



**Navigating the OTC Analgesic Aisle:
What a Pain in the Aspirin!**

Laura Meyer-Junco, PharmD, BCPS, CPE
University of Illinois Chicago (UIC) College of Pharmacy—Rockford

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Disclosure

- Nothing to disclose



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Learning Objectives

At the completion of this presentation, participants should be able to:

- Identify available nonprescription products marketed for pain relief, including their dosage, formulations, indications, and safety and efficacy considerations
- Describe the place of various nonprescription analgesics in the treatment of common painful conditions
- Summarize how to prepare patients to navigate the OTC analgesic aisle on their own



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It's a Jungle Out There!



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Reading the Label

ACTIVE INGREDIENT
Therapeutic substance in product; amount of active ingredient per unit

PURPOSE
Product action or category (such as an anti-inflammatory, antacid, or cough suppressant)

USE
Symptoms or diseases the product will treat or prevent

DIRECTIONS
Specific age categories, how much to take, how often, and how long to take

OTHER INFORMATION
How to store the product properly and required information about certain ingredients (such as the amount of calcium, potassium, or sodium the product contains)

INACTIVE INGREDIENTS
Substances such as colors or flavors

WARNINGS
When not to use the product; conditions that may require advice from a doctor before taking the product; possible interactions or side effects; when to stop taking the product and when to contact a doctor; if you are pregnant or breastfeeding, seek guidance from a health care professional; keep product out of children's reach

www.fda.gov/drugs/understanding-over-the-counter-medicines/educational-resources-understanding-over-the-counter-medicine

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Patient Education on Nonprescription Analgesics

- <https://www.knowyourdose.org/common-medicines/how-to-read-your-medicine-label/>
- <https://www.fda.gov/drugs/understanding-over-the-counter-medicines/educational-resources-understanding-over-the-counter-medicine>
- <https://www.fda.gov/drugs/drug-information-consumers/otc-drug-facts-label>
- <https://www.getrelieffresponsibly.com/pain-medicine-safety>



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Acetaminophen

OTC Systemic Analgesics: the Major Players

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Acetaminophen Dose/Fls

- **Pharmacologic category:** analgesic and antipyretic
- **Nonprescription indications:** mild to moderate pain and fever
- **Mechanism of Action:** central inhibition of prostaglandin synthesis
 - As a result, lacks anti-inflammatory properties and not associated with platelet inhibition and gastric side effects

"APAP (acetaminophen/paracetamol), which has long been regarded as a mainstay of OA treatment, was not recommended by the majority of the Voting Panel for any OA phenotype or comorbidity subgroup."
 —2019 Osteoarthritis Research Society International (OARS) Osteoarthritis Guidelines

"The 2007 review concluded that acetaminophen was effective for acute low back pain... However, this update included a placebo-controlled RCT in patients with low back pain that showed no difference in effectiveness between acetaminophen and placebo"
 —2017 American College of Physicians Low Back Pain Guideline

BUT it may be helpful in combination with NSAIDs in certain settings and even NSAID-sparing... STAY TUNED!

PainWeek Ann Intern Med. 2017;166:514-530 Osteoarthritis and Cartilage. 2019;27:1578-1589. Kinsley et al, eds. Handbook of Nonprescription Drugs, 20 ed. Washington, DC: American Pharmacists Association, 2020.
Minerva Anestesiol. 2009;75:644-653 Acetaminophen. Clinical Pharmacology database.

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Acetaminophen Pharmacokinetic Profile

- **Pharmacokinetics:**
 - Rapidly absorbed from the GI tract
 - Extensive hepatic metabolism to inactive glucuronic and sulfuric acid conjugates
 - Small amount of drug metabolized by CYP2E1 to hepatotoxic metabolite, N-acetyl-p-benzoquinoneimine (NAPQI)
 - Rapidly detoxified by glutathione at therapeutic doses
 - Supratherapeutic or repeated therapeutic doses of acetaminophen, fasting, and alcoholism may deplete glutathione stores, resulting in increased concentrations of NAPQI and hepatotoxicity.
 - CYP2E1 substrate (inducers: ethanol and isoniazid)
 - Renally excreted as the glucuronide conjugate (40% to 65%) and sulfate metabolite (25% to 35%).

PainWeek Acetaminophen. Clinical Pharmacology database. Kinsley et al, eds. Handbook of Nonprescription Drugs, 19th ed. Washington, DC: American Pharmacists Association, 2018.

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OTC Acetaminophen—Boxed Warnings

- Potentially hepatotoxic in doses > 4 g/d, particularly with chronic use
- Conservative dosing (≤ 2 g/d) or avoidance
 - Liver disease
 - Concurrent hepatotoxic medication use
 - Poor nutritional intake
 - ≥ 3 alcoholic drinks per day
 - 1 drink = 12 ounces beer, 5 ounces wine, 1.5 ounces of 80 proof liquor
- Rare but serious skin reactions

FDA requires manufacturers include warnings:

Warnings

Liver warning: This product contains acetaminophen. Severe liver damage may occur if you take

- more than 6 caplets in 24 hours, which is the maximum daily amount
- with other drugs containing acetaminophen
- 3 or more alcoholic drinks every day while using this product

Allergy alert: Acetaminophen may cause severe skin reactions. Symptoms may include:

- skin reddening
- blisters
- rash

If a skin reaction occurs, stop use and seek medical help right away.

650 mg ER product

Kinsky et al, eds. Handbook of Nonprescription Drugs, 18th ed. Washington, DC: American Pharmacists Association, 2018.



