

NSAIDs, including COX-2 selective agents

Cyclo-oxygenase inhibitors that relieve pain, fever and inflammation by blocking prostaglandin synthesis, at the cost of gastrointestinal, renal and cardiovascular risk that defines how the class is prescribed.

Online guide: <https://www.medguideglobal.com/pharmacology/analgesia-and-anaesthesia/nsaids>

Content updated: 2026-08-24

Quick revision

One Liner: NSAIDs inhibit cyclo-oxygenase and reduce prostaglandin, prostacyclin and thromboxane synthesis; that single mechanism explains the anti-inflammatory benefit and the GI, renal and cardiovascular harm together.

1. Mechanism: inhibition of cyclo-oxygenase (COX-1 and/or COX-2), which converts arachidonic acid into prostaglandins, thromboxanes and prostacyclin. [1]
2. COX-1 is constitutively expressed and protects gastric mucosa, renal blood flow and platelet function; COX-2 is induced mainly during inflammation. [1]
3. Non-selective agents (ibuprofen, naproxen, diclofenac, indomethacin, ketorolac, meloxicam) inhibit both isoenzymes; celecoxib is COX-2 selective. [1]
4. Every prescription NSAID, selective or not, carries an FDA boxed warning for serious cardiovascular thrombotic events and for serious GI bleeding, ulceration and perforation. [3]
5. GI and CV risk both can occur without warning symptoms, and CV risk can appear early in treatment and rise with duration of use. [3]
6. All NSAIDs are contraindicated in the setting of coronary artery bypass graft surgery. [3]
7. Aspirin is the exception within the class: it irreversibly acetylates COX, so its antiplatelet effect lasts the roughly week-long lifespan of the platelet, unlike the reversible inhibition from other NSAIDs. [2]
8. Combining an NSAID with an ACE inhibitor or ARB and a diuretic - the "triple whammy" - raises acute kidney injury risk by blunting both the renin-angiotensin and the prostaglandin-dependent renal compensations at once. [1]

Overview

1. NSAIDs are among the most widely used medicines in the world, valued for treating pain, fever and inflammation across conditions from muscle strain and dysmenorrhoea to arthritis and gout. The class spans older non-selective agents such as ibuprofen, naproxen, diclofenac, indomethacin, ketorolac and meloxicam, and the newer COX-2 selective agent celecoxib, developed specifically to reduce the gastrointestinal toxicity of the older agents. [1]
2. Every member works through the same core mechanism: inhibition of cyclo-oxygenase, the enzyme that converts arachidonic acid into prostaglandins, thromboxanes and prostacyclin. COX-1 is constitutively expressed and its products protect gastric mucosa, maintain renal blood flow and support platelet aggregation; COX-2 is induced mainly during inflammation. Non-selective agents block both isoenzymes, so the anti-inflammatory benefit of blocking COX-2 comes bundled with the loss of COX-1's protective functions. [1]
3. That trade-off is why every prescription NSAID - selective or not - carries an FDA boxed warning for serious cardiovascular thrombotic events and for serious gastrointestinal bleeding, ulceration and perforation, either of which can occur without warning symptoms. Aspirin sits apart from the rest of the class mechanistically: unlike every other NSAID, it inhibits COX irreversibly, which is what gives low-dose aspirin its durable antiplatelet effect rather than a purely anti-inflammatory one. [3][2]

Classification and drug examples

Intro: Best learned by COX selectivity, since selectivity predicts which of the class's two headline risks - gastrointestinal

or cardiovascular - dominates for a given agent, though both risks apply to some degree across the class.

1. Name: Non-selective COX-1/COX-2 inhibitors

1. Note: Block both isoenzymes; carry the class's classic GI ulceration and bleeding risk alongside cardiovascular and renal risk.

