AN OVERVIEW OF NSAIDS USED IN ANTI-INFLAMMATORY AND ANALGESIC ACTIVITY AND PREVENTION GASTROINTESTINAL DAMAGE

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ABSTRACT
Nonsteroidal anti-inflammatory agents/analgesics (NSAIDs) are a class of drugs that provide analgesic, antipyretic (fever-reducing) and in higher doses anti-inflammatory effects. The term "nonsteroidal" distinguishes these drugs from steroids, which among a broad range of other effects, have a similar eicosanoid-depressing, anti-inflammatory action. As analgesics, NSAIDs are unusual in that they are non narcotic. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most highly prescribed drugs in the world. Their analgesic, anti-inflammatory, and antipyretic actions may be beneficial, they are associated with severe side effects including gastrointestinal injury and peptic ulceration. The most prominent members of this group of drugs are aspirin, ibuprofen, and naproxen. All of the drugs are available over the counter in most countries. NSAIDs are usually indicated for the treatment of acute or chronic conditions where pain and inflammation are present. In 2001, NSAIDs accounted for 70,000,000 prescriptions and 30 billion over-the-counter doses sold annually in the United States. In this paper, the mechanism of action of NSAIDs and their critical gastrointestinal complications have been reviewed. This paper also provides the information on different preventive measures prescribed to minimize such adverse effects and analyses the new suggested strategies for development of novel drugs to maintain the anti-inflammatory functions of NSAIDs along with effective gastrointestinal protection.

Keyword- Analgesic, anti-inflammatory, NSAIDs, Gastrointestinal Damage.

INTRODUCTION:
Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most well recognized drugs worldwide for the treatment of pain, inflammation and fever. NSAIDs are commonly administered for treatment against inflammatory diseases, rheumatoid arthritis, osteoarthritis, dysmenorrhea, and ischemic cerebrovascular disorders. These drugs inhibit prostaglandin biosynthesis and produce their therapeutic effects. NSAIDs possess certain common pharmacologic properties. Mostly they are organic acids with pKa in the range of 3–5. They contain an acidic group mostly carboxylic acids or enols. The acidic moiety is essential for COX inhibitory activity.

ANALGESIC:
An analgesic is commonly known as PAINKILLER, it is member of diverse group of drugs used to relieve pain and to achieve analgesia. This is derives from Greek words an- “without”, and algeia- “pain”.

Analgesics are the drugs that selectively relieve pain by acting on the CNS (central nervous system) or on peripheral pain mechanisms, without significantly altering consciousness. Pain is an ill-defined, unpleasant, sensation usually evoked by an external or internal noxious stimulus. It is a warning signal and primarily protective in nature, but causes discomfort. Analgesics are the drugs that selectively relieve pain by acting on the CNS (central nervous system) or on peripheral pain mechanisms, without significantly altering consciousness.

Analgesic drugs act on a various ways on the peripheral and central nervous system, they include nonsteroidal anti-inflammatory drugs (NSAIDs) such as Salicylate, Narcotic drugs such as Morphine, synthetic drugs with narcotic properties such as Tramadol.

Pain relieving agents are also called as antinociceptives. The effect of pain-killing is known as Analgesia. The effect is brought about by increasing the threshold of pain which is felt when an internal or external stimulus is given.
Inflammation:

Inflammation is defined as the local response of living mammalian tissue to injury due to any agent.\textsuperscript{16} Inflammation is derived from the Latin word – \textit{Inflammare}, means burn. The agent causing inflammation may be:\textsuperscript{16}

2. Chemical agent- Organic and Inorganic poisons.
3. Infective agent- Bacteria, Virus and their toxins.
4. Immunological agent- cell-mediated and antigen-antibody.

It is localized protective response elicited by injury or destruction of tissue, which serves to destroy, dilute, wall off (sequester) both the injurious agent and injured tissue.\textsuperscript{9,11}

Earlier it was believed that inflammation was contemplated as a single disease caused by disturbances of body fluids. According to the modern concept, inflammation is a healthy process resulting from some disturbance or disease.

Any form of injury to the human body can elicit a series of chemical changes in the injured area. Inflammation usually involves a sequence of events which can be categorized under three phases viz. acute transient phase, delayed sub acute phase and chronic proliferate phase.\textsuperscript{8,10,13}

It is characterized in the acute form by the cardinal signs (mohan)\textsuperscript{1} such as Pain (dolor), Heat (calor), Redness (rubor), Swelling (tumor), Loss of function (functio laesa). Inflammation is part of the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. It is a localized reaction that produces redness, warmth, swelling, and pain as a result of infection, irritation, or injury. Inflammation can be external or internal.\textsuperscript{8,9} Inflammation is usually devided in to acute, chronic inflammation and repair.

