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An updated review on NSAIDs

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Abstract
Nonsteroidal anti-inflammatory drugs (NSAIDs) represent a widely utilized class of agents for the treatment of pain, inflammation, and various medical conditions [1]. This overview summarizes their mechanism of action, clinical applications, and associated risks. NSAIDs exert their effects by inhibiting cyclooxygenase (COX) enzymes, which mediate prostaglandin synthesis, with varying selectivity toward COX-1 and COX-2 isoforms [8, 15]. Clinically, they are employed for analgesia, antipyresis, anti-inflammatory purposes, and in certain cardiovascular settings [1]. However, NSAID use is linked to adverse effects, including gastrointestinal irritation, renal impairment, cardiovascular complications, bleeding tendencies, hypersensitivity reactions, and hepatic toxicity[2].The pharmacokinetic and pharmacodynamic profiles of NSAIDs vary widely, influencing their clinical applications and safety profiles. Recent advancements include the investigation of COX-3 as a novel target and the integration of personalized medicine to improve therapeutic safety and efficacy [14]. The use of willow leaves containing salicylate, highly selective cyclooxygenase-2 (COX-2) inhibitors, and the newest dual-acting anti-inflammatory drugs have all undergone rapid and continuous change [7]. Even with the tremendous progress made over the past two decades, researchers continue to strive for the creation of safer and more effective treatments for inflammatory diseases. For NSAID therapy to reduce risk and maximize results, a patient-specific strategy is necessary. Ongoing research aims to develop more selective and safer NSAID options to enhance clinical benefit while reducing harm.

Keywords: NSAIDs, inflammation, prostaglandins, inhibitors, COXIBs, cardiovascular risk, cyclooxygenase

Introduction
NSAIDs, or nonsteroidal anti-inflammatory drugs, are a vital component of contemporary medicine's toolkit for treating a wide range of illnesses and managing pain and inflammation [1]. The effectiveness and adaptability of these drugs have won them a place in healthcare. One of the most popular classes of therapeutic agents for the management of fever, inflammation, and pain is non-steroidal anti-inflammatory medications (NSAIDs) [3]. These medications achieve their anti-inflammatory, analgesic, and antipyretic actions mainly by blocking the cyclooxygenase (COX) enzymes that are involved in the manufacture of prostaglandins [8, 15]. Since the late 19th century, when aspirin was discovered, NSAID development has advanced dramatically, producing a wide variety of drugs with different levels of potency, toxicity profiles, and COX-1/COX-2 selectivity [6, 10]. Cyclooxygenases (COX) are essential enzymes involved in the synthesis of prostaglandins, and NSAIDs mainly work by inhibiting their activity [8, 13]. Prostaglandins are lipid molecules [as messengers in the body, controlling temperature, inflammation, and even pain perception [16]. NSAIDs have well-documented side effects, including cardiovascular risks, renal failure, and gastrointestinal (GI) bleeding, despite their clinical usefulness [2, 20]. The non-selective suppression of COX-1, which is physiologically essential for stomach protection and platelet aggregation, is the main cause of these safety issues. Consequently, medicinal chemists have concentrated on creating NSAIDs with better safety profiles, especially those that specifically block COX-2, the isoform primarily linked to inflammation [17].
About 3, 500 years ago, the Greek physician Hippocrates employed a willow bark and leaf extract to treat fever and inflammation for the first time [4]. In the 17th century, salicylic acid was discovered to be the extract's active ingredient [9]. Bayer first released acetylsalicylic acid, the acetyl derivative of salicylic acid (aspirin), in 1869, but the drug's mode of action was unknown [6].

After nearly a century, Vane and colleagues investigated the molecular mechanism of aspirin [13]. Their discovery that all these NSAIDs block the COX enzyme has now served as a foundation for the development of new NSAIDs [8].Many COX inhibitors have been developed to combat undesired inflammation in response to these facts, and some of them are also being used as treatment. The first-generation COX inhibitors include nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin and diclofenac, which inhibit both COX-I and COX-II enzymes [1]. However, due to this nonselective targeting of COX-I, these agents trigger undesirable side effects of peptide ulcers and stomach bleeding to name a few [2].To address the potential adverse effects of nonselective COX inhibitors, COX-II selective anti-inflammatory drugs (COXIBs) have been developed. Some of the typical examples of these second-generation NSAIDs include Celecoxib, Valdecoxib, and Rofecoxib [17]. Compared to COX-I, these medications exhibit strong selectivity indices for COX-II inhibition. With the identification of COX-2, an inducible isoform, it became evident that there are two isoforms of COX. The constitutive isoform, COX-1, mediates several physiological functions and is cytoprotective, while the inducible isoform, COX-2, promotes inflammation. Conventional NSAIDs inhibit both isoforms of COX-1 and COX-2 [8]. The discovery of COX-2 paved the way for the creation of selective COX-2 inhibitors (COXIBs); these included the blockbuster medications celecoxib, co-developed by G. D. Searle and Pfizer in 1999, rofecoxib by Merck, and numerous more [18].The purpose of this review is to examine the chemical diversity of NSAIDs, their modes of action, structure-activity correlations (SAR), and the continuous attempts to improve its therapeutic index through prodrug strategies, molecular changes, and innovative formulations.

