The 411 on Nonprescription Analgesics: When to Hold ‘Em, When to Fold ‘Em

Alexandra L. McPherson, PharmD, MPH

Disclosure

The Nothing Club
Learning Objectives

- At the conclusion of this presentation the participant will be able to:
  - Describe the mechanism of action of common nonprescription analgesics.
  - List and explain contraindications to self-treatment for tension headache and musculoskeletal pain.
  - Given a simulated patient with a complaint of pain, select a nonprescription analgesic and provide dosing and use instruction.

OTC Analgesic Facts

- OTC analgesics are the most frequently used of all OTCs
- About 20% of the population uses OTC analgesics weekly
- 87% of women vs. 80% men used OTC analgesics in past year
- Most commonly used OTC in children were analgesics/antipyretics
- About 50% of patients who use OTC analgesics do not read the labels of these products

OTC Analgesic Facts

- 43% of those surveyed were not aware of potential adverse effects of taking OTCs with Rx medications
- 40% did not know about potential drug interactions or GI side effects
- 60% did not know the precautions for these drugs for those with hepatic or renal disease
- 80% did not know about potential for adverse effects when aspirin is used in asthmatics

Jerome

- Jerome is a 26 year old man who presents in the pharmacy asking for advice to treat this “relentless” headache he’s had for the past several days
- Jerome has graduated from law school, and he is studying furiously for the law bar exam
- He denies having chronic headaches, but notices a pattern of headache when he is stressed and anxious (like now)
Jerome

- He describes the pain as bilateral, extending over the top of his head and the base of his skull
- Jerome describes the pain as constricting, like his hat is too tight
- He states the pain evolved gradually over 4-6 hours, and has been present for two days
- He denies any throbbing sensation, pressure behind his eyes or face, and the pain is not worsened by light or sound

Sounds like a TENSION HEADACHE
Acetaminophen – Mechanism of Action

- Increases pain threshold
- Reduces nitric oxide pathway
- Selectively inhibits COX-2
- Interacts with the endocannabinoid system
- Reduces PG in the CNS, inhibiting endogenous pyrogens


Acetaminophen – Adverse Effects

- Hepatotoxicity
  - Nausea, vomiting
  - Abdominal pain, jaundice
  - Fatigue
  - Skin rashes and/or itching of skin
  - Fluid retention
**Acetaminophen**

- Analgesic/antipyretic
- Preferred analgesic for the elderly
- Preferred analgesic in patients taking warfarin
- Do not exceed 4 grams a day; consider all drugs
  - Found in over 600 OTC and prescription products
- Caution/avoid with liver disease
- Caution/avoid with alcohol use

**NSAID Mechanism of Action**

- Ibuprofen, Naproxen
  - Inhibits cyclooxygenase (COX), reducing prostaglandin & thromboxane synthesis
  - Interacts with the endocannabinoid system
- Aspirin
  - Nonselective and irreversibly inhibits COX reducing PG and thromboxane A2 synthesis producing analgesic, anti-inflammatory, and antipyretic effects and reducing platelet aggregation

**Analgesic, Antipyretic**
**Anti-inflammatory, Antiplatelet**
NSAID – Adverse Effects

- Gastrointestinal toxicity, bleeding
  - Diarrhea, epigastric/abdominal pain, nausea/vomiting,
- Platelet inhibition
- Cardiovascular toxicity – hypertension, MI
- Renal toxicity

- Respiratory (aspirin)

NSAIDs

- Analgesic, anti-inflammatory, antipyretic, antiplatelet
- Avoid with CVD (hyperlipidemia, diabetes, hypertension, other macrovascular disease)
  - PRECISION trial showed celecoxib non-inferior to ibuprofen and naproxen for CV adverse outcomes
- Caution/avoid in GI disorders/bleeding
- Caution with renal impairment
### OTC Analgesics for Adults and Children > 12