Inflammatory diseases include different types of rheumatic disorders such as rheumatic fever, rheumatoid arthritis, ankylosing spondylitis, polyarthritis nodosa, systemic lupus erythematosus and osteoarthritis.

Most of the anti-inflammatory drugs now available are potential inhibitors of cyclooxygenase (COX) pathway of arachidonic acid metabolism which produces prostaglandins. Prostaglandins are hyperalgesic, potent vasodilators and also contribute to erythema, edema and pain. Hence for treating inflammatory diseases analgesic and anti-inflammatory agents are required.\textsuperscript{13}

NSAIDs have three major actions, all of which are due mainly to the inhibition of arachidonic acid cyclooxygenase in inflammatory cells (the COX-2 isoenzyme), and the resultant decrease in prostanoid synthesis.

COX:

COX is responsible for formation of important biological mediators called prostanoids, including prostaglandins, prostacyclin and thromboxane. Pharmacological inhibition of COX can provide relief from the symptoms of inflammation and pain. Non-steroidal anti-inflammatory drugs, such as aspirin and ibuprofen, exert their effects through inhibition of COX. The names "prostaglandin synthase (PHS)" and "prostaglandin endoperoxide synthetase (PES)" are still used to refer to COX. There are three known isoforms-COX-1, COX-2 and COX-3 as well as some non-catalytic species.

COX-1:

It is a constitutive enzyme expressed in most tissues, including blood platelets. It has a 'housekeeping' role in the body, being involved in tissue homeostasis, and is responsible for the production of prostaglandins involved in, for example, gastric cytoprotection, platelet aggregation, renal blood flow autoregulation and the initiation of parturition. Side effects including gastrointestinal erosions, and renal and hepatic insufficiency. Such critical adverse reactions are mostly dependent on COX-1 inhibition. Pain, fever, redness, edema.

COX-2:

COX-2 inhibitors are a subclass of nonsteroidal antiinflammatory drugs (NSAIDs). NSAIDs work by reducing the production of prostaglandins, chemicals that promote inflammation, pain, and fever. Prostaglandins also protect the lining of the stomach and intestines from the damaging effects of acid, promote blood clotting by activating platelets, and also affect kidney function. It is induced in inflammatory cells when they are activated, and the primary inflammatory cytokines-interleukin (IL)-1 and tumour necrosis factor (TNF)-α are important in this regard. Thus the COX-2 isoform is responsible for the production of the prostanoid mediators of inflammatory although there are some significant exceptions. For example, there is a considerable pool of 'constitutive' COX-2 present in the central nervous system (CNS) and some other tissues, although its function is not yet completely clear.

Common side effects of COX-2 inhibitors include:

Insomnia, abdominal pain, flatulence (gas), headache, nausea, diarrhea, heart attacks, stroke, fainting, kidney failure, aggravation of hypertension, ringing in the ears, bleeding, blurred vision, anxiety, light sensitivity, weight gain, water retention, drowsiness, and weakness.

COX-2 inhibitors may increase the risk of serious, even fatal stomach and intestinal adverse reactions, such as ulcers, bleeding, and perforation of the stomach or intestines but to a lesser extent than other nonselective NSAIDs that block both COX-1 and COX-2.
COX-2 inhibitors are used for treating conditions that cause inflammation, mild to moderate pain, and fever. Examples include Sports Injuries, Osteoarthritis, Rheumatoid arthritis, Colorectal polyps, And Menstrual cramps. Unlike aspirin, also an NSAID, they are not effective for preventing strokes and heart attacks in individuals at high risk for such events.

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COX-3

It is the third and most recently discovered cyclooxygenase (COX) isozyme, the others being COX-1 and COX-2. The COX-3 isozyme is encoded by the same gene as COX-1, with the difference that COX-3 retains an intron that is not retained in COX-1. COX-3 actually occurs in humans in a functional form, we will confine the discussion mainly to a consideration of COX-1 and COX-2. While they are closely related (> 60% sequence identity) and catalyse the same reaction, it is clear that there are important differences between the expression and role of these two isoforms.

