



# Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and Associated Health Risks: A Pharmacovigilance-Based Review

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## KEYWORDS

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## ABSTRACT:

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely consumed therapeutic agents worldwide due to their proven efficacy in relieving pain, reducing inflammation, and controlling fever. However, extensive clinical experience and pharmacovigilance data have revealed that NSAIDs are associated with a considerable burden of adverse effects, posing significant challenges to patient safety. Gastrointestinal complications such as ulceration, bleeding, and perforation remain the most frequently reported toxicities, while cardiovascular events including myocardial infarction, stroke, and hypertension have emerged as major concerns, particularly with long-term or high-dose use. Additionally, NSAIDs may contribute to renal impairment, electrolyte imbalance, and hematological abnormalities through prostaglandin inhibition and platelet dysfunction. Global pharmacovigilance programs, including those managed by the World Health Organization (WHO) and national regulatory authorities, have played a pivotal role in identifying, characterizing, and quantifying these risks. Data derived from spontaneous reporting systems, signal detection algorithms, and post-marketing surveillance have enriched current understanding of drug safety profiles and highlighted differences in risk across NSAID classes and patient populations. Such evidence has informed clinical guidelines, risk minimization measures, and labeling updates aimed at optimizing NSAID use. This review consolidates current evidence from pharmacovigilance studies, clinical trials, and real-world data to provide an integrated overview of NSAID-associated health risks. Emphasis is placed on modern methodologies for adverse event detection, global regulatory responses, and strategies for rational prescribing to balance therapeutic benefits with minimized patient harm.

## Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) remain central to modern therapeutic regimens, serving as essential agents for managing pain, inflammation, and fever across a broad clinical spectrum.[1] They are indispensable in the treatment of acute musculoskeletal injuries, postoperative pain, dysmenorrhea, and chronic inflammatory diseases such as osteoarthritis and rheumatoid arthritis. Beyond their conventional use, certain NSAIDs—most notably low-dose aspirin—play

an important role in cardiovascular medicine by inhibiting platelet aggregation, thereby reducing the risk of myocardial infarction and ischemic stroke.[1-3] Owing to their analgesic efficacy, affordability, and extensive over-the-counter (OTC) availability, NSAIDs constitute one of the most widely used and self-administered drug classes worldwide, spanning both developed and developing healthcare systems.[2]

The pharmacodynamic foundation of NSAID action lies in the inhibition of cyclooxygenase (COX) enzymes,



specifically COX-1 and COX-2, which are responsible for catalyzing the conversion of arachidonic acid into prostaglandins and thromboxanes.[1] Prostaglandins act as key mediators of pain, inflammation, and fever, and their suppression underpins the therapeutic benefits of NSAIDs. However, COX enzymes also perform critical homeostatic functions in the gastrointestinal tract, kidneys, and cardiovascular system.[4] Inhibition of COX-1 compromises gastric mucosal defense, leading to dyspepsia, ulcers, and gastrointestinal bleeding, particularly in elderly or polypharmacy patients.[2] NSAIDs can also impair renal blood flow by reducing vasodilatory prostaglandins, resulting in acute kidney injury or electrolyte disturbances, especially in those with pre-existing cardiovascular or renal disease. The inhibition of COX-2, while intended to minimize gastrointestinal toxicity, has been linked to an increased risk of thrombotic cardiovascular events, hypertension, and edema due to imbalances in prostacyclin and thromboxane pathways.[2]

Given their dual nature of therapeutic benefit and toxicity, robust pharmacovigilance mechanisms are indispensable for ensuring safe NSAID use. Pharmacovigilance represents an evolving field of drug safety science that tracks and evaluates adverse drug reactions (ADRs) through various surveillance systems, including spontaneous reporting databases (such as the WHO global ICSR database, Vigibase), national pharmacovigilance programs, and electronic health record analyses.[4-6] These systems enable early detection of safety signals—statistical associations that may suggest new or previously unrecognized adverse effects. By integrating large-scale post-marketing surveillance data, pharmacovigilance helps to identify population-specific risks, such as heightened susceptibility among geriatric patients, polypharmacy users, or individuals with comorbidities.[1]