1. Name: Ibuprofen

1. Route: Oral/topical

1. Note: The most widely used non-selective NSAID, available both by prescription and over the counter. [1]

2. Name: Naproxen

2. Route: Oral

2. Note: Longer half-life than ibuprofen, allowing less frequent dosing; among the non-selective agents with a comparatively lower reported cardiovascular signal in some analyses. [1]

3. Name: Diclofenac

3. Route: Oral/topical

3. Note: Carries the highest hepatotoxicity risk within the class. [1]

4. Name: Indomethacin

4. Route: Oral

4. Note: An older, potent non-selective agent used particularly in gout and certain rheumatologic indications. [1]

5. Name: Ketorolac

5. Route: Oral/IV/IM

5. Note: A parenteral option for short-term moderate to severe pain; duration of use is deliberately limited because of GI and renal risk. [1]

6. Name: Meloxicam

6. Route: Oral

6. Note: More COX-2 preferential than the other non-selective agents at usual doses, though not selective in the way celecoxib is. [1]

7. Name: Aspirin

Acetylsalicylic acid

7. Route: Oral

7. Note: Mechanistically distinct within the class: irreversibly acetylates COX, giving low-dose aspirin a durable antiplatelet effect that outlasts the drug itself. [2] [1]

2. Name: COX-2 selective agents

2. Note: Developed to reduce COX-1-mediated GI toxicity; cardiovascular risk remains and is specifically labelled.

Name: Celecoxib

Route: Oral

Note: The remaining COX-2 selective agent on the US market after rofecoxib and valdecoxib were withdrawn; still carries the class cardiovascular boxed warning and is contraindicated peri-CABG, and in sulfonamide allergy. [3] [3]

Mechanism of action

Summary: NSAIDs inhibit cyclo-oxygenase, reducing conversion of arachidonic acid into prostaglandins, thromboxanes and prostacyclin. Which isoenzyme is inhibited - COX-1, COX-2, or both - determines whether the dominant consequence is protective-mucosa loss, altered renal haemodynamics, or reduced platelet aggregation.

Target: Cyclo-oxygenase (COX-1 and/or COX-2)

Cidal Static: Not applicable - this class is an anti-inflammatory/analgesic/antipyretic, not an antimicrobial.

Kill Kinetics: Not applicable, except for aspirin, whose COX inhibition is irreversible; every other class member's effect is reversible and tracks plasma concentration.

1. Step: 1

1. Title: Cyclo-oxygenase is blocked

1. Detail: The drug binds cyclo-oxygenase and prevents it from converting arachidonic acid into prostaglandin H₂, the shared precursor for the entire downstream family of prostanoids. [1]
2. Step: 2
2. Title: Inflammatory prostaglandin synthesis falls (COX-2 effect)
2. Detail: With less prostaglandin produced at sites of inflammation, the vasodilation, hyperalgesia and hypothalamic temperature-set-point elevation that COX-2-derived prostaglandins drive are reduced, producing the anti-inflammatory, analgesic and antipyretic effects. [1]
3. Step: 3
3. Title: Protective COX-1-derived prostaglandins fall too (non-selective agents)
3. Detail: In non-selective agents the same inhibition removes COX-1-derived PGE₂ and PGI₂, which normally maintain gastric mucous secretion and mucosal blood flow, exposing the stomach lining to injury. [2]
4. Step: 4
4. Title: Renal afferent arteriolar dilation is lost
4. Detail: Prostaglandins normally dilate the afferent arteriole to maintain glomerular filtration when renal perfusion is challenged; losing that dilation reduces glomerular filtration rate, particularly in volume-depleted or already-compromised kidneys. [1]
5. Step: 5
5. Title: Platelet thromboxane synthesis is affected
5. Detail: Thromboxane A₂, also COX-derived, drives platelet aggregation. Non-selective inhibition reduces it; aspirin's irreversible acetylation removes it for the platelet's whole lifespan, which is the pharmacological basis for low-dose aspirin's antiplatelet use. [2]