COX-3 was actually discovered in 2002, and been found to be selectively inhibited by paracetamol, phenacetin, antipyrine, dipyrone, and some NSAIDs in rodent studies. Classification of NSAIDs:

NSAIDs can be classified based on their chemical structure or mechanism of action. Older NSAIDs were known long before their mechanism of action was elucidated and were for this reason classified by chemical structure or origin. Newer substances are more often classified by mechanism of action.

1. Nonselective irreversible inhibitor of Cox: Aspirin (Acetylsalicylic Acid), Sodium Salicylate, Sulfasalazine, Methylsalicylate, Olsalazine.


3. Weak inhibitor of Cox-1 and Cox-2- Nimesulide(5-10 fold cox-2 selective)


5. Selective Cox-2 inhibitors- (>50 fold cox-2 selective) - Celecoxib, Rofecoxib, Valdecoxib, Etoricoxib.

6. Cox-3 inhibitor or reversible inhibitor of Cox-1- (except in inflammatory condition where these are weak inhibitor of cox-1) - Paracetamol, Metamizol (analgin).

7. NSAIDs which do not inhibits prostaglandin synthesis - Nefopam.

8. Others 4,13 Pravadolin, Salazopyrin, Fosfosa, Tenoxicam, Liofeleone acts by inhibiting LOX (lipooxygenase) & COX and hence known as 5- LOX/COX inhibits or Lysine clonixinate.

Mechanism of action of NSAIDs:

The mechanism of action of NSAIDs are based on inhibition of prostaglandin (PG) synthesis PG is one of the main mediators of inflammation, pain, and fever and is synthesized from arachidonic acid. The reaction is
catalyzed by the enzyme, cyclooxygenase (COX) earlier referred to as PGH synthase. NSAIDs block PG formation by binding and inhibiting COX. The analgesic activity of the NSAIDs has been demonstrated to be due to the interference of PGE1 and PGF2 in animal pain models. It has also been observed that NSAIDs are effective against pain because of their ability to inhibit PG-mediated cerebral vascular vasodilation. Several studies have shown that the antipyretic action of NSAIDs is via inhibition of PGE2 synthesis in and near the preoptic hypothalamic area in circumventricular organs.

**Epidemiology of Nonsteroidal Anti-inflammatory Drug:**

Nonsteroidal Anti-inflammatory Drug are among the most frequently used drugs in many countries. Population-based studies have shown that, on any given day, 10–20% of elderly people (≥65 years old) have a current or recent NSAID prescription. Over a 6-month period in Alberta, Canada, 27% of elderly people were prescribed NSAIDs.

NSAIDs cause a wide variety of side-effects. The most clinically important side-effects are upper gastrointestinal tract dyspepsia, peptic ulceration, hemorrhage, and perforation, leading to death in some patients.

Gastrointestinal side-effects are common, the most common NSAID-associated side-effect is epigastric pain/indigestion. In two population-based studies of people aged ≥65 years, the use of agents to prevent peptic ulcers or relieve dyspepsia was nearly twice as common in regular NSAID users (20–26%) than in non-NSAID users (11%).

In the United States alone, there are an estimated 41,000 hospitalizations and 3,300 deaths each year among the elderly that are associated with NSAIDs. Approximately half of patients who regularly take NSAIDs have gastric erosions, and 15%–30% have ulcers when they are examined endoscopically. However, the incidence of clinical gastrointestinal (GI) events caused by NSAIDs is much lower.

Clinical upper GI events may occur in 3%–4.5% of patients taking NSAIDs, and serious complicated events develop in approximately 1.5%. However, the risk varies widely in relationship to clinical features such as history of ulcers or GI events, age, concomitant anticoagulant or steroid use, and NSAID dose.

**Common Side Effects of NSAIDs:**

1. GI (side effects decreased with COX-2–selective drugs)-
   - Abdominal pain, GI hemorrhage, GI hemorrhage,
   - Perforation, Diarrhea, Nausea, Anorexia, Gastric erosions/ulcers, Anemia.
2. Renal-
Salt and water retention, Edema, worsening of renal function in renal/cardiac and cirrhotic patients, Decreased effectiveness of antihypertensive medications, Decreased effectiveness of diuretic medications, Decreased urate excretion (especially with aspirin), Hyperkalemia.

3. CNS
Headache, Vertigo, Dizziness, Confusion, Depression, Lowering of seizure threshold, Hyperventilation (salicylates).