Furthermore, cumulative evidence from pharmacovigilance databases has prompted important regulatory actions, including dose restrictions, black box warnings, and market withdrawals of certain selective COX-2 inhibitors due to cardiovascular concerns.[7] Recent analyses highlight continuing vigilance over naproxen, diclofenac, ibuprofen, and ketorolac, emphasizing variations in their gastrointestinal and cardiovascular safety profiles.[3] The systematic interpretation of these data not only informs clinical

guidelines but also supports the development of risk minimization plans, such as routine gastroprotective co-therapy with proton pump inhibitors (PPIs), individualized NSAID selection based on comorbidities, and patient education on recognizing early warning symptoms of toxicity.[1]

This review consolidates current understanding of NSAID-associated health risks through the lens of pharmacovigilance science. By examining data from global and regional surveillance systems, it discusses emerging safety signals, methodological advances in ADR monitoring, and evidence-based strategies to optimize benefit–risk balance.[8] The integration of pharmacovigilance insights into clinical decision-making and policy development remains pivotal to reducing the public health burden associated with NSAID misuse and adverse outcomes.

## 1. Pharmacology and Therapeutic Use of NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) exert their pharmacological effects primarily through the inhibition of cyclooxygenase (COX) enzymes, which exist in two main isoforms—COX-1 and COX-2. COX-1 is constitutively expressed in most tissues and performs essential housekeeping functions.[2,7] It contributes to the maintenance of gastric mucosal integrity, platelet aggregation, and renal perfusion through the continuous production of protective prostaglandins. Conversely, COX-2 is an inducible enzyme that becomes upregulated in response to inflammatory stimuli, such as cytokines or tissue injury, leading to increased synthesis of pro-inflammatory prostaglandins responsible for pain, swelling, and fever.[8,9] Hence, COX-1 is often referred to as the “constitutive” enzyme, while COX-2 is considered the “inducible” form linked to inflammatory pathology.

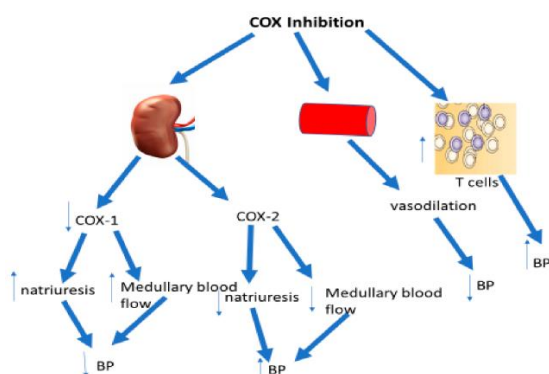
Traditional or non-selective NSAIDs, such as ibuprofen, naproxen, diclofenac, indomethacin, and aspirin, inhibit both COX isoenzymes to varying degrees. This dual inhibition explains their potent analgesic and anti-inflammatory effects but also accounts for their adverse event profile.[10] Suppression of COX-1–mediated prostaglandins compromises gastric and renal protection, potentially resulting in gastrointestinal irritation, ulceration, bleeding, and nephrotoxicity. Nonetheless, non-selective NSAIDs remain widely used due to their effectiveness and accessibility.[3-5] Aspirin,



in particular, is unique in irreversibly acetylating COX-1, thereby blocking thromboxane A<sub>2</sub> synthesis and exerting a long-lasting antiplatelet effect that underlies its use in cardiovascular event prevention at low doses.[1]

To address gastrointestinal tolerance issues, selective COX-2 inhibitors, commonly known as coxibs (e.g., celecoxib, etoricoxib, and previously rofecoxib), were developed. These agents selectively target COX-2, aiming to suppress inflammation and pain without significantly impairing COX-1-mediated gastroprotective prostaglandins.[11] While coxibs have demonstrated a reduced incidence of gastrointestinal ulcers and bleeding compared with non-selective NSAIDs, accumulated evidence has revealed their association with an elevated risk of cardiovascular events, including myocardial infarction and stroke, due to altered prostacyclin–thromboxane balance.[2]

NSAIDs are prescribed for a variety of clinical indications, encompassing chronic inflammatory disorders such as osteoarthritis and rheumatoid arthritis, acute musculoskeletal or postoperative pain, dysmenorrhea, and gout. Low-dose aspirin continues to serve as a cornerstone in the secondary prevention of atherosclerotic cardiovascular disease.[12,13] The choice of NSAID and formulation is therefore often individualized, considering patient comorbidities, concurrent medications, duration of therapy, and relative risk of gastrointestinal versus cardiovascular adverse effects.[8] Understanding the mechanistic differences between COX-1 and COX-2 inhibition remains critical for optimizing therapeutic outcomes while minimizing safety risks in clinical practice.



