PHARMACOLOGY

Not all nonsteroidal anti-inflammatory drugs are created equally

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Anti-inflammatory drugs have their origins in pharmacognosy and the serendipitous discovery that certain plants and their extracts have utility in the relief of pain, inflammation, and fever. Historically, investigation into the active components found in the bark of the willow tree led to the discovery of salicylates and, ultimately, synthesis of the first nonsteroidal anti-inflammatory drug (NSAID), known as *acetylsalicylic acid* (ASA).[1] Although ASA was first developed in 1853 by the French chemist Charles Gerhardt, it was not until almost 50 years later, in 1897, that Felix Hoffmann, a chemist at the German life science firm Bayer, synthesized the more familiar, pure, and stable form, which was marketed in 1899 with the tradename Aspirin.

While ASA is the progenitor of the NSAID drug class, the term *NSAID* was not coined until many years after its development, and many textbooks still mistakenly refer to phenylbutazone as the first nonsteroidal anti-inflammatory medication, despite its much later development by J.R. Geigy in Basel, Switzerland, in 1946. The research that ultimately led to the discovery of ibuprofen was driven, in part, by the need to find a safer form of aspirin, avoid the serious adverse effects of phenylbutazone (bone marrow depression, including agranulocytosis and aplastic anemia), and avoid corticosteroids in the treatment of inflammation.[2]

Dr Stewart Adams and his team at the Boots Company in Nottingham, England, discovered ibuprofen in the 1960s, but it was not marketed until 1969. In the United States, the Upjohn Company launched ibuprofen as Motrin in 1974. The US Food and Drug Administration (FDA) approved the drug for over-the-counter use in 1984, and it was marketed as Advil (Pfizer).[3] To date, more than 20 NSAIDs are on the market, available in many more formulations, and they continue to be some of the most commonly prescribed medications worldwide for managing pain, inflammation, and fever. Ibuprofen is on the World Health Organization's *Model List of Essential Medicines* and is 1 of the world's best-selling medications.[4] Dr Adams died in January 2019 at age 95 years.[5]

One mechanism of action, many different effects

All NSAIDs have the same mechanism of action, which explains both their therapeutic and adverse effects. They all competitively inhibit both cyclooxygenase (COX) isoenzymes, COX-1 and COX-2, by blocking arachidonic acid binding, resulting in analgesic, antipyretic, and anti-inflammatory pharmacologic effects.[6]

The enzymes COX-1 and COX-2 catalyze the conversion of arachidonic acid to prostaglandin G_2, the first step in the synthesis of prostaglandins, and thromboxanes, which are involved in rapid physiologic responses. COX-1 is constitutively expressed in almost all tissues, while COX-2 appears to be constitutively expressed only in the brain, bones, kidney, reproductive organs, and some neoplasms (eg, colon and prostate cancers). COX-1 is responsible for prostaglandin synthesis in response to stimulation by circulating hormones as well as maintenance of normal renal function, hemostasis, and gastric mucosal integrity. COX-2 is inducible in many cells in response to certain mediators of inflammation (eg, interleukin 1, tumor necrosis factor, lipopolysaccharide, mitogens, and reactive oxygen intermediates).

The anti-inflammatory mechanism of NSAIDs is due to decreased prostaglandin synthesis via inhibition of COX-1 and COX-2, although it is the inhibition of the COX-2 isoenzyme that is primarily responsible for the anti-inflammatory effects. COX-1 is expressed at some sites of inflammation, such as the joints (especially the synovial lining) of patients with rheumatoid arthritis and osteoarthritis, and it is the primary enzyme of prostaglandin synthesis in human bursitis. However, it is the inhibition of COX-2 that primarily mediates the anti-inflammatory effect of NSAIDs.

The antipyretic activity of NSAIDs promotes a return to a normal body temperature set point in the hypothalamus by suppressing the synthesis of prostaglandins, specifically prostaglandin E_2, in circumventricular organs in and near the hypothalamus.

The gastrointestinal (GI) adverse effects of NSAIDs are primarily related to COX-1 inhibition; a potential role of COX-2 inhibition in the GI tract has not been fully elucidated.