4. Platelets (side effects absent with COX-2–selective drugs)
Inhibited platelet activation, Propensity for bruising, Increased risk of hemorrhage.

5. Uterus
Prolongation of gestation, Inhibit labor.

6. Vascular
Closure of ductus arteriosus.

7. Hypersensitivity -
Vasomotor rhinitis, Asthma, Urticaria, Hypotension, Shock, Asthma, Angioneurotic edema.

SOME COMMON DRUGS USED IN NSAIDS:

- **ASPIRIN:**
  Trade name: Excedrin
  Aspirin (acetylsalicylic acid) is a drug in the family of salicylate, often used as an analgesic(pain & aches), antipyretic(fever), and anti-inflammatory. first isolated in 1829 by Leroux from willow bark. 
  Aspirin (acetylsalicylic acid) is the oldest non-steroidal anti-inflammatory drug.
  In addition to its anti-inflammatory actions, aspirin inhibits platelet aggregation, and its main clinical importance now is in the therapy of myocardial infarction. It is given orally and is rapidly absorbed; 75% is metabolised in the liver. 

**Disease state leading to increase vasoconstrictors**

- Renal disease
- Cardiovascular disease

**Response of renal blood flow.**

- Decrease renal blood flow
- Increase vasoconstrictor.
- Angiotensin –II.
- Vasopressin.
- Catacholamine.

**Prostaglandin synthesis normly antagonize intrarenal effect of vasoconstrictor.**

**NSAID inhibits prostaglandin synthesis leaving action of vasoconstrctor unopposed.**

**Vasoconstrctor**

**Renal effect of Aspirin inhibition of prostaglandin synthesis**

**MECHANISMS OF ACTION:**

It acts by irreversibly inactivating both cyclooxygenase (COX)-1 and COX-2, is also indicated for inhibition of platelet aggregation. This is useful in the management of arterial thrombosis and prevention of adverse cardiovascular events. Aspirin inhibits platelet aggregation by inhibiting the action of Thromboxane A2. In other tissues, synthesis of new COX replaces the inactivated enzyme so that ordinary doses have a duration of action of 6–12 hours.
Clinical Uses:
Aspirin decreases the incidence of transient ischemic attacks, unstable angina, coronary artery thrombosis with myocardial infarction, and thrombosis after coronary artery bypass grafting. Epidemiologic studies suggest that long-term use of aspirin at low dosage is associated with a lower incidence of colon cancer, possibly related to its COX-inhibiting effects.6

Adverse Effects:
In addition to the common side effects dizziness, deafness and tinnitus (‘salicylism’); aspirin’s main adverse effects at antithrombotic doses are gastric upset (intolerance) and gastric and duodenal ulcers. Hepatotoxicity, asthma, rashes, gastrointestinal bleeding, and renal toxicity rarely if ever occur at antithrombotic doses. The antiplatelet action of aspirin contraindicates its use by patients with hemophilia. Although previously not recommended during pregnancy, aspirin may be valuable in treating preeclampsia-eclampsia

Aspirin has been linked with a postviral encephalitis (Reye’s syndrome) in children. If given concomitantly with warfarin, aspirin can cause a potentially hazardous increase in the risk of bleeding.7, 13

PARACETAMOL- (called acetaminophen)
Trade name: Tylenol, Vicodin Acetaminophen + Hydrocodone.
It can be traced to inhibition of CNS prostaglandin synthesis, it has weak anti-inflammatory activity (except in some specific instances) and does not share the gastric or platelet side effects of the other NSAIDs.9, 10, 12

It is similar in analgesic and antipyretic efficacy to acetylsalicylic acid. It is used for mild to moderate pain including headache and acute migraine attacks and for reducing fever, including post-immunization pyrexia.

Paracetamol is particularly useful in patients in whom salicylates or other NSAIDs are contraindicated, such as asthmatics and those with a history of peptic ulcer, or for children under the age of 16 years in whom salicylates should be avoided because of the risk of Reye syndrome.8

Paracetamol has analgesic and antipyretic actions but only weak anti-inflammatory effects.7, 9

Adverse Side Effects:
Normal doses adverse effects are rare, but overdosage with a single dose of 10–15 g is particularly dangerous because it may cause hepatocellular necrosis and, less frequently, renal tubular necrosis.