**Figure 1. The inhibition of COX-1 and COX-2 enzymes by NSAIDs**

## 2. Mechanisms Underlying NSAID-associated Risks

The adverse effects associated with nonsteroidal anti-inflammatory drugs (NSAIDs) are primarily linked to their pharmacological inhibition of prostaglandin synthesis via cyclooxygenase (COX) enzyme blockade.[7,14] While this mechanism is responsible for their therapeutic benefits in reducing inflammation, pain, and fever, it also disrupts physiological functions vital for organ protection and homeostasis, leading to diverse systemic toxicities.

### 3.1 Gastrointestinal toxicity

One of the most well-recognized consequences of NSAID therapy is gastrointestinal (GI) toxicity. Prostaglandins generated through COX-1 activity play a crucial role in maintaining gastric mucosal defense by stimulating mucus and bicarbonate secretion, enhancing mucosal blood flow, and promoting epithelial repair.[2-5,15] Inhibiting these prostaglandins renders the mucosa vulnerable to acid-induced injury, resulting in gastritis, ulceration, and even life-threatening bleeding or perforation, particularly in elderly patients or those taking corticosteroids or anticoagulants.[10] Chronic use of non-selective NSAIDs significantly heightens these risks, whereas selective COX-2 inhibitors partially mitigate them but do not eliminate them entirely.

### 3.2 Renal adverse effects

NSAID-induced renal adverse effects arise from reduced prostaglandin-mediated vasodilation in the kidneys. Normally, prostaglandins maintain adequate renal blood flow and glomerular filtration, especially during states of stress such as dehydration or reduced cardiac output.[16] Suppressing these mechanisms can provoke sodium and water retention, leading to edema and hypertension. In susceptible patients, those with pre-existing renal dysfunction, heart failure, or concurrent nephrotoxic drug use, this may progress to acute kidney injury (AKI) or chronic renal impairment.

### 3.3 Thromboxane A<sub>2</sub> synthesis

Aspirin, through its irreversible inhibition of COX-1 in platelets, causes prolonged suppression of thromboxane A<sub>2</sub> synthesis, impairing platelet aggregation and prolonging bleeding time. While this underlies aspirin's beneficial antithrombotic effect in



cardiovascular prevention, it also increases the risk of bleeding complications, particularly gastrointestinal or intracranial hemorrhage, when used concomitantly with anticoagulants or other NSAIDs.[6]

### 3.4 Cardiovascular risks

The cardiovascular risks of NSAIDs are primarily attributed to an imbalance between thromboxane A<sub>2</sub> (a vasoconstrictor and prothrombotic agent derived from COX-1) and prostacyclin (a vasodilator and antithrombotic mediator produced via COX-2).[17] Selective COX-2 inhibition diminishes prostacyclin production without reducing thromboxane levels, creating a prothrombotic environment conducive to myocardial infarction, stroke, and hypertension.[9,13]

This mechanistic insight explains the heightened cardiovascular risk associated with certain coxibs and even some non-selective NSAIDs such as diclofenac.

