Nonopioid Analgesics: Antidepressants, Adjuvant Therapies, and Muscle Relaxants

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Disclosure

- Nothing to disclose
Learning Objectives

- Describe where adjuvant analgesics act in the pain pathways
- State which adjuvants are considered first-line analgesics
- Compare risks and benefits of different adjuvant analgesics for a given patient
Who’s Up for an Adjuvant Analgesic?

Non-opioids...Adjuvants and Co-Analgesics

- Acetaminophen
- NSAIDs
- Antidepressants
- Anticonvulsants
- Anesthetics
- Skeletal Muscle Relaxants
- Antipsychotics
- Others
What is an Adjuvant?

- What is an adjuvant?
  - “Serving to help or assist; auxiliary.”
  - “Serving to aid or contribute.”

- What is an adjuvant analgesic?
  - “Drugs with a primary indication other than pain that have analgesic properties in some painful conditions.”
  - “Medications whose primary indication is the treatment of a medical condition, with secondary effects of analgesia.”

- Also referred to as “co-analgesics”
Where Do Adjuvants Work?

### Peripheral Desensitization
- Anticonvulsants
- Local anesthetics
- Capsaicin
- Corticosteroids

### Descending Modulator
- TCA’s
- SNRI’s
- Skeletal muscle relaxants

### Antinociceptive
- Opioids
- NSAIDS
- APAP
- Cannabinoids

### Antihyperalgesic
- NMDA antagonists

Putting it all together…

Acetaminophen Mechanism of Action

- Active metabolite of phenacetin
- Not clearly understood; centrally active
  - Weak COX-1 and COX-2 inhibitor
- Equivalent to ASA as an analgesic and antipyretic agent
  - Lacks anti-inflammatory properties
  - Does not affect uric acid levels
  - Does not inhibit platelet function

Acetaminophen Pharmacokinetics

- **Absorption / Distribution**
  - IR acetaminophen is rapidly absorbed
  - Peaks 30-60 minutes
  - Distributes throughout most bodily fluids
  - Slightly bound to plasma proteins

http://en.wikipedia.org/wiki/Paracetamol
Acetaminophen Liver Toxicity

- Highly reactive metabolite (NAPQI)
- 26,000 hospitalizations/450 deaths in U.S. annually; 40% of acute liver failure cases
- Unintentional overdose
  - 38% taking 2 or more OTC products
  - 1/3 of narcotic users also taking OTC APAP
  - Most commonly prescribed: hydrocodone/APAP
- Risk Factors for Overdose
  - Acute ingestion
  - Concurrent use of other hepatotoxic drugs
  - Pre-existing liver disease
  - Poor nutritional intake
  - Ingestion of > 3 alcoholic drinks per day
  - Genetic mutations

LFTs at Therapeutic Dosing

- Prospective, randomized, single-blind, placebo-controlled longitudinal study
- Healthy adults receiving 4 grams PO APAP
  - 81/106 (76%) developed ≥ 1 elevation in ALT above the upper limit of normal (ULN)
- In 53% ALT levels peaked at ≥ 2 times ULN (>80 U/L),
  - 39% greater than 3 times (>120 U/L),
  - 25% greater than 5 times (>200 U/L),
  - 8% greater than 8 times (>320 U/L).

Watkins PB et al. JAMA 2006;296:87-93
Unintentional Overdose

- Surveys on overdoses of APAP in the U.S.
  - One survey: 48% unintentional, 44-70% intentional
  - Prescriptions of combination tablets accounts for ≥4 gm of APAP/day in 8% of all prescriptions
  - In the U.K., APAP sales restricted to blister packs
    - 765 fewer deaths/11 years (43% reduction)

- Cross-sectional study - interviews and literacy assessment
  - Nearly 1 in 4 patients would exceed maximum amount of APAP (1000 mg/dose (17.5%) vs 500 mg/dose (6.4%))
  - Lower literacy → increased risk of overdose (RR 1.65, CI 1.03-2.66)

Acetaminophen Overdose

- Acute ingestion > 7.5 grams
- Chronic overuse of acetaminophen
- Four stages of overdose:
  - Stage 1 – onset within a few hours of ingestion; resolves within 24 hours (GI symptoms; LFTs normal)
  - Stage 2 – 24-36 hours post acute ingestion; liver injury with right upper quadrant pain and increased LFTs
  - Stage 3 – 72-96 hours post acute ingestion; hepatotoxicity peaks and is evidenced by fulminant hepatic failure, encephalopathy, coma, LFTs elevated. Fatal 3-5 days.
  - Stage 4 – recovery stage for those who survive stage 3
More Than Just The Liver

