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# Toxicity of Non-Steroidal Anti-Inflammatory Drugs

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**Abstract:**
The analgesic, anti-inflammatory, and antipyretic properties of nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used. In many parts of the world, they are commonly taken in excess. The vast majority of patients with acute NSAID overdose will be asymptomatic or will experience minor self-limiting gastrointestinal symptoms. However, serious clinical sequelae such as convulsions, metabolic acidosis, coma, and acute renal failure have been reported in patients with acute NSAID overdose. There appears to be some variation in the relative risk of these complications among the NSAIDs; in particular, mefenamic acid is most commonly associated with convulsions. There are no specific antidotes for acute NSAID toxicity, so management of these serious clinical features is largely supportive.

**Keywords**: Toxicity, Non-Steroidal, Anti-Inflammatory Drugs, NSAID

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## Introduction

As a class, Nonsteroidal anti-inflammatory drugs, commonly abbreviated as NSAIDs, are chemically varied, yet share similar therapeutic and adverse effects. All drugs within the class work to reduce inflammation, pain, and fever through inhibition of endoperoxide synthesis enzymes, known as cyclooxygenase (COX) enzymes. Both cyclooxygenase isozymes, COX-1 and COX-2, convert arachidonic acid into its endoperoxide metabolites, which include prostacyclin, prostaglandins, and thromboxane; these all have diverse biologic activity, ranging from inflammation, smooth muscle tone, and thrombosis. COX-1 is constitutively expressed and is considered the primary source of prostanoids needed for physiologic homeostases, such as protection of gastric epithelium. COX-2, on the other hand, is inducible, and its production of prostanoids is significantly upregulated during conditions of stress and inflammation. Despite the distinct roles of each isozyme, COX-1 and COX-2 can work together, and both contribute to the development of an inflammatory response.[1][2]

## Nonsteroidal Anti-Inflammatory Drugs Toxicity

Nonsteroidal anti-inflammatory drugs, sometimes known as NSAIDs, are a class of medications with a wide range of chemical compositions but similar therapeutic and negative effects. By inhibition of the cyclooxygenase (COX) enzymes, which are responsible for the endoperoxide synthesis, all medications in this family work to reduce inflammation, pain, and fever. Arachidonic acid is transformed by the cyclooxygenase isozymes COX-1 and COX-2 into its endoperoxide metabolites, prostacyclin, prostaglandins, and thromboxane, which have a variety of biological activities, such as inflammation, smooth muscle tone, and thrombosis.

**Types of NSAIDs**

| NONSTEROIDAL ANTIINFLAMATORY DRUG TYPE | EXAMPLE AGENTS |
|---|---|
| Non–Cox-2 selective NSAID | - Ibuprofen<br>- Naproxen<br>- Indomethacin<br>- Ketoprofen<br>- Ketorolac |
| NSAIDs with some Cox-2 activity | - Diclofenac (not traditionally considered a Cox-2–specific agent, but has been associated with a cardiovascular risk profile similar to the Cox-2–specific agents)<br>- Piroxicam<br>- Diflunisal<br>- Meclofenamate |
| Cox-2–selective NSAIDs | - Celecoxib (Celebrex, Pfizer)<br>- Meloxicam<br>- Etodolac<br>- Valdecoxib (no longer available)<br>- Etorocoxib (investigational)<br>- Rofecoxib (no longer available)<br>- Lumiraxocib (investigational) |

**Figure 1:** Types of NSAIDs

Because COX-1 is constitutively produced, it is thought to be the main source of prostanoids required for maintaining physiologic homeostases, including the defense of the stomach epithelium. On the other hand, COX-2 can be induced, and stress and inflammation dramatically increase this enzyme's ability to produce prostanoids. The same pharmacology that makes NSAIDs so effective therapeutically can potentially cause toxicity. The interprofessional team's involvement in assessing, diagnosing, and treating the illness is discussed in this exercise, along with the origin, presentation, evaluation, and management of NSAID toxicity.