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Recommended Nonprescription Dosing

- Acetaminophen 325 -1000 mg every 4-6 hours prn
- In 2011, manufacturer of Tylenol voluntarily reduced maximum dosage:

TYLENOL [®] PRODUCT	REGULAR STRENGTH TYLENOL [®] TABLETS 325 mg	REGULAR STRENGTH TYLENOL [®] LIQUID GELS 325 mg	EXTRA STRENGTH TYLENOL [®] 500 mg	TYLENOL [®] 8 HR ARTHRITIS PAIN 650 mg	TYLENOL [®] 8 HR MUSCLE ACHES & PAIN 650 mg
DIRECTIONS	2 Tablets Every 4-6 hours while symptoms last.	2 Capsules Every 4-6 hours while symptoms last.	2 Caplets Every 6 hours while symptoms last.	2 Caplets Every 8 hours while symptoms last.	2 Caplets Every 8 hours while symptoms last.
	Not to exceed 10 tablets in 24 hours, unless directed by a doctor.	Not to exceed 10 capsules in 24 hours, unless directed by a doctor.	Not to exceed 6 caplets in 24 hours, unless directed by a doctor.	Not to exceed 6 caplets in 24 hours.	Not to exceed 6 caplets in 24 hours.
	Max: 3250 mg/day		Max: 3000 mg/day	Max: 3900 mg/day	



https://www.tylenol.com/health/education/tylenol-dosage-for-adults

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The "What's in There?" Gameshow

Which acetaminophen product(s) contains the diuretic, pamabrom?

Acetaminophen 500 mg
Pamabrom 25 mg (diuretic)

Acetaminophen 500 mg
Caffeine 60 mg (diuretic)
Pyrilamine maleate 15 mg (antihistamine)

Acetaminophen 500 mg
Pamabrom 25 mg (diuretic)
Pyrilamine maleate 15 mg (antihistamine)



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NSAIDs and Salicylates

OTC Systemic Analgesics: the Major Players

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Nonselective NSAIDs Profile

- **FDA-approved nonprescription NSAIDs:** ibuprofen (Motrin, Advil), naproxen (Aleve), ketoprofen (not commercially available)
 - Plus in combination products galore!
- **NSAID class:** Propionic acids (phenyl-propionic acid)
- **Pharmacologic category:** analgesic, antipyretic, and anti-inflammatory
- **Nonprescription indications:** fever and minor pain associated with arthritis, muscle ache, backache, toothache, headache, common cold, and menstrual cramps
- **Mechanism of action:** central and peripheral inhibition of prostaglandin synthesis
 - Reversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes
- **Pharmacokinetics:**
 - Rapidly absorbed from the GI tract
 - Highly protein-bound (>90%)
 - Extensive hepatic metabolism (primarily glucuronidation) to inactive metabolites
 - CYP2C9 substrate (inhibitors: fluconazole, amiodarone)
 - Excreted in urine

PainWeek Lange Top 100 Nonprescription Drugs, 2018-2019. Kirnsky et al, eds. Handbook of Nonprescription Drugs, 19th ed. Washington, DC: American Pharmacological Association, 2018.

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Salicylates Profile

- **Nonprescription members:**
 - Aspirin/acylsalicylic acid (Bayer, Ecotrin, St. Joseph)
 - Nonacetylated salicylates: magnesium salicylate (Doan's, Percogesic), sodium salicylate (Cystex)
- **Pharmacologic category:** analgesic, antipyretic, and anti-inflammatory
- **Nonprescription indications:** fever and minor pain associated with backache, headache, arthritis, and muscle ache; prevention of cardiovascular events
- **Mechanism of action:** primarily peripheral inhibition of prostaglandin synthesis, and possibly a central mechanism.
 - Aspirin irreversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes
- **Pharmacokinetics:**
 - Passive absorption of non-ionized drug through the GI tract
 - Affected by dosage form, dissolution time, gastric pH, acid-suppressive drugs, gastric emptying, and food
 - Once absorbed, aspirin is hydrolyzed to salicylic acid and widely distributed to all tissues
 - Salicylic acid is highly protein bound (and concentration dependent, decreasing protein binding at higher concentrations)
 - Hepatic metabolism (primarily conjugation)
 - Largely eliminated through kidneys (half-life 2-3 hours for single low dose; 12 hours for anti-inflammatory doses)

PainWeek Lange Top 100 Nonprescription Drugs, 2018-2019. Aspirin. Clinical Pharmacology database. Handbook of Nonprescription Drugs, 19th ed. 2018.

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Ibuprofen Single-Entity Products: Adult OTC Formulations

¹Time to peak delayed by food, opioids, anticholinergics
²Anti-inflammatory time to peak: 2-3 weeks

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<https://www.ada.org/ibuprofen-200mg-capsules-1041466>
 Drug Design, Development and Therapy 2017:11:135-141
 Ibuprofen, Clinical Pharmacology database.
 Drugs R D 2014; 14:283-290 Ibuprofen, Micromedex database.
 Kogil A, Patel NB, et al. Guide to Pain in Low Resource Settings. IASP 2010
 PAIN 2014; 155: 14-21

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<https://www.ada.org/ibuprofen-200mg-capsules-1041466>
 Drug Design, Development and Therapy 2017:11:135-141
 Ibuprofen, Clinical Pharmacology database.
 Drugs R D 2014; 14:283-290

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“New” Kid on the Block

- Per tablet:
 - Acetaminophen 250 mg
 - Ibuprofen 125 mg
- Indication: minor aches and pains
- Dosing: 2 tablets q 8 h
- Max: 6 tablets/day

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www.advil.com/our-products/advil-dual-action/

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OTC Non-Aspirin NSAID Label Change in 2016

Stomach bleeding warning
(Refer to full Drug Facts Label or product for complete list of warnings)

Heart attack and stroke warning
NSAIDs, except aspirin, increase the risk of heart attack, heart failure, and stroke. These can be fatal. The risk is higher if you use more than directed or for longer than directed.