- Skin reactions
- Age-related metabolic changes
- Pregnancy
- Asthma
- Drug-Drug interactions
# Drug Interactions with Acetaminophen

<table>
<thead>
<tr>
<th>Precipitant Drug</th>
<th>Objective Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbiturates</td>
<td>Acetaminophen</td>
<td>Increase risk of hepatotoxicity with large/chronic doses of barbiturates. Possibly reduced acetaminophen therapeutic effect.</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Acetaminophen</td>
<td>Increased risk of acetaminophen-induced liver damage.</td>
</tr>
<tr>
<td>Hydantoins</td>
<td>Acetaminophen</td>
<td>Increased risk of hepatotoxicity; possibly reduced acetaminophen therapeutic effect.</td>
</tr>
<tr>
<td>Sulfinpyrazone</td>
<td>Acetaminophen</td>
<td>Increased risk of hepatotoxicity; possibly reduced acetaminophen therapeutic effect.</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Lamotrigine</td>
<td>With chronic acetaminophen use, may require lamotrigine dosage increase to maintain effect.</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Warfarin</td>
<td>Weekly doses of acetaminophen of 2.275 grams or higher warrant INR monitoring and possibly warfarin dosage adjustment (increase).</td>
</tr>
</tbody>
</table>
## Dosing Acetaminophen

<table>
<thead>
<tr>
<th>Population</th>
<th>Usual Dosage</th>
<th>MDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults and Children ≥ 12 years of age</td>
<td>325-650 mg by mouth q4-6h IR or 1300 mg q8h XR</td>
<td>4,000 mg (3,000 mg OTC)</td>
</tr>
<tr>
<td>Adults and adolescents ≥ 13 years of age, ≥ 50 kg</td>
<td>Up to 1000 mg intravenously q6h</td>
<td>4,000 mg</td>
</tr>
<tr>
<td>Adults and adolescents ≥ 13 years of age, ≤ 50 kg</td>
<td>15 mg/kg intravenously q6h</td>
<td>75 mg/kg</td>
</tr>
<tr>
<td>Children 2-12 years of age</td>
<td>10 mg/kg by mouth q4-6h</td>
<td></td>
</tr>
<tr>
<td>Children ≥ 2-12 years of age</td>
<td>15 mg/kg intravenously q6h</td>
<td>75 mg/kg</td>
</tr>
</tbody>
</table>

Caution with acetaminophen/opioid combination analgesics (Vicodin, Lortab, etc.)

January 2011 FDA mandated limiting acetaminophen to no more than 325 mg/tab or cap (3 year phase-in)

Role in Therapy

- Acetaminophen is first line for mild pain
  - Similar to aspirin in analgesic and antipyretic activity
  - Modestly inferior to NSAIDs for pain control
- Dose limit of 4 g/d for OA
  - American College of Rheumatology, American Pain Society, EULAR, OARSI and the American Geriatrics Society
  - Lacks GI toxicity of NSAIDs, but poses a risk of hepatotoxicity; do not exceed MDD (consider all acetaminophen-containing products)
- May be combined with opioids for the treatment of moderate to severe pain
  - Where is the line in the sand when combined with opioids?

EULAR - European League Against Rheumatism; OARSI - Osteoarthritis Research Society International
Nonsteroidal Anti-inflammatory Drugs (NSAIDs) Agents

- Diclofenac*
- Indomethacin
- Sulindac
- Tolmetin
- Celecoxib **
- Meclofenamate
- Mefenamic acid
- Nambumetone
- Piroxicam

- Meloxicam
- Fenoprofen
- Flurbiprofen
- Ibuprofen ***
- Ketoprofen
- Naproxen
- Oxaprozin
- Etodolac
- Ketorolac ***

Analgesic  
Antipyretic  
Anti-inflammatory  
Antiplatelet

*Available as topical; **COX-2 selective; ***Available as injectable
### NSAID Chemical Classes

—Allergic reactions

<table>
<thead>
<tr>
<th>Non-acetylated salicylates</th>
<th>Propionic acids</th>
<th>Acetic acids</th>
<th>Enolic acids</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diflunisal</td>
<td>Ibuprofen</td>
<td>Diclofenac</td>
<td>Meloxicam</td>
<td>Medroxyprogesterone</td>
</tr>
<tr>
<td>Choline Mg Trisalicylate</td>
<td>Naproxen</td>
<td>Etodolac</td>
<td>Piroxicam</td>
<td>Mefenamic acid</td>
</tr>
<tr>
<td>Salsalate</td>
<td>Ketoprofen</td>
<td>Tolmetin</td>
<td></td>
<td>Nabumetone</td>
</tr>
<tr>
<td></td>
<td>Flurbiprofen</td>
<td>Sulindac</td>
<td></td>
<td>Celecoxib</td>
</tr>
<tr>
<td></td>
<td>Oxaprozin</td>
<td>Indomethacin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ketorolac</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Arachidonic Acid