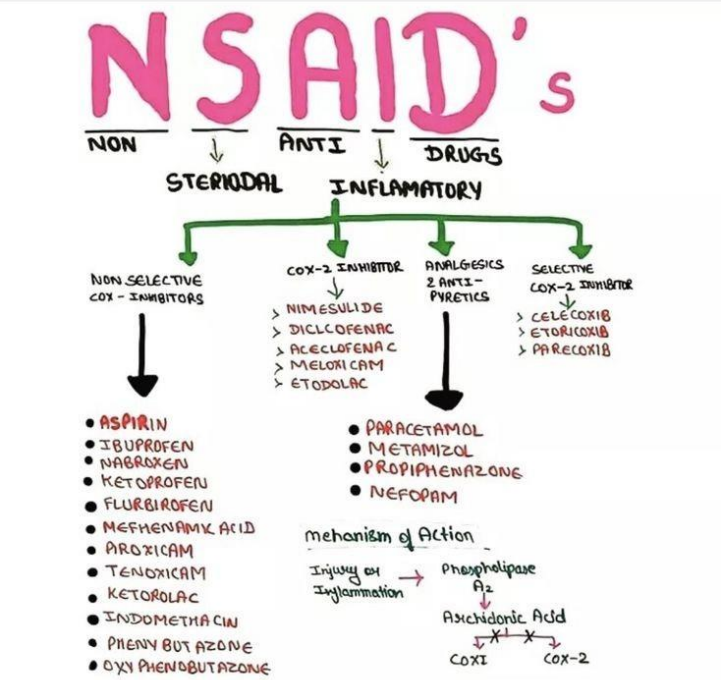


**Figure 2:** Drug discovery cycle.

**Objectives:**

- Describe the various pharmacologic mechanisms by which NSAIDs can cause toxicity.
- Summarize the evaluation for a patient who may be showing signs of NSAID toxicity.
- Go over methods for managing and treating NSAID toxicity as well as precautions to try to avoid it.
- Explain the importance of improving care coordination among the interprofessional team to improve outcomes for patients who either have or are potential candidates for developing NSAID toxicity.

**Etiology**

The majority of NSAIDs are made from organic acids and are quickly absorbed from the GI tract. These medications are eliminated through glomerular filtration and tubular secretion after undergoing significant hepatic metabolism. NSAIDs are often contraindicated in patients with severe renal and hepatic impairment for these reasons. As NSAIDs are predominantly linked to plasma proteins, they accumulate easily and quickly in sites of inflammation, resulting in acute analgesia within 30 to 60 minutes.

**Epidemiology**

Long used as safe and efficient over-the-counter and prescription medications for pain relief and fever reduction, NSAIDs are now widely accepted as such. An estimated 14 million people in the world use NSAIDs on a regular basis. The Centers for Disease Control and Prevention (CDC) predict that as the population ages, the use of this medicine class will significantly grow, mirroring the anticipated rise in the prevalence of painful disorders including osteoarthritis and inflammatory diseases. Therefore, it should come as no surprise that the frequency of side effects linked to NSAID use will probably increase. Prior research has revealed that medication toxicity is the cause of 5%–7% of hospital admissions, with non-aspirin NSAIDs accounting for 11%–12% of those admissions. [3] [4]

**Pathophysiology**

Depending on the chemical make-up of specific drugs, the mechanisms of action differ slightly. A conformational shift caused by aspirin's covalent and hence irreversible binding to cyclooxygenase stops further arachidonic acid processing. Aspirin is generated from salicylic acid. As opposed to aspirin, NSAIDs (also known as classic NSAIDs) like ibuprofen reversibly inhibit COX-1 and COX-2, lowering the synthesis of prostanoids. In order to prevent unintended GI side effects, a subclass of NSAIDs, which includes celecoxib, was designed as selective COX-2 inhibitors with little COX-1 affinity.

NSAIDs are frequently employed to treat mild to moderate pain. Acute musculoskeletal injury, headache, arthralgia, surgical pain, pain from inflammation, and menstrual pain are all common conditions for which these medications are prescribed. Prostanoids, including PGE2, are well known for their ability to cause pain and inflammation. Rubor, calor, tumor, and dolor, which are recognizable signs of inflammation, are caused by increased blood flow and vascular permeability as a result of PGE2-mediated arterial dilation, whereas it has been discovered that the perception of pain is partially caused by PGE2's excitation of peripheral sensory neurons as well as of certain sites within the central nervous system. The ability of the medication class to reduce PGE2-triggered hypothalamic increase of body temperature in response to infection or inflammation contributes to the antipyretic effects of NSAIDs. The function of NSAIDs in thrombosis and cardioprotection draws attention to aspirin's unique effects on mature platelets, where COX-1 is irreversibly blocked, inhibiting the production of thromboxane A2 and its powerful effects on platelet activation and vasoconstriction. Due to aspirin's irreversibility, its effects typically last one week on average, or the life of the platelet.Because of this, regular aspirin dosages result in a cumulative antiplatelet action. In addition to these main applications, NSAIDs provide therapeutic benefits for a number of additional diseases, including systemic mastocytosis resistant to antihistamines, uncommon disorders of increased prostaglandin production, and newborn cases of patent ductus arteriosus. [5] [6][7][8]

**Toxicokinetics**

Prostanoids have extensive impacts on smooth muscle tonicity in the vascular, respiratory and Gastrointestinal tracts, reproductive organs, and even the kidneys, as was previously mentioned. Furthermore, thromboxane has particular effects on platelet function. As a result, NSAIDs have a

tremendous therapeutic usefulness but may also be more toxic and have negative side effects due to these wide physiologic impacts.