Origin and development of nsaids

Every day, more than 30 million NSAIDs, either aspirin or non-aspirin, are used intentionally or unknowingly. (Emery 2001; Bjarnason *et al*. 2018) [2]. Aspirin™, the NSAID's progenitor, has been the most used medication for more than 120 years (Desborough and Keeling 2017)[3].The origin of aspirin or non-aspirin NSAIDs can be traced back to accidental discoveries made in antiquity The Sumerians were the first people to use willow leaves (Salix species) to treat inflammatory rheumatic diseases (Montinari *et al*. 2019)[4].The Ebers Papyrus (1534 B.C.) also mentions willow leaves as being beneficial for reducing inflammatory symptoms (Bryan 1974) [5].The Greek physician Hippocrates (c. 400 B.C.), who is considered the father of medicine, suggested using extracts from the leaves and bark of Salix plants to treat pain and fever a few years later [4, 6].
Furthermore, Pliny the Elder (23 CE), Dioscorides (40 CE), and Galen (129 CE) all documented several reports highlighting the extracts' medical effectiveness, and these reports have been passed down from one generation to the next (Lichterman 2004) [6]. The clinical use of willow bark extract on fifty patients suffering from fever or ague in the seventeenth century was made possible by these pre-records. Edward Stone, the first writer to document the therapeutic potential of willow bark as an antipyretic in a scientific way, presented the trial's findings in this way (Stone 1764) [7].Due to advancements in chemistry, German pharmacologist Joseph Buchner isolated willow's active constituent, known as "salicin, " in the middle to late nineteenth century (Vane and Botting 1992) [8]. Salicylic acid, the main component used to make aspirin, was extracted from salicin a few years later by the Italian chemist Raffaele Piria (Piria1838) [9].
Salicylic acid's chemical synthesis was significantly advanced in 1958 by German scientist Hermann Kolbe and his assistant Rudolf Wilhelm Schmitt (Sneader 2005) [10].Synthetic salicylate was the subject of multiple clinical trials during the same years due to its industrial manufacturing. The compound's efficacy stimulated additional research to create salicylate derivatives with fewer side effects. Pharmaceutical scientist Felix Hoffmann identified the parameters of the synthesis that produced acetylsalicylic acid in Bayer's laboratory in 1897 (Zündorf and Bayer AG 1997) [11]. Bayer AG patented this pure, stable, and affordable substance, which is produced as tablet form named Aspirin.Due to its strong anti-inflammatory, antipyretic, and antiplatelet therapeutic effects, about 100 billion conventional aspirin tablets are still sold annually, despite the passage of time (Bjarnason *et al*. 2018; Casey 2019) [2, 12]. Classical NSAIDs were developed because of both clinical results and the aspirin's commercial success. In the pre-prostaglandin (PG) era, medications including ibuprofen, indomethacin, and phenylbutazone eventually made their way into the market (Desborough and Keeling 2017) [3]. The mechanism of action of aspirin and a class of NSAIDs was first satisfactorily explained by John R. Vane and his colleagues in 1971 (Piper and Vane 1969; Vane 1971) [12, 13]., showing that these drugs impede the production of PG in a dose-dependent way (Vane 1971).Prostacyclins were later discovered by Vane and Moncada, and Vane, together with Samuelsson and Bergstrom, shared the 1982 Nobel Prize in Physiology and Medicine for his studies on "prostaglandins and related biologically active substances.". "When Hemler *et al*. identified the biological target of aspirin and NSAIDs, proving that cyclooxygenase (COX) is the primary enzyme in the manufacture of PG, the problem was finally solved (Hemler and Lands 1976) [14]. The process of classifying and evaluating NSAIDs has changed from focusing on chemical and structural similarities to considering the biological target. Moreover, the molecular mechanisms that underlie the adverse effects of NSAIDs have been found.