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage Forms</th>
<th>Usual Adult Dose (maximum daily dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Immediate-release tablets</td>
<td>325-1000 mg every 4-6 hours (suggested 3250 mg; FDA max)</td>
</tr>
<tr>
<td></td>
<td>Extended-release tablets</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Effervescent tablets</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disintegrating tablets</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rapid-release tablets</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chewable tablets</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Capsules</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liquid drops</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elixir</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Suspension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Suppositories</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Immediate release and chewable</td>
<td>200-400 mg every 4-6 hours (1200 mg)</td>
</tr>
<tr>
<td></td>
<td>tablets</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Suspension; liquid drops</td>
<td></td>
</tr>
<tr>
<td>Naproxen sodium</td>
<td>Tablets</td>
<td>220 mg every 8-12 hours (660 mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Over age 65: 220 mg every 12 hours (440 mg)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Immediate-release, buffered, enteric-coated, film-coated, effervescent and chewable tablets</td>
<td>650-1000 mg every 4-6 hours (4000 mg)</td>
</tr>
<tr>
<td></td>
<td>Suppositories</td>
<td></td>
</tr>
<tr>
<td>Magnesium salicylate</td>
<td>Tablets</td>
<td>650 mg every 4 hours or 1000 mg every 6 hours (4000 mg)</td>
</tr>
</tbody>
</table>

### FDA Approved Doses for OTC Analgesics in Children < 12 years

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Weight (lb)</th>
<th>Ibuprofen (mg) Dose by body weight (mg/kg): 5-10 mg/kg</th>
<th>Acetaminophen (mg) 10-15 mg/kg</th>
<th>Aspirin (mg) 10-15 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2</td>
<td>&lt; 24</td>
<td>Ask prescriber</td>
<td>Ask prescriber</td>
<td>Ask prescriber</td>
</tr>
<tr>
<td>2-3</td>
<td>24-35</td>
<td>100</td>
<td>160</td>
<td>160</td>
</tr>
<tr>
<td>4-5</td>
<td>36-47</td>
<td>150</td>
<td>240</td>
<td>240</td>
</tr>
<tr>
<td>6-8</td>
<td>48-59</td>
<td>200</td>
<td>320</td>
<td>320</td>
</tr>
<tr>
<td>9-10</td>
<td>60-71</td>
<td>250</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>11</td>
<td>72-95</td>
<td>300</td>
<td>480</td>
<td>480</td>
</tr>
</tbody>
</table>
## Clinically Important Drug-Drug Interactions

<table>
<thead>
<tr>
<th>Analgesic/Antipyretic</th>
<th>Drug</th>
<th>Potential Interaction</th>
<th>Management/Preventive Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Alcohol</td>
<td>Increased risk of hepatotoxicity</td>
<td>Avoid concurrent use if possible; minimize alcohol intake when using acetaminophen</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Warfarin</td>
<td>Increased risk of bleeding (↑ INR)</td>
<td>Limit acetaminophen to occasional use; monitor INR for several weeks when acetaminophen 2-4 grams daily is added or discontinued in patients on warfarin</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Valproic acid</td>
<td>Displacement from protein-binding sites and inhibition of valproic acid metabolism</td>
<td>Avoid concurrent use; use naproxen instead of aspirin (no interaction)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>NSAIDs, including COX-2 inhibitors</td>
<td>Increased risk of gastroduodenal ulcers and bleeding</td>
<td>Avoid concurrent use is possible; consider use of gastroprotective agents (e.g., PPIs)</td>
</tr>
</tbody>
</table>

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<th>Management/Preventive Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>Aspirin</td>
<td>Decreased antiplatelet effect of aspirin</td>
<td>Aspirin should be taken at least 30 minutes before or 8 hours after ibuprofen. Use acetaminophen (or other analgesic) instead of ibuprofen</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Phenytoin</td>
<td>Displacement from protein-binding sites</td>
<td>Monitor free phenytoin levels; adjust dose as indicated</td>
</tr>
<tr>
<td>NSAIDs (several)</td>
<td>Bisphosphonates</td>
<td>Increased risk of GI or esophageal ulceration</td>
<td>Use caution with concomitant use</td>
</tr>
<tr>
<td>NSAIDs (several)</td>
<td>Digoxin</td>
<td>Renal clearance of digoxin inhibited</td>
<td>Monitor digoxin levels; adjust dose as indicated</td>
</tr>
<tr>
<td>Salicylates and NSAIDs (several)</td>
<td>Antihypertensive agents; beta-blockers, ACE inhibitors, vasodilators, diuretics</td>
<td>Antihypertensive effect inhibited; possible hyperkalemia with potassium-sparing diuretics and ACE inhibitors</td>
<td>Monitor BP, cardiac function, and potassium levels</td>
</tr>
</tbody>
</table>

