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Key Inforbits

- What are NSAIDs
- Common NSAIDs
- NSAID Benefits
- NSAID Risks
- NSAID Mechanisms
- NSAID Uses



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What's New in the World of NSAIDs?

But first, what are NSAIDs?

NSAIDs (Non-Steroidal anti-inflammatory drugs) are a class of drugs that reduce inflammation, reduce fever, and can prevent blood coagulation, without a corticosteroid as an ingredient. There are two classes of NSAIDs: Cyclo-Oxygenase (COX) 1 inhibitors and COX-2 inhibitors; the class of the NSAID will determine the effects and benefits of the drug. Cyclo-Oxygenase is produced in the arachidonic acid metabolic pathway; as injury occurs, arachidonic acid is released and inflammatory mediators, including COX-1 and 2, are formed. By inhibiting COX-1 or 2, a cascade is prevented that causes the development of prostanooids which lead to the production of prostacyclin, prostaglandin, and thromboxane.

COX-1 inhibitors have the most cardiovascular effect, but in turn also cause the most gastrointestinal issues due to their antiplatelet effects. Selective COX-1 inhibitors, such as low dose aspirin, are used as primary and secondary prevention for cardiovascular disease due to COX-1 being directly related to platelet formation and aggregation.

COX-2 inhibitors' effects are seen more on inflammation. The COX-2 isoform is found predominantly in inflammatory cells; therefore, selective COX-2 inhibition has the most effect on inflammation and regulation of inflammatory cells.

The majority of NSAIDs fall within both of these categories. Most NSAIDs are not selective for COX 1 or 2; rather, they are non-selective COX 1 and 2 but exert variable effect on one or the other pathway.¹⁻⁵

Table 1: Brief Overview of the Mechanism of Action⁶

Irreversible Non-Selective COX Inhibitors:	Inhibits cyclooxygenase-1 and 2 enzymes irreversibly. It does this by acetylation that causes a decrease in the formation of prostaglandin precursors. Additionally, irreversible inhibition of thromboxane A2 occurs due to acetylation of platelet COX. This causes inhibition of platelet aggregation and lasts for 7 to 10 days after drug discontinuation.
Non-Selective & Semi-Selective COX Inhibitors:	Reversibly binds to COX 1 & 2 enzymes. It causes decreased formation of prostaglandin precursors. Mechanisms behind antipyretic, analgesic and anti-inflammatory are not well understood. Proposed MOA of the anti-inflammatory effects include obstructed chemotaxis, lymphocyte altered activity, stalled neutrophil aggregation and-or activation, and decreased proinflammatory cytokines.
Selective COX Inhibitors:	Decreases activity of COX-2 by inhibition which decreases formation of prostaglandin precursors. Does not inhibit COX-1 at therapeutic concentrations.
Acetaminophen:	The MOA is not fully understood. It is believed the analgesic effects are due to activation of the descending serotonergic inhibitory pathways in the CNS. And the antipyretic effects are due to hindered activity of the heat-regulating portion of the hypothalamus.

COX 1&2 = cyclooxygenase 1 & 2; MOA = mechanism of action; CNS = central nervous system

Table 2: Commonly Used NSAIDs^{6,7}

Drug (Selected Brand Names)	Usual analgesic dose (oral)	Maximum dose per day (mg)	Important Pearls:
Irreversible Non-selective COX Inhibitors:			
Aspirin (Bayer, Ecotrin, St. Joseph's)	325 to 650 mg every 4 to 6 hours	4000 mg	<ul style="list-style-type: none"> • Available OTC and Rx • Dosage forms: tablet (enteric coated and chewable) and suppository • Used in low dose (81 mg) for primary and secondary prevention of cardiovascular disease; avoid concomitant use with other NSAIDs • Avoid in children and teenagers to prevent Reye's syndrome who are being treated for a viral illness or infection

