IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A Comprehensive Review Of Nsaids: Therapeutic Uses, Mechanisms, Advances, And Safety Challenges

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1.Abstract: Nonsteroidal anti-inflammatory drugs (NSAIDs) represent one of the most widely prescribed and self-administered classes of medications worldwide, primarily utilized for their analgesic, anti-inflammatory, and antipyretic properties. Their clinical relevance spans diverse conditions ranging from musculoskeletal disorders and postoperative pain to chronic inflammatory diseases. The pharmacological effects of NSAIDs are largely mediated through inhibition of cyclooxygenase (COX) enzymes, thereby reducing prostaglandin synthesis, although this same mechanism underlies many of their adverse events, including gastrointestinal irritation, renal impairment, and increased cardiovascular risk. This review summarizes key aspects of NSAIDs, including classification, mechanisms of action, and therapeutic applications, while emphasizing both their benefits and safety concerns. Recent advances have focused on developing novel agents such as nitric oxide–releasing NSAIDs, dual COX/LOX inhibitors, and selective COX-2 inhibitors, as well as improved formulations like topical, extended-release, and nanocarrier-based delivery systems aimed at enhancing efficacy and minimizing toxicity. Current practice trends also involve risk stratification, co-therapy with gastroprotective agents, and patient-specific prescribing to optimize outcomes. Despite progress, challenges remain regarding long-term safety, individualized therapy, and regulatory oversight. Future research directions include identifying biomarkers for predicting adverse events, exploring precision medicine approaches, and expanding the clinical utility of safer NSAID derivatives. Collectively, NSAIDs remain indispensable in modern pharmacotherapy, but their use demands a balance between therapeutic benefits and risk management through continued innovation and evidence-based practice.

Keywords : Nsaids, Cyclooxygenase, Analgesia, Gastrointestinal Toxicity, Cardiovascular Risk, No-Nsaids, Dual Inhibitors, Formulation Advances

2.Introduction: Nonsteroidal anti-inflammatory drugs (NSAIDs) represent one of the most widely used therapeutic categories in modern medicine, owing to their efficacy in relieving pain, reducing inflammation, and lowering fever. Their use spans across diverse clinical settings, from the management of acute conditions such as headache, dysmenorrhea, and musculoskeletal injuries to chronic disorders including osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and other inflammatory diseases. Globally, NSAIDs account for a substantial share of over-the-counter (OTC) and prescription drug sales, second only to acetaminophen (paracetamol) among non-opioid analgesics, reflecting their indispensable role in both self-care and clinical practice.(1)

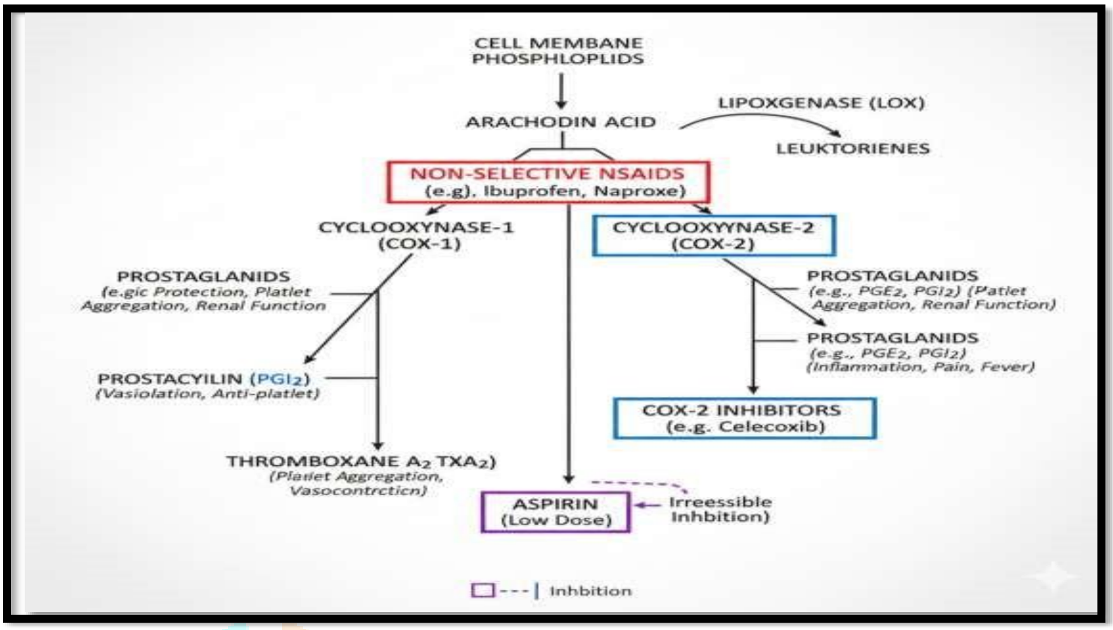

Figure 1 : Mechanism of Action of NSAID

The pharmacological activity of NSAIDs is primarily mediated through inhibition of cyclooxygenase (COX) enzymes, which exist in at least two wellcharacterized isoforms: COX-1 and COX-2. COX-1 is constitutively expressed and plays an essential role in maintaining gastric mucosal protection, platelet aggregation, and renal function, whereas COX-2 is inducible at sites of inflammation and injury, driving the synthesis of pro-inflammatory prostaglandins. Traditional NSAIDs inhibit both isoforms to varying degrees, providing therapeutic benefits but also contributing to adverse effects. Inhibition of COX-1 is strongly linked to gastrointestinal complications such as gastritis, ulceration, and bleeding, while suppression of COX-2 has been associated with cardiovascular risks including hypertension, myocardial infarction, and stroke. Renal adverse events, ranging from reduced glomerular filtration to acute kidney injury, are also well documented. Thus, despite their clinical utility, NSAIDs pose a significant challenge in balancing efficacy with safety.(2)