Mechanism of action

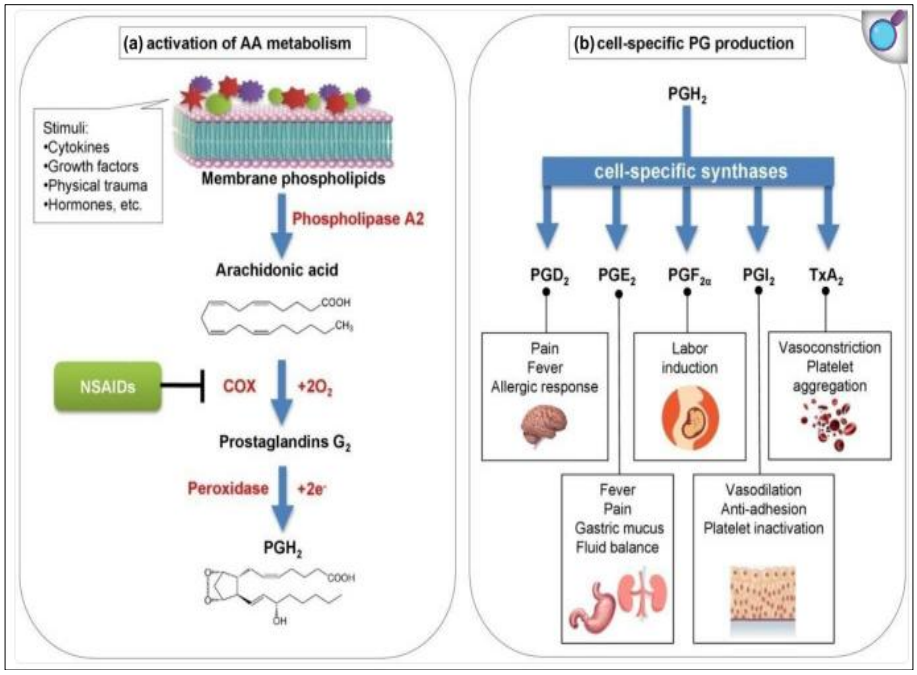

Fig 1: NSAIDS's mechanism of action

NSAIDs are a class of pharmaceuticals that share a common molecular mechanism but have a wide range of structural and pharmacological characteristics [1].NSAIDs work by preventing the cyclooxygenases (COX) enzymes from producing prostaglandins, which are lipid molecules that control analgesic, antipyretic and anti-inflammatory properties [8, 15]. Inhibition of cyclooxygenase (COX) reduces inflammation, fever, and pain by inhibiting the synthesis of prostaglandin and other eicosanoid molecules [13, 15]. Prostaglandins increase the hypothalamic thermostat set point, promote vasodilation, and are important in anti-nociception, whereas thromboxane contribute to platelet adhesion [8, 13]. Prostaglandin endoperoxide H synthase (PGHS), another name for the cyclooxygenase (COX) enzyme, comes in two isoforms: PGHS-1, also called COX-1, and PGHS-2, also called COX-2[15]. Only 60% of their structures are similar, indicating a substantial structural difference.Both isoforms are membrane-bound glycoproteins that catalyze the conversion of arachidonic acid to prostanoid COX-1, which is found in most tissues and is essential for preserving the integrity of the stomach lining and controlling blood coagulation, even though their genes are different. The generation of prostaglandins linked to pain and inflammation is mainly caused by COX-2, which is activated at inflammatory sites [15, 17].

Platelets, endothelium, and seminal vesicles are among most mammalian cells and organs that constitutively express COX-1 [15]. Under dormant conditions, it carries out continuous regulatory tasks known as "housekeeping duties." COX-1 activity produces prostaglandins that have a variety of uses, including mucus synthesis, platelet aggregation, macrophage differentiation, and gastro and renal protection [15, 17]. Molecular studies have shown that COX-1 mRNA and protein expression remain unchanged in inflammatory circumstances, confirming their limited participation in the inflammatory process [14]. Constitutively expressed COX-1 catalyses the synthesis of prostaglandins, which include pro-aggregatory thromboxane A2 in platelets, mucosal protection in the gastrointestinal tract, and the maintenance of normal renal function in the kidneys. However, COX-1 continues to be relevant in both clinical and experimental settings because of the negative consequences caused by certain NSAIDs' nonselective inhibition of cyclooxygenase enzymes.

Tissue damage and other stimuli like lipopolysaccharide (LPS), interleukin-1, and tumour necrosis factor alpha (TNFα) can activate the inducible enzyme COX-2. It mediates inflammatory, pain, fever, and carcinogenic responses and is active at injury sites and in a range of tissues, including rheumatoid synovial endothelial cells and the vascular endothelium [17, 18]. In inflammatory processes, COX-2 levels rise significantly, which leads to a rise in the production of pro-inflammatory prostaglandins. Originally believed to be solely inducible, research has revealed that COX-2 also plays some constitutive or regulatory roles [16].COX-2 expression is thought to play a part in the modulation of pain, inflammation, and fever and can be triggered by cytokines and other inflammatory mediators in a variety of tissues, including endothelial cells.The potential existence of a third isoform, COX-3, has been proposed as an explanation for the mechanism of action of acetaminophen, a mild inhibitor of COX-1 and COX-2 [14].

The presence of AA at the site of action is necessary to produce the PGs and TxAs. The enzymes known as secretory and cytoplasmic phospholipases A2, which balance the levels of eicosanoid, are activated when the cell is stimulated by different stimuli. This results in the conversion of membrane-bound arachidonate into free AA. When AA is released, COX pathways are triggered, allowing COXs to oxygenate these molecules and produce prostaglandin G2. This molecule is immediately converted by peroxidase into prostaglandin H2 (PGH2), which serves as a substrate for the enzymes specific to the cell to produce bioactive PG species, including prostacyclin (PGI2), PGD2, PGE2, and PGF2α, thromboxane A2 (TxA2), (Smith and Langenbach 2001) [15].These eicosanoids are considered inadequate for the treatment of NSAIDS. According to earlier research, the AA cascade contains prostanoids derived from COX-2, such as PGE2 and PGI2, which are significantly elevated in inflammatory tissues. These

prostanoids increase local blood flow, vascular permeability, leukocyte infiltration, and heat production, all of which contribute to inflammation, pain, and fever response (Smyth *et al*. 2009; Ricciotti and FitzGerald 2011; Aoki and Narumiya2012) [16, 18]. Conversely, prostanoids generated from COX-1 are physiological regulators of platelet aggregation, renal balance, and the digestive mucosal barrier.

