk.
- NSAIDs are contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.

Gastrointestinal Risk
- NSAIDs cause an increased risk of serious gastrointestinal adverse events including inflammation, bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

GI Adverse Events: Risk Factors

- **Low risk**
  - No risk factors

- **Moderate risk (1-2)**
  - > 65 years of age
  - High dose NSAID therapy
  - History of prior uncomplicated ulcer
  - Concurrent use of low-dose aspirin, anticoagulants, or corticosteroids

- **High risk patients**
  - History of previously complicated ulcer
  - Multiple risk factors (>2)

GI Adverse Events: Prevention

<table>
<thead>
<tr>
<th>Low CV Risk</th>
<th>Low GI Risk</th>
<th>Moderate GI Risk</th>
<th>High GI Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low CV Risk</td>
<td>NSAID alone</td>
<td>NSAID + PPI or misoprostol</td>
<td>Alternative therapy or COX-2 + PPI or misoprostol</td>
</tr>
<tr>
<td>High CV Risk</td>
<td>Naproxen + PPI or misoprostol</td>
<td>Naproxen + PPI or misoprostol</td>
<td>Avoid NSAIDs or COX-2 inhibitors. Use alternative therapy</td>
</tr>
</tbody>
</table>

NSAIDs and Renal

Avoid in people with GFR < 30 ml/min

Long-term therapy is not recommended in people with GFR < 60 ml/min

Avoid with lithium

Avoid in people taking RAAS blocking agents


Topical NSAIDs: Agents

<table>
<thead>
<tr>
<th>Medication</th>
<th>Indication</th>
<th>Dosing</th>
</tr>
</thead>
</table>
| Diclofenac gel 1%                 | Joint amenable to topical application (knee and hands) | 2 g for each elbow, wrist or hand  
4 g for each knee, ankle, or foot  
Max 32 mg/day                          |
| Diclofenac sodium topical solution| OA of knee                                        | 10 drops at a time on each of 4 sides of knee  
40 drops QID                             |
| Diclofenac epolamine patch 1.3%   | Topical treatment of acute pain due to minor strains, sprains, and contusion | 1 patch to painful area BID |

Pain Med. 2013;14:S35-S39
Topical NSAIDs: Place in Therapy

- American College of Rheumatology
  - Initial management of hand or knee OA may include topical NSAID
- American Geriatric Society
  - May consider topical NSAID for localized, non-neuropathic persistent pain
- European League Against Rheumatism (EULAR)
  - Hand OA: topical NSAIDs over systemic
  - Hand or Knee OA: topical NSAIDs with clinical efficacy and safety
- National Institute for Health and Clinical Excellence (NICE)
  - Topical NSAIDS considered in addition to nonpharmacological
  - Consider topical NSAIDs or acetaminophen prior to PO NSAIDs

Topical NSAIDs: Pharmacokinetics

Absorption
- Gel: 6-10%
- Solution: 2-3%
- Patch
- Half-life: ~12h
- Time to peak
  - Gel ~ 10-14h
  - Solution 5-17h
  - Patch 10-20h

## Drug-Drug Interactions

<table>
<thead>
<tr>
<th>Anticoagulants, anti-platelets,</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs)</td>
</tr>
<tr>
<td>Cyclosporine, tacrolimus</td>
</tr>
<tr>
<td>Methotrexate</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs)</td>
</tr>
<tr>
<td>Lithium</td>
</tr>
<tr>
<td>Diuretics</td>
</tr>
<tr>
<td>Ibuprofen + aspirin</td>
</tr>
</tbody>
</table>


## Anticonvulsants
**Anticonvulsants: Gabapentinoids**

- 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

Micromedex 2.0 Online.

---

**Gabapentin**

<table>
<thead>
<tr>
<th>Gabapentinoid Medication</th>
<th>FDA-Approved Indications</th>
<th>Dosing</th>
<th>Renal Dose Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin (Neurontin®)</td>
<td>PHN</td>
<td>Initiate at 100-300 mg PO QHS or TID. Doses can be increased by 100-300 mg/day every 1-7 days / Maximum dose 3600 mg/day Exceeding 1800 mg/day may not provide further benefit owing to saturable nonlinear kinetics</td>
<td>≥60 mL/min – no change 30-59 mL/min – 400-1400 mg/day in 2 divided doses 15-29 mL/min 200-700 mg in 1 daily dose</td>
</tr>
</tbody>
</table>