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Clinically Important Drug-Drug Interactions

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<th>Drug</th>
<th>Potential Interaction</th>
<th>Management/Preventive Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salicylates and NSAIDs</td>
<td>Anticoagulants</td>
<td>Increased risk of bleeding, especially GI</td>
<td>Avoid concurrent use, if possible; risk is lowest with salsalate and choline magnesium trisalicylate</td>
</tr>
<tr>
<td>Salicylates and NSAIDs</td>
<td>Alcohol</td>
<td>Increased risk of GI bleeding</td>
<td>Avoid concurrent use, if possible; minimize alcohol intake when using salicylates and NSAIDs</td>
</tr>
<tr>
<td>Salicylates and NSAIDs (several)</td>
<td>Methotrexate</td>
<td>Decreased methotrexate clearance</td>
<td>Avoid salicylates and NSAIDs with high-dose methotrexate therapy; monitor levels with concurrent treatment</td>
</tr>
<tr>
<td>Salicylates (moderate-high doses)</td>
<td>Sulfonylureas</td>
<td>Increased risk of hypoglycemia</td>
<td>Avoid concurrent use, if possible; monitor blood glucose levels when changing salicylate dose</td>
</tr>
</tbody>
</table>


Does Jerome have exclusions for self-tx?

- Severe head pain
- Headaches that persist for 10 days with or without treatment
- Last trimester of pregnancy
- ≤ 8 years of age
- High fever or signs of serious infection
- History of liver disease or consumption of ≥ 3 alcoholic drinks per day
- Headache associated with underlying pathology (secondary headache), except for minor sinus headache
- Symptoms consistent with migraine but no formal diagnosis

Pick a drug…any drug?

- Asthma & nasal polyps, chronic/recurrent GI ulcers, gout, coagulation disorder or anticoagulant therapy, hypertension, CHF, kidney disease, h/o allergy
  - Avoid salicylates and NSAIDs
- < 12 years of age – avoid naproxen
- ≤ 15 years of age – avoid salicylates if symptoms of viral illness are present
- Recommend acetaminophen or NSAID; non-pcol tx

Topical Analgesics
Sally

- Sally is a 68 year old woman who presents to the pharmacy on Monday with complaints of an aching back. She is inquiring as to what she can take to “make the pain go away!”
- She states that since the weather was so gorgeous on Saturday, she spent all day outside gardening. Then on Sunday, she babysat her toddler grandson and was constantly chasing him and picking him up.
- She denies other signs/symptoms, including weakness.
- She has a past medical history of hypertension (uncontrolled), dyslipidemia and osteoarthritis.

What are our options?

Sally

- She describes her pain as “achy” and “sore,” and states it’s mostly located in her mid to lower back.
- She rates her pain as a 5/10.
- She tried the ThermaCare® HeatWrap but has not experienced any significant relief.
Counterirritants – Mechanism of Action

- Paradoxical pain-relieving effect – produce a less severe pain to counter a more intense one
- Relieve pain indirectly by stimulating cutaneous receptors to induce sensations of cold, warmth, or even itching and distracting from deep-seated pain in muscles, tendons, joints, etc.
- Psychological component