The inhibition of platelet aggregation seen with NSAIDs is due to

dose-dependent inhibition of COX-1 in platelets, leading to decreased levels of platelet thromboxane A_2 and an increase in bleeding time. The inhibition of platelet aggregation is reversible on drug discontinuation except in the case of ASA, which irreversibly binds to COX-1 in platelets, thus inhibiting this enzyme for the life of the platelet. Consequently, it is important for patients to take their daily cardioprotective dose of ASA before any additional NSAID. If an NSAID is taken prior to the ASA, the ASA will have limited binding capacity and be eliminated from the body without being completely effective when the reversible binding of the first NSAID wears off.[7]

In the kidneys, prostaglandins are produced by both COX-1 and COX-2 and are important regulators of sodium and water reabsorption through prostaglandin E_2. Prostaglandins are also important regulators of renal function and hemodynamics via prostaglandin I_2 in response to vasoconstrictive factors (eg, endothelin 1, a factor that increases peripheral vascular resistance) and through effects on the renin-angiotensin system. In conditions in which renal blood flow depends on prostaglandin synthesis, administration of NSAIDs can result in significant decreases in renal blood flow, leading to acute renal failure.

Five NSAID pearls

Although all NSAIDs have the same mechanism of action, they are not created equally. There are specific differences based on the drug's chemical structure or varying affinities for the different cyclooxygenase isoforms, which give some of these molecules distinct advantages in particular clinical situations.

Patient is allergic/ pseudoallergic

Allergenicity is among the most common concerns of oral healthcare professionals, especially because NSAIDs are the preferred medications for managing orofacial pain.[8,9] While NSAIDs are a class of drugs with a shared mechanism of action, this class of drugs is actually composed of 7 specific subclasses based on the drug's chemical structure: acetic acids, propionic acids, COX-2 inhibitors, nonacidic agents, salicylic acid derivatives, oxicams, and fenamates (Table 1). For patients who report a history of allergy to NSAIDs, the prudent practitioner should determine the type of reaction and the specific causative agent (Table 2).[10]

Reactions to NSAIDs can be categorized as pseudoallergic (types I-IV) or allergic (types V and VI).[11] In an individual patient, pseudoallergic reactions are induced by multiple different NSAIDs, while allergic reactions are usually induced by a single NSAID or a small number of structurally similar agents. Pseudoallergic reactions are nonimmunologic reactions that are related to the COX-1–inhibiting properties of the drug. In susceptible individuals, these reactions may be elicited by any NSAID that primarily inhibits COX-1, including ASA. Affected patients are believed to have acquired alterations in the biochemical pathways affected by COX-1 inhibitors, although the precise mechanism underlying pseudoallergic reactions has not been established.

Allergic NSAID reactions are presumed to be immunoglobulin E–mediated immunologic reactions based on their clinical characteristics. These reactions are elicited by a single NSAID in a susceptible individual. NSAIDs that similarly inhibit COX-1 over COX-2 are said to be cross-reactive (Box).[12] In many cases, patients who report a pseudoallergic history to a specific NSAID may respond appropriately to another NSAID from a different chemical subclass. A pseudoallergic reaction to 3 or more of the chemical subclasses of NSAIDs often is required before a patient can be described as being allergic to NSAIDs. These types of medication challenges are best managed by an allergist, unless the dentist believes the patient's allergic history does not describe a life-threatening reaction or airway compromise (type V or VI allergic reaction).

In instances of suspected type I-IV pseudoallergic reactions, treatment options include the following: acetaminophen only; a weak COX-1 inhibitor (salsalate, up to 2000 mg daily, divided into 2 or 3 doses; choline magnesium trisalicylate, up to 2000 mg daily, divided into 2 or 3 doses; or diflunisal, up to 1000 mg daily, divided into 2 or 3 doses); highly selective COX-2 inhibitors (celecoxib, up to 400 mg daily, divided into 2 doses); or desensitization in cooperation with medical colleagues. Patients who are found to be truly allergic to NSAIDs may have to rely on acetaminophen, glucocorticoids, or opioids to meet their analgesic needs.

Patient has renal issues

In patients with a history of renal disease, as well as those undergoing dialysis or who have received a kidney transplant, renal blood flow may depend primarily on prostaglandin synthesis. Administration of NSAIDs can result in significant decreases in renal blood flow, leading to acute renal failure. As a result, healthcare professionals historically have avoided prescribing NSAIDs to such patients.[13]

Certain NSAIDs, however, are said to be renal-sparing, and may be an appropriate choice for patients with renal insufficiency. Sulindac (200 mg twice a day) is a prodrug that is converted to an active sulfide metabolite, which is responsible for most of the pharmacologic activity. The active metabolite of sulindac competitively inhibits both COX-1 and COX-2 by blocking arachidonic acid binding, resulting in analgesic, antipyretic, and anti-inflammatory effects. The parent drug has a minimal inhibitory effect on COX, whereas the sulfide metabolite is 500 times more potent.