### Gabapentin ER

<table>
<thead>
<tr>
<th>Gabapentinoid Medication</th>
<th>FDA-Approved Indications</th>
<th>Dosing</th>
<th>Renal Dose Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin (Gralise®)</td>
<td>PHN</td>
<td>Take once daily with evening meal. Day 1: 300 mg Day 2: 600 mg Day 3-6: 900 mg Days 7-10: 1200 mg Days 11-14: 1500 mg Day 15: 1800 mg Maximum dose 1800 mg/day</td>
<td>• &gt; 60 mL/min – none • 30-60 mL/min – 600-1800 mg • &lt; 30 mL/min do not use • Hemodialysis: do not use</td>
</tr>
</tbody>
</table>


### Gabapentin enacarbil

<table>
<thead>
<tr>
<th>Gabapentinoid Medication</th>
<th>FDA-Approved Indications</th>
<th>Dosing</th>
<th>Renal Dose Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin enacarbil (Horizant®)</td>
<td>Moderate to severe RLS PHN</td>
<td>600 mg in AM x 3 days Then increase to 600 mg PO BID. Maximum dose 1200 mg/day</td>
<td>• &gt; 60 mL/min no change • 30-59 mL/min – initiate at 300 mg QAM x 3 days, may increase up to 600 mg BID • 15-29 mL/min – 300 mg in QAM x 3 days then increase to 300 mg BID • &lt; 15 mL/min – 300 mg every other day, may increase to 300 mg QAM • Hemodialysis – 300 mg after dialysis may increase to 600 mg after dialysis</td>
</tr>
</tbody>
</table>

**Pregabalin**

<table>
<thead>
<tr>
<th>Gabapentinoid Medication</th>
<th>FDA-Approved Indications</th>
<th>Dosing</th>
<th>Renal Dose Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregabalin (Lyrica)</td>
<td>• DPN</td>
<td>• Initiate at 150 mg/day in 2 or 3 divided doses.</td>
<td>• &gt; 60 mL/min – no change needed</td>
</tr>
<tr>
<td></td>
<td>• PHN</td>
<td>• Increase dose to 300 mg/day within 1 week.</td>
<td>• 30-60 mL/min – 75-300 mg divided BID or TID</td>
</tr>
<tr>
<td></td>
<td>• Adjunctive therapy for</td>
<td>• Maximum doses vary depending on indication</td>
<td>• 15-30 mL/min – 25 – 150 mg divided daily or BID</td>
</tr>
<tr>
<td></td>
<td>partial onset seizures</td>
<td></td>
<td>• &lt; 15 mL/min – 25-75 mg daily</td>
</tr>
<tr>
<td></td>
<td>• Fibromyalgia</td>
<td></td>
<td>• Hemodialysis – provide supplemental doses after dialysis based on daily dose</td>
</tr>
<tr>
<td></td>
<td>• Neuropathic pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>associated with SCI</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


**Pregabalin CR**

<table>
<thead>
<tr>
<th>Gabapentinoid Medication</th>
<th>FDA-Approved Indications</th>
<th>Dosing</th>
<th>Renal Dose Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregabalin CR</td>
<td>• PHN</td>
<td>• DPN: Starting dose: 165 mg/day, Maximum dose: 330 mg/day</td>
<td>Renal dosage adjustments needed</td>
</tr>
<tr>
<td></td>
<td>• DPN</td>
<td>• PHN: Initial dose: 165 mg/day. Maximum dose: 330-660 mg/day</td>
<td></td>
</tr>
</tbody>
</table>

Gabapentinoid Pharmacokinetics

<table>
<thead>
<tr>
<th>Medication</th>
<th>F</th>
<th>Tmax</th>
<th>Half-life</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin IR</td>
<td>900</td>
<td>60%</td>
<td>1200 mg</td>
<td>47%</td>
</tr>
<tr>
<td>(Neurontin)</td>
<td>2400</td>
<td>34%</td>
<td>3600</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5-7h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bioavailability is not dose proportional</td>
</tr>
<tr>
<td>Gabapentin ER</td>
<td></td>
<td>8h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Gralise)*</td>
<td></td>
<td></td>
<td></td>
<td>Bioavailability is not dose proportional. Cmax increased 33-8% and AUC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>33-118% with food depending on fat content. Absorbed from proximal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>small bowel by a saturable L-amino transport system.</td>
</tr>
<tr>
<td>Gabapentin enacarbil*</td>
<td>75%</td>
<td>7.3 h with</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>food</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.1-6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prodrug. Dose-proportional and extended exposure to gabapentin. Nonsaturable absorption</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.3 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Linear Cmax and AUC, independent of dose</td>
</tr>
</tbody>
</table>