Therefore, during long-term NSAID therapy, undesirable inhibition of COX-1 causes a sharp decline in the levels of gastroprotective PGs, leading to serious side effects like stomach erosions, bleeding, and gastrointestinal tract perforations [2, 19]. In fact, it is estimated that 15.3 deaths occur for every 100, 000 NSAID users in Europe (Lanas *et al*. 2006). Researchers have created a different strategy to treat and prevent inflammation-based disorders because of these growing concerns. A possible tactic was selective COX-2 inhibition, which spares the gastroprotective prostaglandin production mediated by constitutive COX by blocking the release of excess pro-inflammatory PGE2 [17, 18].

Pain, fever, and inflammation

Though several studies in the literature suggest a possible and substantial central analgesic effect, NSAIDs are primarily considered of as peripheral pain inhibitors [1, 13]. In reaction to electrical, chemical, or physical stimuli, nociception is triggered by a variety of mediators at the periphery. Prostaglandins sensitize nociceptors by working in concert with other mediators [15, 17]. Several animal models of pain have shown central analgesic benefits from some NSAIDs. This is explained by a disturbance in the production of central prostaglandins and other modulators of the nociceptive pathway [13]. Evidence supporting central activity includes studies that demonstrate the antinociceptive effect of spinally administered ibuprofen and the inhibitory effect of NSAIDs on prostaglandin expression in cerebrospinal fluid induced by N-methyl-D-aspartate (NMDA) receptor activation [14].

NSAIDs have shown promise in treating inflammatory diseases such arthritis, severe trauma, and inflammatory pain [2]. Vasodilation, the extravasation of protein exudates, and nociception are all mediated by inflammatory mediators at the site of damage. Prostaglandins, which are important in this process, are suppressed here [16, 17]. Although the primary mechanism for NSAIDs' anti-inflammatory effects is still thought to be COX inhibition, other processes that are loosely referred to as non-COX mechanisms have been documented in the literature. NNF-κB, a transcription factor for pro-inflammatory proteins like chemokines, adhesion molecules, and cytokines, has been shown to be suppressed by NSAIDs. Additionally, some membrane stability, activator protein 1 inhibition, and a decrease in reactive oxygen species (ROS) formation are demonstrated by NSAIDs [1].

By preventing COX-mediated prostaglandin production, NSAIDs reduce fever [8, 15]. Cells of the innate immune system react to exposure to exogenous pyrogens, primarily pathogen-associated molecular patterns (lipopolysaccharide, peptidoglycan, viral RNA, etc.), by releasing endogenous pyrogens to cause pyrexia. In the preoptic hypothalamic area of the brain, circulating interleukin-1, interleukin-6, and TNFα reach the brain and trigger prostaglandin production by cyclooxygenase [15, 17]. To reset the body's thermoregulation, prostaglandin E2 (PGE2) attaches itself to an EP-3 receptor on the hypothalamic endothelium [18]. To reach this desired temperature, a subsequent physiological procedure takes place. NSAIDs have been effective in reducing the negative effects of high and prolonged temperatures because they interfere with this process by inhibiting COX [8]. It's crucial to remember that they don't affect either the atypical rise in body temperature or abnormal ones like heat stroke and malignant hyperthermia. These situations include mechanisms that are not related to the inflammatory pathway of COX/prostaglandin.

Classification of NSAIDs

Numerous attributes, such as COX selectivity and chemical and pharmacological features, can be used to categorize NSAIDs.Many chemical similarities exist across NSAIDs because they are weak acids that are relatively lipid soluble. However, some variations in pharmacokinetic characteristics are clinically significant [1, 8].

Classification of NSAIDs based on structure

Based on their chemical structure, NSAIDs can be generally divided into

1. **Salicylic acid derivates:** Acetylsalicylic acid (aspirin), sulfasalazine
2. **Para-aminophenol derivates:** Acetaminophen* (paracetamol)
3. **Note:** While paracetamol is structurally related to NSAIDs and often grouped with them, it lacks significant anti-inflammatory activity. Unlike traditional NSAIDs, which inhibit both COX-1 and COX-2 enzymes peripherally, paracetamol is believed to act mainly in the central nervous system, possibly via COX-3 inhibition. Therefore, it is not considered a true NSAID pharmacologically.
4. **Indole and indene acetic acids:** Etodolac, indomethacin, sulindac
5. **Hetero-aryl acetic acids:** Ketorolac, diclofenac, tolmetin
   Aryl-propionic acids ketoprofen, ibuprofen, flurbiprofen, naproxen, fenoprofen, oxaprozin, fenclofenac, aceclofenac,
6. **Anthranilic acids (fenamates):** mefenamic acid, meclofenamic acid
7. **Enolic acids (oxicam):** piroxicam, tenoxicam, meloxicam
8. **Alkanones:** nabumetone
9. **Pyrazolidinediones:** Phenylbutazone, oxyphenylbutazone
10. **Diary heterocycles (selective COX-2 inhibitors):** celecoxib, rofecoxib, valdecoxib, lumiracoxib, parecoxib, eterocoxib.