Prostaglandin G/H Synthase 1 & 2

COX-1

Low-dose ASA

COX-2

Coxibs

Prostaglandin H2 (PGH₂)

PGD₂

PGE₂

PGF₂α

TXA₂

PGI₂

Lipoygenases
Nonsteroidal Anti-inflammatory Drugs (NSAIDs) Indications

- Actinic keratosis
- Acute gout
- Acute shoulder pain
- Ankylosing spondylitis
- Bursitis
- Fever
- Juvenile idiopathic arthritis
- Menorrhagia
- Migraine (abortive, menstrual, prophylactic)
- Osteoarthritis
- Pain
- Patent ductus arteriosus
- Primary dysmenorrhea
- Rheumatoid arthritis
- Tendinitis
NSAID Pharmacokinetics

- **Absorption / Distribution**
  - Rapidly and almost completely absorbed
    - Naproxen sodium vs. naproxen
  - Food delays absorption but does not affect total amount absorbed
    - In general, take NSAIDs with meals to minimize GI effects (e.g., gastritis)
  - All NSAIDs are > 90% protein bound

- **Metabolism / Excretion**
  - Most NSAIDs have negligible hepatic metabolism
    - Exceptions: etodolac, ketorolac, nabumetone, oxaprozin, meloxicam
    - Celecoxib and mefenamic acid undergo metabolism via P450 2C9 isoenzymes
    - Sulindac and nabumetone are inactive prodrugs converted by the liver to active metabolites

www.online.factsandcomparisons.com, accessed 8/24/16
“NSAIDs can upset your tummy, but they aren’t dangerous like the opioids.”

- Have we become immune to the toxicities of NSAIDs in favor of the sensational news of opioid overdose and death?
NSAID Use

- 8 out of 10 Americans use OTC NSAIDs to some extent every year
  - Up to 60% of these individuals are unaware of any risks or are not concerned about adverse events
- 4 out of 10 users take doses > recommended on the warning labels and 22% falsely believe alerting sx will always preceded NSAID complication.
- Clinically significant upper GI complications in up to 2% of NSAID users
  - More than 80% of patients developing GI complications have no prior symptoms or warning signs.
NSAID Toxicity

- Gastro-intestinal dyspepsia/bleeding
- Risk factors include:
  - Prior PUD
  - Prior NSAID GI-complication
  - Advanced age
  - Concurrent CCS or AC
  - High doses of NSAIDs
  - Combinations of NSAIDs
  - ?? In combination with SSRI antidepressant

- Renal impairment and acute renal failure
- Salt and water retention
- Bronchial spasm/asthma
- Platelet inhibition
- Cardiovascular risk
GI Adverse Effects / Precautions

- “NSAID gastropathy” – mild dyspepsia or abdominal discomfort to perforation and hemorrhage
- Risk increases with
  - Age (particularly > 60 years old)
  - History of ulcers (especially bleeding ulcers)
  - High NSAID dose; H. pylori infections
  - Concurrent use of antiplatelet agents, aspirin, steroids

- Nonselective vs. COX-2 selective NSAIDs

- Nonselective NSAID therapy
  - 10-30% develop peptic ulcers
  - Mortality rate for nonselective-NSAID induced ulceration is 35% (double non-users of NSAIDs)

GI Adverse Effects / Precautions

- 5-20% of NSAID-users experience dyspepsia, diarrhea, and other GI symptoms
- > 100,000 hospitalizations/year secondary to NSAIDs

Strategies to prevent GI events include:
- Misoprostol (Cytotec, a prostaglandin E1 analog)
- Proton pump inhibitors (PPIs)
  - Long-term PPI use associated with osteoporotic hip fractures
  - Increases cost of regimen and tablet burden
- Higher dose H2 antagonists
- Avoid long half-life NSAIDs (piroxicam)
<table>
<thead>
<tr>
<th>More COX-1 Selective</th>
<th>Nonselective</th>
<th>5-50 fold COX-2 selective</th>
<th>&gt; 50 fold COX-2 selective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketorolac</td>
<td>Ibuprofen</td>
<td>Sulindac</td>
<td>Etoricoxib</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>Fenoprofen</td>
<td>Diclofenac</td>
<td></td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Sodium salicylate</td>
<td>Celecoxib</td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Diflunisal</td>
<td>Meloxicam</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
<td>Etodolac</td>
<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td></td>
<td>Increased GI effects</td>
<td></td>
</tr>
<tr>
<td>Tolmetin</td>
<td></td>
<td>Increased CV effects</td>
<td></td>
</tr>
<tr>
<td>Piroxicam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meclofenamate</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Behnen EM. Prac Pain Manage 2013.
Prothrombotic hypothesis