Choline magnesium trisalicylate (Trilisate)	750 mg every 8 to 12 hours	3000 mg	<ul style="list-style-type: none"> • Available Rx • Dosage forms: liquid and tablet • Less frequently associated with GI bleeding than other non-selectives • Slow onset of action
Salsalate (Disalcid)	750 to 1000 mg every 8 to 12 hours	3000 mg	<ul style="list-style-type: none"> • Available Rx • Dosage forms: tablet • Less frequently associated with GI bleeding than other non-selectives • Slow onset of action • 500 mg is comparable to 650 mg of acetaminophen or aspirin
Non-selective COX Inhibitors:			
Diflunisal (Dolobid)	500 mg every 8 to 12 hours	1500 mg	<ul style="list-style-type: none"> • Available Rx • Dosage forms: tablet • Less frequently associated with GI bleeding than nonselective • Slow onset of action
Flurbiprofen (Ansaid)	50 to 100 mg every 6 to 12 hours	300 mg	<ul style="list-style-type: none"> • Available Rx • Dosage forms: tablet and solution (ophthalmic)
Ibuprofen (Advil, Motrin)	400 to 800 mg every 4 to 6 hours	3200 mg acute, 2400 mg chronic	<ul style="list-style-type: none"> • Available OTC and Rx • Dosage forms: tablet (chewable), solution (IV), suspension, cream, and capsule • 200 to 400 mg is comparable to 650 mg of acetaminophen or aspirin • Short duration of action • Useful alternative to naproxen in patients without cardiovascular risks • Lowest risk of hepatotoxicity
Ketoprofen (Orudis)	50 mg every 6 hours OR 75 mg every 8 hours	300 mg	<ul style="list-style-type: none"> • Available: Rx • Dosage forms: capsule (extended release) and cream • 25 mg is comparable to 400 mg of ibuprofen • Short duration of action
Naproxen (Aleve)	250 to 500 mg every 12 hours (naproxen base) 275 to 550 mg every 12 hours (naproxen sodium)	1250 mg acute, 1000 mg chronic (naproxen base) 1375 mg acute, 1100 mg chronic (naproxen sodium)	<ul style="list-style-type: none"> • Available OTC and Rx • Dosage forms: tablet (extended and delayed release), capsule, cream, and suspension • Good choice for acute or chronic pain and inflammation • High doses may have less cardiovascular toxicity than other NSAIDs • Rheumatologic disorders may use up to a maximum of 1500 mg

			<p>(naproxen base) OR 1650 mg (naproxen sodium)</p> <ul style="list-style-type: none"> • Naproxen sodium has more rapid onset of action and absorption compared to naproxen base
Oxaprozin (Daypro)	1200 mg once daily	26 mg/kg up to 1800 mg (whichever is lower)	<ul style="list-style-type: none"> • Available Rx • Dosage forms: tablet • Long duration of action; dosed once daily
Semi-Selective COX Inhibitors:			
Diclofenac sodium/potassium (Cambia, Zipsor, Zorvolex, Voltaren)	50 mg every 8 hours	150 mg For rheumatoid arthritis: 200 mg	<ul style="list-style-type: none"> • Available OTC and Rx • Dosage forms: patch, solution (ophthalmic and IV), gel (oral), capsule, packet, cream, and tablet (delayed release and extended release) • Gel is available OTC • Used for musculoskeletal pain and osteoarthritis of superficial joints • Interacts with strong CYP2C9 inhibitors and inducers
Etodolac (Lodine)	IR: 200 to 400 mg every 6 to 8 hours ER: 400 to 1000 mg once daily	IR: 1000 mg ER: 1200 mg	<ul style="list-style-type: none"> • Available Rx • Dosage forms: capsule and tablet (extended release) • 200 mg is comparable to 400 mg of ibuprofen • Relatively COX-2 selective at lower doses (600 to 800 mg)
Indomethacin (Indocin, Tivorbex)	IR: 25 to 50 mg every 8 to 12 hours CR: 75 mg once or twice daily	150 mg	<ul style="list-style-type: none"> • Available Rx • Dosage forms: capsule (extended release), solution (IV), suppository, and suspension • Useful for acute gout attacks and specific types of headaches • More frequently associated with central nervous system side effects (e.g. headaches) • Potent inhibitory effects on renal prostaglandin synthesis • Carefully monitor to reduce renal and cardiovascular toxicities
Ketorolac (Toradol)	≥50 kg AND <65 years of age: 20 mg once, followed by 10 mg every 4 to 6 hours <50 kg OR ≥65 years of age: 10 mg every 4 to 6 hours	40 mg	<ul style="list-style-type: none"> • Available Rx • Dosage forms: solution (nasal, IV, IM) and tablet • Used for acute pain • Maximum duration is 5 days • Use only as continuation of IV or IM therapy • Avoid in elderly patients (Beers Criteria)