<table>
<thead>
<tr>
<th>Group</th>
<th>Ingredients</th>
<th>Concentration (%)</th>
<th>Mechanism of Action</th>
<th>Frequency and Duration of Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Allyl isothiocyanate, Ammonia water, Methyl salicylate, Turpentine oil</td>
<td>0.5-5 1-2.5 10-60 6-50</td>
<td>Rubefacients (increase blood flow)</td>
<td>Apply no more than 3-4 times daily for up to 7 days</td>
</tr>
<tr>
<td>B</td>
<td>Camphor, Menthol</td>
<td>3-11 1.25-16</td>
<td>Produce cooling sensation</td>
<td>Same as group A</td>
</tr>
<tr>
<td>C</td>
<td>Histamine dihydrochloride, Methyl nicotinate</td>
<td>0.025-0.1 0.25-1</td>
<td>Cause vasodilation</td>
<td>Same as group A</td>
</tr>
<tr>
<td>D</td>
<td>Capsicum oleoresin, Capsaicin</td>
<td>0.025-0.25 0.025-0.25 0.025-0.25</td>
<td>Incite irritation without rubefaction; are as potent as group A ingredients</td>
<td>Acute pain: Same as group A Chronic pain: Apply 3-4 times daily for duration of pain</td>
</tr>
</tbody>
</table>
Counterirritants – Adverse Effects

- Skin irritation and/or rash
- Erythema
- Blistering
- Thermal hyperalgesia
- Systemic reactions
  - Salicylate toxicity

Counterirritants - Application

- If pain, swelling, or blistering of the skin occurs after application of a topical analgesic, patients should immediately discontinue use of the product and seek medical attention.
- Do not bandage the area tightly where the product has been applied.
- Do not use any heat where the product has been applied.
- Do not apply to wounded, damaged, broken, or irritated skin.
- Do not allow these medications to come in contact with the eyes, or inside the nose, mouth, or genitals.
Counterirritants

- **Methyl salicylate**
  - Occurs naturally as wintergreen oil or sweet birch oil
  - Usually combined with other ingredients (e.g., menthol and/or camphor)
  - Responsible for the “hot” action in many topical counterirritant products
  - **Mechanism of action:**
    - Vasodilation of cutaneous vasculature → reactive hyperemia + increase in localized skin temperature = counterirritant effect
    - Inhibition of central and peripheral prostaglandin synthesis
  - **Contraindications/Precautions:**
    - Avoid heat exposure and exercise after application
    - Avoid use in children and patients with aspirin sensitivities, severe asthma or nasal polyps due to possible percutaneous absorption

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Counterirritants

- **Camphor**
  - Obtained naturally from camphor tree, but majority is synthetic
  - **Mechanism of action** – Dose-dependent effect
    - **Camphor 0.1-3%**: Depresses cutaneous receptors and acts as a topical analgesic, anesthetic, and antipruritic
    - **Camphor > 3%**: Stimulates nerve endings in the skin and induces relief of pain and discomfort by masking moderate-severe deeper visceral pain, with a milder pain arising from the skin at the level of innervation
  - **Precautions:**
    - Camphor toxicity – tonic-clonic seizures, nausea, vomiting, colic, headache, dizziness, delirium, coma, and death
Counterirritants

- **Menthol**
  - Extracted from peppermint oil or prepared synthetically
  - Also used as a flavoring agent and permeability enhancer
  - Responsible for the “cold” action in many topical counterirritant products
  - **Mechanism of action** – Dose-dependent effect
    - Menthol <1%: Depresses cutaneous receptor response (anesthetic)
    - Menthol >1.25%: Stimulates cutaneous receptor response (counterirritant)
    - Activates TRPM8 menthol receptor, triggering the sensation of cold.
  - **Contraindications/Precautions:**
    - C/I in patients with hypersensitivity or sensitization to the agent (e.g., urticaria, erythema, and other cutaneous lesions)

Counterirritants: Examples

<table>
<thead>
<tr>
<th>Product</th>
<th>Ingredients</th>
<th>Packaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bengay Ultra Strength Pain Relieving Cream</td>
<td>Methyl salicylate 30% Menthol 10% Camphor 4%</td>
<td><img src="Bengay.png" alt="Bengay" /></td>
</tr>
<tr>
<td>Icy Hot Cream Extra Strength/Precise Pain Relieving Cream</td>
<td>Methyl salicylate 30% Menthol 10%</td>
<td><img src="IcyHot.png" alt="Icy Hot" /></td>
</tr>
<tr>
<td>Salonpas Pain Relief Patch</td>
<td>Methyl salicylate 10% Menthol 3%</td>
<td><img src="Salonpas.png" alt="Salonpas" /></td>
</tr>
</tbody>
</table>
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<th>Packaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiger Balm Arthritis Rub Cream</td>
<td>Camphor 11%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Menthol 11%</td>
<td></td>
</tr>
<tr>
<td>Aspercreme Heat Pain Relieving Gel</td>
<td>Menthol 10%</td>
<td></td>
</tr>
<tr>
<td>Mineral Ice</td>
<td>Menthol 2%</td>
<td></td>
</tr>
</tbody>
</table>