Ask a doctor before use if

- stomach bleeding warning applies to you
- you have problems or serious side effects from taking pain relievers or fever reducers
- you have a history of stomach problems, such as heartburn; you have high blood pressure, heart disease, liver problems, kidney disease, asthma, or had a stroke
- you are taking a diuretic

When using this product

- Use with food or milk if stomach upset occurs

The risk of heart attack or stroke may increase if you use more than directed or for longer than directed (this statement is required by the "Heart attack and stroke warning" above)

Stop use and ask a doctor if

- you experience any of the following signs of stomach bleeding:
 - feel faint
 - vomit blood
 - have bloody or black stools
 - have stomach pain that does not get better
- you have symptoms of heart problems or stroke:
 - chest pain
 - trouble breathing
 - weakness in one part or side of body
 - slurred speech
 - leg swelling

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https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/010116s010_label_2016.pdf

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NSAIDs — Boxed Warnings

Prescription Label

Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, 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 greater risk (see **WARNINGS**).
- MOTRIN tablets are contraindicated for treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including 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 (see **WARNINGS**).

https://www.fda.gov/drugs/infos-safety-and-availability/fda-drug-safety-communication-fda-strengthens-warning-non-aspirin-nsaids-prescription-label

PainWeek
https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/017593s1028b.pdf

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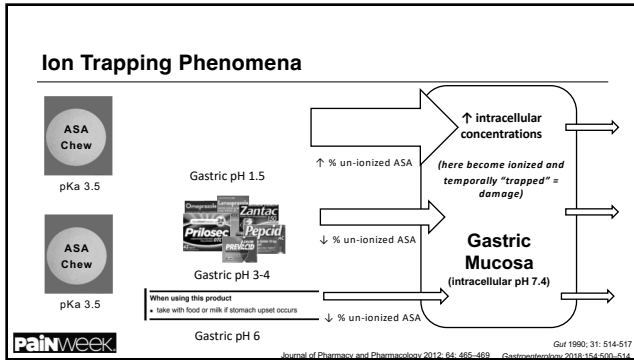
Mechanisms of Aspirin/NSAID Induced GI Injury/Bleed

- Local irritation
 - Low pH of gastric contents (pH 1-3 when fasted) + low pKa of drug = NSAID/ASA phospholipid interaction and permeation into the gastric epithelium
 - The lower the pKa of the NSAID, the greater the "topical toxicity"
 - Aspirin pKa 3.5
 - Naproxen pKa 4.15
 - Ibuprofen pKa 5.2
- Inhibition of cyclooxygenase and reduction in production of prostaglandins responsible for inhibiting acid secretion by the stomach and promoting the secretion of cytoprotective mucus
- Impaired of platelet aggregation (increased bleeding tendency) — aspirin

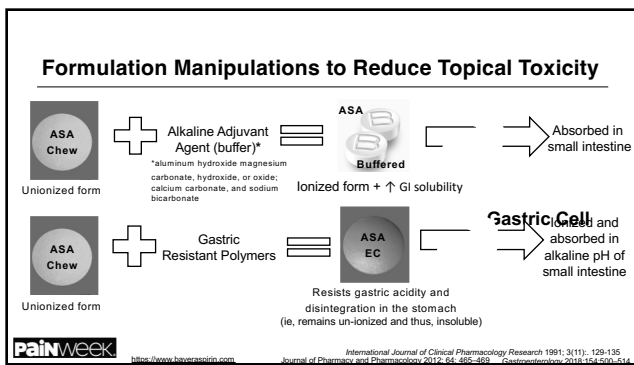
pKa = logarithmic transformed acid dissociation constant.

PainWeek
Gastroenterology 2018;154:500-514
Journal of Pharmacy and Pharmacology 2012; 64: 465-469
Lancet 1996; 348:1413-1416

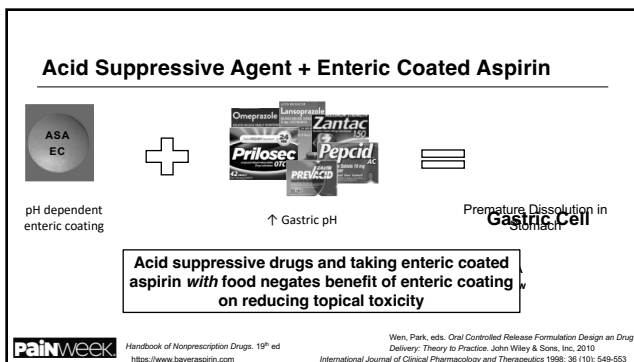
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Aspirin

Trade Name	Generic Name	Strength	Formulation	Manufacturer
Bayer Aspirin	Aspirin	325 mg	Tablet	Bayer
St. Joseph Aspirin	Aspirin	325 mg	Tablet	St. Joseph
Bayer Safety Coated Aspirin	Aspirin	325 mg	Tablet	Bayer
Ecotrin	Aspirin	325 mg	Tablet	Ecotrin

Uses

- for the temporary relief of minor aches and pains or as recommended by your doctor. Because of its delayed action, this product will not provide fast relief of headaches or other symptoms needing immediate relief.
- ask your doctor about other uses for Bayer Safety Coated 325 mg Aspirin

PainWeek Handbook of Nonprescription Drugs, 19th ed. Applied Biopharmaceutics & Pharmacokinetics, 7e Aspirin, Micromedex database, <https://www.bayeraspirin.com/usa/otc> Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e