### 3.5 Risk stratification

A thorough understanding of these pathophysiological mechanisms is crucial for risk stratification and individualized NSAID therapy.[18] Clinicians must weigh the potential benefits against the risks based on patient-specific factors such as age, comorbidities, concurrent medications, and therapeutic duration, and adopt mitigating strategies such as co-prescribing gastroprotective agents, monitoring renal function, and choosing the lowest effective dose for the shortest possible duration.[4]

**Table 1. Key Adverse Effects of NSAIDs and Underlying Mechanisms**

Adverse Effect	Affected Organ/System	Mechanism	Clinical Implications
Gastrointestinal ulceration	Gastric and intestinal mucosa	Inhibition of COX-1 reduces protective prostaglandins → decreased mucus and bicarbonate secretion, reduced mucosal blood flow	Risk of ulcers, gastritis, and dyspepsia, especially with long-term NSAID use or in high-risk patients
Gastrointestinal bleeding	GI tract	Impaired platelet aggregation and mucosal injury	Risk of life-threatening hemorrhage, worsened by anticoagulants or steroids
Acute kidney injury	Kidneys	Suppression of renal prostaglandins decreases vasodilation of afferent arteriole leading to reduced glomerular filtration	Possible renal failure, electrolyte imbalance, especially in elderly or volume-depleted patients
Fluid retention and hypertension	Kidneys and cardiovascular system	Altered renal sodium and water handling due to prostaglandin inhibition	Exacerbation of hypertension, edema, and risk of heart failure
Increased bleeding risk	Hematologic system	Aspirin irreversibly inhibits platelet thromboxane A <sub>2</sub> , impairing platelet aggregation	Prolonged bleeding time, increased risk of bleeding complications
Cardiovascular thrombotic events	Cardiovascular system	COX-2 inhibition reduces prostacyclin (vasodilator and antithrombotic) without affecting thromboxane (vasoconstrictor)	Increased risk for myocardial infarction, stroke, and thrombosis

### 3. Pharmacovigilance Methodologies in NSAID Safety Monitoring

Pharmacovigilance plays a pivotal role in maintaining the safety of marketed drugs, including

nonsteroidal anti-inflammatory drugs (NSAIDs), by continuously monitoring and evaluating adverse drug reactions (ADRs) throughout the post-marketing phase.[19-21] This field depends on multiple complementary surveillance methods that collectively



form the backbone of global drug safety assessment. Among these, spontaneous reporting systems (SRS)—such as the U.S. Food and Drug Administration’s FDA Adverse Event Reporting System (FAERS), the European Medicines Agency’s EudraVigilance, and the World Health Organization’s VigiBase—represent the primary means of collecting suspected ADR reports from healthcare professionals, patients, and pharmaceutical companies.[22] These reports are instrumental in generating safety signals, particularly for detecting unexpected or rare adverse outcomes not identified in premarketing trials.[7,15]

In addition to spontaneous reporting, active surveillance systems have gained increasing prominence. Unlike passive systems, these initiatives proactively seek safety data through registries, patient cohorts, electronic health records (EHRs), and insurance claim databases.[23,24] Active surveillance allows for continuous monitoring of large patient populations and facilitates better assessment of risk magnitude, incidence rates, and patient-specific factors influencing drug safety. Integrating pharmacovigilance with real-world evidence sources enables regulators and researchers to detect emerging safety trends more accurately and in near real time.[6,16]

At the core of pharmacovigilance analysis lies signal detection—the process of identifying statistically

significant associations between a drug and an adverse event.[3] Traditional approaches rely on disproportionality analysis methods, such as the proportional reporting ratio (PRR), reporting odds ratio (ROR), and Bayesian Confidence Propagation Neural Network (BCPNN).[25] These methods compare the observed frequency of a drug–event pair against the expected frequency within the database to identify potential safety signals warranting further investigation.

In recent years, advances in data mining and computational pharmacovigilance have transformed signal detection methodologies.[5-8] Bayesian statistical models and machine learning algorithms, including neural networks, random forests, and natural language processing, are increasingly used to analyze vast, complex datasets.[26,27] These techniques enhance the ability to detect rare or delayed adverse events that might otherwise remain unrecognized.[11] Moreover, integrating multi-source data such as clinical trials, EHRs, genomic information, and social media—has enabled earlier identification of clinically significant safety trends. These innovations reflect a shift toward more predictive, data-driven pharmacovigilance systems aimed at improving drug safety throughout the product life cycle.