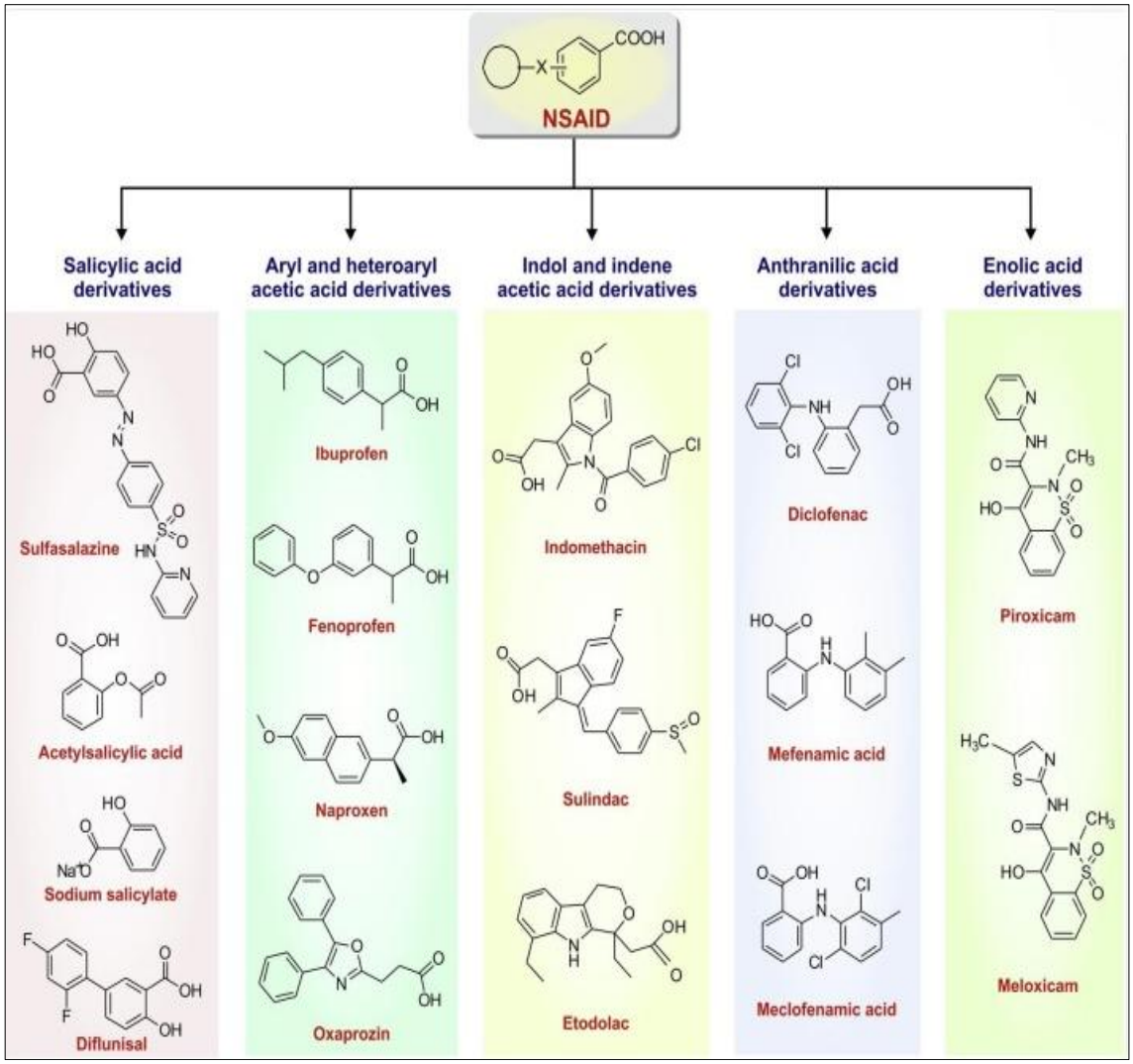

Fig 2: NSAID (non-steroidal anti-inflammatory medication) classification based on structure.

Classification of NSAIDs based on plasma half-life (t½)

NSAIDs are weak acids that are comparatively lipid-soluble and share many chemical characteristics, though their pharmacokinetic characteristics may differ. They undergo a variety of hepatic transformations by CYP3A and CYP2C and/or glucuronidation, but the majority are fully absorbed, have limited distribution volumes, are strongly bound to serum proteins, and have negligible first-pass hepatic metabolism. NSAIDs can be categorized as "long-acting" (lasting more than six hours) or "short-acting" (lasting less than six hours), though their half-lives also vary. NSAIDs can also be divided into two groups: short-acting (plasma half-life < 6 h) such as aspirin, diclofenac, and ibuprofen, and long-acting (half-life approximately > 10 h) such as naproxen and celecoxib. Ibuprofen and other medications with short half-lives have a rapid onset of action, making them appropriate for treating acute pain. However, NSAIDs, like naproxen, have a longer half-life and are helpful in treating chronic problems [1].

Classification of NSAIDS according to their COX inhibitory activity: [8, 15].