Major clinical uses

1. Drug: Ibuprofen
 1. Indication: Mild to moderate pain, fever, and inflammatory conditions including musculoskeletal pain and dysmenorrhoea
 1. Line: first-line for many common types of acute pain
 1. Note: Available over the counter at lower doses; prescription strength for more severe indications. [1]
2. Drug: Naproxen
 2. Indication: Osteoarthritis, rheumatoid arthritis, and other chronic inflammatory joint conditions
 2. Line: maintenance therapy
 2. Note: Longer half-life supports twice-daily dosing. [1]
3. Drug: Diclofenac
 3. Indication: Osteoarthritis and soft-tissue pain, including topical formulations for localised joint pain
 3. Line: targeted
 3. Note: Topical formulations reduce systemic exposure relative to oral dosing. [1]
4. Drug: Celecoxib
 4. Indication: Osteoarthritis and rheumatoid arthritis, particularly when GI risk is a greater concern than cardiovascular risk
 4. Line: alternative to non-selective NSAIDs
 4. Note: Choice between celecoxib and a non-selective agent should weigh individual GI versus cardiovascular risk factors. [3]
5. Drug: Ketorolac
 5. Indication: Short-term moderate to severe acute pain, often post-operatively
 5. Line: short-course only
 5. Note: Duration is deliberately restricted because of accumulating GI and renal risk with longer use. [1]
6. Drug: Aspirin

6. Indication: Low-dose antiplatelet therapy for cardiovascular risk reduction, distinct from its higher-dose analgesic/anti-inflammatory use

6. Line: specialist- or guideline-directed

6. Note: The antiplatelet indication depends on the irreversible mechanism unique to aspirin within this class. [2]

Pharmacokinetics

1. Drug: Ibuprofen

1. Route: Oral/topical

1. Absorption: Well absorbed orally

1. Csf Penetration: Not clinically relevant to its use

1. Metabolism: Hepatic

1. Elimination: Renal

1. Half Life: See prescribing reference

1. Dose Adjust: Renal and hepatic impairment; caution with concurrent nephrotoxic or antihypertensive therapy [1]

2. Drug: Diclofenac

2. Route: Oral/topical

2. Absorption: Well absorbed orally; topical formulations give lower systemic exposure

2. Csf Penetration: Not clinically relevant to its use

2. Metabolism: Hepatic

2. Elimination: Renal and biliary

2. Half Life: See prescribing reference

2. Dose Adjust: Highest hepatotoxicity risk in the class; monitor liver function with prolonged use [1]

3. Drug: Celecoxib

3. Route: Oral

3. Absorption: Well absorbed orally

3. Csf Penetration: Not clinically relevant to its use

3. Metabolism: Hepatic, chiefly CYP2C9

3. Elimination: Hepatic/renal

3. Half Life: See prescribing reference

3. Dose Adjust: Sulfonamide allergy is a contraindication; contraindicated peri-CABG [3]

1. This page gives no dose regimens by design. NSAID dosing depends on indication, renal and hepatic function, cardiovascular risk and concurrent medications, and belongs in a prescribing reference used by the treating clinician.

2. Combining any NSAID with an ACE inhibitor/ARB and a diuretic - the 'triple whammy' - is a recognised, specifically named cause of acute kidney injury and warrants particular caution or avoidance. [1]

Adverse effects

1. Effect: Gastrointestinal upset

1. Detail: Dyspepsia, nausea and abdominal discomfort are common even without frank ulceration or bleeding. [1]

2. Effect: Fluid retention and blood pressure elevation

2. Detail: Prostaglandin-mediated sodium and water retention can raise blood pressure and worsen heart failure. [1]

1. Effect: Serious cardiovascular thrombotic events

1. Detail: Myocardial infarction and stroke, which can be fatal; risk may occur early in treatment and increase with duration of use, and is present with COX-2 selective and non-selective agents alike.

1. Action: Assess cardiovascular risk before starting and use the lowest effective dose for the shortest duration consistent with treatment goals. [3]

2. Effect: Serious gastrointestinal bleeding, ulceration and perforation

2. Detail: Can occur at any time during use and without warning symptoms; elderly patients and those with a prior

history of peptic ulcer disease or GI bleeding are at greater risk.

2. Action: Consider gastroprotection in higher-risk patients and monitor for signs of GI bleeding. [3]

3. Effect: Acute kidney injury

3. Detail: From loss of prostaglandin-dependent afferent arteriolar dilation, particularly in volume depletion, existing renal impairment, or the 'triple whammy' combination.