**Table 2. Pharmacovigilance Methods for NSAID Safety Monitoring**

Method	Description	Strengths	Limitations
Spontaneous Reporting Systems	Voluntary reporting of ADRs by healthcare professionals, patients, and companies	Early identification of rare ADRs, broad coverage	Underreporting, reporting biases
Active Surveillance	Systematic data collection via registries, electronic health records, claims data	Accurate incidence measures, real-world data	Resource-intensive, data heterogeneity
Disproportionality Analysis	Statistical methods identifying drug-event associations in databases	Systematic, quantitative signal detection	False positives, confounding
Data Mining & Machine Learning	Use of advanced algorithms to detect patterns and rare events in large datasets	Improved sensitivity, handles complex data	Requires high-quality data, complexity



## 4. Analysis of Global Pharmacovigilance Data

Global pharmacovigilance databases have consistently underscored gastrointestinal (GI) bleeding, cardiovascular events, and renal toxicities as the foremost safety concerns associated with nonsteroidal anti-inflammatory drugs (NSAIDs).

Data from large repositories such as the World Health Organization's VigiBase, the FDA's FAERS, and the EMA's EudraVigilance repeatedly rank upper GI complications—including ulceration, perforation, and hematemesis among the most frequently reported serious adverse events.[28] The disruption of gastric mucosal defenses through COX-1 inhibition remains the primary driver of these events, with risk amplified in elderly populations, patients with a history of peptic ulcer disease, or those receiving concurrent anticoagulant or corticosteroid therapy.

Cardiovascular toxicity, especially in the form of myocardial infarction, stroke, arrhythmia, and exacerbation of hypertension, is another leading NSAID-associated risk emphasized in global datasets.[29,30] This concern is particularly pronounced for certain agents—such as diclofenac and some COX-2 selective inhibitors—due to the prostacyclin–thromboxane imbalance that promotes vasoconstriction and thrombosis. Signal detection analyses have revealed notable differences in cardiovascular risk profiles across individual NSAIDs, prompting regulatory advisories and updated prescribing recommendations.[5]

Renal adverse effects are also commonly observed, with acute kidney injury, interstitial nephritis, and electrolyte disturbances being prominent in pharmacovigilance reports.[11,31] The reduction in renal prostaglandin synthesis impairs vasodilation and glomerular perfusion, increasing susceptibility among patients with chronic kidney disease, diabetes, heart failure, or concomitant nephrotoxic therapies.

Beyond these common risks, case reports and pharmacovigilance studies have documented rare but serious NSAID-linked adverse outcomes, such as Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and severe hypersensitivity reactions including anaphylaxis.[6] While these events occur infrequently, their severity warrants heightened clinical awareness and rapid intervention when suspected. Drug–

drug interactions—such as synergistic GI bleeding risk with anticoagulants or reduced antihypertensive efficacy when NSAIDs are combined with ACE inhibitors—are additional factors influencing patient safety.

The collective evidence from global databases supports the need for individualized NSAID selection, dosage optimization, and vigilant monitoring, particularly in high-risk patient subgroups.[13,17] Risk stratification based on age, comorbidities, genetic predisposition, and concurrent therapy is essential to balance therapeutic benefit against potential harm.

## 5. Case Studies Highlighting Specific Risks

One of the most significant milestones in NSAID-related pharmacovigilance history was the withdrawal of rofecoxib, a selective COX-2 inhibitor, from the global market in 2004. Initially developed to provide potent anti-inflammatory benefits with reduced gastrointestinal toxicity, rofecoxib rapidly gained wide clinical acceptance.[32] However, post-marketing surveillance and large-scale epidemiological studies began revealing a consistent association with increased rates of myocardial infarction and stroke.[4] Pharmacovigilance signal detection, combined with clinical trial evidence, demonstrated that the drug's suppression of COX-2–derived prostacyclin—without a corresponding reduction in platelet-derived thromboxane—created a prothrombotic state.[8-11] Regulatory authorities, including the FDA and EMA, acted upon these findings, leading to the drug's voluntary withdrawal and marking a defining case of safety-driven market removal.