Early studies demonstrated that in the kidney, the active sulfide metabolite is converted back to sulindac, thereby protecting the kidney from prostaglandin inhibition.[14] Some other clinical studies have yielded conflicting results regarding the effect of sulindac on renal function, but it is still considered to be the most renal-sparing of all available NSAIDs.[13,14] According to a recent review article on pain management in patients with chronic kidney disease, sulindac is indicated for relief of mild pain.[15] Alternatively, these patients can be treated with acetaminophen, tramadol, or perhaps opioids.

Patient has GI issues

There are differences in the extent to which a particular NSAID inhibits each isoform of COX, which may affect the drug's activity and toxicity. Specific to their ulcerogenic profile, NSAIDs that favor COX-1 inhibition over COX-2 inhibition—ketorolac, ketoprofen, indomethacin, and ASA—may be more prone to causing gastroduodenopathies.[16-18]

Table 1. Nonsteroidal anti-inflammatory drugs for mild to moderate nociceptive pain.[a]

Chemical class	**Acetic acid**					
Generic name	Diclofenac immediate release	Diclofenac delayed release	Etodolac	Indomethacin immediate release		Indomethacin sustained release
Usual adult dosage	Oral: 50 mg every 8-12 h	Oral: 50 mg every 12 h	Oral: 200-400 mg every 6-8 h	Oral: 25-50 mg every 6-8 h		Oral: 75 mg every 12-24 h
MRDD (mg)	225	200	1000	200		150
Notes	Zipsor 25-mg capsules administered every 6 h	Do not crush or chew	200 mg comparable to ibuprofen 400 mg	Liquid: 5 mg/mL		Do not crush or chew
Chemical class	**Propionic acid**					
Generic name	Fenoprofen	Flurbiprofen	Ibuprofen	Ibuprofen		Ketoprofen
Usual adult dosage	Oral: 50–100 mg every 8-12 h	Oral: 100 mg every 12 h	Oral: 200-400 mg every 4-6 h	IV: 400-800 mg every 6 h		Oral: 50 mg every 6 h or 75 mg every 8 h
MRDD (mg)	3200	300	3200	1200		300
Notes			Liquid: 20-40 mg/mL Rx and OTC	IV solution: 100 mg/mL		25 mg comparable to ibuprofen 400 mg
Chemical class	**Nonacidic agent**	**Salicylic acid derivative**		**Oxicam**		**Fenamate**
Generic name	Nabumetone	Diflunisal	Salsalate	Meloxicam	Piroxicam	Meclofenamate
Usual adult dosage	Oral: 500-750 mg every 8-12 h	Oral: 500 mg every 12 h	Oral: 1000 mg every 8 h	Oral: 7.5-15 mg every d	Oral: 10-20 mg every 12-24 h	Oral: 50-100 mg every 4-6 h
MRDD (mg)	2000	1500	3000	15	20	400
Notes	FDA-approved only for osteoarthritis and rheumatoid arthritis			FDA-approved only for osteoarthritis and rheumatoid arthritis		

Abbreviations: FDA, US Food and Drug Administration; IM, intramuscular; IN, intranasal; IV, intravenous; MRDD, maximum recommended daily dose; OTC, available over the counter; Rx, prescription required.

[a]All listed drugs require a prescription in the United States unless otherwise noted. Dosage is based on 70-kg adult with normal hepatic and renal function.

[b]Ketorolac is approved for moderate to severe pain.

[c]Acetaminophen is included in multiple prescription and over-the-counter products for treatment of pain, cough, cold, flu, migraine, insomnia, and so forth, increasing the risk of accidental overdose. The Food and Drug Administration is asking drug manufacturers to limit the amount of acetaminophen in prescription products to 325 mg and to perhaps reduce the maximum recommended daily dose to < 3250 mg.

Acetic acid			
Ketorolac[b]	Ketorolac[b]	Sulindac	Tolmetin
Oral: 10 mg every 4-6 h IM: 30 mg every 6 h	IN: 1 spray in each nostril every 6-8 h	Oral: 200 mg every 12 h	Oral: 400-600 mg every 8 h
Oral: 40 IM: 120	126	400	2000
IM: 5-d maximum	15.75 mg per spray	Should be taken with food	
Propionic acid			**COX-2 inhibitor**
Naproxen	Naproxen sodium	Oxaprozin	Celecoxib
Oral: 250 mg every 6-8 h or 500 mg every 12 h	Oral: 275 mg every 6-8 h or 550 mg every 12 h	Oral: 1200 mg every d	Oral: 200 mg every 12 h
1250 mg first day, then 1000 mg	1375 mg first day, then 1100 mg	1800	600 mg first day then 400 mg
Liquid: 25 mg/5 mL	Rx and OTC; Aleve 220-mg capsules are OTC	Patients < 50 kg should receive 600 mg/d	Less effective than full doses of naproxen or ibuprofen