Gabapentin Increases Overdose Odds

- Population-based nested case-control study
- Cases (1,256 cases) were opioid users who died of an opioid-related cause matched with up to 4 controls (4,619 controls)
- Primary exposure was gabapentin use 120 days preceding index date
- 12.3% of cases and 6.8% of control were prescribed gabapentin
- Odds increased 49% if prescribed gabapentin + opioid
- High dose gabapentin (1800 mg/day) about 60% increased odds compared to moderate dose
- Very high dose (2,200 mg/day) associated with 2-fold increased odds

Pregabalin Increases Overdose Odds

- Population-based, nested, case-control study in patients received opioid
- 1417 cases: died of an opioid-related cause, excluding suicide or homicide
- 5097 controls: matched on several characteristics
- Primary exposure: pregabalin 120 days prior to index date
- Case patients more likely to receive CNS depressants, more medications annually, and have more comorbidities
- Exposure to pregabalin 120 days prior increased odds of opioid-related death 1.68 (95% CI 1.19-2.26)
- High dose of pregabalin (> 300 mg/day) associated with 2.51 increased odds (95% CI 1.24-5.06)

Gabapentinoid Abuse

- Prevalence
  - General population 1.1%
  - Opioid use disorder
    - 15-22% gabapentin misuse
    - 40-65% abuse of gabapentin with prescription
- Dosing – variety
  - Therapeutic range – no prescription
  - Supratherapeutic range
  - 3-20 times clinically used amounts
  - Taken as one large dose

Addiction. 2016;111:1160-1174. CNS
Drugs. 2014;28:491-496.
Drugs. 2017;77:403-426.
Gabapentinoid Abuse

- Typically ingested with other substances
- Often used to increase high or treat withdrawal
- 90% of fatalities involve opioids
- Withdrawal treatment involves tapering gabapentinoid


Anticonvulsants:
Carbamazepine and Oxcarbazepine

- MOA: inhibit voltage-gated sodium channels and potentiate GABA
- Role
  - CBZ drug of choice for trigeminal neuralgia
  - OXCBZ
    - Trigeminal neuralgia
    - Specialist setting/4th line NICE neuropathic pain guidelines

Eur J Neurol. 2010;17(9):1113-e1188.
Anticonvulsants:
Carbamazepine and Oxcarbazepine

CBZ IR and XR
- Initial: 100 mg PO BID
- Titrate by 100 mg PO BID
- Target dose 300-900 mg/day
- Max dose: 1200 mg/day

OXCBZ IR
- Initial: 150 mg PO BID
- Titrate by 300 mg q3 days
- Target: 300-600 mg PO BID
- Max dose: 1800 mg/day

OXBZ XR
- Initial dose: 600 mg PO daily
- Titrate by 600 mg/day weekly
- Max dose: 2400 mg/day

- CBZ
  - Metabolized by CYP3A4
  - Active metabolite carbamazepine 10,11, epoxide autoinducer
  - Induces CYP3A4, CYP1A3, CYP2B6, CYP2C9, CYP2C19
- OXCBZ
  - Keto-derivative of CBZ
  - Metabolized to active metabolite 10-monohydroxy oxcarbazepine which avoids CYP metabolism
  - May be better tolerated
  - 20-30% have cross-reactivity with OXCBZ if allergic to CBZ
**Anticonvulsants: Carbamazepine and Oxcarbazepine**

- **Common ADE**
  - Diplopia, abnormal vision
  - Fatigue
  - Dizziness
  - Somnolence
  - N/V
  - Ataxia
  - Headache
  - Nystagmus
  - Tremor
  - Abnormal gait

- **Serious ADE**
  - Hyponatremia
  - Allergic reactions
  - Pancytopenia
  - Agranulocytosis
  - Leukopenia
  - Serious dermatological reactions
    - HLA-B*1502 testing for those with Asian ancestry
  - Cardiac (BP, CHF, arrhythmias, AV block) (CBZ)
  - Elevation LFTS (CBZ)