Table 1: NSAID classification based on PGHS-selective inhibitory effect

Group 1	Poorly selective NSAIDs that fully inhibit both COX-1 and COX-2 (< 5-fold COX-2 selectivity)	Ibuprofen, diclofenac, aspirin, piroxicam, naproxen
Group 2	NSAIDs capable of inhibiting both COX-1 and COX-2 with a preferential selectivity toward COX-2 (5-to-50-fold COX-2 selectivity)	Celecoxib, meloxicam, nimesulide, etodolac
Group 3	NSAIDs with >50-fold COX-2 selectivity that highly inhibit COX-2 but only weakly inhibit COX-1	Rofecoxib, NS-398
Group 4	NSAIDs that appear to only weakly inhibit COX-1 and COX-2	Sodium salicylate, nabumetone

NSAIDS are classified as either non-selective or selective COX-2 inhibitors based on the isoenzyme's selectivity.

1. Non-selective COX inhibitors: This class has less adverse effects and lacks specific inhibitory impact on COX isoforms and lacks the selectivity. Ibuprofen, ketoprofen, naproxen, and aspirin 23 are well-known members of this class. These drugs have major negative effects on the gastrointestinal tract, even though they are still advised for use as analgesics and anti-inflammatory agents in rheumatoid arthritis, degenerative joint disease, ankylosing spondylitis, and periarticular diseases like tendinitis. The

two main causes of gastrointestinal tract injury are the direct attack of the carboxylic acid moiety (-COOH) on GIT mucosal cells and the decrease in PG production in tissues, which diminishes the cytoprotective effect of PGs on GIT health [2, 19].

2. Selective cyclooxygenase-2 enzyme (COX-2) inhibitors (COXIBs)

To prevent the adverse effects of non-selective NSAIDs on the gastrointestinal tract, researchers began searching for other options The structural differences between the COX-1 and COX-2 isoenzymes are substantial yet negligible. The cavity that arachidonic acid occupies in both enzymes is the same. However, the primary distinction is found in the existence of a little extra pocket in the structure of the COX-2 enzyme. Therefore, having an extension that binds to the COX-2 extra pocket specifically is essential for improving selectivity towards the COX-2 enzyme.One feature of COXIBs, which are selective COX-2 inhibitors, is their pharmacophore, a carboxylic or heterocyclic five-membered ring. Substituted sulfonyl groups are also thought to be pharmacophores that can detect the COX-2 active site pocket, based on studies of structure-activity relationships.

First generation COXIBs

Celecoxib® and rofecoxib® are two of the first and best-known COX-2 inhibitors.

Second generation COXIBs

Among this class, valdecoxib, parecoxib, and etoricoxib are the most effective.

Administration

The most popular form of NSAIDs is an oral tablet. The following are the dosages for the most popular over-the-counter NSAIDs, per the package insert: [1, 15].

- **Ibuprofen:** Ibuprofen: Take one or two 200 mg tablets of ibuprofen every four to six hours as long as symptoms last. Ibuprofen dosages cannot exceed 1200 mg per day.
- **Aspirin:**325 mg tablets of aspirin at regular strength, taken once or twice every four hours, or three times every six hours. The daily limit for aspirin is 4000 mg.
- **Naproxen:** One to two 220 mg pills of naproxen sodium should be taken every eight to twelve hours. 660 milligrams of naproxen sodium is the daily maximum.

Topical NSAIDs are also available (diclofenac sodium gel 1%, diclofenac sodium hydroxyethyl pyrrolidine 1.3% patch, and diclofenac sodium 1.5% topical solution). In order to help manage pain and reduce temperature, several NSAIDs can also be administered intravenously. For example, ibuprofen can be administered as a 30-minute infusion and utilized as a non-opioid analgesic. Studies have shown that combining ibuprofen and morphine in postoperative adult patients can reduce the amount of morphine used overall; the recommended dosage for treating pyrexia is 400 mg initially, followed by 400 or 100 to 200 mg every 4 to 6 hours as needed, and for treating pain, 400 to 800 mg every 6 hours as needed. Ketorolac can also be given parenterally.

Safety Concerns and Toxicities: Non-steroidal anti-inflammatory drugs (NSAIDs) have several adverse effects despite their therapeutic advantages, particularly when taken often or in larger dosages. NSAID use raises the risk of renal disease, unfavorable cardiovascular events, and a variety of gastrointestinal (GI) issues.

Cardiovascular risks

COX-2 inhibitors have been associated with an increased risk of cardiovascular events, such as heart attack and stroke, hypertension [17, 18].The mechanism for this has been proposed to be the effect of COX inhibition on the equilibrium between the production of anti-aggregatory prostaglandin I2 in endothelial cells and pro-aggregatory thromboxane in platelets mediated by COX-2 [15, 17]. Aside from aspirin, NSAIDs raise the risk of stroke and myocardial infarction. After using it for at least a week, this happens. Because they raise the risk of death or recurrent MI, they are not advised for people who have already experienced a heart attack. Research suggests that naproxen might be the least dangerous of them [17, 18]. NSAIDs are linked to a doubled risk of heart failure in individuals without a history of heart disease, except for (low dose) aspirin. Except for low-dose aspirin, NSAID use was linked to a more than ten-fold increase in heart failure in people with such a history. Naproxen and ibuprofen raise mortality risk (hazard ratio) in heart failure patients by about 1.2-1.3, rofecoxib and celecoxib by 1.7, and diclofenac by 2.1 [19].

