Nonopioid Analgesics: The Selection and Use of Adjuvant Therapies

Developed by: Abigail Brooks, PharmD, BCPS, & Courtney Kominek, PharmD, BCPS, CPE

Disclosures

- Courtney Kominek:
  - Consultant, Axial Healthcare
- 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
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


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

## 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:


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## Opioids are not a 1st line treatment option...

[Link: https://www.youtube.com/watch?v=MI1myFQPdCE]

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## 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 anesthetic</td>
<td>Peripheral desensitization</td>
</tr>
<tr>
<td>Mood stabilizers</td>
<td>Antinociceptive</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Antinociceptive</td>
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<tr>
<td>Antidepressants</td>
<td>Antikonvulsant</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>Peripheral desensitization</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Antinociceptive</td>
</tr>
<tr>
<td>Skeletal muscle relaxants</td>
<td>Descending modulator</td>
</tr>
</tbody>
</table>

Where Do Adjuvants Work?

Pain Types

- Nociceptive
- Inflammatory
- Mechanical
- Bone
- Muscular
- Neuropathic
- Psychogenic

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
  - Swell

Drug Management
- NSAID
  - Ibuprofen
  - Naproxen
  - Ketorolac (IV form)
  - Meloxicam
  - Celecoxib (COX-2 inhibitor)
- Corticosteroids
  (if not contraindicated by infection)
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

**Figure 1** NSAIDs—Mechanism of Action

- COX-1
- COX-2
- COX-1 and COX-2
- COX-2
- Celecoxib
- Meloxicam
- Nimesulide

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

**Figure 2** NSAIDs—COX Selectivity and Associated Risk

- Cardiovascular Risk
- Gastrointestinal Risk
- Thrombosis, myocardial infarction
- Nausea
- Blood pressure increase
- COX-1
- COX-2

*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

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 tablet: 50 mg TID QID  OR: 150-300 mg/day in 2-4 doses OR: 100 mg/day</td>
<td>IR: 150-200 mg/day OR: 300 mg/day OR: 200 mg/day</td>
</tr>
<tr>
<td>Etodolac</td>
<td>IR: 300-600 mg q6-8h</td>
<td>IR: 1000 mg/day</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>400-600 mg q8-4q12h</td>
<td>2.4-3.2 g</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>IR: 35-50 mg BID-TID OR: 75 BID or 150 mg daily</td>
<td>IR: 200 mg/day OR: 150 mg/day</td>
</tr>
</tbody>
</table>

NSAIDs—Dosing (cont’d)

<table>
<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 q6-8h OR: 30 mg once or 15-30mg q8h OR: 60 mg once or 30 mg q6-8h</td>
<td>PO: 40 mg/day OR: 75 mg/day OR: 120 mg/day MAX: ≤5 DAYS</td>
</tr>
<tr>
<td>Naproxen</td>
<td>250 mg q6-8h, 500 mg q12h OR: 1000 mg/day</td>
<td>OR: 1000-1500 mg/day OR: 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>150-300 mg BD</td>
<td>400 mg/day</td>
</tr>
</tbody>
</table>

Lexi-Comp, Inc. (Lexi-Drugs™). Lexi-Comp, Inc.; Hudson, OH; 22 April 2015.
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. Elderly patients are at greater risk for serious gastrointestinal events.
- Strategies to prevent gastric mucosal damage in chronic NSAID users:
  - Proton pump inhibitor (PPI)
    - Examples: omeprazole, pantoprazole
  - Histamine-2 receptor antagonist (H2RA)
    - Example: ranitidine
  - Use of COX-2 selective NSAID
    - Example: celecoxib
- 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
  - Concurrent use of corticosteroids, aspirin, or anticoagulants

Topical NSAIDs
- Diclofenac sodium 1% gel
  - Indications: osteoarthritis pain
  - Dose:
    - Upper extremity (hands, elbows, wrists): 2g applied QID up to 8g on any one joint
    - Lower extremity (knees, ankles, 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
  - Indications: topical treatment of acute pain due to minor strains, sprains, and contusions
  - Dose: 1 patch applied BD 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.