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Aspirin Single-Entity Products: Adult OTC Formulations

Trade Name	Generic Name	Strength	Formulation	Manufacturer
Bayer Aspirin	Aspirin	325 mg	Tablet	Bayer
Bayer Extra Strength Aspirin	Aspirin	325 mg	Tablet	Bayer

PainWeek Handbook of Nonprescription Drugs, 19th ed. <https://www.bayeraspirin.com/products/>

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Aspirin

Trade Name	Generic Name	Strength	Formulation	Manufacturer
Bufferin	Aspirin	325 mg	Tablet	Bufferin
Alka-Seltzer	Aspirin	325 mg	Tablet	Alka-Seltzer

PainWeek Am J Cardiol 1999; 84:404-409. Br J Clin Pharmacol 1984; 17:697-701. <https://www.alka-seltzer.com/>, <https://www.bayeraspirin.com/products/>, 2019 Wolters Kluwer Clinical Drug Information, Inc.

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The "Brand Extension" Gameshow

Which of these is the analgesic?

HEARTBURN

Anhydrous citric acid 1000 mg (antacid)
Sodium bicarbonate 1940 mg (antacid)

GOLD

Anhydrous citric acid 1000 mg (antacid)
Potassium bicarbonate 344 mg (antacid)
Sodium bicarbonate 1050 mg (antacid)

LEMON LIME

Anhydrous citric acid 1000 mg (antacid)
Aspirin 325 mg (analgesic)
Sodium bicarbonate 1700 mg (antacid)

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Do these strategies reduce topical toxicity?

- **Enteric coated**
 - Endoscopic studies in *healthy, younger* adults demonstrate reduced gastric irritation and micro-bleeding compared to plain aspirin
 - ASA EC 300 mg x 5 days has the least evidence of gastric injury vs plain aspirin (75-300 mg) (*Aliment Pharmacol Ther* 1999; 13: 187-193)
 - Effectiveness not demonstrated in endoscopic studies of *older, long-term* aspirin users (possibly due to hypochlorhydria in older adults) (*Interactive CardioVascular and Thoracic Surgery* 2007; 6: 518-5)
 - Greater evidence of less mucosal damage in high doses (3.9 g/day) vs buffered or plain aspirin in older studies (*NewM* 1980;3(3):136-8)
- **Buffered tablets or effervescent solution**
 - Early studies showed reduced GI side effects and mucosal injury in healthy volunteers on high doses (aspirin 650 mg TID) vs plain aspirin, but didn't hold true for lower aspirin doses (80-100 mg/day—not available in US) (*Neth Heart J* (2014) 22:107-112; *Neth Heart J* (2014) 22:105-106; *Qut* 1996; 38: 11-14; *Clinical Gastroenterology and Hepatology* 2008;6:309-313)
- **Taking nonenteric coated aspirin with food**
 - Lack of data (*Journal of Pharmacy and Pharmacology* 2012; 64: 465-469)

PainWeek Oral Controlled Release Formulation Design and Drug Delivery: Theory to Practice, 2010

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Effect of Aspirin Formulation on Upper GI Bleed (UGIB)

Aspirin Formulation	Dose	Frequency	Relative Risk of UGIB	Relative Risk of Gastric Bleed	Relative Risk of Duodenal Bleed
Plain	≤325 mg/day	Regular Overall	4.1 (3.0-5.5)		
		Regular	2.6 (1.7-4.0)	2.6 (1.5-4.3)	2.4 (1.2-4.6)
		Regular	5.8 (3.9-8.6)	5.7 (3.6-8.9)	5.1 (2.9-8.9)
		Occasional	1.8 (1.3-2.5)		
Enteric Coated	≤325 mg/day	Regular Overall	2.3 (1.3-4.3)		
		Regular	2.7 (1.4-5.3)	3.2 (1.5-7.0)	2.6 (1.0-7.0)
		Regular	Insufficient data	--	
		Occasional	Insufficient data	--	
Buffered	≤325 mg/day	Regular Overall	4.9 (2.6-9.0)		
		Regular	3.1 (1.3-7.6)	3.6 (1.3-9.8)	2.6 (0.7-9.9)
		Regular	7.0 (3.0-16)	7.8 (3-20)	7.0 (2.2-22)
		Occasional	2.2 (1.3-3.9)		

PainWeek Regular = at least every other day x 1 week Lancet. 1996;348:1413-1416.

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Magnesium Salicylate Products: Adult OTC Formulations

Product Name	Product	Strength	Form	Time to Onset	Duration	Contraindications
DOAN'S		162.5 mg	Tablet	15-30 min	4-6 hrs	None listed
Percogesic		162.5 mg	Tablet	15-30 min	4-6 hrs	None listed


Low incidence of GI effects and does **NOT have a clinically significant effect on platelets*

PainWeek Magnesium Salicylate Micromedex database.
Magnesium Salicylate Clinical Pharmacology database.