All NSAIDs should be used at the lowest dosage recommended by the American Heart Association. According to these and other guidelines, such as those issued by the American College of Rheumatology, patients with cardiovascular risk factors (such as hypertension, hypercholesterolemia, angina, edema, recent bypass surgery, and a history of myocardial infarction or other cardiovascular events) should avoid all NSAIDs, and in particular, COX-2-selective agents, whenever possible [19].They should only be employed when the benefits outweigh the elevated cardiovascular risk and alternative therapy have not been able to adequately relieve pain. Naproxen is the recommended NSAID of choice when NSAID medication is necessary for patients who are at risk of cardiovascular problems.

Gastrointestinal toxicity

NSAIDs have the potential to cause ulcers, gastritis, and gastrointestinal bleeding by irritating the stomach lining. The inhibition of COX-1, which stops the production of prostaglandins that shield the gastric mucosa, is probably the cause of the negative effects in the stomach [1, 2]. The damage is more likely in a patient who has a prior history of peptic ulcers [15]. The usage of COX-2 selective NSAIDs is a less dangerous option because it is COX-1 specific. High NSAID dosage, advanced age, Helicobacter pylori infection, a history of ulcer or ulcer-related complications, and concurrent use of over-the-counter NSAIDs, low-dose aspirin, anticoagulants, or corticosteroids are among the risk factors for NSAID-associated gastrointestinal injury [15, 18]. NSAID users frequently use low-dose aspirin concurrently for cardiovascular prevention (about 20-25% in clinical studies. however, this eliminates the gastrointestinal advantages of COX-2-selective drugs and raises the risk of mucosal injury.Inhibiting COX-1 and COX-2 lowers the amounts of protecting prostaglandins, whereas the acidic

chemicals directly irritate the stomach mucosa [18].Inhibiting prostaglandin synthesis in the GI tract results in increased secretion of stomach acid, decreased secretion of bicarbonate, decreased secretion of mucus, and decreased trophic effects on the epithelial mucosa.

While ibuprofen (at lower doses) and diclofenac seem to have lower rates of gastric adverse effects, the use of indomethacin, ketoprofen, and piroxicam appears to have the highest rate [2, 15].

GI protective agents such Misoprostol, H2-receptor antagonists (H2RA), or proton pump inhibitors (PPI) can help avoid gastroduodenal ulcers caused by NSAIDs. Approximately 20% of elderly patients taking chronic NSAIDs employ this tactic [4]. Another tactic to reduce GI side effects is to use COX-2 selective NSAIDs instead of nonselective ones. Luminacoxib, celecoxib, and rofecoxib are examples of COX-2 inhibitors that have been shown in numerous studies to cause less harm to the GI mucosa than non-selective NSAIDs [12, 15]. These results were supported by Rhame *et al*.'s study of elderly people taking low-dose aspirin. They observed that compared to non-selective NSAIDs, celecoxib has a better GI safety profile.

Risk of renal injury

Acute kidney injury (AKI) and chronic kidney disease (CKD), which includes electrolyte imbalance, glomerulonephritis, renal papillary necrosis, fluid retention-induced hypertension, renal tubular acidosis, hyponatremia, and hyperkalaemia, are among the numerous nephrological complications that NSAIDs carry in addition to CVD and GI issues [15, 16].Renal adverse effects are because COX-1 and COX-2 facilitate the production of prostaglandins that play a role in renal hemodynamic. Inhibiting prostaglandin synthesis does not present a significant issue in patients with normal renal function; however, in patients with renal failure, prostaglandins are more important and can cause issues when lowered with NSAIDs [15]. The glomerular afferent arterioles are often dilated by prostaglandinsThis contributes to the maintenance of normal glomerular perfusion and glomerular filtration rate (GFR), which are indicators of kidney function. In kidney failure, this is especially crucial since the kidney is attempting to maintain renal perfusion pressure by raising angiotensin II levels [18]. Angiotensin II ordinarily constricts the efferent arteriole, but at these high levels it also constricts the afferent arteriole entering the glomerulus.Because NSAIDs prevent the prostaglandin-mediated impact of afferent arteriole dilatation, particularly in kidney failure, they promote unopposed constriction of the afferent arteriole, which lowers RPF (renal perfusion flow) and GFR [16].

Hepatic toxicity

Although it happens less frequently than gastrointestinal toxicity, hepatic toxicity is another NSAID-related side effect (Sriuttha *et al*., 2018).Hepatotoxicity, or elevated aminotransferase levels, is a rare side effect of NSAIDs, and hospitalization for liver-related reasons is extremely uncommon.Compared to the other NSAIDs, diclofenac has a higher rate of hepatotoxic consequences [15]. NSAIDs should not be taken by patients with liver impairment. Hepatic failure, liver necrosis, fulminant hepatitis, and jaundice are among the severe reactions that have been documented. While infrequent, liver toxicity caused by NSAIDs is clinically important and typically idiosyncratic, meaning it arises unpredictably and does not correlate with dosage [16]. This adverse effect is believed to result from reactive metabolites-especially those formed by drugs like diclofenac and nimesulide-which can covalently bind to liver proteins, triggering oxidative damage, mitochondrial injury, or immune-mediated reactions. Individual susceptibility, influenced by factors such as HLA genotypes and CYP2C9 enzymevariants, also plays a key role. AmongNSAIDs, diclofenac is most linked to liver injury, whereas nimesulide has shown more severe hepatotoxic potential, prompting regulatory limitations in several regions [15, 16].