3. Action: Avoid in significant renal impairment and monitor renal function when risk factors are present. [1]

1. Drug: Diclofenac

1. Effect: Highest hepatotoxicity risk within the class. [1]

2. Drug: Aspirin

2. Effect: Irreversible antiplatelet effect lasting the life of the platelet, distinct from the reversible effect of other NSAIDs; raises bleeding risk accordingly. [2]

3. Drug: Celecoxib

3. Effect: Contraindicated in patients with sulfonamide hypersensitivity, unlike non-selective NSAIDs. [3]

Contraindications, precautions and interactions

1. Known hypersensitivity to the specific agent, or a history of asthma, urticaria, or other allergic-type reaction after aspirin or another NSAID. [3]

2. Use in the setting of coronary artery bypass graft (CABG) surgery. [3]

3. Sulfonamide hypersensitivity, specific to celecoxib. [3]

1. History of peptic ulcer disease or gastrointestinal bleeding. [3]

2. Established cardiovascular disease or cardiovascular risk factors. [3]

3. Renal impairment, volume depletion, or concurrent ACE inhibitor/ARB and diuretic use ('triple whammy'). [1]

4. Third-trimester pregnancy. [1]

1. With: ACE inhibitors, ARBs and diuretics

1. Effect: Combined use raises acute kidney injury risk through the 'triple whammy' mechanism, and NSAIDs blunt the antihypertensive effect of ACE inhibitors and ARBs. [1]

2. With: Anticoagulants and aspirin

2. Effect: Additive bleeding risk, particularly gastrointestinal. [3]

3. With: Lithium and methotrexate

3. Effect: NSAIDs can reduce renal clearance of both, raising the risk of toxicity. [1]

Comparison tables

Title: COX selectivity and its dominant risk

Caption: Both cardiovascular and GI risk apply across the class to some degree; this shows which risk each agent's mechanism emphasises. A prescribing reference and the treating clinician govern actual therapy.

1. Key: drug

1. Label: Drug

1. Is Row Header: true

2. Key: selectivity

2. Label: COX selectivity

3. Key: dominant_risk

3. Label: Emphasised risk

1. Drug: Ibuprofen / naproxen / indomethacin

1. Selectivity: Non-selective

1. Dominant Risk: GI ulceration/bleeding, renal effects [1]

2. Drug: Diclofenac

2. Selectivity: Non-selective, more COX-2-preferential in practice

2. Dominant Risk: Hepatotoxicity, plus class GI/CV/renal risk [1]
3. Drug: Celecoxib
3. Selectivity: COX-2 selective
3. Dominant Risk: Cardiovascular thrombotic risk; lower GI risk than non-selective agents [3]
4. Drug: Aspirin
4. Selectivity: Non-selective, irreversible
4. Dominant Risk: Bleeding, from a durable antiplatelet effect distinct from other NSAIDs [2]

High-yield exam pearls

1. Pearl: One enzyme, two faces.
1. Why: COX-1 is the housekeeping isoform protecting the stomach, kidney and platelets; COX-2 is the inflammation-driven isoform. A non-selective NSAID gets the anti-inflammatory benefit of blocking COX-2 but pays for it by also blocking COX-1's protective roles. [1]
2. Pearl: COX-2 selectivity trades GI risk for cardiovascular risk, not eliminates all risk.
2. Why: Celecoxib spares COX-1-dependent gastric protection but still carries the same boxed warning for serious cardiovascular thrombotic events as non-selective NSAIDs - selectivity changes which risk dominates, not whether the class-wide risks apply. [3]
3. Pearl: Aspirin is the odd one out mechanistically.
3. Why: Every other NSAID inhibits COX reversibly; aspirin acetylates it irreversibly. That is why low-dose aspirin can produce a lasting antiplatelet effect for the life of the platelet, while ibuprofen's antiplatelet effect disappears as the drug clears. [2]
4. Pearl: "Triple whammy" is a named, testable interaction.
4. Why: An ACE inhibitor or ARB plus a diuretic plus an NSAID removes two separate compensatory mechanisms that protect renal perfusion, and the combination is a recognised, specifically named cause of acute kidney injury. [1]
5. Pearl: GI and CV risk can strike without warning.
5. Why: The FDA boxed warning states both serious GI events and serious cardiovascular events can occur at any time during use, without warning symptoms - a reason NSAIDs are not treated as harmless because a patient 'feels fine'. [3]