Vascular prostacyclin

Platelet TXA₂

Partial block

Conventional NSAIDs

COX-2 Specific inhibitors
No block of TXA₂

Vasodilation and endothelial function

Platelet aggregation and vasoconstriction

Misbalance can lead to prothrombotic state and can increase the cardiovascular risk


Adverse Effects / Precautions

- Cardiovascular adverse events
  
  - Both COX-2 selective and nonselective systemic NSAIDs increase CV risk
  
  - Less risk than gastropathy
  
  - CV effects due to imbalance between thromboxane and prostacyclin on the endothelium
  
  - Risk factors include:
    
    - COX-2 selectivity
    
    - Dose, longer plasma half-life
    
    - Effect on BP
    
    - Interaction with concomitant aspirin

  Increased risk for cerebrovascular accidents as well.

Adverse Effects / Precautions

- Renal adverse events
  - All systemic NSAIDs increase risk of renal AE
  - Fenoprofen, indomethacin > other nonselective NSAID risk
  - Electrolyte retention, reduced GFR, nephrotic syndrome, renal papillary necrosis, hyperkalemia, chronic renal failure
  - Risks include: older adults (especially with comorbid conditions), renal insufficiency, CHF, DM

- Other adverse events
  - Hepatic complications (transaminitis, synthetic impairment)
  - Clotting problems (contributing to bleeding)
  - Respiratory (aspirin-exacerbated respiratory disease)
  - Prolonged pregnancy or labor, fetal effects from antiplatelet activity
### Drug Interactions with NSAIDs

<table>
<thead>
<tr>
<th>Precipitant Drug</th>
<th>Objective Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors, ARBs</td>
<td>NSAIDs</td>
<td>Reduced antihypertensive effects; risk of nephrotoxicity increased.</td>
</tr>
<tr>
<td>Alcohol</td>
<td>NSAIDs</td>
<td>Increased risk of GI bleeding</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>NSAIDs</td>
<td>Increased risk of GI bleeding and GI ulceration</td>
</tr>
<tr>
<td>Salicylates, Corticosteroids, anticoagulants</td>
<td>NSAIDs</td>
<td>Increased risk of GI bleeding</td>
</tr>
<tr>
<td>Hepatotoxic agents</td>
<td>NSAIDs</td>
<td>Increased risk of hepatotoxicity</td>
</tr>
<tr>
<td>SSRIs</td>
<td>NSAIDs</td>
<td>Increased risk upper GI bleeding</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Aminoglycosides</td>
<td>Increased risk of renal toxicity</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Diuretics, anti-hypertensives</td>
<td>Diminished antihypertensive effect</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Lithium, MTX</td>
<td>Reduced renal clearance; increased toxicity</td>
</tr>
</tbody>
</table>
# Dosing Selected NSAIDs

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Usual Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac</td>
<td>50 mg three times a day</td>
</tr>
<tr>
<td></td>
<td>100 mg daily</td>
</tr>
<tr>
<td>Etodolac</td>
<td>200 mg – 400 mg three times daily</td>
</tr>
<tr>
<td></td>
<td>600 mg daily</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>400 mg - 800 mg three times daily</td>
</tr>
<tr>
<td>Naproxen</td>
<td>250 mg three times daily;</td>
</tr>
<tr>
<td></td>
<td>500 mg two or three times daily</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>100 – 200 mg twice daily</td>
</tr>
</tbody>
</table>

Role in Therapy

- Analgesic, anti-inflammatory effects
- Acute and chronic pain, particularly with an inflammatory component
- Mild to moderate pain; 30-50% opioid-sparing with severe pain
- Consider use of topical NSAIDs
- Judicious use of NSAIDs (if at all)
  - Limit doses to lowest effective dose and shortest duration possible
  - Caution/avoid with high risk co-morbid conditions
Topical vs. Systemic NSAID

- Topical NSAID bioavailability < 10%
- Diclofenac topical solution vs. oral diclofenac
  - Comparable efficacy, lower adverse effects
- Incidence GI adverse effects 3 times lower with topical vs. oral NSAID
  - Systemic adverse effects are rare, = placebo
- Topical NSAIDs are a good option for osteoarthritis pain, while minimizing systemic exposure to drugs
  - Flector (1.3%) topical patch – acute pain (sprains, strains and bruises)
  - Pennsaid (1.5%) topical solution - OA
  - Voltaren (1%) topical gel - OA
  - Solaraze (3%) topical gel – actinic keratoses