Uses:
Mild to moderate pain including dysmenorrhea, headache; pain relief in osteoarthritis and soft tissue lesions; pyrexia including post-immunization pyrexia; acute migraine attack

Dose: Tablets, paracetamol 500 mg12

DICLOFENAC:
Diclofenac is a phenylacetic acid derivative that is relatively nonselective as a COX inhibitor.10, 19 It is an analgesic, antipyretic and anti-inflammatory drugs, similar in efficacy to naproxen.
Its inhibits prostaglandin synthesis. It is well absorbed orally, 99% protein bound, metabolized and excreted both in urine and bile.8 Gastrointestinal ulceration may occur less frequently than with some other NSAIDs.
A preparation combining diclofenac and misoprostol decreases upper gastrointestinal ulceration but may result in diarrhea.13, 18

Another combination of diclofenac and omeprazole was also effective with respect to the prevention of recurrent bleeding, but renal adverse effects were common in high-risk patients. Diclofenac, 150 mg/d, appears to impair renal blood flow and glomerular filtration rate.
Elevation of serum aminotransferases occurs more commonly with this drug than with other NSAIDs.9

In Europe, diclofenac is also available as an oral mouthwash and for intramuscular administration of aspirin in anti-inflammatory effect.

Adverse effects: Pain, Nausea, Headache, Dizziness, Rashes, Gastric Ulceration and bleeding are less common.

Nimesulide:
The government has banned the paediatric use of the common fever and pain drug nimesulide for its adverse effects on the liver, in a much-delayed move.
The decision was taken by the Union health ministry after experts on the Drug Technical Advisory Board recommended banning the drug along with five others. The ministry decided last week to ban the sale, distribution and manufacture of nimesulide’s paediatric formulation along with cisapride, phenylpropanolamine, human placenta extract and sibutramine and R-sibutramine. A notification on the ban is expected in a day or two,” officials said. But experts said the decision has come too late. Nimesulide causes liver failure, while cisapride, an anti-acidity drug causes heart abnormality and the risk of hepatotoxicity, Nimesulide has been withdrawn from market in many countries. These drugs should have been banned 10 years ago. They are banned in all developed countries. Because it is an nsaid and it may cause serious drug reaction like vomiting, rash, ulcer, kidney damage so not to be given to children
1. Nimesulide is long banned in other countries.
2. It is NSAID. Almost all NSAID (Non-Steroidal anti inflammatory drugs ) are Liver Loxic pain killers.
3. One must not take any NSAID without doctor’s prescription.
4. Safest pain killer is Paracetamol (Crocin) and in acute pain it is DOLO (Paracetamol 650 mg).
5. Almost all the al the allopathic medicines are either Liver Toxic or Nephro (Kidney) Toxic and must not be taken without prescription by a qualified doctor who checks pros and cons of prescribing the medicine.
6. Pain Killers (NSAID) should be avoided for prolonged used.

On September 13, 2011 Madras High Court has revoked a ban on manufacture and sale of paediatric drugs nimesulide and phenylpropanolamine (PPA). Side effect:
Nimesulide is known to be hepatotoxic (damaging to the liver). The use of nimesulide in children under the age of 12 is contraindicated.
The drug has certain side effects, that can affect individuals in different ways. The following are some of the side effects, that are often associated with the drug: Diarrhoea, Vomiting, Skin rash, Pruritis, Dizziness, Bitterness in mouth. Women should use the drug with caution during lactation and it is contraindicated during pregnancy.

CELECOXIB:
Trade name: Excedrin:
Celecoxib is a selective COX-2 inhibitor—about 10–20 times more selective for COX-2 than for COX-1. Reducing substances in the body that cause pain, fever, and inflammation. Celecoxib is associated with fewer endoscopic ulcers than most other NSAIDs. Probably because it is a sulfonamide, celecoxib may cause rashes. It does not affect platelet aggregation at usual doses. It interacts occasionally with warfarin—as would be expected of a drug metabolized via CYP2C9.

Indications:
Fever and relieve mild to moderate pain from conditions such as muscle aches, toothaches, common cold, and headaches. It may also be used to reduce pain and swelling conditions such as arthritis.

IBUPROFEN:
Its have analgesic, anti-inflammatory and antipyretic properties. Ibuprofen is used in the treatment of mild to moderate pain and in the management of pain and inflammation in rheumatoid arthritis and juvenile arthritis. Ibuprofen is also used to reduce pain in children.