Over the decades, researchers have sought to improve this therapeutic index by developing selective COX-2 inhibitors, novel derivatives with additional protective properties (e.g., nitric oxide–donating NSAIDs, dual COX/LOX inhibitors), and advanced formulations designed to reduce systemic toxicity. Parallel to drug innovation, advances in clinical guidelines emphasize stratifying patients based on risk factors, employing the lowest effective dose for the shortest duration, and combining NSAIDs with gastroprotective agents such as proton pump inhibitors or misoprostol where necessary. Recent trends also highlight the exploration of personalized and precision-based approaches, including biomarker-driven therapy, pharmacogenomic profiling, and safer delivery systems like topical gels, transdermal patches, and nanocarrier-based formulations.

Despite these innovations, the widespread and often indiscriminate use of NSAIDs continues to contribute to a significant burden of drug-related morbidity worldwide. Hospital admissions due to NSAID-related gastrointestinal bleeding and renal impairment remain common, and concerns about cardiovascular safety persist, particularly in high-risk populations. These challenges underscore the need for continuous evaluation of clinical practices, development of safer drug candidates, and dissemination of evidence-based prescribing strategies.(3)

3. literature review

1. **Morita I. etal (2002)** explored the distinct physiological and pathological roles of cyclooxygenase isoenzymes COX-1 and COX-2. The study highlighted COX-1 as primarily involved in homeostatic functions such as gastric protection and platelet aggregation, whereas COX-2 is mainly induced during inflammation, pain, and fever, suggesting isoform-selective therapeutic targets for NSAIDs.

2. **Adelizzi RA. etal (1999)** discussed the differential roles of COX-1 and COX2 in health and disease. The review emphasized that while COX-1 maintains normal physiological functions, COX-2 expression is closely associated with inflammatory conditions, supporting the rationale for selective COX-2 inhibitors to reduce adverse gastrointestinal effects.

3. **Pilotto A etal. (2007)** investigated genetic susceptibility to NSAID-related gastroduodenal bleeding, focusing on cytochrome P450 2C9 polymorphisms. The study found that specific genetic variants significantly increased the risk of NSAID-induced gastrointestinal complications, highlighting the importance of pharmacogenomics in personalized NSAID therapy.

4. **Krasniqi V etal. (2016)** reviewed how polymorphisms in cytochrome P450 genes influence ibuprofen and diclofenac metabolism and toxicity. The authors concluded that genetic variations in metabolizing enzymes could alter drug efficacy and increase adverse reactions, suggesting that genotyping may improve safety and therapeutic outcomes.

5. **Yiannakopoulou E. etal (2013)** provided insights into the pharmacogenomics of acetylsalicylic acid and other NSAIDs, focusing on clinical implications. The review summarized evidence that genetic differences affect drug response and adverse effect profiles, underscoring the potential for individualized dosing strategies in clinical practice.

6. **Davis JS etal. (2017)** analyzed trends in NSAID use among US adults, noting demographic variations over time. Their findings indicated an increasing use of NSAIDs in older populations and highlighted the need for monitoring and education regarding long-term risks associated with chronic NSAID consumption.

7. **Pirmohamed M etal. (2004)** conducted a large prospective analysis of adverse drug reactions (ADRs) leading to hospital admissions. NSAIDs were identified as a major contributor to ADR-related hospitalizations, stressing the importance of careful prescribing and monitoring, particularly among vulnerable populations.

8. **Komagamine J. etal (2024)** studied the prevalence of urgent hospitalizations due to ADRs in a cross-sectional design. NSAID-induced complications were among the significant causes of hospitalization, reinforcing the ongoing public health concern regarding the safety profile of commonly used anti-inflammatory drugs.

9. **Salis Z & Sainsbury A. etal (2024)** examined the association between longterm NSAID use and knee osteoarthritis progression in a multi-cohort study over 4–5 years. Results suggested that chronic NSAID exposure might not prevent osteoarthritis progression and highlighted the need to balance symptomatic relief with potential long-term joint effects.

10. **Harirforoosh S etal. (2013)** provided an updated review of NSAID-related adverse effects, focusing on gastrointestinal, cardiovascular, and renal complications. The study emphasized that while NSAIDs are effective antiinflammatory agents, their long-term use requires careful risk assessment and monitoring to minimize serious organ-specific toxicities.