**Anticonvulsants: Lamotrigine**

- **MOA**: voltage-gated sodium channels
- **Role**
  - 4th line/specialist setting for neuropathic pain
  - 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

- **Dosing**
  - TITRATE DOSE SLOWLY
  - Initiate at 25 mg PO daily x 2 weeks then increase to 50 mg/day for 2 weeks
  - Then titrate by 50 mg/day q1-2 weeks
  - May need to titrate to 200-400 mg/day

---


Eur J Neurol. 2010;17(9):1113-e1188.
Anticonvulsant: Lamotrigine

- **Common ADE**
  - Dizziness
  - Nausea
  - Insomnia
  - Somnolence
  - Fatigue
  - Diplopia
  - Ataxia

- **Severe ADE**
  - FATAL OR LIFE-THREATENING HYPERSENSITIVITY
  - Blood dyscrasias
  - Aseptic meningitis


Anticonvulsants: Topiramate

- **MOA**
  - Inhibits voltage-gated sodium channels
  - AMPA/kainate subtype of glutamate receptor
  - Carbonic anhydrase inhibitor
  - Increases activity at GABA-A receptor

- **Role**
  - Alcohol use disorder
  - Migraine prophylaxis
  - Neuropathic pain

Anticonvulsants: Topiramate

Dosing

– Topiramate IR
  • Initial dose: 25 mg po daily x 1 week
  • Titrate by 25-50 mg/day
  • Target dose
    – Migraine: 50 mg PO BID
    – Neuropathic pain 200-400 mg/day

– Topiramate XR
  • Initial dose: 25 mg PO daily
  • Titrate by 25mg/day q week
  • Target dose: 100 mg/day


Anticonvulsants: Topiramate

Dose-related ADE

– Paresthesia
– Fatigue
– Nausea
– Anorexia
– Dizziness
– Difficulty with memory
– Diarrhea
– Weight loss
– Concentration/attention
– Somnolence

Caution

– Secondary angle glaucoma
– Metabolic acidosis
– Hyperammonemia
– Kidney stones
– Oligohidrosis
– Hypo/hyperthermia
– Cognitive dysfunction
– Renal adjustments CrCl < 70 mL/min

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

Tricyclic Antidepressants (TCAs)
Role in Pain Management

First-line for neuropathic pain

- NICE
- Canadian Pain Society Guidelines
- Neuropathic Pain Special Interest Group of the International Association for the Study of Pain
- European Federation of Neurological Societies

Second-line for neuropathic pain

- American Academy of Neurology
- American Diabetes Association

Role in Pain Management

Effects independent of BH disorder

Low back pain

Migraine prophylaxis

Fibromyalgia

Effects independent of BH disorder

Lower doses compared to MDD


Pharmacodynamics

Ach M=acetylcholine muscarinic receptor, α₁=alpha-1 adrenergic receptor, H₁=histamine-1 receptor,

<table>
<thead>
<tr>
<th>Medication</th>
<th>Ach M</th>
<th>α₁</th>
<th>H₁</th>
<th>5-HT₁</th>
<th>NE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary amines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desipramine</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Tertiary amines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Doxepin</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Imipramine</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++++</td>
<td>+++</td>
</tr>
</tbody>
</table>


Tricyclic Antidepressants (TCAs)

May initiate as follows:
- **Nortriptyline** 10mg PO at bedtime
- **Desipramine** 25mg PO at bedtime
- **Amitriptyline** 10-25mg PO at bedtime
  - Increase by 10-25mg PO every 3-5 days
  - Use doses <100mg/day when possible
  - Do not exceed 50mg/day in patients on SSRI or SNRI
  - Use with caution in BPH, glaucoma, cardiac disease, and those at risk for suicide

Lancet Neurol 2015; 162–73.
Adverse Drug Effects (ADE)

Cardiac → Avoid in CV disease

<table>
<thead>
<tr>
<th>Sudden cardiac death with doses &gt; 100 mg/day</th>
<th>QTc prolongation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Baseline ECG recommended by some in those &gt;40-50 years of age</td>
<td></td>
</tr>
<tr>
<td>Routine ECG monitoring not recommended</td>
<td></td>
</tr>
</tbody>
</table>

| Arrhythmias | Tachycardia | Orthostatic hypotension |


ADE

Anticholinergic → Elderly

- Dry mouth
- Constipation
- Urinary retention → BPH
- Tachycardia
- Confusion
- Blurred vision → Glaucoma