NSAIDs and GI Adverse Effects

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Corticosteroids

Pretaglandin inhibition
Cell membrane stabilization

Corticosteroid MOA in Analgesia

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


Corticosteroids (cont’d)

- Intro-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
  - Eg, in acute disc herniation, acute or persistent migraine, flares of rheumatic pain
  - Goal: Use the lowest effective dose for the shortest period of time necessary

1. Arthritis Care & Research. Vol. 64, No. 4, April 2012, pp 465–474
Corticosteroids (cont’d)

- **Dexamethasone:**
  - Oral, IV: in divided doses q6-12h. Dose depends on condition
  - Intra-articular: 0.4-6mg/day
- **Prednisone:** 5-60mg PO daily. Dose depends on condition
- **Note:** 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


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**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
  - Topiramate
- **Antidepressants**
  - TCAs
  - SNRIs
- **Local anesthetics**
  - Capsaicin

* Drug of choice for trigeminal neuralgia

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**Anticonvulsants**
Anticonvulsants Gabapentin & Pregabalin

- Structurally related to GABA but it does not bind to GABA\_α or GABA\_β receptors or influence the degradation or uptake of GABA
- Binds to the α2-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

1. Micromedex 2.0 Online.

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Anticonvulsants

**Gabapentin**
- Initial dose: 300mg PO at bedtime
- Increase by 300-600mg every 3-7 days, as tolerated, to lowest effective dose
- Maximum total daily dose: 3600mg
- 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: 75mg PO BID
- Titrate up to 150mg PO BID or TID
  - Doses up to 600mg have been evaluated with no significant additional benefit (increase in ADRs)
- Renal dose adjustment required
- Recommended 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: 400-1400mg/day
  - CrCL >15-29 mL/min: 200-700mg administered as one daily dose
  - CrCL 15 mL/min: 100-300mg 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


Gabapentin ER

- FDA-approved indication: postherpetic neuralgia
- Do not use interchangeably with other gabapentin products
- Max dose: Up to 3600mg/day in single dose with evening meal

- Titration recommendations:
  - Day 1: 300mg
  - Day 2: 600mg
  - Days 3-6: 900mg
  - Days 7-10: 1200mg
  - Days 11-14: 1500mg
  - Day 15: 1800mg

- Renal dose adjustment:
  - CrCL 30-60 mL/min: 600-1800mg
  - CrCL <30 mL/min: not recommended for use
  - Hemodialysis not recommended for use


Anticonvulsants (cont’d)
Pregabalin

- Renal dose adjustment:
  - CrCL (mL/min) Total Pregabalin Daily Dose (mg/day) Dose Regimen
    - ≥60 150 300 450 600 BID or TID
    - 30-60 75 150 225 300 BID or TID
    - 15-30 25-50 75 100-150 150 QD or BID
    - <15 25 25-50 50-75 75 QD

- 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: 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**
  - Data supports use in refractory trigeminal neuralgia, central poststroke pain, SI pain with trigeminal and facial visceral allodynia, HIV-associated neuropathy in patients on anti-retroviral therapy, and diabetic neuropathy
  - Most effective at doses between 200-400mg/day
  - Not effective at doses between 50-100mg/day
  - Note: follow strict titration schedule to reduce the risk of serious skin reactions

- **Topiramate**
  - 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** 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

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TCAs

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

- Muscarinic Ach 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 pre-existing disease or established conduction abnormalities
- Unlikely increased 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 10x prescribed
- Risk of “switching” to mania but small

SSRI/SNRI

<table>
<thead>
<tr>
<th>Selective Serotonin Reuptake Inhibitors (SSRIs)</th>
<th>Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>Venlafaxine</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Duloxetine</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Desvenlafaxine</td>
</tr>
<tr>
<td>Paroxetine*</td>
<td>Milnacipran</td>
</tr>
<tr>
<td>Citalopram*</td>
<td>Levomilnacipran</td>
</tr>
<tr>
<td>Escitalopram*</td>
<td></td>
</tr>
</tbody>
</table>

*Small RCT data to support use in chronic musculoskeletal or neuropathic pain
**SSRI**

- **Fluoxetine**
  - Initial: 20mg PO QAM
  - Titration: Increase by 10-20mg PO at 2-week intervals
  - Optimal: 30-80mg PO QAM
  - Maximum: 80mg PO QAM
  - Requires dose adjustment in hepatic impairment

- **Citalopram**
  - Initial: 20mg PO daily
  - Titration: Increase by 20mg at weekly intervals
  - Optimal: 20-40mg PO daily
  - Maximum: 40mg PO daily
  - Requires dose adjustment in renal and hepatic impairment