4. Classification of NSAIDs: NSAIDs represent a structurally diverse group of agents, and several classification systems have been proposed to better understand their pharmacological profiles, therapeutic applications, and safety considerations. They can be categorized according to COX selectivity, chemical structure, and mechanism of enzyme inhibition.(3,5)

1. Based on COX Selectivity

- **Non-selective (traditional) NSAIDs**: These inhibit both COX-1 and COX-2 isoforms without significant preference. While they are highly effective in alleviating pain, fever, and inflammation, their non-specific inhibition of COX-1 contributes to gastrointestinal and renal side effects. Examples include **ibuprofen, naproxen, diclofenac, indomethacin**, and **piroxicam**.
- **Preferential COX-2 inhibitors**: These agents exhibit somewhat higher affinity for COX-2 over COX-1, aiming to provide anti-inflammatory efficacy with a reduced incidence of gastric toxicity, though cardiovascular risks remain a concern. Drugs such as **meloxicam** and **nimesulide** fall into this category.
- **Highly selective COX-2 inhibitors (coxibs)**: Designed to specifically block COX-2, these drugs demonstrate improved gastrointestinal tolerability. However, long-term use has been associated with an increased risk of thrombotic cardiovascular events. Examples include **celecoxib, etoricoxib,** and **parecoxib**.
- **Novel hybrids and derivatives**: Recent advances have introduced nextgeneration NSAIDs, including **nitric oxide–donating NSAIDs (NONSAIDs or CINODs)**, which couple anti-inflammatory action with vasoprotective effects; **dual COX/LOX inhibitors**, which target both cyclooxygenase and lipoxygenase pathways to suppress broader inflammatory mediators; and **COX-2/soluble epoxide hydrolase (sEH) hybrids**, under investigation for enhanced anti-inflammatory efficacy with reduced toxicity.(5)

2. Based on Chemical Class

NSAIDs are often grouped by their underlying chemical structure, as this influences both pharmacokinetic properties and clinical activity:

- **Salicylates**: The oldest NSAID group, with **aspirin (acetylsalicylic acid)** as the prototype. Aspirin uniquely acts as an irreversible COX inhibitor and is widely used for analgesia, anti-inflammation, and cardioprotection.
- **Propionic acid derivatives**: A widely prescribed group with favorable tolerability and safety profiles; examples include **ibuprofen, naproxen, and ketoprofen**.
- **Acetic acid derivatives**: Potent agents often used in arthritis and acute inflammation, including **diclofenac, indomethacin, sulindac,** and **etodolac**.
- **Enolic acid derivatives (oxicams)**: Known for long half-lives and oncedaily dosing; examples include **piroxicam, meloxicam,** and **tenoxicam**.
- **Fenamates (anthranilic acid derivatives)**: Include **mefenamic acid** and **tolfenamic acid**, used for dysmenorrhea and acute pain.
- **Sulfonanilides and others**: Include agents such as **nimesulide**, which exhibit preferential COX-2 inhibition but carry hepatotoxicity risks.(6)

3. Based on Mechanism of Inhibition

- **Reversible inhibitors**: Most NSAIDs, including ibuprofen and diclofenac, bind reversibly to COX enzymes, leading to temporary suppression of prostaglandin synthesis.
- **Irreversible inhibitors**: **Aspirin** is unique among NSAIDs in irreversibly acetylating COX enzymes, providing long-lasting platelet inhibition and a well-established role in cardiovascular prophylaxis.(4)