Fenamate	Aminophenol
Mefenamic acid	Acetaminophen[c]
Oral: 250 mg every 6 h	Oral: 650 mg every 6 h or 1000 mg every 8 h
1250 mg first day, then 1000 mg	4000 mg
Maximum therapy of 1 wk	OTC

Ketorolac (10 mg 4 times a day) greatly favors COX-1 inhibition over COX-2 inhibition more so than any other NSAID; therefore, it is considered the most ulcerogenic of all the NSAIDs. Because of this, ketorolac has an FDA black box warning limiting its use to the short-term management (up to 5 days in adults) of moderately severe acute pain to avoid this adverse effect.[19] Moving down the continuum from ketorolac to other NSAIDs that favor COX-2 inhibition over COX-1 inhibition, these agents (eg, etodolac, celecoxib, and meloxicam) are considered to be much safer in patients with a history of gastroduodenopathies, such as peptic ulcerations and bleeds. Alternatively, these patients can be treated with acetaminophen, tramadol, or perhaps opioids.

The discovery of the COX-2 isoform in the early 1990s led an effort to develop NSAIDs that preferentially inhibited COX-2, the isoform that is upregulated in inflammatory states and involved in the production of inflammatory mediators, while sparing COX-1, which is important for gastric cytoprotection. These newer drugs were termed *COX-2 selective NSAIDs* and were also referred to as *COX-2 inhibitors*, *selective COX-2 inhibitors*, and *coxibs*. The coxibs demonstrate at least a 200- to 300-fold selectivity for inhibition of COX-2 over COX-1 at their defined therapeutic doses. In the doses used clinically, they provide analgesia comparable to that offered by the nonselective NSAIDs and result in less gastroduodenal toxicity. In the United States, only 1 agent remains in this class of drugs: celecoxib (Celebrex, Pfizer; 200 mg orally twice a day).[20]

Patient takes an anticoagulant

As discussed earlier, NSAIDs inhibit platelet aggregation but this effect is reversible on drug discontinuation except in the case of ASA, which inhibits COX-1 for the life of the cell (approximately 8-9 days). The COX-2–selective NSAIDs such as celecoxib have little to no inhibitory effect on platelet function. Generation of prostaglandins by activated platelets plays an important role in platelet function and in promoting vasoconstriction. Production of thromboxane A_2 specifically depends on COX-1, and inhibition of COX-2 alone produces little

Table 2. Pseudoallergic (types I-IV)[a] and allergic (types V and VI)[b] reactions to nonsteroidal anti-inflammatory drugs (NSAIDs).

Type of reaction	Eliciting NSAID	Signs and symptoms	Onset	Patient comorbidities
Type I	Multiple (including aspirin)	Common: • Severe rhinitis, nasal obstruction • Bronchospasm • Conjunctival injection • Facial flushing Uncommon: • Throat tightness/laryngospasm • Nausea/vomiting • Diarrhea • Hypotension	Delayed: 30 min to 3 h after ingestion or administration	• Asthma (present in most but not all patients) • Chronic rhinosinusitis with nasal polyposis (patients usually have extensive sinusitis on CT and often report anosmia) • AERD
Type II	Multiple (including aspirin)	Urticaria and/or angioedema	30-90 min	Chronic urticaria (patients may report being able to tolerate NSAIDs when urticaria is in remission)
Type III	Multiple (including aspirin)	Urticaria and/or angioedema	30-90 min	None
Type IV	Multiple (including aspirin)	Symptoms affecting both the respiratory tract and skin, including patients with AERD who develop cutaneous symptoms in the context of respiratory reactions	Variable, depending on the type of reaction: 30-90 min	Some patients have AERD and experience systemic reactions with cutaneous symptoms, while other patients have no underlying conditions
Type V	A single NSAID (not aspirin)	Cutaneous: urticaria, pruritus, angioedema	Variable: minutes to a few hours after ingestion/ administration	None
Type VI	A single NSAID (not aspirin)	Anaphylaxis (probably a more severe form of type V)	Variable: minutes to a few hours after ingestion/ administration	None

Abbreviations: AERD, triad of asthma, chronic rhinosinusitis with nasal polyposis, and aspirin (or NSAID)-induced type I pseudoallergic reactions; CT, computed tomography; NSAID, nonsteroidal anti-inflammatory drug.