Corticosteroids

- Inflammatory neuropathic pain from peripheral nerve injuries; spinal cord compression
- Bone pain
- Pain from bowel obstruction, lymphedema
- Pain from headache associated with increased intracranial pressure

- Stimulation of appetite
- Weakness
- Nausea, vomiting
- Fatigue
- General affect

Wide range of uses in advanced illness
Corticosteroid Adverse Effects

Box 1. Common side effects of dexamethasone

Most frequent side effects include the following:
- increased appetite or weight gain
- proximal muscle weakness
- insomnia
- gastrointestinal side effects
- psychiatric side effects, such as delirium, depression, anxiety, and psychosis
- osteoporosis with long-term use

Less frequent side effects include the following:
- infections
- hyperglycemia
- Cushing syndrome

Life-threatening side effects include the following:
- gastrointestinal bleeds
- thromboembolism

Corticosteroids

- **Glucocorticoids reduce pain by:**
  - Inhibiting prostaglandin synthesis (which leads to inflammation)
  - Reducing vascular permeability that results in tissue edema
  - Reduce spontaneous discharge in an injured, nerve, which reduces neuropathic pain

- **Dexamethasone vs. prednisone**
  - Dexamethasone more potent glucocorticoid; least mineralocorticoid
  - Dexamethasone has a long half-life (t1/2 ~ 60 hours)
    - Dose once or twice daily (2-8 mg)
  - Dexamethasone 0.75 mg ~ prednisone 5 mg
  - Dexamethasone may be administered PO, IV, SQ, epidural
  - Need to taper, need to discontinue?

Adjuvant Analgesics

- **Multipurpose Analgesics**
  - Antidepressants, CCS, NSAIDs, α-2 adrenergic agonists, neuroleptics

- **Adjuvants for Neuropathic Pain**
  - Anticonvulsants, Na+ channel blockers, NMDA antagonists, cannabinoids

- **Topical Analgesics**
  - Capsaicin, local anesthetics, NSAIDs

- **Adjuvants for Bone Pain**
  - CCS, NSAIDs, calcitonin/bisphosphonates, Radiopharmaceuticals

- **Other**
  - Adjuvants for bowel obstruction, musculoskeletal pain

**Conclusion:**

Overall, the absolute risk benefit (ARB) of antidepressants, anticonvulsants and other adjuvant analgesics, or opioids **GREATLY** outweighed the absolute risk harm.
NEUROPATHIC PAIN
Multipurpose Analgesics - Antidepressants

- **SNRI**
  - Venlafaxine
  - Desvenlafaxine
  - Duloxetine
  - Milnacipran
  - Levomilnacipran

- **Atypicals**
  - Bupropion
  - Mirtazapine
  - Trazodone
  - Vilazodone

- **TCAs (tertiary vs. secondary)**
  - Doxepin
  - Imipramine
  - Amitriptyline
  - Clomipramine
  - Protriptyline
  - Nortriptyline
  - Desipramine

- **SSRIs ??**
  - Paroxetine
  - Escitalopram
  - Citalopram
Antidepressants

- Provide pain relief independently of mood effects
  - Effective in non-depressed patients
  - Effective at lower doses than antidepressant doses (TCAs)
  - Pain relief seen more quickly than antidepressant action (TCA’s)

- Mechanisms of action include:
  - Increase neurotransmitter availability in endogenous monoamine-mediated pain-modulating brain pathways that use serotonin or norepinephrine
  - TCAs have pharmacokinetic interaction resulting in increased opioid serum levels (e.g., morphine, due to competitive protein binding)
  - Blocking sodium channels (TCAs)
  - Secondary p’dyn effect (anticholinergic \(\rightarrow\) sleep, itch, nausea)
Tricyclic Antidepressants (TCAs)

- Secondary amines tolerated better than tertiary amines
- Secondary amines equally effective in pain as tertiary amines
- Therapeutic drug monitoring of questionable utility

<table>
<thead>
<tr>
<th>Tertiary Amines</th>
<th>Secondary Amines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxepin</td>
<td>Protriptyline</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Nortriptyline</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Desipramine</td>
</tr>
<tr>
<td>Clomipramine</td>
<td></td>
</tr>
</tbody>
</table>

Risks of TCAs

- 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 yrs of age)
  - Cardiac (QTc) and anticholinergic toxicity at doses as little as 10x prescribed