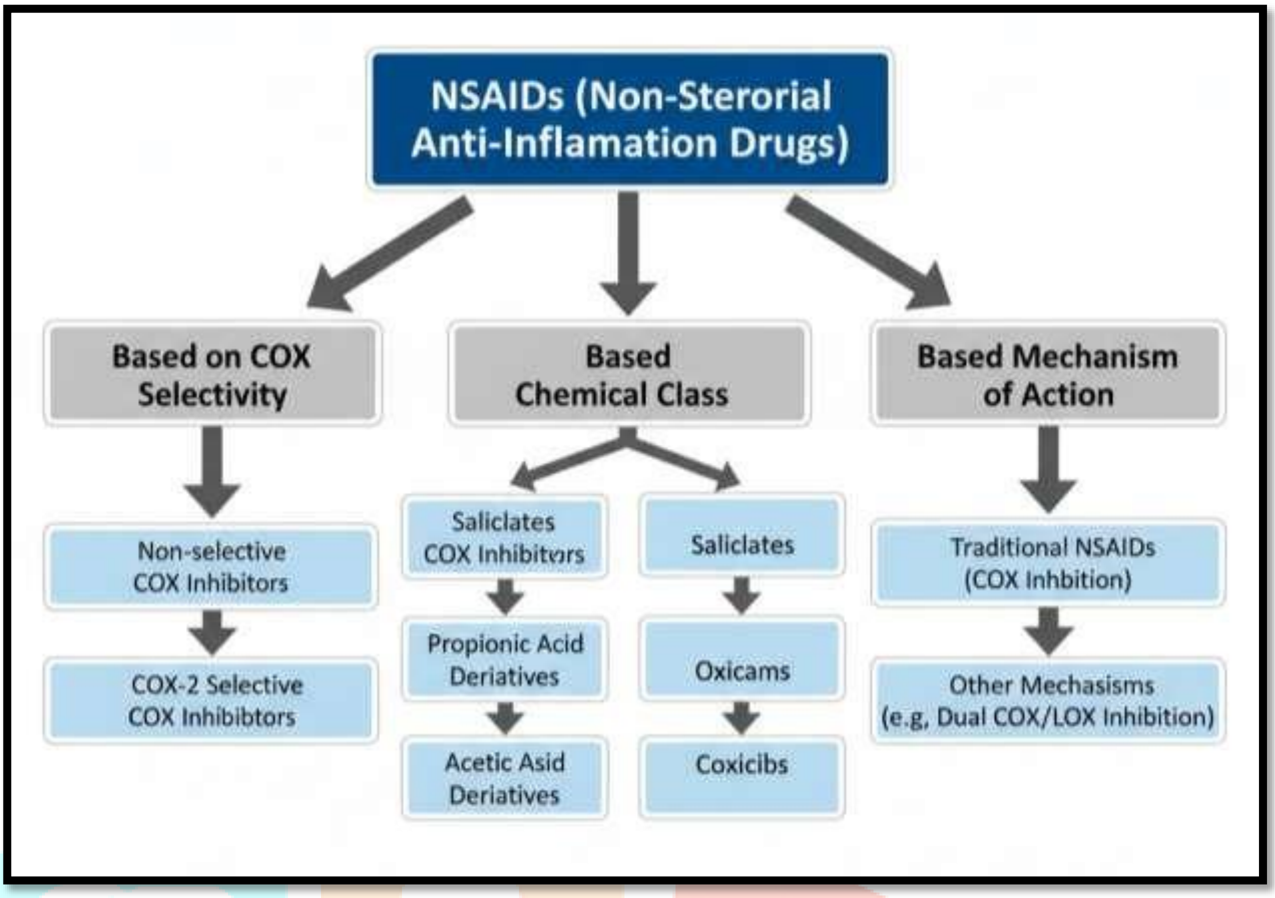

Figure 2 : The Classification Of Nsaids By Chemical Class.

Classification Feature	**Chemical Class**	**Examples of Agents**	**COX Selectivity**	**Key Clinical Notes**
Non-Selective (Traditional) NSAIDs	**Salicylates**	**Aspirin** (Acetylsalicylic Acid), Salsalate	Irreversible Inhibitor (Aspirin)	**Aspirin:** Anti-platelet effect is primary mechanism for low-dose cardiovascular protection. High GI toxicity risk.
	Propionic Acid Derivatives	**Ibuprofen, Naproxen,** Ketoprofen, Flurbiprofen	Non-Selective (&)	**Ibuprofen:** Low GI risk at OTC doses. Short halflife. **Naproxen:** Longer half-life (Twice-daily dosing). Lower CV risk among tNSAIDs.

	Acetic Acid Derivatives	**Diclofenac, Indomethacin,** Ketorolac, Sulindac	Non-Selective (But Diclofenac has some preference)	**Diclofenac:** Good efficacy; one of the highest CV risks. **Indomethacin:** High incidence of side effects (headache). **Ketorolac:** Highly potent; use limited to days (high GI/renal risk).
	Enolic Acid (Oxicam) Derivatives	**Piroxicam, Meloxicam**	& (Meloxicam is mildly preferential)	**Piroxicam:** Very long half-life (once daily). High GI risk. **Meloxicam:** Mild preference provides a slight GI benefit over non-selectives.
Selective NSAIDs	**Coxibs**	**Celecoxib** (only one currently available in the US)	Highly Selective	**Low GI risk** (due to sparing). Increased risk of events (, stroke) due to disrupting / balance.
Other Class	**Non-Acidic Prodrug**	Nabumetone	Non-Selective (active metabolite)	Long half-life. Lower incidence of GI adverse effects due to non-acidic nature.

Table 1: Classification of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

5. Therapeutic Uses

NSAIDs remain indispensable in clinical medicine due to their broad spectrum of pharmacological actions, including analgesic, antipyretic, anti-inflammatory, and antiplatelet effects. Their widespread use reflects not only their effectiveness in managing common symptoms such as pain and fever but also their role in chronic disease management and preventive medicine.(7)

1. Analgesia / Pain Relief

NSAIDs are among the most commonly prescribed and self-administered analgesics for the management of mild to moderate acute pain. They are effective in conditions such as musculoskeletal pain, dental pain, headache, and soft tissue injuries. In chronic pain states, including osteoarthritis and rheumatoid arthritis, NSAIDs improve functional outcomes and quality of life by reducing pain and stiffness. They are also widely prescribed for primary dysmenorrhea, where suppression of uterine prostaglandin synthesis significantly alleviates menstrual cramps. In the postoperative setting, NSAIDs are frequently used as part of a multimodal analgesic regimen, allowing for opioid-sparing effects and improved pain control. Evidence from controlled studies confirms that NSAIDs are superior to placebo and often demonstrate greater efficacy compared to acetaminophen for musculoskeletal and inflammatory pain conditions.