Meclofenamate (Meclomen)	50 mg every 4 to 6 hours	400 mg	<ul style="list-style-type: none"> • Available Rx • Dosage forms: capsule • Alternative for acute or chronic pain, inflammation, and dysmenorrhea • Higher incidences of GI disturbances (diarrhea, nausea, etc.)
Mefenamic acid (Ponstel)	250 mg every 4 to 6 hours	1000 mg	<ul style="list-style-type: none"> • Available Rx • Dosage forms: capsule • Alternative for acute pain and dysmenorrhea • Not preferred for anti-inflammatory effects • Do NOT exceed 7 days for acute pain or 3 days for dysmenorrhea
Meloxicam (Mobic, Anjeso, Qmiiz ODT, Vivlodex)	7.5 to 15 mg once daily (tablet or ODT) 5 to 10 mg once daily (capsule)	15 mg (tablet or ODT) 10 mg (capsule)	<ul style="list-style-type: none"> • Available Rx • Dosage forms: capsule, tablet (orally disintegrating), suspension, and solution (IV) • Slow onset, long duration of action (not preferred for acute pain) • Relatively COX-2 selective at lower doses (7.5 mg) • Capsules are approved for osteoarthritis
Nabumetone (Relafen)	500 to 750 mg every 8 to 12 hours OR 1000 to 1500 mg once daily	2000 mg	<ul style="list-style-type: none"> • Available Rx • Dosage forms: tablet • Slow onset, moderate duration of action • Relatively COX-2 selective at lower doses (≤ 1000 mg)
Piroxicam (Feldene)	10 to 20 mg once daily	20 mg	<ul style="list-style-type: none"> • Available Rx • Dosage forms: capsule • Long duration of action (good for chronic pain and inflammation) • High doses (≥ 20 mg) increase risk of serious GI complications • Gastroprotection is suggested • Prescribing should be limited to specialists with experience in treatment of chronic pain and inflammation
Sulindac (Clinoril, Sulin)	150 to 200 mg every 12 hours	400 mg	<ul style="list-style-type: none"> • Available Rx • Dosage forms: tablet • Higher incidences of hepatic inflammation • Prescribing should be limited to specialists with experience in treatment of chronic pain and inflammation
Tolmetin (Tolectin)	400 to 600 mg every 8 hours	1800 mg	<ul style="list-style-type: none"> • Available Rx • Dosage forms: tablet and capsule

Selective COX-2 Inhibitors:			
Celecoxib (Celebrex)	200 mg once daily OR 100 mg every 12 hours	400 mg	<ul style="list-style-type: none"> • Available Rx • Dosage forms: capsule • Lowest GI toxicity risk • No effect on platelet function→aspirin required for cardio-protection if indicated
NSAID Alternative:			
Acetaminophen (Tylenol, Mapap, Midol, Pharbetol, Acephen, Cetafen)	325 to 650 mg every 4 to 6 hours OR 1000 mg every 6 hours up to three times per day	4000 mg	<ul style="list-style-type: none"> • Available OTC and Rx • Dosage forms: capsule, elixir, gel, solution (oral and IV), suppository, suspension, and tablet (chewable, extended release, and orally disintegrating) • Limited anti-inflammatory effects • <2000 mg doses do not increase GI complications • Can cause hepatotoxicity in acute and chronic overdose • Avoid or use lower doses (2000 mg/day) for older adults, patients with high risk of hepatotoxicity (i.e., regular alcohol use or malnourished), or organ dysfunction • Interacts with warfarin, isoniazid, and CYP450 inducing drugs • Also known as Paracetamol in most of the world outside the United States.

OTC=over the counter; Rx=requires prescription; GI=gastrointestinal; IV=intravenous; IM=intramuscular

Table 3: Considerations in Special Populations ^{5,6}

Special Populations:	NSAIDs	Acetaminophen
Pregnancy	<ul style="list-style-type: none"> • AVOID, especially in 1st and 3rd trimesters 	<ul style="list-style-type: none"> • Safe for all stages of pregnancy
Lactation	<ul style="list-style-type: none"> • Very low or nonexistent embryo-fetal risk 	<ul style="list-style-type: none"> • Very low or nonexistent embryo-fetal risk
Pediatrics	<ul style="list-style-type: none"> • Ibuprofen: 4 to 10 mg/kg/dose every 6 to 8 hours • Maximum 40 mg/kg/day →maximum 400 mg/dose 	<ul style="list-style-type: none"> • 12 years and younger: <ul style="list-style-type: none"> ○ 10 to 15 mg/kg/dose every 4 to 6 hours ○ Maximum: 75 mg/kg (not to exceed 4000 mg/day or 5 doses in 24 hours)

		<ul style="list-style-type: none"> ● 12 years and older: <ul style="list-style-type: none"> ○ Regular strength: 650 mg every 4 to 6 hours ○ Extra strength: 1000 mg every 6 hours ○ Extended release: 1300 mg every 8 hours ○ Maximum: 4000 mg/day (under health care provider supervision)
Geriatrics	<ul style="list-style-type: none"> ● Use with caution 	<ul style="list-style-type: none"> ● Avoid or use lower doses (2000 mg/day maximum)

Notable NSAID Benefits:

- Pain reduction without the need for opioids and without the risk of dependence.
- Reduction of inflammation without the use of a corticosteroid.
- Flexible dosing.
- Ability to use in children and adolescents without the added risks or unwanted side effects of corticosteroids.
- Cardiac benefits with COX-1 selective drugs; i.e., low dose aspirin.
- OTC availability.