- Risk of “switching” to mania but small

TCAs – Anticholinergic & Sedation

- Antihistaminergic effects (sedation, delirium)
- Start low with dosing
  - 10-25 mg at bedtime
  - Usual effective dose 50-150 mg nightly
- Tertiary metabolized by 1A2/2C19; secondary metabolized by 2D6 – large interindividual variability
- Muscarinic - acetylcholine receptor antagonists
  - Blurred vision, constipation, dry mouth, urine retention, constipation, tachycardia, confusion, delirium, increased ocular pressure
  - Secondary amines < tertiary amines
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 > 100mg / day amitriptyline equivalents

- Avoid in those with cardiovascular disease or established conduction abnormalities

- Taper off if possible (abrupt DC = headache, malaise, N/V)

SNRI Antidepressants

- Neuropathic pain and depression (and additional effects)
  - Venlafaxine, Duloxetine
  - Desvenlafaxine, Milnacipran, Levomilnacipran
  - Lack anticholinergic/antihistaminic effects seen with TCAs

- Duloxetine
  - Balanced and potent dual reuptake inhibitor 5HT/NE
  - Efficacy comparable to gabapentin/pregabalin in neuropathic pain
  - Start with 30 mg po qd; increase to 60 mg (no need to increase to 120 mg)
  - Dose limiting AE include sedation and nausea

- Venlafaxine
  - Weaker norepinephrine reuptake effects; nausea and somnolence AE
  - Effective at doses between 150-225 mg/day
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, clonus
- Severity may range from benign to lethal
- Solely a clinical diagnosis
- Patient and caregiver education is KEY!!
- Consider serotonin active herbal / OTC products!!

Hunter Criteria

Serotonergic agent + one below:
- 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)

Bupropion (Wellbutrin)

- Inhibits neuronal NE and 5HT, and less potently DA reuptake
- Commonly used for smoking cessation and depression
- Can be activating; useful in patients with hypoactive depression, fatigue or sedation
- Shown to be effective in treating neuropathic pain
- Low risk for somnolence or sexual dysfunction (common with other antidepressants)
- AE – dry mouth, insomnia, nausea, headache, rash, agitation, excitement, lowers seizures threshold
- Starting dose 100-150 mg/day; 150-450 mg/day effective dose
## Antidepressants activating vs sedating

<table>
<thead>
<tr>
<th>Sedating</th>
<th>Activating</th>
</tr>
</thead>
</table>
| • Paroxetine  
  • Mirtazapine | • Fluoxetine  
  • Venlafaxine  
  • Bupropion |
| • Sertraline  
  • Citalopram |
SSRI/SNRI: Other Concerns

- **Hyponatremia**
  - Sg/Sx (SIADH mediated): fluid and CNS status
  - Recommendations for monitoring vary (most opinion): consider Na+ within first month if at risk (diuretics, female, age, low BMI, CYP3A4 DI, if low K at initiation)

- **QTc prolongation (citalopram > escitalopram)**
  - dose limits in place, may consider baseline ECG if cardiac hx

- **Bleeding risk**
  - Minimal risk if monotherapy, higher if used with NSAIDS (acid suppression decreases risk)

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# Anticonvulsants

(available in US, excluding benzodiazepines)

<table>
<thead>
<tr>
<th>1st Generation Anticonvulsants</th>
<th>2nd / 3rd Generation Anticonvulsants</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Carbamazepine</td>
<td>• Eslicarbazepine</td>
</tr>
<tr>
<td>• Ethosuximide</td>
<td>• Ezogabine</td>
</tr>
<tr>
<td>• Phenobarbital</td>
<td>• Felbamate</td>
</tr>
<tr>
<td>• Phenytoin / Fosphenytoin</td>
<td>• Gabapentin</td>
</tr>
<tr>
<td>• Primidone</td>
<td>• Lacosamide</td>
</tr>
<tr>
<td>• Valproic Acid</td>
<td>• Lamotrigine</td>
</tr>
<tr>
<td></td>
<td>• Levetiracetam</td>
</tr>
<tr>
<td></td>
<td>• Oxcarbazepine</td>
</tr>
<tr>
<td></td>
<td>• Perampanel</td>
</tr>
<tr>
<td></td>
<td>• Pregabalin</td>
</tr>
<tr>
<td></td>
<td>• Rufinamide</td>
</tr>
<tr>
<td></td>
<td>• Tiagabine</td>
</tr>
<tr>
<td></td>
<td>• Topiramate</td>
</tr>
<tr>
<td></td>
<td>• Vigabatrin</td>
</tr>
<tr>
<td></td>
<td>• Zonisamide</td>
</tr>
</tbody>
</table>
Anticonvulsants

- Used to treat neuropathic pain for over 2 decades
- Helpful in:
  - Lancinating, sharp and burning neuropathic pain syndromes
  - May be secondary to direct neoplastic invasion of peripheral nerves or spinal cord
  - Compression due to bony involvement and vertebral collapse
  - Secondary to radiation- or chemotherapy-induced nerve injury