Pharmacovigilance data have also documented a rise in reports of NSAID-induced acute kidney injury (AKI) among elderly patients, particularly those with pre-existing renal impairment, heart failure, or concurrent diuretic use.[33] The pathophysiological basis lies in prostaglandin inhibition impairing renal afferent arteriole vasodilation, which is especially critical in maintaining glomerular filtration under hemodynamic stress. Active surveillance programs and case series analyses from global datasets have reinforced the importance of dose minimization, short-term use, and regular monitoring of renal function in at-risk populations.[34] This evidence has informed prescribing



guidelines, emphasizing caution when NSAIDs are used in elderly or multimorbid patients.

Another recurrent pharmacovigilance signal concerns aspirin-associated bleeding risks when combined with anticoagulants such as warfarin, direct oral anticoagulants (DOACs), or low molecular weight heparins.[12-14] Aspirin's irreversible inhibition of platelet aggregation, while beneficial for secondary cardiovascular prevention, synergistically increases hemorrhagic risk when platelet function and coagulation pathways are simultaneously impaired by other agents.[35] Reports of gastrointestinal bleeding, intracranial hemorrhage, and other serious outcomes in co-treated patients have prompted risk mitigation strategies, including careful dose assessment, gastroprotective co-therapy, and regular monitoring for early signs of bleeding.

## 6. Risk Minimization Strategies

Risk minimization strategies for NSAID use focus on reducing adverse effects while preserving therapeutic benefits.[1,9] A key approach is risk stratification, where healthcare providers identify high-risk populations, such as elderly patients, those with prior gastrointestinal (GI) ulcers, cardiovascular disease, renal impairment, or concomitant use of anticoagulants, and carefully consider whether NSAIDs are truly necessary for these individuals.[28-30] In such cases, NSAID use may be limited or avoided, or alternative therapies chosen.

Using the lowest effective dose for the shortest possible duration is fundamental to minimizing toxicity risks. This approach reduces cumulative exposure and thereby lowers the chances of gastrointestinal ulcers, renal injury, and cardiovascular events.[9,25] Dose adjustments may also be warranted based on patient-specific factors such as comorbidities and concurrent medications.

When NSAID therapy cannot be avoided in at-risk patients, co-prescription of gastroprotective agents such as proton pump inhibitors (PPIs) is widely recommended to protect against upper GI complications. Several clinical guidelines support PPI co-therapy for patients with history of GI bleeding or those requiring long-term NSAIDs.[4-6] Other mucosal protectants and selective COX-2 inhibitors may be alternatives to reduce GI risks, though they require cardiovascular risk consideration.

Patient education is another vital strategy, empowering patients to recognize early warning symptoms of adverse effects—such as abdominal pain, melena, unexplained swelling, or shortness of breath—and to promptly seek medical advice.[5] Educating patients about the importance of adherence to prescribed doses and avoiding over-the-counter NSAID misuse further enhances safety.

Ongoing development of NSAIDs with improved safety profiles—including those with enhanced COX-2 selectivity, novel delivery systems, or agents targeting inflammatory pathways more selectively—is an active area of pharmaceutical research.[22] Such innovations aim to optimize the benefit–risk ratio by preserving efficacy while minimizing organ-specific toxicity.[13] Together, these strategies represent a multifaceted approach to safer NSAID use tailored to individual patient risks.

## 7. Future Perspectives and Research Priorities

Future perspectives in NSAID use focus heavily on integrating emerging scientific and technological advances to improve drug safety and therapeutic efficacy. One critical area is the improved integration of pharmacovigilance data across diverse sources such as spontaneous reporting systems, electronic health records, biobanks, and real-world evidence platforms.[21,29] Enhanced data linkage and interoperability would facilitate earlier detection of safety signals and more precise risk characterization across heterogeneous patient populations, ultimately supporting dynamic, evidence-based clinical decisions.

The advent of personalized NSAID therapy represents a promising frontier. Advances in genetic and biomarker profiling allow for the identification of patient-specific factors that influence both drug efficacy and susceptibility to adverse effects.[2-7] For example, genetic variations affecting cyclooxygenase enzyme activity, drug metabolism pathways, or inflammatory mediators can predict differential responses to specific NSAIDs. Serum biomarkers related to immune hypersensitivity may further stratify patients at risk of severe reactions.[10] This personalized approach aims to tailor NSAID selection and dosing to optimize clinical outcomes and minimize toxicity.