<https://www.doan.com/>

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Other OTC Nonacetylated NSAID Products



Cystex
Urinary Pain Relief (NSAID)

Max Strength+
Fast relief of pain & burning plus helps control infection

40 Tablets



AZO
Urinary Tract Defense

ANTIBACTERIAL PROTECTION

✓ HELPS CONTROL THE INFECTION
✓ PLUS GENERAL PAIN RELIEVER

24 TABLETS

Active Ingredients:

- Methenamine 162 mg (antibacterial)
- Sodium salicylate 162.5 mg

Instructions:
Take 2 tablets with a full glass of water 3 times a day

PainWeek <https://www.azo-products.com/> <https://www.cystex.com/>

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The Side Kick: Caffeine

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Caffeine Profile

- OTC products containing caffeine may also contain:
 - Acetaminophen
 - Aspirin
 - Acetaminophen + aspirin
- Caffeine dose range in OTC products per unit: 32 mg-65 mg
- Proposed mechanism of action:
 - Improved drug absorption by increased gastric blood flow and lower gastric pH
 - Reduced hepatic blood flow resulting in reduced drug metabolism
 - Direct effect from blocking central adenosine receptors that influence pain signaling or from blockade of peripheral adenosine receptors in sensory afferents.
 - Inhibiting cyclooxygenase (COX) activity at some sites
 - Changes in perception of pain as result of changes in mood/emotional state

PainWeek Cochrane Database of Systematic Reviews 2014, Issue 12, Art. No.: CD009281, Anesth Pain Med 2016; 6(3): e33163.

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OTC Analgesic Plus Caffeine vs Analgesic Alone


Primary Outcome	No. studies (No. of participants)	Proportion of patients with at least 50% of max pain relief		NNT
		+ caffeine*	- caffeine	
Any Pain Condition	16 (4262)	48%	41%	14
Postoperative/postpartum	10 (2139)	60%	51%	10
Headache	5 (1503)	33%	25%	13
Dysmenorrhea	1 (620)	43%	39%	---
Drug				
Acetaminophen (500-1500 mg)	8 (2186)	62%	54%	14
Ibuprofen (100-400 mg)	4 (707)	46%	32%	7.2
Aspirin (650 mg)	1 (134)	26%	25%	--
Aspirin (500 mg) + APAP (400 mg)	1 (980)	89%	77%	8

PainWeek *Benefit of caffeine in doses \geq 100 mg; no increase in benefit > 200 mg
Cochrane Database of Systematic Reviews 2014, Issue 12, Art. No.: CD009281

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Caffeine Beverage Refresher

- Coffee (100 to 150 mg caffeine per mug)
- Tea (75 mg caffeine per mug)
- Cola/soda/pop drinks (up to 40 mg caffeine per can)
- Energy drinks (~80 mg caffeine per can)
- Plain chocolate (up to 50 mg caffeine per bar)
- Caffeine tablets (100 mg caffeine per tablet)



PainWeek Cochrane Database of Systematic Reviews 2014, Issue 12, Art. No.: CD009281.

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Arch Intern Med 1991;151(4):733-7.

Indication	Drug	Strength	Formulation	Manufacturer
Analgesic Antipyretic Anti-inflammatory Antirheumatic Anticancer	BAYER BACK-TO-BODY	325 mg	Tablet	Bayer
	ANACIN	500 mg	Tablet	Parke-Davis

PainWeek Arch Intern Med 1991;151(4):733-7. <https://www.anacin.com/> <https://www.bayerusa.com/>

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Arch Intern Med 1991;151(4):733-7.

Indication	Drug	Strength	Formulation	Manufacturer
Analgesic Antipyretic Anti-inflammatory Antirheumatic Anticancer	BC	325 mg	Tablet	Bayer
	BC	500 mg	Tablet	Parke-Davis

PainWeek Arch Intern Med 1991;151(4):733-7. <https://www.bcpowder.com/>

Caffeine warning: The recommended dose of this product contains about as much caffeine as a cup of coffee. Limit the use of caffeine-containing medications, foods, or beverages while taking this product because too much caffeine may cause nervousness, irritability, sleeplessness, and, occasionally, rapid heart beat.

Each product contains caffeine warning

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Arch Intern Med 1991;151(4):733-7.

Indication	Drug	Strength	Formulation	Manufacturer
Analgesic Antipyretic Anti-inflammatory Antirheumatic Anticancer	Goody's	325 mg	Tablet	Parke-Davis
	Goody's CODEINE	325 mg	Tablet	Parke-Davis

PainWeek Arch Intern Med 1991;151(4):733-7. <https://www.bcpowder.com/> <https://www.bcpowder.com/>

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Which of these products contain the same active ingredients?

EXCEDRIN EXTRA STRENGTH Acetaminophen 250 mg Aspirin 250 mg Caffeine 65 mg Take 2 tabs q6h (max 8 tabs/day)	EXCEDRIN MIGRAINE Acetaminophen 250 mg Aspirin 250 mg Caffeine 65 mg Take 2 tabs with water (max 2 tabs/day)	EXCEDRIN TENSION HEADACHE Acetaminophen 500 mg Caffeine 65 mg Take 2 tabs q6h (max 6 tabs/day)
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The "Brand Extension" Gameshow

PainWeek "Clinically proven formula of 2 pain fighters plus a booster" www.excedrin.com

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OTC Systemic Analgesics: Efficacy

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Nonprescription Efficacy for Acute Pain*

- Review of all Cochrane reviews of RCTs of single dose oral analgesics for acute post operative pain (including dental pain, inpatient surgery, and day surgery) in adult patients
- Number needed to treat (NNT) for at least 50% pain relief over four to six hours following a single dose

Non-prescription (OTC) oral analgesics for acute pain - an overview of Cochrane reviews (Review)