Common exam traps

1. Trap: "COX-2 selective NSAIDs have no boxed warning because they spare the stomach."
1. Correction: Celecoxib's label carries the same boxed warning for cardiovascular thrombotic events as non-selective NSAIDs, and is specifically contraindicated in the setting of CABG surgery. Selectivity changes the risk profile; it does not remove the warning. [3]
2. Trap: "Adding aspirin to another NSAID lowers cardiovascular risk further."
2. Correction: There is no consistent evidence that concurrent aspirin mitigates the cardiovascular thrombotic risk of another NSAID, and combining aspirin with an NSAID increases the risk of serious GI events instead. [3]
3. Trap: "NSAID-related kidney injury only happens with long-term daily use."
3. Correction: NSAIDs reduce prostaglandin-dependent afferent arteriolar dilation acutely; combined with an ACE inhibitor/ARB and a diuretic (the 'triple whammy'), acute kidney injury can occur within days, not only after chronic use. [1]
4. Trap: "All NSAIDs inhibit COX the same permanent way aspirin does."
4. Correction: Aspirin is uniquely irreversible. Ibuprofen, naproxen, diclofenac, celecoxib and the rest are reversible COX inhibitors whose effect tracks plasma drug concentration rather than platelet lifespan. [2]

Self-test questions

1. Question: What is the core enzymatic mechanism shared by all NSAIDs?

1. Inhibition of lipoyxygenase, blocking leukotriene synthesis
 2. Inhibition of cyclo-oxygenase (COX-1 and/or COX-2), reducing prostaglandin, prostacyclin and thromboxane synthesis from arachidonic acid
 3. Blockade of voltage-gated sodium channels in peripheral nerves
 4. Antagonism of the mu-opioid receptor
1. Explanation: NSAIDs inhibit cyclo-oxygenase, the enzyme that converts arachidonic acid into prostaglandins, thromboxanes and prostacyclin. Whether an agent inhibits COX-1, COX-2 or both determines its specific benefit and risk profile. [1]
2. Question: Why does inhibiting COX-1 specifically raise gastrointestinal bleeding risk?
1. COX-1 produces the acid that neutralises stomach protection
 2. COX-1 is constitutively expressed and its prostaglandin products maintain gastric mucosal blood flow and mucous secretion; blocking it removes that protection
 3. COX-1 has no role in the gastrointestinal tract
 4. COX-1 inhibition increases gastric acid production directly
2. Explanation: COX-1-derived prostaglandins such as PGE2 and PGI2 maintain gastric mucous secretion and mucosal blood flow. Removing that constitutive protection is what makes non-selective COX-1 inhibition ulcerogenic, independent of any anti-inflammatory action. [2]
3. Question: Why is celecoxib still contraindicated in the setting of coronary artery bypass graft (CABG) surgery despite being COX-2 selective?
1. Celecoxib has no cardiovascular risk and the contraindication is outdated
 2. COX-2 selective inhibition still carries a boxed warning for serious cardiovascular thrombotic events, and celecoxib's label specifically contraindicates it in the CABG setting
 3. Celecoxib causes excessive bleeding through irreversible COX-1 inhibition, exactly like aspirin
 4. Celecoxib is metabolised only by the kidney, which fails during CABG
3. Explanation: COX-2 selectivity reduces GI risk relative to non-selective NSAIDs but does not remove cardiovascular thrombotic risk. Celecoxib's FDA label carries the same class-wide cardiovascular boxed warning and specifically contraindicates use in the CABG surgical setting. [3]
4. Question: What makes aspirin's antiplatelet effect different from that of ibuprofen?
1. Aspirin has no effect on platelets; only ibuprofen does
 2. Aspirin irreversibly acetylates COX, so its effect lasts the roughly week-long lifespan of the platelet; ibuprofen's inhibition is reversible and tracks plasma concentration
 3. Ibuprofen's antiplatelet effect is permanent while aspirin's is reversible
 4. Both drugs have an identical, reversible antiplatelet duration
4. Explanation: Aspirin irreversibly binds cyclo-oxygenase, so a platelet exposed to aspirin cannot regenerate the enzyme for the rest of its roughly seven-to-ten-day lifespan. Other NSAIDs inhibit COX reversibly, so their antiplatelet effect disappears as the drug is cleared. [2]
5. Question: A patient taking an ACE inhibitor and a diuretic is started on an NSAID and develops acute kidney injury within days. What is this interaction called, and why does it happen?
1. The 'triple whammy' - the NSAID removes prostaglandin-dependent afferent arteriolar dilation while the ACE inhibitor and diuretic remove the other renal compensatory mechanisms
 2. Serotonin syndrome, from combined serotonergic activity
 3. The 'double cover' effect, from combined COX-1 and COX-2 inhibition alone
 4. This combination has no recognised interaction risk
5. Explanation: This is the named 'triple whammy': an NSAID blunts prostaglandin-mediated afferent arteriolar dilation, while an ACE inhibitor/ARB and a diuretic remove other renal protective mechanisms, together raising acute kidney injury risk sharply and quickly. [1]
6. Question: Why does the FDA boxed warning emphasise that serious GI and cardiovascular NSAID events can occur