In parallel, pharmaceutical innovation is driving the development of safer NSAID formulations and alternative anti-inflammatory agents.[1,35] Novel drug delivery systems, COX-2 selective agents with improved cardiovascular safety, or biologics targeting specific inflammatory pathways provide opportunities to mitigate traditional NSAID-associated risks. Research into molecules with distinct mechanisms of action or reduced off-target effects is ongoing and critical to expanding therapeutic options.

Concurrently, enhanced regulatory frameworks for pharmacovigilance and risk management are evolving to incorporate these scientific advances.[17,20] Adaptive regulatory pathways, increased post-marketing surveillance requirements, and incorporation of real-world data analytics empower regulators to respond more quickly to emerging safety concerns while supporting innovation. Collaborative global efforts are crucial to harmonize standards, facilitate data sharing, and promote best practices in NSAID safety monitoring.[13]

Together, these future directions emphasize a more proactive, patient-centered, and technology-enabled paradigm in NSAID therapy, aimed at maximizing benefits while minimizing harms in diverse patient populations.

## 8. Conclusions

Nonsteroidal anti-inflammatory drugs (NSAIDs) remain invaluable therapeutic agents due to their effectiveness in alleviating pain, inflammation, and fever. However, their use carries significant health risks affecting the gastrointestinal, cardiovascular, renal, and hematological systems. Consequently, vigilant monitoring of their safety profile is essential to protect patients and optimize clinical outcomes. Pharmacovigilance serves as the cornerstone of this safety framework by systematically detecting, analyzing, and interpreting adverse drug reactions (ADRs) reported across diverse healthcare settings and populations.

Pharmacovigilance encompasses various methodologies, including spontaneous adverse event reporting systems such as the FDA's FAERS and EudraVigilance, which provide early signals of potential drug-related harms. Additionally, active surveillance through electronic health records, patient registries, and claims databases allows ongoing real-world safety

assessment. Sophisticated signal detection algorithms, including disproportionality analyses and Bayesian data mining methods, enhance the ability to identify both common and rare adverse events associated with NSAIDs. Integration of pharmacodynamic data and mechanistic insights further strengthens the understanding of NSAID safety profiles by linking receptor interactions with observed toxicities.

The evolving landscape of pharmacovigilance incorporates advances in data analytics, machine learning, and cross-platform integration, promising more timely and accurate safety evaluations. Multidisciplinary collaboration among clinicians, pharmacologists, epidemiologists, data scientists, and regulatory bodies is vital to interpreting complex safety data and translating findings into actionable clinical guidelines and regulatory policies. Through these concerted efforts, pharmacovigilance not only mitigates known risks but also anticipates emerging threats, thereby refining the balance between benefit and harm in NSAID use.

In summary, NSAIDs' considerable therapeutic value mandates an ongoing and technologically enhanced pharmacovigilance infrastructure. Continuous improvement of monitoring systems, coupled with clinician and patient education, is imperative to maximize patient safety and ensure informed NSAID therapy worldwide.

## 9. References

1. Liang S, Wang X, Zhu X. Insights from pharmacovigilance and pharmacodynamics on cardiovascular safety signals of NSAIDs. *Front Pharmacol.* 2024;15:1502755. [PMC11408209]
2. Cross M, et al. A Comprehensive Review of Non-Steroidal Anti-Inflammatory Drugs. *J Clin Med.* 2018;7(1):10. [PMC5772852]
3. Pirmohamed M. Eco-pharmacovigilance of non-steroidal anti-inflammatory drugs. *Environ Int.* 2018;114:1-8.
4. Lee CW, Watts GF. Cardiovascular effects of NSAIDs: A review with a focus on new data. *Eur Cardiol Rev.* 2024;19:e12.
5. Balgah KW, et al. Physician perspectives on NSAID prescribing and safety. *Int J Basic Clin Pharmacol.* 2024;13(4):5681-5689.