2. Antipyretic / Fever Reduction

NSAIDs exert their antipyretic action by inhibiting prostaglandin E_2 synthesis within the hypothalamic thermoregulatory center, thereby lowering the set-point for body temperature. They are effective in both infectious and non-infectious causes of fever, often used when acetaminophen alone is insufficient.(8)

3. Anti-inflammatory / Disease-Modifying Effects

The anti-inflammatory properties of NSAIDs form the basis of their use in chronic inflammatory disorders. They are integral to the management of inflammatory arthropathies such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and gout. In acute gout flares, NSAIDs remain a first-line treatment to rapidly suppress pain and inflammation. While not considered disease-modifying in the strict sense, their long-term use in inflammatory conditions provides symptomatic relief and enhances patient functionality. Some evidence also supports their adjunctive role in cancer-related pain, although their benefits in tumor biology and disease progression remain under investigation.

4. Cardioprotection / Antiplatelet Effect (Aspirin-Specific)

Low-dose aspirin has a unique therapeutic role due to its irreversible inhibition of platelet COX-1, leading to sustained suppression of thromboxane A_2 production and reduced platelet aggregation. This property underpins its widespread use in the primary and secondary prevention of myocardial infarction, ischemic stroke, and other thromboembolic events. Interestingly, this cardioprotective benefit contrasts with the potential cardiovascular risks associated with other non-aspirin NSAIDs, particularly with long-term or highdose use, highlighting the complexity of class-specific safety profiles.(2.7)

5. Emerging and Investigational Uses

Beyond established indications, NSAIDs are being explored for novel therapeutic roles. Epidemiological and experimental studies suggest potential benefits in neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease) through modulation of neuroinflammation. There is also growing interest in their role in metabolic disorders such as diabetes, and in oncology, where NSAIDs are investigated for their anti-neoplastic properties via COXdependent and COX-independent pathways. Hypotheses regarding perioperative NSAID use to reduce cancer recurrence are under active study, though clinical evidence remains preliminary.Thus, NSAIDs occupy a central place in both symptomatic and adjunctive therapy, although with important risk considerations.(9)

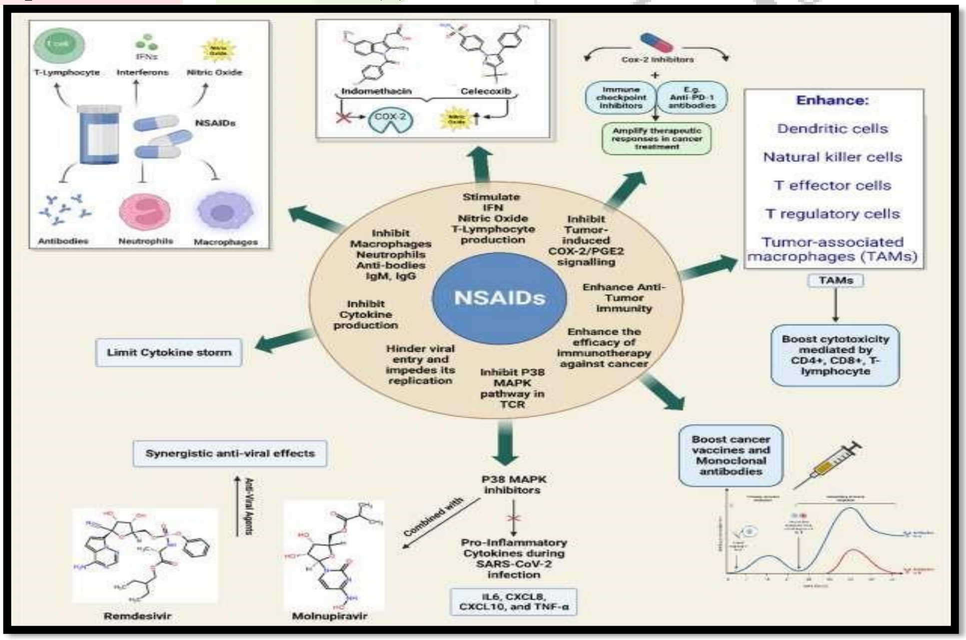

Figure 3: Immunomodulatory effects of NSAIDs in tumor management and viral infections, providing an overview of the synergistic potentials when combined with various therapeutic agents

Table 2 : Therapeutic Uses of NSAIDs

Condition	Preferred NSAIDs	Notes
Acute pain (dental, musculoskeletal)	Ibuprofen, Diclofenac	Rapid relief
Chronic pain (OA, RA)	Naproxen, Celecoxib	Consider risk profile
Dysmenorrhea	Ibuprofen, Mefenamic acid	Commonly prescribed
Gout (acute attack)	Indomethacin, Naproxen	Avoid aspirin
Cardioprotection	Low-dose aspirin	Secondary prevention

6. Mechanism of Action

The therapeutic effects of NSAIDs are primarily mediated through inhibition of cyclooxygenase (COX) enzymes, which catalyze the conversion of arachidonic acid into prostaglandin H_2 (PGH_2), the precursor of biologically active prostaglandins, prostacyclin (PGI_2), and thromboxanes (TXA_2). By suppressing prostaglandin synthesis, NSAIDs reduce key mediators of pain, inflammation, and fever, making them effective across a range of clinical conditions.(4,10)

A COX Isoforms and Their Roles

- ✓ COX-1 is constitutively expressed in various tissues and plays essential "housekeeping" roles, including protection of the gastrointestinal mucosa, maintenance of platelet function, and regulation of renal blood flow. Inhibition of COX-1 is largely responsible for gastrointestinal, renal, and hematological adverse effects associated with traditional NSAIDs.