[a]Pseudoallergic NSAID reactions are elicited by multiple NSAIDs (including aspirin) in a susceptible patient. They are related to the pharmacologic ability of NSAIDs to inhibit the cyclooxygenase 1 enzyme.

[b]Allergic NSAID reactions are elicited by a single NSAID (or rarely by more than 1 agent with similar structure) in a susceptible patient. Allergic reactions are not reported with aspirin and are presumed to be immunoglobulin E mediated.

or no effect on platelet function, including platelet aggregation and adhesion.[21] As a result, anticoagulant-treated patients who are treated concurrently with a coxib are at less risk of bleeding than patients receiving a concurrent nonselective NSAID.[22] Etodolac, meloxicam, or any of the glucocorticoids are also beneficial alternatives.

Patient is pregnant or breastfeeding

Many analgesics are available over the counter. As a result, patients and prescribers alike often forget about the wide-ranging effects of analgesics and do not consider them in the context of being potentially dangerous during pregnancy or breastfeeding. In a review of human studies focusing on the ingestion of ibuprofen during pregnancy, Thorpe et al found a risk of embryonic implantation disturbances, inhibition of parturition, and contraction of the ductus arteriosus, leading to maternal pulmonary hypertension.[23]

Gastroschisis is a congenital and often ibuprofen-related malformation in which fetal organs develop outside the abdominal wall.[24] Other drug-related cases of gastroschisis have been linked to maternal use of other NSAIDs, including ASA and the decongestants pseudoephedrine and phenylpropanolamine.[24] For these reasons, the FDA historically listed NSAIDs as pregnancy risk factor category C or D.[25] Category C means one of two things: Either studies in animals have revealed adverse effects on the fetus (teratogenic, embryocidal, or other) and there are no controlled studies in women, or no controlled studies are available in women or

Box. NSAID cross-reactivity (strength of COX-1 and COX-2 inhibition).

NSAIDs that preferentially inhibit COX-1 and cross-react with aspirin

- Diclofenac
- Etodolac
- Fenoprofen
- Flurbiprofen
- Ibuprofen
- Indomethacin
- Ketoprofen
- Ketorolac
- Meclofenamate
- Mefenamic acid
- Naproxen
- Oxaprozin
- Piroxicam
- Sulindac
- Tolmetin

Nonopioid analgesics and nonacetylated salicylates that are poor inhibitors of COX-1 and only with higher concentrations of drug; cross-reactions with aspirin at higher doses

- Acetaminophen
- Choline magnesium trisalicylate
- Diflunisal
- Salsalate

NSAIDs that preferentially inhibit COX-2 but also inhibit COX-1 when higher doses administered; cross-reactions with aspirin at higher doses

- Meloxicam
- Nabumetone

Highly selective COX-2 inhibitor that does not inhibit COX-1; cross-reactions with aspirin are rare (may occur at the highest doses)

- Celecoxib

Abbreviations: COX, cyclooxygenase; NSAIDs, nonsteroidal anti-inflammatory drugs.

animals.[26] Drugs in this category should be administered only if the potential benefit justifies the potential risk to the fetus. Category D means that there is positive evidence of human fetal risk, but the benefits in pregnant women may outweigh the risk (for example, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).[26] The A, B, C, D, and X risk categories, which were introduced in 1979, have been replaced with narrative sections and subsections in each product monograph.[27]

The results of 3 large-scale epidemiologic studies indicate that acetaminophen is the safest analgesic for a pregnant patient.[28-30] The American Academy of Pediatrics (AAP) also considers acetaminophen to be compatible with breastfeeding.[31] Alternatively, if needed, these patients can be treated with oxycodone, which also is in FDA pregnancy risk category B (animal studies show no risks, but there are no controlled studies in pregnant women).[26]

The AAP, however, reported that use of NSAIDs is safe during breastfeeding; the only exception is aspirin, daily doses of which should not exceed 100 mg because of the associated risk of platelet dysfunction and Reye syndrome.[31] Alternatively, these patients can be treated with acetaminophen, codeine, or glucocorticoids.

Conclusion

While all NSAIDs have the same mechanism of action, they are not the same. Specific differences, based on either their chemical structure or varying affinities for the different cyclooxygenase isoforms, give some of these molecules distinct advantages in particular clinical situations. The prudent oral healthcare practitioner should be aware of these characteristics when prescribing NSAIDs to manage orofacial pain, especially for patients who report an allergic history, have renal compromise or some type of GI pathology, are being treated with an anticoagulant agent, or are pregnant or breastfeeding.

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Disclaimer

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