Notable NSAID Risks:

- Class associated risk of gastrointestinal (GI) issues such as peptic ulcer disease and GI bleeding.
- Irreversible non-selective COX inhibitors (aspirin) have the potential to cause cardiac arrhythmias, hypotension, and tachycardia.
- COX-2 selective agents (celecoxib) have the potential to lead to severe cardiac issues such as acute myocardial infarction, angina, coronary artery disease, edema, exacerbated blood pressure, and tachycardia.
- Overall potential bleeding risk increased.
- Overall potential increased risk of renal damage in some patients.

NSAID Uses:

NSAIDs vs. Opioids

With the opioid crisis at a high, there has been increased pressure to find an alternative to prescribing opioid pain relievers in most patients. One of the alternatives are NSAIDs. There is evidence to suggest that the use of NSAIDs in many situations is as good as the use of opioids without the long-term negative issues that the use of opioids brings. In one meta-analysis, it was shown that for knee osteoarthritis, the use of NSAIDs had very similar overall pain reduction compared to opioid pain relievers. The use of opioids comes with the risk of dependence and negative outcomes due to the dependence. Using NSAIDs gives pain and inflammation control, without a risk of becoming dependent or overdosing on the drug.⁸⁻¹⁰

For patients experiencing chronic noncancer pain, treatment with opioids is considered a last line option. Both NSAIDs and acetaminophen are preferred for treatment of a variety of mild-moderate chronic pain-inducing conditions such as osteoarthritis. For some patients NSAIDs show benefits for managing cancer-related bone pain and chronic low back pain.^{13,14}

NSAIDs remain highly recommended and are often considered a first line agent in those afflicted with osteoarthritis. They are highly effective at managing joint pain associated with inflammation. Since arthritis is defined as the inflammation of a joint, the use of an anti-inflammatory agent that is also a pain reliever, such as an NSAID, is a great choice. NSAIDs have been shown to be as efficacious as opioid analgesics in relieving pain associated with arthritis and osteoarthritis.^{8,11}

Opioids are often prescribed by dentists and oral surgeons for short term use after dental procedures for pain management. Studies comparing NSAIDs and opioids prescribed to patients undergoing dental procedures showed that NSAIDs were just as effective as opioids, if not more so, with minimal side effects and reduced risks of dependency. Opioids prescribed by dentists and oral surgeons are sometimes the first exposure patients have to opioids. By implementing programs aimed to decrease opioid use post-surgery, such as educating patients on appropriate opioid use and proper disposal and providing non-opioids, such as NSAIDs and acetaminophen, for step down therapy, the number of self-administered opioids are reduced, patients are more aware of the use of NSAIDs in pain management, and intentional disposal of opioids are increased.¹⁵⁻¹⁷

Cardiology

For years, low dose aspirin has been used for primary and secondary prevention of strokes. Its use stems from its COX-1 selectivity which causes an anti-platelet effect that prevents blood clot formation. Aspirin is also used in patients that are not a candidate for clot buster therapy such as tPA (tissue-plasminogen activator) medications. However, recent studies discussing and comparing ticagrelor, clopidogrel, and aspirin have suggested that aspirin may not be the best candidate for primary prevention of stroke. Aspirin still has its place in cardiovascular health, but it is not the cornerstone of therapy as it once was. Some studies have now shown that in healthy individuals, the use of aspirin may actually increase the risk of bleeds and all-cause mortality.^{14,18-21}

In short, NSAIDs remain a staple drug in the world of pain management. The way they behave mechanistically can have drastic or subtle differences depending on their sub-class. This can also allow their adverse effects to be more easily monitored and predicted. While some controversy exists on their use in general, because of fears of overprescribing, it cannot be denied they remain a reliable medication for osteoarthritis and a potential class to decrease the abuse of opioid medications.



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The last “dose” ...

“Pain is inevitable. Suffering is optional.”
-Haruki Murakami [Japanese author, 1949 -]

“There is a thin line that separates laughter and pain, comedy and tragedy, humor and hurt.”
-Erma Bombeck [American humorist, 1927 – 1996]

“The rewards for those who persevere far exceed the pain that must precede the victory.”
-Ted Engstrom [American evangelical leader and author, 1916 – 2006]

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