- ✓ COX-2 is predominantly inducible at sites of inflammation, where it mediates the production of pro-inflammatory prostaglandins such as PGE_2. Selective COX-2 inhibitors were developed to preserve COX-1mediated physiological functions while targeting inflammation. However, COX-2 also has constitutive roles, particularly in vascular endothelium and homeostasis, meaning that selective inhibition can alter the balance between prostacyclin (PGI_2) and thromboxane A_2 (TXA_2), potentially increasing the risk of cardiovascular events.(11)

B Additional Mechanistic Insights

- ✓ Certain novel NSAID derivatives modulate complementary pathways beyond COX inhibition, such as the lipoxygenase (LOX) pathway, nitric oxide (NO) signaling, and soluble epoxide hydrolase pathways, aiming to enhance anti-inflammatory efficacy while minimizing toxicity.
- ✓ Within the central nervous system (CNS), NSAIDs reduce prostaglandin synthesis in the hypothalamus and spinal cord, contributing to antipyretic effects and modulation of pain perception at both peripheral and central levels.
- ✓ Overall, the pharmacological actions of NSAIDs result from a complex interplay between COX inhibition, prostaglandin suppression, and modulation of secondary signaling pathways, which collectively explain both their therapeutic benefits and their adverse effect profiles.(12)

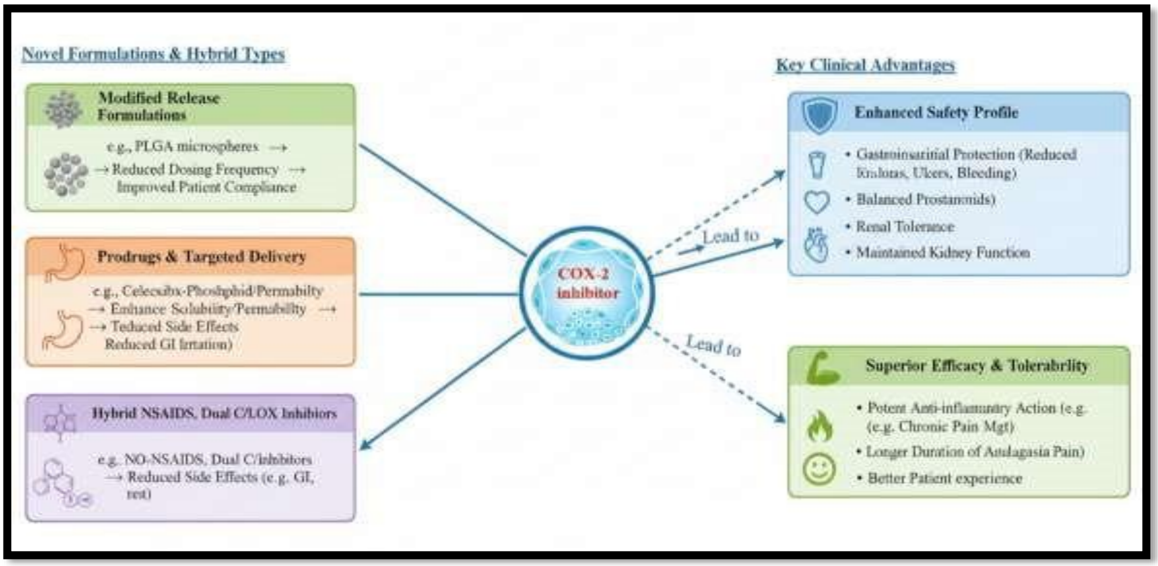

Figure 4 :Recent Advances in NSAID Formulations and Hybrid Types, and their mechanisms for improving safety and efficacy.

7. Recent Advances in Clinical Application & Formulation

In recent years, substantial research has focused on enhancing the **therapeutic efficacy** of NSAIDs while minimizing their **adverse effects**, reflecting a growing emphasis on safer and more patient-specific applications. Advances span pharmaceutical formulation, novel drug derivatives, precision prescribing strategies, and exploration of emerging indications.

1. Formulation and Pharmaceutical Modifications

Innovative drug delivery systems have significantly improved NSAID pharmacokinetics and safety. Submicron or nanoparticle formulations, such as SoluMatrix diclofenac, enable faster absorption, lower effective doses, and reduced systemic exposure, thereby decreasing gastrointestinal and renal toxicity. Similarly, topical and local delivery systems provide targeted antiinflammatory effects at the site of pain or inflammation, limiting systemic absorption and associated adverse effects. These strategies optimize the benefit– risk ratio, particularly in patients who require long-term therapy.(13)

2. Novel NSAID Derivatives and Hybrids : Chemical modification has led to the development of next-generation NSAIDs with improved safety profiles:

- **Nitric oxide–donating NSAIDs (NO-NSAIDs or CINODs)**: These molecules combine traditional NSAID structures with NO donors, promoting vasodilation and protecting the gastrointestinal mucosa and vascular endothelium. While none are currently approved for clinical use, preclinical studies demonstrate promising safety and efficacy.
  - **Dual COX/LOX inhibitors**: By simultaneously targeting cyclooxygenase and lipoxygenase pathways, these agents may prevent shunting of arachidonic acid into leukotriene pathways, potentially reducing gastrointestinal complications.
  - **COX-2/soluble epoxide hydrolase (sEH) hybrids**: These hybrids aim to enhance anti-inflammatory potency while preserving cardiovascular and gastrointestinal safety by combining COX-2 inhibition with modulation of sEH-mediated signaling.(14)

3. Precision and Safer Use Strategies

Clinical advances also emphasize personalized and risk-stratified NSAID therapy. Strategies include:

- Patient stratification based on gastrointestinal, renal, and cardiovascular risk to guide NSAID selection and dosing.
- Co-prescription of gastroprotective agents such as proton pump inhibitors or misoprostol in high-risk populations.
- Adherence to the principle of shortest effective duration at the lowest effective dose.
- Enhanced monitoring and pharmacovigilance, including improved adverse event reporting systems, to detect and mitigate complications early. (15)

4. Emerging and Repurposing Applications

Beyond conventional indications, NSAIDs are under investigation for novel therapeutic roles:

- Modulation of neurodegenerative diseases, metabolic disorders such as diabetes, and cancer prevention or adjunct therapy, leveraging anti inflammatory and anti-proliferative pathways.
- Perioperative use to potentially reduce tumor recurrence, an area supported by preliminary evidence.
- Adjunctive use in cancer pain management, offering opioid-sparing benefits and improved analgesic efficacy. (16)

8. Adverse Effects

Adverse Effects of NSAIDs

NSAIDs, while highly effective for pain, inflammation, and fever, are associated with a spectrum of adverse effects affecting multiple organ systems. The risk of toxicity is influenced by dose, duration of therapy, and individual patient factors, including age, comorbidities, and concomitant medications. Awareness of these risks is essential for safe clinical use.(8,17)

1. Gastrointestinal Toxicity

NSAID use is strongly associated with gastrointestinal (GI) complications, ranging from dyspepsia and gastritis to peptic ulcers, gastrointestinal bleeding, and, in severe cases, perforation. NSAID-induced enteropathy can affect both the small and large intestines, leading to ulcers, strictures, and bleeding. Strategies to reduce GI toxicity include the use of selective COX-2 inhibitors, co-administration of gastroprotective agents such as proton pump inhibitors or misoprostol, and enteric-coated or slow-release formulations to minimize direct mucosal irritation.

2. Renal Adverse Effects

NSAIDs can impair renal function by reducing renal perfusion and altering glomerular hemodynamics. Complications include acute kidney injury, interstitial nephritis, papillary necrosis, fluid retention, and exacerbation of hypertension. Risk is elevated in patients with pre-existing renal disease, volume depletion, or concomitant use of nephrotoxic drugs. (18)

3. Cardiovascular Risks: NSAID therapy is linked to increased cardiovascular morbidity, including hypertension, exacerbation of heart failure, myocardial infarction, and stroke. Selective COX-2 inhibitors, in particular, have been associated with heightened cardiovascular risk, exemplified by the withdrawal of rofecoxib.

Mechanistically, these effects are related to disruption of the prostacyclin (PGI_2)
thromboxane A_2 balance and altered platelet function

4. Hepatic Toxicity: Although uncommon, NSAIDs can induce hepatotoxicity, ranging from asymptomatic transaminitis to severe liver injury in susceptible individuals.

Routine monitoring may be warranted in long-term therapy or high-risk patients.

5. Hematologic Effects

NSAIDs can impair platelet aggregation, primarily via COX-1 inhibition, increasing bleeding risk. Rarely, NSAID use may cause anemia or neutropenia, particularly with chronic exposure.

6. Other Adverse Effects

Additional complications include hypersensitivity reactions, asthma exacerbation, and dermatologic manifestations. NSAID use during late pregnancy is contraindicated due to the risk of fetal renal impairment and premature closure of the ductus arteriosus. Non-medical misuse, such as overuse by athletes, can further amplify these adverse outcomes.(19)