Most frequently, NSAID use increases the risk of serious gastrointestinal side effects such ulceration, bleeding, or perforation. Despite the fact that individuals of any age can experience these dangers at any moment, elderly people tend to experience these adverse events more frequently. Additional unpleasant GI symptoms that can result from erosion of the alimentary canal include nausea, dyspepsia, appetite loss, stomach discomfort, and diarrhea. The constitutive contribution of prostanoids like PGE2 and PGI2 to GI mucous production is well known. Moreover, these prostanoids encourage vasodilation, which improves blood flow and the supply of bicarbonate to mucosal surfaces. These cytoprotective outcomes are diminished by primary COX-1 inhibition.

Use of NSAIDs may also be linked to serious cardiovascular side effects. Myocardial infarction and stroke incidence have historically received a great deal of attention, particularly in relation to the selective COX-2 inhibitor rofecoxib, which was taken off the market in 2004. Since then, comparable enquiries into the cardiovascular safety of non-selective NSAIDs and celecoxib, the last selective COX-2 inhibitor, have been made. Celecoxib is not linked to a greater rate of cardiovascular events when compared to non-selective medications, according to a 2016 study known as the PRECISION (Prospective Randomized Assessment of Celecoxib Integrated Safety vs Ibuprofen or Naproxen) trial. However, well-known negative consequences include blood pressure increase and potentiation or aggravation of congestive heart failure due to suppression of naturally occurring prostanoid-induced salt excretion and modifications in renal arteriolar tone. These dangers typically depend on the dose and time period. In the end, it's critical to show that using tobacco, drinking alcohol, and engaging in other unhealthy behaviors all raise the risk of adverse cardiovascular events linked to NSAID usage.

Those who take NSAIDs may occasionally develop negative effects on their kidneys. As previously mentioned, it has been discovered that NSAIDs interfere with prostanoid-regulated systems that impact afferent arterioles within nephrons, lowering the glomerular filtration rate. Due to decreased renal blood flow, drug usage reduces the reno-protective effects of prostanoid and raises the risk of acute kidney injury. Renal papillary necrosis and interstitial nephritis are further signs of NSAID-induced renal damage. The decrease of renal blood flow is known to cause the renal papillae to become sensitive. Gross hematuria can be caused by ischemic damage from drug-associated vasoconstriction. Those who are hypersensitive to the analgesic class may develop interstitial nephritis, which is characterized by acute kidney inflammation, eosinophilic pyuria, and azotemia.

In addition to these separate toxicities, using NSAIDs at the same time as many other medications can have negative consequences. Due to their pharmacokinetics, NSAIDs may displace other high plasma protein-bound medications, increasing the free serum concentration of these medications. When displaced in this way, medications having limited therapeutic windows, such warfarin or phenytoin, theoretically may reach toxic concentrations. Moreover, some NSAIDs decrease renal perfusion and inhibit cytochrome P450 (CYP) enzymes or glucuronidation, which can make medications more dangerous that depend on renal clearance (like lithium) or hepatic metabolism.
Additional prominent drug interactions occur when NSAIDs and antihypertensives are used together, as well as when anticoagulants and antiplatelets, selective serotonin receptor inhibitors (SSRIs), GI mucosa-damaging drugs, and anticoagulants and antiplatelets. The capacity of NSAIDs to lower natriuresis reduces the effectiveness of several antihypertensives. In addition to decreased effectiveness, the use of NSAIDs in particular combinations with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may worsen potassium retention, which is known to have serious cardiac effects. Due to decreased platelet aggregation, using NSAIDs plus anticoagulants or antiplatelets together can increase the risk of bleeding. Because serotonin is one of many chemicals taken up by and released by platelets to induce aggregation and hemostasis, bleeding risk is also enhanced by concurrent use of SSRIs and NSAIDs. Last but not least, using NSAIDs along with alcohol

or glucocorticoids, which prevent the activation of phospholipase A2, increases the risk of peptic ulcer disease or a GI bleed significantly. [9] [10] [11] [12][13]