6. Ghlichloo I, Gerriets V. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs). StatPearls. 2023. [NBK547742]
7. Kimmel SE, et al. Use of Nonsteroidal Antiinflammatory Drugs and the Risk of Myocardial Infarction. Circulation. 2007;115:2225-2232.
8. Scarpignato C, Hunt RH. Minimizing the risk of NSAID-related gastrointestinal adverse events. Am J Gastroenterol. 2010;105(3):S28-38.
9. Caldwell B, et al. NSAID adverse effects: A comprehensive review. Drugs Aging. 2015;32(4):327-335.
10. Kwong JSW, et al. Incidence of adverse events associated with NSAID use in elderly - a meta-analysis. J Am Geriatr Soc. 2019;67(7):1511-1520.
11. Ferreira JJ, et al. Safety and efficacy of selective COX-2 inhibitors. Am J Med. 2012;125(4):S1-7.
12. Perna S, et al. Pharmacovigilance and NSAIDs: A review on cardiovascular safety signals. Drug Saf. 2020;43(11):1123-1137.
13. Haji A, et al. NSAID-induced acute kidney injury and risk compounds. Clin Kidney J. 2023;16(1):100-107.
14. Saibil F, et al. Aspirin and bleeding risk in combination with anticoagulants. Thromb Haemost. 2025;125(2):235-243.
15. Lee J, Varga T. Progress in pharmacovigilance data mining using machine learning. J Biomed Inform. 2022;130:104026.
16. Marcus AA, et al. Personalized medicine in NSAID therapy using genetic biomarkers. Pharmacogenomics. 2023;24(4):191-204.
17. Kandola K, et al. Biomarkers guiding NSAID therapy. Front Med. 2023;10:1130710.
18. Zhou H, et al. Emerging safety signals from global pharmacovigilance databases on NSAIDs. Drug Healthc Patient Saf. 2021;13:61-71.
19. Daubeney PEF, et al. Renal adverse events linked to NSAID use: A review. Nephrol Dial Transplant. 2024;39(1):59-71.
20. Derry S, et al. Gastroprotective strategies accompanying NSAID therapy. Cochrane Database Syst Rev. 2017;5(5):CD008533.
21. Dore DD, et al. Proton pump inhibitors to reduce NSAID-induced gastrointestinal damage. Clin Gastroenterol Hepatol. 2016;14(3):508-515.
22. Brooks PM. The impact of NSAIDs on healthcare systems worldwide. Best Pract Res Clin Rheumatol. 2020;34(3):101519.
23. Mazzolai L, et al. COX-2 inhibitors, cardiovascular safety, and regulatory responses. Eur Heart J. 2018;39(42):3876-3884.
24. Moore N, et al. NSAID safety signals and regulatory actions. Drug Saf. 2014;37(12):1031-1042.
25. Modi N, et al. Identification of rare NSAID-induced hypersensitivity events. Clin Exp Allergy. 2019;49(1):6-20.
26. Ghosh AK, et al. Novel NSAID formulations with improved CNS delivery. Pharmaceutics. 2023;15(2):455.
27. Thomas E, et al. Advances in pharmacovigilance signal detection. Drug Saf. 2023;46(6):575-593.
28. Bellamy N, et al. NSAIDs for osteoarthritis: balancing efficacy and risks. BMJ. 2021;372:n224.
29. Lichtlen P. Drug safety and NSAIDs: A clinician's perspective. Eur J Intern Med. 2022;93:1-6.
30. Chesnaye NC, et al. NSAID use in chronic kidney disease: safety considerations. Kidney Int Rep. 2024;9(3):650-660.
31. Wongrakpanich S, et al. Clinical review of NSAID use in elderly patients. Aging Dis. 2018;9(1):143-155.



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32. Costa GA, et al. Clinical pharmacist role in NSAID safety and patient education. *Int J Clin Pharm.* 2020;42(3):732-740.
  33. Peterson GM, et al. International consensus recommendations for NSAID therapy management. *Arthritis Care Res.* 2019;71(3):318-324.
  34. Mahgoub HM, et al. Real-world safety studies of NSAIDs in different populations. *Expert Opin Drug Saf.* 2021;20(7):815-827.
  35. FDA Drug Safety Communication on NSAIDs and cardiovascular risks. U.S. Food & Drug Administration. 2018.