Moore RA, Wiffen PJ, Derry S, Maguire T, Roy YM, Tyrrell L

Cochrane Database Syst Rev 2015 Nov 4;(11):CD010784


PainWeek *Excludes migraine pain, headache, and menstrual pain

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Studied Drug	Associated Product (s)	Dose (mg)	NNT (95% CI)
Ibuprofen + Acetaminophen	Regular release 200 mg ibuprofen and Tylenol extra strength 500 mg tab/caplets	400 + 1000	1.5 (1.4 to 1.7)
Ibuprofen + Acetaminophen	Tylenol extra strength 500 mg tab/caplets	200 + 500	1.6 (1.5 to 1.8)
Ibuprofen Fast Acting	Advil liquid-gels	400	2.1 (1.9 to 2.3)
Ibuprofen Fast Acting	Advil Migraine (solubilized ibuprofen)	200	2.1 (1.9 to 2.4)
Ibuprofen + Caffeine	Combination product not available in US	200 + 100	2.1 (1.9 to 3.1) [NNH 19]
Ibuprofen	Advil 400 mg tablet/caplet	400	2.5 (2.4 to 2.6)
Naproxen	Aleve liquid gels, tab/caplets	440	2.7 (2.2 to 3.5)
Ibuprofen	Advil 200 mg tablet	200	2.9 (2.7 to 3.2)
Naproxen	Aleve liquid gels, tab/caplets	220	3.4 (2.4 to 5.8)
Acetaminophen	Tylenol extra strength 500 mg tab/caplets	500	3.5 (2.7 to 3.5)
Acetaminophen	500 mg or 325 mg (regular strength) tab/caplets	975-1000	3.6 (3.2 to 4.1)
Aspirin	Regular strength 325 mg tablet and enteric coated	650	4.2 (3.8 to 4.6)
Aspirin	Bayer Extra Strength 500 mg coated caplets	1000	4.2 (3.8 to 4.6) [NNH 7.5]
Acetaminophen	Tylenol Arthritis/8 hour (extended release)	650	4.6 (3.9 to 5.5)
Aspirin	Bayer Extra Strength 500 mg coated caplets	500	Not better than placebo

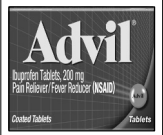
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**Higher or Lower Doses in Acute Pain?
Direct Comparison Studies**



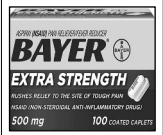
APAP 1000 vs 500/650 mg

NNT 9



Ibuprofen 800 vs 400 mg

NNT 10



ASA 1000/1200 vs 500/600 mg

NNT 16

US Food and Drug Administration, 382GB1 13 Mefenamic Acid; www.accessdata.fda.gov/drugsatfda_docs/nda/020383Orig1s001/MefenamicAcid.cfm
 Pain 2012; 153: 1384-1387 Br J Clin Pharmacol 2007 Mar; 63(3):271-8.

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OTC Topical Analgesics

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American College of Rheumatology (ACR) 2019 Osteoarthritis Guidelines

HIP Osteoarthritis
1st Line: Oral NSAIDs

HAND Osteoarthritis
1st Line: Oral NSAIDs
2nd Line: **Topical NSAIDs**

KNEE Arthritis
1st Line: **Topical NSAIDs**
2nd Line: Oral NSAIDs

PHARMACOLOGIC APPROACHES

HAND	KNEE	HIP
Oral NSAIDs		
Topical NSAIDs	Topical NSAIDs	
I-A Steroids	I-A Steroids (Imaging-Guidance for Hip)	
Acetaminophen		
Tramadol		
Duloxetine		
Chondroitin	Topical Capsaicin	

Arthritis Care & Research. 2020. 72(2):149-162

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What's the story with trolamine?




Table 2. Pharmacologic recommendations for the initial management of hand OA*

We conditionally recommend that health professionals should use one or more of the following:
Topical capsaicin
Topical NSAIDs, including trolamine salicylate
Oral NSAIDs, including COX-2 selective inhibitors
Tramadol

We conditionally recommend that health professionals should not use the following:
Intra-articular therapies
Opioid analgesics

We conditionally recommend that persons age ≥75 years should use topical rather than oral NSAIDs. In persons age <75 years, the TEP expressed no preference for using topical rather than oral NSAIDs.

* No strong recommendations were made for the pharmacologic management of hand osteoarthritis (OA). For patients who have an inadequate response to initial pharmacologic management, please see the Benefits for alternative strategies. NSAIDs = nonsteroidal anti-inflammatory drugs; COX-2 = cyclooxygenase 2; TEP = Technical Expert Panel.

2012 ACR Recommendations for Management of Hand, Hip, and Knee OA

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Arthritis Care & Research 2012; 64 (4): 465-474

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Counterirritants: Paradoxical Pain Relief

- Labels indicate for "the temporary relief of minor-moderate aches and sprains of muscles and joints."
- When applied to the skin, produce a local, mild inflammatory reaction to counter or distract from pain at the site (in muscles, joints, tendons)

Group A	Group B	Group C	Group D
<ul style="list-style-type: none"> Rubefacients Redness/warm due to vasodilation Methyl Salicylate 	<ul style="list-style-type: none"> Produce cooling sensation Menthol Camphor 	<ul style="list-style-type: none"> Cause vasodilation Histamine dihydrochloride [Methyl nicotinate] 	<ul style="list-style-type: none"> TRPV1 agonists Substance P Depletors Capsaicin <1% Capsicum

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Kinsky et al, eds. Handbook of Nonprescription Drugs. 19th ed. Washington, DC: American Pharmacists Association, 2018.