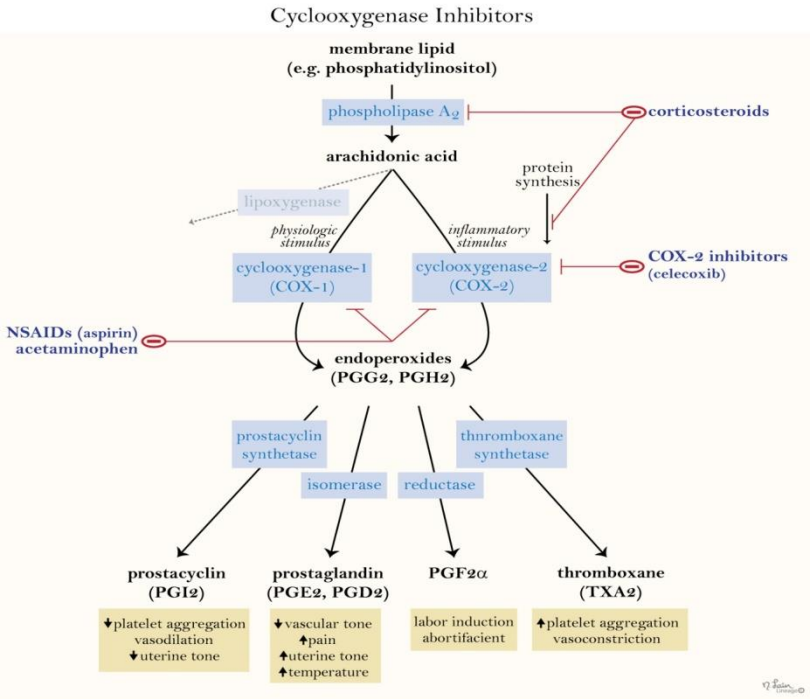


**Figure 3:** Cyclooxygenase Inhibitors.

**History and Physical**

The right history must contain the precise medication taken, the quantity consumed, and the time it was ingested in cases of suspected drug poisoning. To rule out any potentially fatal drug interactions or overdoses, further information about the history of the presenting condition, such as potential co-ingestants, is also essential. A patient's physical examination is typically uneventful unless there has been a sudden shift in their mental state. Additional clinical signs of Gastrointestinal distress could include nausea, vomiting, sleepiness, dizziness, and blurred vision. Nevertheless, various comorbidities that may affect NSAID toxicity may affect the clinical characteristics of toxicity. Healthcare professionals must be diligent when taking a patient's history to find risk factors or comorbidities that could exacerbate the negative effects of NSAIDs or potential drug interactions. [14]

**Evaluation**

Evaluation for suspected NSAID toxicity should include applicable laboratory tests for levels of common co-ingestants such acetaminophen and salicylate after a history and physical have been taken. Clinical presentation may serve as a guidance for additional laboratory tests. For symptomatic patients or those who have consumed significantly high doses of the medication (i.e., more than 6 grams in an adult or more than 400 milligrams/kg in a child), a baseline assessment of renal function determined by blood urea nitrogen, creatinine, and electrolyte levels may be helpful. A complete blood count will enable the monitoring of hemoglobin and platelet counts in patients who present with bleeding that was probably brought on by the use of NSAIDs. If there is a concern for massive ingestion, an arterial blood gas can help determine the patient's acid-base status, and an electrocardiogram can show evidence of QT interval prolongation in the case of potential co-ingestant consumption that could have dangerous effects on the cardiac conduction system. Last but not least, professionals should always think about other potential causes of changed mental status and may request testing to check for other probable diseases including hypoglycemia.

**Treatment / Management**

Patients who present with acute NSAID toxicity must be evaluated for their airway, breathing, and circulation as with any acute ailment, and any issues with their hemodynamic stability must be taken care of. Determining the necessity for decontamination depends on how long ago a patient consumed the substance. If there are no contraindications, individuals who appear within two hours of consumption may be treated with activated charcoal. In the absence of a specific antidote, these situations typically call for supportive care, such as resolving electrolyte imbalances, replenishing intravascular volume, or treating any existing acid-base problems. On the other hand, NSAIDs should be kept to a minimum or, if possible, totally removed from a patient's medical regimen in order to treat chronic toxicity. [19] [20]

**Differential Diagnosis**

- Elderly individuals' abdominal pain
- • Acute lactose intolerance
- Anxiety disorders
- Chronic anaemia
- Emergency medicine's use of delirium, dementia, and amnesia
- Delirium, dementia and amnesia in emergency medicine
- Encephalitis
- Stevens-johnson syndrome
- Toxic epidermal necrolysis