Anticonvulsant Mechanisms of Action

- Secondary to decreasing ectopic neuronal activity
- Providing stabilization of neuronal cell membranes through modulation of voltage-gated ion channels
  - Sodium (Phenytoin, lamotrigine, carbamazepine, oxcarbazepine, lamotrigine)
  - Calcium (Gabapentinoids – gabapentin and pregabalin)
- Injured nerves with evidence of demyelination and remyelination demonstrate a redistribution of sodium channels, which may be involved in ectopic hyperexcitability
  - In area of damaged nerve, and in the dorsal root ganglion
  - Increase in A and C fiber discharge after nerve transection

Anticonvulsant Mechanisms of Action: Gabapentinoids

- **Mechanism of gabapentinoids (gabapentin, pregabalin)**
  - Bind selectively to the 2 delta subunit of voltage-gated Ca+ channels
  - Reduce Ca2+ influx into presynaptic nerve terminals
  - Inhibiting the release of nociceptive neurotransmitters such as glutamate and substance P

- **Efficacy of gabapentin**
  - Decreasing acute post-op pain s/ craniotomy
  - Post-herpetic neuralgia, other types of neuropathic pain

Gabapentinoids

- Gabapentin limitations
  - Poor oral bioavailability with original formulation
  - AE – dizziness, somnolence, headache, diarrhea, nausea, edema, blurred vision
  - Dosing – start low (100-300 mg qhs); increase to 1800-3600 mg/day

- Pregabalin
  - Binds to 2 delta subunit protein of voltage-gated calcium channels in various regions of the brain and superficial dorsal horn of spinal cord
  - Often used when gabapentin not effective
  - AE – dizziness, somnolence, peripheral edema
  - Can escalate dose more quickly; 150 bid = preferred dose

Morphine, Gabapentin, or Both

- 41 patients with neuropathic pain randomized to four groups (x 5 weeks)
  - SR morphine
  - Gabapentin
  - SR morphine + gabapentin
  - Placebo (lorazepam)

<table>
<thead>
<tr>
<th>Group</th>
<th>Pain Rating (0-10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>5.72</td>
</tr>
<tr>
<td>Placebo</td>
<td>4.49</td>
</tr>
<tr>
<td>SR morphine</td>
<td>4.15</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>4.15</td>
</tr>
<tr>
<td>MS + Gabapentin</td>
<td>3.06</td>
</tr>
</tbody>
</table>

- Morphine + gabapentin doses were lower than the morphine or gabapentin arms, with better pain relief.
- Combination treatment had more constipation and dry mouth.

NEJM 2005;352:1324-1334
Other Anticonvulsants

- **Topiramate**
  - Acts on central pain pathway by slowing neuronal firing via inhibition of gamma-aminobutyric acid pathway
  - Modulates voltage-dependent sodium conduction
  - AE – nausea, somnolence, dizziness, paresthesia, cognitive dysfunction, increased nephrolithiasis (increase fluid intake)

- **Carbamazepine**
  - Effective in a variety of neuropathic pain states; trigeminal neuralgia
  - AE – drowsiness, dizziness, constipation, ataxia, rash, leukopenia, hepatic toxicity; autoinduces its own metabolism

Other Anticonvulsants (sodium channel blockers)

- Oxcarbazepine
  - Effective in painful diabetic neuropathy
  - AE – hyponatremia; check baseline sodium levels at baseline, 6 and 8 weeks

- Lamotrigine (sodium channel blocker)
  - Effective in various neuropathic pain states; mixed results
  - AE – CNS AE, Stevens-Johnson, TEN

- Phenytoin (sodium channel blocker)
  - AE – gait abnormalities, nausea, vomiting, sedation, nystagmus at toxic levels
  - Complicated pharmacokinetics; 90% bound to albumin
  - Check FREE/unbound level (therapeutic target 1-2 ug/ml)

Sodium Channel Blockers

- Mexiletine
  - Poorly tolerated (GI adverse effects – diarrhea, nausea)
  - Contraindicated in second- and third-degree AV conduction blocks

- Lidocaine
  - Can be used to determine sodium channel blockade responsiveness
  - Has an effect on both spontaneous pain and evoked pain
  - Analgesia achieved at subtherapeutic doses
    - Lidocainesuppresses the frequency rather than the duration of sodium channel opening
  - Parenteral, topical (post-herpetic neuralgia, PDN, CRPS, postmastectomy pain, HIV-related neuropathy)
Anticonvulsants- Other Concerns

- **Suicidality:**
  - Risk of suicidal thoughts/behaviors ~ doubles
    - May present 1 week after initiation
    - Controversial (Drug vs epilepsy?)