Counterirritants

- **Capsaicin**
  - Major ingredient in hot chili peppers
  - Available OTC in a roll-on applicator or patch formulation
  - Available Rx as Qutenza® (capsaicin 8% patch)
  - **Mechanism of action:**
    - Depletion of substance P from sensory neurons
    - When substance P is released, burning pain occurs but diminishes with repeated application
Counterirritants

- **Capsaicin**
  
  - **Patient counseling points:**
    - Instruct patients to wear gloves during application and wash hands following use; if the hands are the site of application, the patient should wait 30 minutes after application and then wash their hands.
    - Do not allow capsaicin to come into contact with eyes or mucous membranes.
    - Pain relief is usually noted within 14 days but can take up to 6 weeks.
    - Adherence is important – once capsaicin has begun to relieve pain, its use must be continued regularly 3-4 times daily.

### Counterirritants: Examples

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<thead>
<tr>
<th>Product</th>
<th>Ingredients</th>
<th>Packaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capzasin Arthritis Pain Relief No-Mess Applicator</td>
<td>Capsaicin 0.15%</td>
<td><img src="image1" alt="Capzasin" /></td>
</tr>
<tr>
<td>Capzasin-HP Arthritis Pain Relief Cream</td>
<td>Capsaicin 0.1%</td>
<td><img src="image2" alt="Capzasin-HP" /></td>
</tr>
<tr>
<td>Zostrix Arthritis Pain Relief Cream</td>
<td>Capsaicin 0.025%</td>
<td><img src="image3" alt="Zostrix" /></td>
</tr>
</tbody>
</table>
Heat/Thermal Wraps

- Non-pharmacologic option
- May help reduce pain by increasing blood flow
- Has been studied in the treatment of acute low back pain (< 4 weeks duration) with favorable effects.
- Osteoarthritis guidelines recommend heat as adjunct non-pharmacologic treatment for pain and stiffness.
- Apply for 15-20 minutes 3-4 times daily (regular heat); ThermaCare® products can be worn for up to 8-12 hours.
- Should not be applied to recently injured (< 48 hours) or inflamed areas; should not be used with other topical agents or over broken skin.

Transcutaneous Electrical Nerve Stimulation (TENS)

- Class II Medical Device FDA-approved for the relief of pain associated with sore, aching muscles, joint pain, or chronic intractable pain.
- **Mechanism of action:**
  - Alteration of pain transmission
  - Increase in production of natural endorphins
- Typically used for 15-30 minutes up to 3 times daily.
- Should not be used in patients with internal or attached medical devices (e.g., pacemakers, defibrillators), pregnant patients or in the pediatric population.
Does Sally have any exclusions for self tx?

- Moderate-to-severe pain (pain score > 6)
- Pain that lasts > 10 days
- Pain that continues > 7 days after tx w/ a topical analgesic
- Increased intensity or change in character of pain
- Pelvic or abdominal pain (other than dysmenorrhea)
- Accompanying nausea, vomiting, fever or other signs of systemic infection or disorder
- Visually deformed joint, abnormal movement, weakness in any limb, or suspected fracture
- Third trimester of pregnancy
- < 2 years of age

Sally

- She does not have any exclusions to self-treatment
- But she has a history of uncontrolled hypertension
  - Avoid NSAIDs, can recommend acetaminophen instead
- Recommend a topical analgesic
  - Apply SalonPas original patch (methyl salicylate 6.3%, menthol 5.7%, and camphor 1.2%) to back 3-4 times a day.
    - This is just one example. Any available OTC patch would work!
  - Can use for up to 7 days.
  - Do not use heat when you are using this medication.
The 411 on Nonprescription Analgesics: When to Hold ‘Em, When to Fold ‘Em

Alexandra L. McPherson, PharmD, MPH