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Group A Agents: Methyl Salicylate 10-60%*

ICYHOT

Cream or Gel Stick
Methyl Salicylate 30%
Menthol 10%
Balm
Methyl Salicylate 29%
Menthol 7.6%
Apply up to 4 times/day

Salonpas

Patch: Methyl Salicylate 10%
Menthol 3% (FDA approved)
1-2 patch for 8-12 hours
(max 2 patches/day do not use more than 3 days in a row)
Spray: Methyl Salicylate 10%,
Menthol 3%
Up to 4 time/day (Hold 4 inches away from skin to avoid frostbite)


BENGAY

Cream: Methyl Salicylate 15%,
Menthol 10%
Apply up to 4 times/day

Appreciable dermal absorption
Camphor/Menthol as well as heat may increase absorption

PainWeek *Usually in combination with other products US Pharm. 2019;44(3):15-2 <https://www.icyhot.com/>
Clin Ther 2010; Jan;32(1):34-43. <https://us.hisamitsu.com/>

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FDA Approved

Methyl salicylate 10%, menthol 3% patch (Salonpas) vs placebo study of 208 patients with mild to moderate muscle strain demonstrated 40% significantly greater pain relief through 8 hours with movement (p=0.005)

Kritsky et al. eds. Handbook of Nonprescription Drugs, 20th ed. Washington, DC: American Pharmacists Association, 2020. Clin Ther 2010; 32(1):34-43

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Efficacy Outcome	No. studies (No. of participants)	Proportion of patients with 50% pain relief		NNT
		Drug	Placebo	
Topical Salicylates* [Cochrane Review]				
Acute pain (sprains, sprains, acute low back pain)	4 (324) [low quality evidence]	64% (25%-95%) at 7 days	34% (0%-59%) at 7 days	3.2
Chronic pain (osteoarthritis, bursitis, back pain)	6 (455) [low quality evidence]	45% (38%-80%) at 14 days	28% (17%-38%) at 14 days	6.2
Safety Outcome	No. studies	Drug	Placebo	NNH
Topical Salicylates				
All adverse events (acute + chronic pain)	11	15% (0%-83%)	9% (0%-52%)	17
Local adverse events (acute + chronic pain)	10	6% (0%-24%)	2% (0%-9%)	31
Methyl salicylate 10%, menthol 3% patch	1	6.7%	5.8%	--

*included trolamine salicylate and methyl salicylate

PainWeek Cochrane Database of Systematic Reviews 2014, Issue 11, Art No.: CD007493. DOI: 10.1002/14651858.CD007493.pub3

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Group B Agents: Menthol 1.25-16%

 <p>Gel: Menthol 2.5% Gel Stick, Roll-On, Spray, Sleeve: Menthol 16% Apply up to 4 times/day Micro-Patch: Menthol 7.5% Up to 4 patches at a time for 12 hours Patch (also in XL): Menthol 5% 1 patch for 8 hours "Advanced Relief" Patch: Menthol 7.5% 1 patch for 12 hours</p>	 <p>Roll-on, Gel, Pump, or "On-the-go" single gel packets: Menthol 4% Use up to 4 times/day Patch: Menthol 5% Up to 4 times/day (1 patch for 8 hours) Cream: Menthol 10% Use up to 4 times/day Spray: Menthol 10.5% Use up to 4 times/day</p>	 <p>Gels: Available in Menthol 2.5% or 5% Apply up to 4 times/day Patch: Menthol 5% Apply up to 4 times/day (label states can cut patch)</p>
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PainWeek <https://www.painweek.com/> <https://www.biofreeze.com> <https://www.bengay.com/> <https://www.tigerbalm.com> US Pharm. 2018-44(3):18-21

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FDA Safety Communication

- Issued in 2012 regarding rare cases of burns with OTC topical products
- In many cases, burns occurred after one application
- Majority of cases with higher concentration menthol as the single ingredient or combination products containing both menthol (>3%) and methyl salicylate (>10%)




FDA Recommendations to Consumers Regarding Topical OTC Products:

- If you experience pain, swelling, or blistering of the skin, stop using the product and seek medical attention immediately. These products should not cause pain or skin damage. These products produce local warmth or coolness.
- Do not bandage the area tightly and do not apply local heat (heating pads, lamps, hot water in bags or bottles) because doing so can increase the risk of serious burns.
- Do not apply to wounds or damaged, broken, or irritated skin. Also do not allow contact with eyes and mucous membranes (such as the skin inside your nose, mouth, or genitals).
- Talk to a health care professional if you have any questions or concerns about using OTC topical muscle and joint pain relievers.

PainWeek <https://www.fda.gov/drugs/otc/safety-and-availability/otc-topical-communication-rare-cases-serious-burns-occur-over-counter-muscle-and-joint>

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Group B Agents: Camphor 3-11%*

 <p>"Advanced Relief" Cream: Camphor 11%, Menthol 16% Apply up to 3 times daily (2-3 hours in between) Lotion: Camphor 4%, Menthol 16% Apply up to 3 times daily</p>	 <p>Patch: Camphor 3.1%, Menthol 6.0%, Methyl Salicylate 10% 1 patch up to 4 times/day (remove after 8 hours) Gel: Camphor 3.1%, Menthol 10%, Methyl salicylate 15% up to 4 times/day</p>	 <p>"Ultra Strength" Cream: Camphor 4%, Menthol 10%, Methyl Salicylate 30% Apply up to 4 times/daily</p>	 <p>Ointment: Camphor 11%, Menthol 11% Apply up to 4 times/daily Patch: Camphor 80 mg, Menthol 24 mg, Capsicum Extract 16 mg Use up to 3 times/daily</p>
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PainWeek <https://www.painweek.com/> <https://www.salonpas.com/> <https://www.bengay.com/> <https://www.tigerbalm.com> *Joint Flex cream contains Camphor 3.1% alone

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Group C Agents: Histamine Dihydrochloride

Australian Dream

Arthritis Relief Cream:
Histamine Dihydrochloride,
0.025%

Arthritis Back Cream:
Histamine Dihydrochloride,
0.05%

Apply up to 4 times daily



PainWeek <https://www.australiandream.com/>

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Group D Agents: Capsaicin 0.025-0.25%