'without warning symptoms'?

1. Because these events are always preceded by clear abdominal pain
2. Because a patient can be at risk of a fatal event without any preceding symptom to prompt a clinical visit, so risk assessment cannot rely on symptoms alone
3. Because the warning applies only to patients already hospitalised
4. Because NSAIDs cause symptoms only after the event has occurred
6. Explanation: The label states these serious events can occur at any time during use and without warning symptoms, which is precisely why risk factors, duration of use and dose are assessed proactively rather than waiting for symptoms to appear. [3]

Frequently asked questions

1. Question: Are COX-2 selective NSAIDs safer overall than non-selective NSAIDs?
1. Answer: They are generally associated with lower gastrointestinal risk, but they carry the same FDA boxed warning for serious cardiovascular thrombotic events as non-selective NSAIDs. 'Safer' depends on which risk matters more for a given patient, which is a decision for the prescribing clinician. [3]
2. Question: Why is aspirin sometimes grouped with NSAIDs and sometimes discussed separately?
2. Answer: Aspirin shares the same COX-inhibition mechanism as other NSAIDs, so it belongs in the class. But its inhibition is irreversible rather than reversible, which gives it a distinct, durable antiplatelet effect that other NSAIDs do not share - that is why low-dose aspirin is used for cardiovascular prevention while other NSAIDs are not. [2]
3. Question: Can NSAID-related GI bleeding happen without any stomach pain first?
3. Answer: Yes. The FDA boxed warning specifically states serious GI events can occur at any time during use, without warning symptoms, which is why risk factors and duration of use are considered proactively rather than waiting for symptoms. [3]
4. Question: Why is it risky to combine an NSAID with a blood-pressure medicine and a diuretic?
4. Answer: This combination - an ACE inhibitor or ARB, a diuretic, and an NSAID - is known as the 'triple whammy' because it removes two separate mechanisms the kidney relies on to maintain blood flow when under stress, and it is a recognised cause of acute kidney injury. [1]
5. Question: What should a patient prescribed an NSAID do if they are worried about side effects?
5. Answer: Any concerns, new symptoms, or other medicines being taken should be discussed with the prescribing clinician or pharmacist rather than adjusting the medicine independently. The clinician can weigh individual GI, renal and cardiovascular risk factors against the benefit of treatment. [3]

References

- [1] Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) (StatPearls). StatPearls Publishing / NCBI Bookshelf 2025.
<https://www.ncbi.nlm.nih.gov/books/NBK547742/>
- [2] Nonsteroidal Anti-Inflammatory Drugs Toxicity (StatPearls). StatPearls Publishing / NCBI Bookshelf 2025.
<https://www.ncbi.nlm.nih.gov/books/NBK526006/>
- [3] Celecoxib Capsules - FDA-approved label (DailyMed). DailyMed, U.S. National Library of Medicine 2026.
<https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=6c56cfd5-f5e2-cbdd-e053-2991aa0a2e1a>

For education only. This guide does not replace professional medical advice. Do not use it to choose or change treatment.