**ADE**

- Withdrawal symptoms
- Suicide risk
- Seizure risk
- Histamine receptor antagonism → Sedation

Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

Role in Pain Management

Duloxetine
- FDA-approved for
  - Diabetic peripheral neuropathy
  - FMS
  - Chronic musculoskeletal pain (LBP, OA)
  - Second-line in American College of Physician guideline on LBP

Milnacipran
- FDA-approved for FMS

Venlafaxine
- LBP
- Diabetic peripheral neuropathy
- FMS
- Chemotherapy-induced neuropathy
- Painful polyneuropathy
- Headaches

ADE

Common
- Nausea
- Somnolence
- Dry mouth
- Hyperhidrosis
- Erectile dysfunction
- Constipation

**ADE**

- Hypertension
- Hyponatremia
- Urinary retention
- Increased bleeding risk
- Withdrawal symptoms with abrupt discontinuation

**Duloxetine Dosing and Considerations**

- **Dosing**
  - Initiate at 30mg PO daily x1 week, then increase to target dose of 60mg PO daily
  - Continue for 2 weeks at 30 mg daily in elderly
  - In fibromyalgia and chronic MSK pain, no evidence that doses >60mg/day provide additional benefit

- **ADE**
  - Hyperglycemia
  - Avoid in chronic hepatic disease or cirrhosis
  - Avoid < 30 mL/min
  - Contraindicated uncontrolled closed-angle glaucoma

Venlafaxine Dosing and Considerations

- **Dosing**
  - Initiate at venlafaxine SA 37.5 mg PO daily
  - Titrate dose q2 weeks to 75 mg daily, 150 mg daily, 225 mg daily
- **QTc prolongation**
  - Consider baseline ECG in those with cardiac disease history
- **Caution with renal disease – reduce doses**
  - Mild to moderate: reduce total daily dose by 25-50%
  - Severe: reduce total daily dose by 50% or more
- **Caution with hepatic disease – reduce doses**
  - Mild to moderate: reduce total daily dose by 50%
  - Severe: reduce total daily dose by at least 50% or more
- **Caution uncontrolled closed-angle glaucoma**

Milnacipran Dosing

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

- Hepatotoxicity – no dose adjustment recommendations
- Use with caution in moderate renal impairment
- Severe renal impairment (CrCl 5-29 mL/min), the maintenance dose should be reduced by 50% to 50 mg/day (25 mg twice daily). May increase to 50 mg BID
- Not recommended in ESRD

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
- Consider serotonin active herbal/OTC products!!!


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


SNRI—Suicidality

- Warnings
- Effected populations
- Timing of risk
- Monitoring and follow-up

http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/UCM096273
SNRI Bleeding Risk

- Block 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


Topical Products
Lidocaine

- Topical anesthetic and Class 1b anti-arrhythmic
- Sodium channel blockade Na(v) 1.7
- Inhibition of acid sensing ion channels (ASIC)
- Available via OTC (0.5%-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
- OTC lidocaine 4% patch
- IV infusion is a potential treatment option


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

Skeletal Muscle Relaxants

Introduction

Heterogeneous group

Structurally not related

2 million people per year report use of SMR

300,000 elderly patients use SMR

Associated with sedation and weakness as well as other adverse effects

## Spasticity vs. Spasms

<table>
<thead>
<tr>
<th>Description</th>
<th>Spasticity</th>
<th>Spasms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Velocity-dependent increase in muscle tone because of increased excitability</td>
<td>Involuntary muscle contraction</td>
</tr>
</tbody>
</table>
| **Etiology** | • Central  
• Upper motor neuron disorder | • Peripheral  
• Muscle sprain or injury  
• Nerve compression |
| **Symptoms** | • Stiffness  
• Hypertonicity  
• Hyperreflexia | • Jerks  
• Twitches  
• Cramps |

*Table adapted from below reference. Used with permission.*

## Spasticity vs. Spasms

<table>
<thead>
<tr>
<th>Description</th>
<th>Spasticity</th>
<th>Spasms</th>
</tr>
</thead>
</table>
| **Cause**   | • Multiple sclerosis  
• Cerebral palsy  
• Spinal cord injury  
• Traumatic brain injury  
• Motor neuron disease  
• Post-stroke syndromes | • Musculoskeletal pain  
• Fibromyalgia  
• Sciatica  
• Mechanical low back pain  
• Herniated disk  
• Spinal stenosis  
• Myofascial pain |

### FDA-approved medications
- • Botulinum toxin  
• Baclofen  
• Dantrolene  
• Diazepam  
• Riluzole  
• Tizanidine  
- • Carisoprodol  
• Chlorzoxasone  
• Cyclobenzaprine  
• Metaxalone  
• Methocarbamol  
• Orphenadrine

*Table adapted from below reference. Used with permission.  