Drug Interactions

One of the most frequent reasons for adverse drug reactions are NSAIDS. Elderly patients should be provided NSAIDs with caution as their ages and medication regimens grow. When taken with certain medications, NSAIDs can change the risk of bleeding and/or gastrointestinal ulcers [16, 17].

In addition to blocking the excretion of methotrexate and lithium, NSAIDs impair kidney blood flow, which diminishes the effectiveness of diuretics. When NSAIDs are taken with other medications that also reduce blood clotting, like warfarin, the reduced capacity to form blood clots can raise the risk of bleeding. NSAIDs have the potential to worsen hypertension, or high blood pressure, which would counteract the effects of antihypertensives such ACE inhibitors. NSAIDs may impair the effectiveness of SSRI antidepressants by interfering with the cytokine derivatives TNFα and IFNγ. When used with SSRIs, NSAIDs increase the risk of adverse gastrointestinal side effects.

When taken with SSRIs, NSAIDs raise the risk of brain haemorrhages and internal bleeding. By Interacting with corticosteroids, they increase the risk of GI bleeding. By Interacting with Angiotensin-converting-enzyme inhibitor and Angiotensin Receptor Blockers they increase the blood pressure.

Recent advances and novel NSAIDs

Considering the adverse gastrointestinal and cardiovascular effects associated with conventional NSAIDs, recent pharmaceutical research has focused on modifying NSAID structures and exploring dual-target therapeutic strategies. Several investigational agents have emerged with improved efficacy and safety profiles.

1. Licofelone [21]

It is a dual-action agent that inhibits both cyclooxygenase and 5-lipoxygenase pathways, thereby reducing the synthesis of prostaglandins and leukotrienes. This mechanism may offer enhanced anti-inflammatory action with reduced gastrointestinal and cardiovascular side effects. It has the potential to treat osteoarthritis and appears to be a safer substitute for conventional NSAIDs, according to phase III trials. "Moreover, preclinical studies have shown that Licofelone may also exhibit chondroprotective effects by slowing cartilage degradation, further supporting its role in joint disease management."

2. Naproxcinod: This naproxen derivative, which releases nitric oxide, is intended to protect the stomach mucosa while also having anti-inflammatory properties. Naproxcinod has shown positive hemodynamic effects, such as blood pressure stabilization, in addition to its anti-inflammatory

and analgesic properties. These effects may be especially advantageous for patients with cardiovascular risk factors.

3. ATB-346: ATB-346 is a derivative of naproxen that releases H_2S.H_2S may have anti-inflammatory and antioxidant properties in addition to its cytoprotective effects on the stomach mucosa. While maintaining similar anti-inflammatory activity, ATB-346 showed a considerably decreased frequency of GI lesions in phase II trials when compared to naproxen [23].

4. Furetoxib: Furetoxib is a more recent selective COX-2 inhibitor that was created for use in veterinary medicine and osteoarthritis. It has proven to be selective for COX-2 and to have a better GI safety profile than other coxibs. Despite being mostly utilized in veterinary medicine, its chemical design encourages more research into COX-2 selective drugs that pose less of a risk to the heart [24].

5. Tepoxalin

Like licofelone, tepoxalin inhibits the COX and 5-LOX enzymes. Although it was first authorized for use in animal medicine, its potential to treat inflammatory human conditions including arthritis has drawn interest. Its dual inhibitory mechanism may minimize negative effects related to prostaglandins and leukotrienes while reducing inflammation.

These emerging agents represent the next generation of NSAIDs that integrate chemical innovation with a focus on improving tolerability and patient outcomes. Their development represents a move away from traditional NSAID therapy's long-standing drawbacks and shift toward multi-targeted, organ-sparing, and prodrug approaches [25].

Conclusion

Non-steroidal anti-inflammatory drugs (NSAIDs) remain a cornerstone in the management of pain, inflammation, and fever due to their proven efficacy and widespread availability. With the advent of COX-2-selective agents, which showed better gastrointestinal tolerability than non-selective NSAIDs, the use of NSAIDs increased significantly at the beginning of the last decade. However, worries about their cardiovascular safety surfaced, which led to a decrease in use and a re-evaluation of the safety and classification of all NSAIDs. It is now commonly known that all NSAIDs have some degree of cardiovascular and gastrointestinal risk, and that patient and drug features should be taken into consideration when making treatment decisions. Future strategies must continue to prioritize a balance between efficacy and safety, with emphasis on personalized medicine, targeted drug delivery, and multi-target mechanisms. As the demand for chronic inflammation management grows, the development of next-generation NSAID with reduced adverse effects and improved therapeutic outcomes remains both a necessity and an opportunity in modern drug design.

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