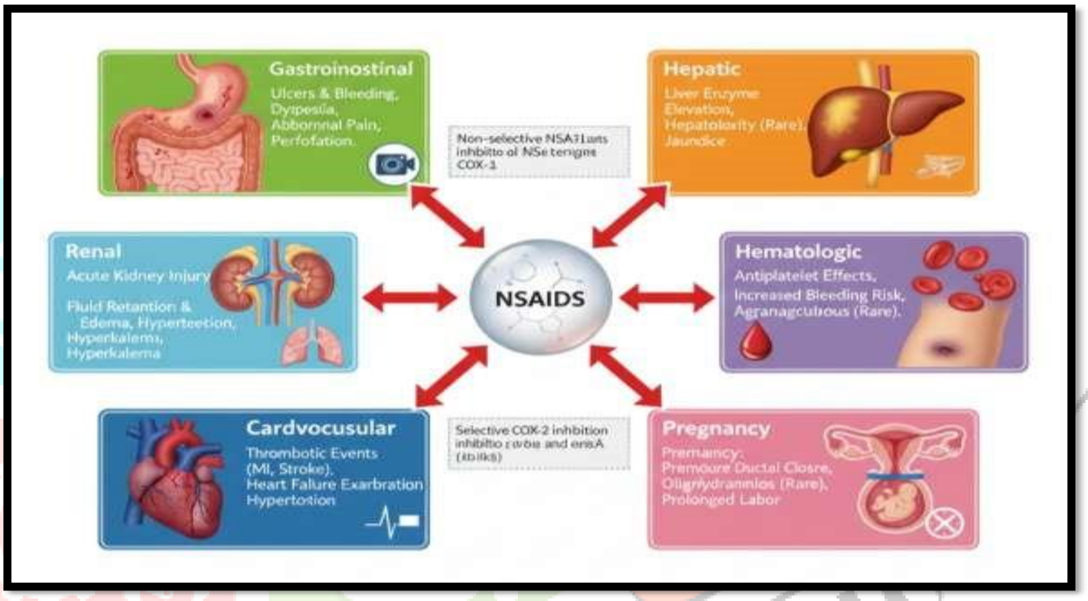

Figure 5 : Overview of Major Systemic Adverse Effects of NSAIDs and Associated Organs.

9.Current Practice and Recent Developments

In contemporary clinical practice, NSAID therapy requires a careful balance between therapeutic efficacy and patient safety, emphasizing a rational, patient-centered approach. Modern strategies integrate individualized risk assessment, evidence-based dosing, and ongoing monitoring to optimize outcomes while minimizing adverse effects.

1. Risk Stratification and Personalized Therapy: Clinicians now routinely evaluate patient-specific gastrointestinal, renal, and cardiovascular risk factors before selecting an NSAID, determining dose, duration, and the need for adjunctive therapy such as proton pump inhibitors (PPIs). This approach allows for individualized therapy and targeted mitigation of potential complications.

2. Lowest Effective Dose, Shortest Duration Principle: To reduce cumulative toxicity, NSAIDs are prescribed at the lowest effective dose for the shortest necessary duration, particularly in populations at elevated risk for adverse events.

3. Co-administration of Gastroprotective Agents: For patients with pre-existing GI risk factors, co-prescription of PPIs or misoprostol remains standard practice, significantly reducing the incidence of NSAID-induced gastrointestinal complications.

4. Selective NSAID Choice: Therapeutic selection increasingly favors agents with lower gastrointestinal or cardiovascular risk profiles. For instance, naproxen may be preferred over diclofenac in patients with cardiovascular concerns, reflecting a nuanced understanding of drug-specific safety profiles. (20)

5. Monitoring and Early Detection: Ongoing surveillance is critical, including renal function tests, blood pressure monitoring, hemoglobin assessment, and vigilance for gastrointestinal symptoms, allowing for early identification and management of adverse effects.

6. Integration of Novel Formulations and Derivatives: Emerging NSAID variants, such as NO-donating NSAIDs (CINODs) and dual COX/LOX inhibitors, are under investigation and may gradually enter clinical practice as evidence of safety and efficacy accumulates. (1,21)

7. Education, Pharmacovigilance, and Stewardship: Patient education on NSAID risks, avoidance of non-medical overuse, and enhanced adverse event reporting systems are integral components of modern NSAID stewardship.

8. Guideline Updates and Regulatory Oversight: Regulatory authorities, including the U.S. Food and Drug Administration (FDA), continue to issue warnings and guidance on NSAID use in high-risk populations, ensuring updated, evidence-based recommendations guide prescribing patterns.(22)

Table 3 : Recent Advances in NSAIDs

Innovation	Example	Advantage	Status
NO-NSAIDs (CINODs)	Naproxcinod	Reduced GI/CV risk	Clinical trials
Dual COX/LOX inhibitors	Licofelone	Balanced prostaglandin/leukotriene inhibition	Investigational
Nanoparticle formulations	Diclofenac submicron	Lower dose, faster onset	Approved in some markets
Topical formulations	Diclofenac gel	Reduced systemic toxicity	Widely available

10. Conclusion: Nonsteroidal anti-inflammatory drugs (NSAIDs) remain a cornerstone of modern pharmacotherapy due to their efficacy in managing pain, inflammation, and fever, with additional roles in cardiovascular protection and emerging therapeutic areas. Their clinical utility, however, is tempered by dose- and duration-dependent adverse effects affecting the gastrointestinal, renal, cardiovascular, hepatic, and hematologic systems. Advances in selective COX inhibitors, novel hybrid derivatives, innovative formulations, and targeted delivery systems aim to improve efficacy while minimizing toxicity. Contemporary practice emphasizes patient-centered approaches, including risk stratification, use of the lowest effective dose for the shortest duration, coprescription of gastroprotective agents, and vigilant monitoring. Ongoing research into new NSAID derivatives, precision therapy, biomarker-guided risk assessment, and expanded indications holds promise for safer and more effective use. Ultimately, optimizing NSAID therapy requires a careful balance between therapeutic benefit and safety, guided by evidence-based strategies, regulatory oversight, and continuous innovation in drug design and clinical practice.

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