## Neurotransmitters Involved in Muscle Spasticity and Spasm

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gamma-aminobutyric acid (GABA)</strong></td>
<td>• Primary inhibitory neurotransmitter from interneurons</td>
</tr>
</tbody>
</table>
| **Glutamate** | • Primary excitatory neurotransmitter from IA afferent fibers in descending corticospinal tract  
• Binds AMPA, kainate, NMDA |
| **Glycine** | • Inhibitory and excitatory roles |
| **Acetylcholine (Ach)** | • Primary neurotransmitter for sending signals from neurons to muscles  
• Changes Na⁺ and Ca²⁺ |

*Adapted from below reference. Used with permission.  
Antispasticity Medications

Baclofen

- Mechanism of Action (MOA)
  - Structurally related to GABA
  - Binds and activates GABA_B receptors that are coupled to Ca^{2+} and K^+ channels leading to membrane hyperpolarization
    - Presynaptic: decreases Ca^{2+} conductance \rightarrow reduces glutamate release \rightarrow decreases activity of alpha-motor neuron
    - Postsynaptic: increases K^+ conductance \rightarrow increases presynaptic inhibition
  - Inhibits substance P
- Dosage Forms
  - Oral
  - Intrathecal (reserved for severe spasticity)

Baclofen

- **Dosing**
  - 5 mg PO TID x 3 days
  - 10 mg PO TID x 3 days
  - 15 mg PO TID x 3 days
  - 20 mg PO TID x 3 days
  - Max: 80 mg/day
  - Avoid CrCl < 30 mL/min
- **Adverse drug events (ADE)**
  - Drowsiness, dizziness, weakness, fatigue, confusion, headache, hypotension,
  - Withdrawal syndrome: hallucinations and seizures if abruptly discontinued


Dantrolene

- **MOA**
  - Hydantoin derivative
  - No direct CNS effects
  - Blocks ryanodine channels $\rightarrow$ inhibits Ca$^{2+}$ release $\rightarrow$ decrease muscle contraction
- **Dosing**
  - 25 mg PO daily x 7 days
  - 25 mg PO TID x 7 days
  - 50 mg PO TID x 7 days
  - 100 mg TID thereafter
- **Kinetics**
  - Half-life 4.1-22.2h
  - CYP3A4 substrate

**Dantrolene**

- **Black box warning: hepatitis**
  - Save for neuroleptic malignant syndrome and malignant hyperthermia
- **Contraindications**
  - Active hepatitis
  - Active cirrhosis
- **ADE**
  - Weakness, dyspnea, dysphasia, somnolence, diarrhea
- **Stop if no benefit within 45 days**


---

**Riluzole**

- **MOA**
  - Inhibits voltage-gated Na\(^+\) channels on glutaminergic nerve terminals → decreases glutamate release
- **Labeling:** amyotrophic lateral sclerosis (ALS)
- **Dosing:** 50 mg PO daily
- **Kinetics**
  - Absorption decreased with high fat meals
  - Metabolized by CYP1A2
- **ADE**
  - Decrease lung function
  - Pruritus
  - Dose-related LFTs increases

Antispasticity-Antispasmodic Agents

Diazepam

- Approvals
  - Spasticity
  - Muscle spasms

- MOA
  - GABA receptor agonist $\rightarrow$ increases chloride conductance $\rightarrow$
    presynaptic inhibition of spinal cord

- Dosing
  - 2 mg PO BID-TID or 5 mg PO QHS
  - Target 40 mg/day divided

*All benzodiazepines have muscle relaxant properties

**Diazepam**

- **Kinetics:**
  - Elimination half-life 20-50 h
  - Active metabolites with half-life up to 100 h
  - Metabolized by CYP3A4 and CYP2C19
- **Avoid**
  - Elderly
  - Renal or hepatic impairment
- **ADE**
  - Abuse potential
  - Dizziness, drowsiness, confusion, amnesia
  - Withdrawal with abrupt cessation