**Enhancing Healthcare Team Outcomes**

Like to other toxicities, prevention is the key to management. Physicians, physician assistants, and nurse practitioners must assist their patients through medical optimization and elimination of risk factors that lead to the development of NSAID adverse effects if NSAID use is necessary in patient case management. Also, pharmacists play a crucial role in the multidisciplinary team that treats patients with acute or chronic diseases that call for the use of NSAIDs. It has been maintained that local pharmacists are best suited to instruct patients on pharmaceutical use. [15] Health literacy assessments and patient counseling are inherently difficult tasks that call for interprofessional help. Nurses on the team are required to be aware of any potential negative effects and alert the other team members if difficulties like gastritis arise. (3rd Level) [16] [17] [18]

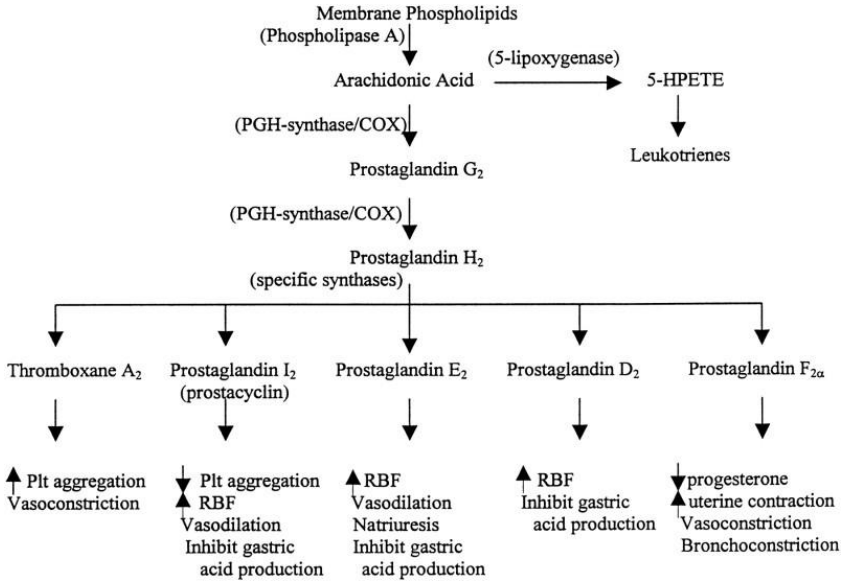


**Figure 4:** Membrane Phospholipids

**CONCLUSION**

The majority of NSAID overdoses have a benign consequence. Large patient series have generally reported modest side effects, but individual case reports have revealed severe toxicity, including seizures, hypotension, apnea, coma, and renal failure. The bulk of these effects happen when adults who are trying suicide consume large amounts. Ibuprofen and piroxicam seldom cause significant poisoning in children who accidentally swallow modest doses. NSAID overdose typically manifests as

nausea, vomiting, headache, sleepiness, blurred vision, and dizziness. With the exception of mefenamic acid (when seizures happen in almost one-third of cases) or after ingesting large amounts of other drugs, seizures are hardly ever reported across all NSAID classes. In severe situations, the propionic acid group of drugs have caused metabolic acidosis, respiratory depression, and coma. Ibuprofen is the medication with the most overdose data that has been published, perhaps as a result of its availability without a prescription in many nations. Until more than 400 mg/kg is consumed, symptoms are often not life-threatening and unlikely to occur after ingestion of 100 mg/kg or less. Plasma concentrations and treatment choices have some correlation but no causal relationship. NSAID overdose is only treated with supportive care. Although gastric lavage followed by the administration of syrup of ipecac is still advised if treatment is given shortly after ingestion, there are a few exceptions: for example, ipecac is contraindicated after ingestion of mefenamic acid or alcohol. Recent trends in emergency department procedures regarding gastric decontamination are evolving towards the recommendation of administration of activated charcoal without gastric emptying in patients presenting more than 1 hour after ingestion. Based on a PKa in the range of 3 to 5, diuresis and urine alkalinization have been advised to improve the clearance of NSAIDs. This method is not likely to be helpful, though, as drugs are almost universally strongly protein bound and have minimal unaltered renal excretion. kidney failure sets in. In order to improve the elimination of NSAIDs with lengthy half-lives, such as piroxicam and sulindac, several doses of activated charcoal may be helpful. Hemodialysis may be necessary if oliguric but is unlikely to improve elimination.

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