MOA: Feeling of warmth via TRPV1 receptor; induces release of substance P (burning sensation), which is depleted after repeated use (at least 2 weeks)

ZOSTRIX

Cream: Capsaicin 0.033%
HP Cream: 0.1%
Foot Cream (marketed for diabetic foot pain): Capsaicin 0.1%
*For optimum relief, apply 3 to 4 times daily
Best results typically occur after 2 to 4 weeks of continuous use

PainWeek <https://www.zostrix.com/>

CAPZASIN

HP: "high potency" Cream: Capsaicin 0.1%
No-mess: 0.15%
Gel: Capsaicin 0.025%, Menthol 10%
*repeat if necessary, but no more than 3-4 times daily"

PainWeek <https://www.chattlam.com/>

PAIN BLOC

Roll-On: Capsaicin 0.25%
Repeat application, as needed, q12 to 24 hours, (max 2x/day)
*May take several days to reach full effect."

PainWeek <https://www.painbloc24.com/>

Salonpas

Gel Patch: Capsicum extract 0.025%, Menthol 1.25%
Use up to 4 times/day (remove after 8 hours)
Patch: Capsicum extract 0.025%
(1 patch up to 4 times/d; max use: 8h)

PainWeek <https://us.bonabest.com/>

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Efficacy Outcome	No. studies (No. of participants)	Proportion of patients with 50% pain relief		NNT
Topical Capsaicin 0.025-0.075%				
Neuropathic pain (0.075%)	4 (313)	57% (53%-75%) at 4 weeks	42% (31%-55%) at 4 weeks	6.4
Musculoskeletal pain (0.025%)	3 (368)	38% (34%-42%) at 4 weeks	25% (17%-37%) at 4 weeks	8.1
Safety Outcome				
Topical Capsaicin 0.075% [Cochrane Review]				
Local skin reaction (over 6-8 weeks of therapy)	6	63% (31% - 93%)	24% (9%-40%)	2.5
Topical Capsaicin 0.025%				
Local adverse effect at 4 weeks	3	49%	10%	2.6

OARS1 2019 guidelines: recommend against capsaicin for osteoarthritis
ACR 2019 guidelines: conditionally recommend capsaicin for knee osteoarthritis

PainWeek <https://www.painweek.com/> <https://doi.org/10.1002/14651858.CD007603>

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Topical Lidocaine 0.5-4%


 <p>Cream or Roll-On: Lidocaine 4%, Menthol 1% Apply q6-8 hours (max 3 applications/day)</p> <p>Patch: Lidocaine 4%, Menthol 1% 1 patch per 24 hours</p> <p>http://www.icyhot.com/</p>	 <p>Gel-Patch: Lidocaine 4% Apply up to 4 times/day (max wear time of 8 hours)</p> <p>Roll-on or Cream: Lidocaine 4%, Benzyl Alcohol 10% Apply up to 4 times/day</p> <p>http://www.kissmybutt.com/</p>	 <p>Cream and Foot Pain Crème (marketed for diabetics): Lidocaine 4% Apply q6-8 hours (max 3 applications/day)</p> <p>Patch (Regular & XL): Lidocaine 4% 1 patch up to 12 hours</p> <p>http://www.icyhot.com/</p>	 <p>Cream: Lidocaine 4% and Emu Oil[®] Apply q6-8 hours (max 3 applications/day)</p> <p>[®]fat from flightless bird (increases drug absorption)</p> <p>http://www.blue-emu.com/</p>
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PAINweek

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Lidocaine OTC Patches


- Double blind placebo controlled study of 87 patients with back pain or arthritis
 - OTC 3.6% lidocaine and 1.25% menthol patch *noninferior* to prescription 5% lidocaine patch
 - Menthol may increase permeability and increase efficient delivery of lidocaine



PAINweek Pain Manag. 2017;7(6):489-498


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Herbal Products for Osteoarthritis



Arnica gel applied twice daily for 3 weeks was found to decrease pain, stiffness, and restriction-of-function compared with baseline in patients with arthritis
Adv. Ther. 2002;19:209-18

Found to be as effective as ibuprofen 5% gel for hand osteoarthritis
Rheumatol Int 2007;27:585-591



Turmeric extract po 500 mg 3-4 times/day x4-6 weeks comparable to ibuprofen 400 mg po 2-3 times/day for reducing knee pain in osteoarthritis
J Altern Complement Med 2009;15:891-7.

PAINweek Topical herbal therapies for treating osteoarthritis. Cochrane Database of Systematic Reviews 2014, Issue 5. Art. No.: CD010538. Oral herbal therapies for treating osteoarthritis. Cochrane Database of Systematic Reviews 2014, Issue 5. Art. No.: CD002047.

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Conclusion

- Reconcile OTC products with patients and frequently
 - Self-care → clinician-assisted self care
- Educate patients on the risks of OTC polypharmacy and on reading labels
- Avoid the brand extension trap (discuss products in terms of active ingredient instead of brand name)
- For acute pain, oral formulation matters (faster = greater pain relief)
- For GI protection, oral formulation may be less important (drug, dose, duration, and risk factors more important)
- Topical diclofenac is now available OTC and recommended by guidelines for OA
- OTC topical counterirritant products may be tried as adjuvant agents, although studies are lacking and often inconsistent
- OTC lidocaine patches may be a cheaper alternative to Rx lidocaine patches



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**Navigating the OTC Analgesic Aisle:
What a Pain in the Aspirin!**

Laura Meyer-Junco, PharmD, BCPS, CPE
University of Illinois Chicago (UIC) College of Pharmacy—Rockford

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