---

**Tizanidine**

- **MOA**
  - Structurally related to clonidine
  - Centrally acting
  - Inhibits presynaptic and postsynaptic α-2 motor neurons
  - Potentiate glycine
- **Dosing**
  - Initial dose: 4 mg
  - Increase by 2-4 mg q6-8h
  - Max 36 mg/day divided

Tizanidine

- **ADE**
  - Hypotension, sedation, asthenia, dry mouth
  - Elevated liver function tests, hepatoxicity
    - Monitor baseline, 1, 3, and 6 months
  - Withdrawal syndrome with abrupt discontinuation
  - Avoid CrCl < 25 mL/min

- **Kinetics**
  - Bioavailability differs based on dosage form and food
  - Metabolized by CYP1A2
    - Contraindicated with ciprofloxacin and fluvoxamine

---


---

Antispasmodics
Carisoprodol

- **MOA**
  - Centrally acting
  - Changes interneuronal activity in spinal cord and descending reticular formation of brain
  - Decreases pain perception

- **Dosing**
  - 350 mg PO QID
  - Max 1400 mg/day

- **Avoid in children < 12 years (or EVERYONE)**

---

Carisoprodol

- **ADE**
  - Abuse potential
  - Drowsiness, headache, vertigo, insomnia
  - Respiratory depression particularly in combo
  - Seizures with overdose, excessive use, withdrawal
  - Idiosyncratic allergic type reactions

- **Kinetics**
  - Metabolized by CYP2C19 to meprobamate among others
    - Subject to pharmacogenetic differences
Chlorzoxazone

- **MOA**
  - Acts at spinal cord and subcortical areas of brain
  - Inhibition of multisynaptic reflex arcs
- **Dosing**
  - 500-75 mg PO TID-QID
- **ADE**
  - Dizziness, drowsiness,
  - Rare hepatotoxicity (monitor LFTs periodically)
  - GI irritation or ulcer
  - Urine discoloration


Cyclobenzaprine

- **MOA**
  - Structurally related to tricyclic antidepressants (TCAs)
  - Not clear likely sedation
  - No direct activity on skeletal muscle
- **Dosing**
  - 5 mg PO TID
  - Increase up to 10 mg PO TID
  - Avoid longer than 3 weeks
- **Kinetics**
  - Metabolized by CYP3A4, CYP1A2, and CYP2D6
- **ADE**
  - Anticholinergic side effects
  - Avoid in patients with cardiac conduction abnormalities or arrhythmias

Metaxalone

- **MOA**
  - Not established
  - No direct action on skeletal muscles or nerve fibers

- **Dosing**
  - 800 mg PO TID-QID

- **Kinetics**
  - Bioavailability increased with high fat meal
  - Metabolized by CYP1A2, CYP2D6, CYP2E1, and CYP3A4

- **ADE**
  - Dizziness, drowsiness (less compared to others), headache,
  - Respiratory depression in combination
  - Rare leukopenia and hemolytic anemia
  - Avoid < 12 yrs of age
  - Avoid in patients with renal or hepatic failures
  - Avoid in anemia


Methocarbamol

- **MOA**
  - Centrally acting
  - Carbamate derivative of guaifenesin
  - Unknown mechanism of muscle relaxation, likely sedation

- **Dosing**
  - 1500 mg PO QID x 2-3 days, then 750 mg PO QID

- **ADE**
  - Discoloration of urine (brown-black or green)
  - Altered mental status
  - Worsen myasthenia gravis

Orphenadrine

- **MOA**
  - Anticholinergic agent
  - Structurally related to diphenhydramine
  - Inhibits antimuscarinic acetylcholine and N-methyl-D-aspartate receptors

- **Dosing**
  - 100 mg PO BID

- **ADE**
  - Anticholinergic
  - GI disturbances
  - Avoid elderly, glaucoma, cardiospasms, myasthenia gravis

- **Contraindicated**
  - Duodenal or pyloric obstruction or stenosing peptic ulcers

---

Antispamodics Place in Therapy

- **Evidence for efficacy limited**
- **Strong evidence for toxicity**
- **Short-term use!!!**
- **American College of Physicians Low Back Pain Guidelines**
  - Role in acute low back pain short-term

---
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