- **Paroxetine**
  - Initial: 10mg PO daily
  - Titration: Increase by 10mg at weekly intervals
  - Optimal: 30-50mg PO daily
  - Maximum: 50mg PO daily
  - Requires dose adjustment in renal and hepatic impairment

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**SNRI**

- **Venlafaxine**
  - Target dose (either IR or SR) is 75mg/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**
  - Initial at 30mg PO daily x 1 week, then increase to target dose of 60mg PO daily
  - In fibromyalgia and chronic WKS pain, no evidence that doses >60mg/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

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**SNRI (cont’d)**

- **Milnacipran**
  - 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

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Serotonin Syndrome

- Mental status changes
  - Anxiety, agitation, 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

SSRI/SNRI—Suicidality

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


Botulinum Toxin A

- MOA:
  - In affected muscles, blocks the presynaptic release of acetylcholine from motor endplates of the lower motor neuron at the myo-neural junction and decreases tone by limiting muscle contraction
- Indication:
  - Peripheral neuropathic pain
- Dose:
  - 50-200 units injected SubQ to the painful area every 3 months
- Recommendation:
  - Third line; specialist use

### Bone Pain

**Diagnosis**
- **Clinical setting**
  - Cancer
  - Compression fracture
  - Sickle cell
  - Osteoporosis
  - Other trauma/fracture
- **Distribution**
  - Limb
  - Spine
  - Rib
  - Hip
- **Quality & timing**
  - Incidental pain
- **Physical findings**
  - Tenderness

**Drug Management**
- **NSAIDs**
- **Corticosteroids**
- **Bisphosphonates**
- **Salmon calcitonin**

### Bone Pain (cont’d)

**Bisphosphonates**
- **MOA:** inhibition of osteoclast bone resorption and overall decrease in osteoclast activity
- **IV or PO administration**
- **Off-label use for acute fracture pain**
- **Dose:** dependent on drug selection
- **Adverse effects:** acute IV infusion reaction, headache, dizziness, N/V, myalgia, arthralgia, pain, hypophosphatemia, hypokalemia, hypocalcemia, hypomagnesemia

**Salmon Calcitonin**
- **MOA:** β-endorphin production, inhibition of prostaglandin and cytokine production, and pain perception modulation via central serotonergic pathways
- **Improved fracture healing?**
- **Intranasal administration**
- **Off-label use for acute fracture and metastatic bone pain**
- **Dose:** 200 IU daily x 4-6 weeks
- **Adverse effects:** nasal tingling or stinging, nasal mucosal erythema, rhinitis, sneezing

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### 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
  - Tendons or ligaments

**Drug Management**
- **Cyclobenzaprine**
- **Methocarbamol**
- **Baclofen**
- **Tizanidine**

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**Muscle Relaxants**

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

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


### Muscle Relaxants (cont’d)

**Baclofen**
- GABA analogue
- Selective GABA-B receptor agonist (↑ K+ conductance, ↓ Ca++ conductance)
- Muscle relaxant and analgesic (reduced substance P)
- May be effective for an acute-on-chronic pain episode
- 5mg PO TID, may titrate every 3 days to effect
- Max dose: 80mg/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
- 2-8 mg PO TID
- Max dose: 36 mg/day
- Side effects: hypotension, asthenia, elevated LFTs, hepatotoxicity


**Cyclobenzaprine**
- MOA: similar structure to tertiary amine, influences both gamma and alpha motor systems by reducing tonic somatic motor activity
- Increased seizure risk with tramadol!
- 5mg PO TID, may increase to 10mg PO TID
- Adverse effects: anticholinergic effects, QT prolongation

**Methocarbamol**
- MOA: mechanism thought to be related to general CNS depression
- 1 500mg PO QID x2-3 days then 750mg PO QID
- May take up to 8g/day in severe conditions
- Adverse effects: adenos, headache, dizziness, drowsiness, hypotension, seizures, N/V, metallic taste

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

Psychogenic Pain

Diagnosis
- Clinical setting
  - High stress
  - Anxiety
  - Depression
- Distribution
  - Widespread
  - Nonanatomical
- Quality & timing
  - Extreme and dramatic descriptors
- Physical findings
  - Anxious
  - Histrionic
  - Normal physical exam

Drug Management
- Antidepressants
  - SSRI
  - SNRI
  - Bupropion
  - Mirtazapine
- Anxiolytics
  - Benzodiazepine
  - Buspirone
  - SSRI
- Atypical antipsychotics
  - Quetiapine
  - Olanzapine

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