- **Bone Disease**
  - Increased risk of fracture vs controls (RR 2.2) and those not on anticonvulsant (RR 2.64)
  - Risk factors (high dose, multiple AEDs, duration, chronic illness, metabolic acidosis, DI with enzyme inducers)
  - National Osteoporosis Foundation recommendations not clear
    - BMD testing >5 yrs (enzyme inducers and VPA)?
    - Routine calcium, phosphate and 25-OHD levels?

Anticonvulsants- Other Concerns

- Dermatologic
  - Stevens-Johnson Syndrome (SJS), Toxic epidermal necrolysis (TEN), Drug rash with eosinophilia and systemic symptoms (DRESS)
  - Typical onset within the first 60 days
  - CBZ/OXC?/PHT/ZON: HLA B*1502 monitoring recommended in Asian ancestry, do not rechallenge (aromatic AED)
  - Lamotrigine (risks higher during titration and in children)

- Neurocognitive
  - Reaction time, learning, memory, executive function, word finding
  - All AED have some effect

NMDA Receptor Antagonists

- Animal experimental studies have shown that central and peripheral N-methyl-D-aspartate (NMDA) receptors play an important role in:
  - Hyperalgesia
  - Chronic pain

- NMDA receptor antagonists include:
  - Dextromethorphan, memantine, methadone, amantadine
  - Ketamine
    - Increases pain relief by 20-30%
    - Allows opioid reduction by 25-50%
    - AE – hallucinations and memory impairment

Cannabinoids

- Delta (9)-trans-tetrahydrocannabinol
  - Most widely studied cannabinoid, may have some analgesic properties
- Analgesic sites of action include in brain areas, spinal cord, periphery
- Positive data in refractory pain
  - Non-cancer pain NNT 3.5-9 for 30% pain reduction
    - Neuropathic pain, fibromyalgia, painful spasticity
  - 2 RCTs in cancer pain
    - NNT 4.5 for 30% pain reduction; 3 fold higher drop out rate

Cannabinoid Adverse Effects

- Psychological
  - Common – depression, euphoria, disorientation, dissociation
  - Uncommon – hallucinations, paranoia, delusions, suicidal ideation

- Neurological
  - Very common – dizziness
  - Common – ataxia, amnesia, drowsiness, blurred vision

- Gastrointestinal
  - Common – increased or decreased appetite, nausea
  - Uncommon – abdominal pain

- Cardiovascular
  - Uncommon – palpitations, tachycardia, syncope, hyper/hypotension

- Buccal irritation (common: ulceration, pain; uncommon: discoloration)

<table>
<thead>
<tr>
<th>Pain Syndrome</th>
<th>Pathway</th>
<th>Symptoms</th>
<th>Potential Adjuvant Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep nociceptive: somatic</td>
<td>Mediated by A delta and C fibers</td>
<td>Well-localized pain with tenderness, swelling, edema</td>
<td>NSAIDs, steroids, opioids</td>
</tr>
<tr>
<td>Deep nociceptive: visceral</td>
<td>Mediated by A delta and C fibers. May be secondary to stretching, ischemia or direct invasion by tumor</td>
<td>Diffuse and poorly localized</td>
<td>NSAIDs, steroids, opioids</td>
</tr>
<tr>
<td>Superficial nociceptive</td>
<td>Mediated by A delta and C fibers</td>
<td>Superficial burning, usually well localized</td>
<td>Topical anesthetics, antidepressants, anticonvulsants</td>
</tr>
<tr>
<td>Neuropathic</td>
<td>Medicated by A delta and A beta fibers, in addition to C fibers</td>
<td>Sharp lancinating pain, burning</td>
<td>Antidepressants, anticonvulsants, systemic anesthetics</td>
</tr>
</tbody>
</table>

Principles of Adjuvant Analgesic Use

- Assess complaint of pain, determine relationship to underlying disease, consider comorbidities
  - Depression?
- Avoid initiating several adjuvant analgesics concurrently
- Initiate treatment with low doses and titrate gradually according to analgesic response and adverse effect
- Select adjuvant analgesics based on knowledge of pharmacology, evidence base, interaction with other drugs, and potential adverse effects

Principles of Adjuvant Analgesic Use

- General principles of adjuvant analgesic use:
  - Multiple pathways of pain transmission provide multiple targets of pain relief
  - Use specific adjuvant for specific condition
  - Titrate only one drug at a time
  - May take several days-weeks to notice improvement in pain
  - Adjuvants usually do not provide full pain relief
  - Educate patients about trial-and-error nature of adjuvant use
  - Select rational combinations of analgesics/adjuvant analgesics

Discussion

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