Adverse effects:
Gastrointestinal disturbances including nausea, diarrhoea, dyspepsia, gastrointestinal hemorrhage, hypersensitivity reactions including rash, angioedema, bronchospasm; headache, dizziness, nervousness, depression, drowsiness, insomnia, vertigo, tinnitus, photosensitivity, raised blood pressure, renal failure; rarely hepatic damage, alveolitis, pulmonary eosinophilia, pancreatitis. Pain and inflammation in rheumatic disease and other musculoskeletal disorder including juvenile arthritis; mild to moderate pain including dysmenorrhoea, headache; pain in children; acute migraine attack.

Ibuprofe-Tablets, ibuprofen 200 mg, 400 mg

NAPROXEN:
Trade name: Aleve, Naprosyn
Pharmacologic class: Nonsalicylate NSAID
Drug action: inhibit both COX 1 and COX-2.
Drug effects: stopping the body's production of a substance that causes pain, fever, and inflammation.
Indications:
Commonly used for the reduction of pain (mild-moderate), fever, inflammation and stiffness caused by conditions such as: osteoarthritis, kidney stones, rheumatoid arthritis, psoriatic arthritis, gout, ankylosing spondylitis, menstrual cramps, tendinitis, bursitis.

Adverse drug reaction:
Easy bruising/bleeding, difficult/painful swallowing, hearing changes (such as ringing in the ears), mental/mood changes, swelling of the ankles/feet/hands, sudden/unexplained weight gain, change in the amount of urine, unexplained stiff neck, vision changes. Ibuprofen Adverse side effect linked to increases in the number of serious and potentially fatal cardiovascular events such as myocardial infarctions and stroke, may interfere and reduce efficiency of SSRI antidepressants.

KETOPROFEN:
Ketoprofen is a propionic acid derivative that inhibits both COX (nonselectively) and lipoxygenase. Concurrent administration of probenecid elevates ketoprofen levels and prolongs its plasma half-life. The effectiveness of ketoprofen at dosages of 100–300 mg/d is equivalent to that of other NSAIDs. In spite of its dual effect on prostaglandins and leukotrienes, ketoprofen is not superior to other NSAIDs in clinical efficacy. Its major adverse effects are on the gastrointestinal tract and the central nervous system.

Prevention of anti-inflammatory drug-induced gastrointestinal damage:
Patients who take non-steroidal anti-inflammatory drugs (NSAIDs) may develop serious gastrointestinal (GI) side effects in both the upper and lower GI tract. Those at risk should be considered for prevention with misoprostol, proton pump inhibitor (PPI) or COX-2 selective inhibitor (coxib) therapy. are effective in the prevention of upper GI events in endoscopy trials and in a few, small, outcome trials in patients at risk. Coxibs have been evaluated in endoscopic ulcer studies and clinical outcome trials, and shown to...
significantly reduce the risk of upper GI ulcer and complications. Moreover, unlike PPIs, coxibs significantly reduce toxicity in the lower GI tract compared with NSAIDs. PPI therapy must be considered for the treatment and prevention of NSAID-induced dyspepsia.

**Strategies to Reduce NSAID-associated Gastrointestinal:**

Two main strategies have been employed to prevent the development of gastrointestinal mucosal injury in NSAID users: cotherapy with a high-dose H$_2$ antagonist, a PPI, or a synthetic prostaglandin analogue, misoprostol; or substitution of a traditional NSAID with a COX-2 inhibitor. Patients with no gastrointestinal risk factors should receive traditional NSAIDs. For patients with high gastrointestinal risk factors who need NSAIDs, including those with a prior bleeding ulcer, or on concurrent anticoagulant therapy, COX-2 inhibitor plus a PPI provide the most promising gastrointestinal protection. Although COX-2 inhibitor plus a PPI provide the most promising gastrointestinal protection in patients at high risk of ulcer bleeding, fewer than 50% of NSAID users with gastrointestinal risk factors were given protective cotherapy, even when prescribers were reminded and cost was not an issue.

**Gastrointestinal injury from NSAID therapy:**

Use of nonsteroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin is accompanied by risk of upper and lower gastrointestinal (GI) complications, some of which can be serious or even fatal. Management strategies to reduce this risk include gastroprotective pharmacotherapy, use of safer NSAIDs, and eradication of Helicobacter pylori infection.

NSAIDs are widely used around the world in patients with rheumatic and musculoskeletal conditions. The primary care physician prescribes far more NSAIDs than the rheumatologist or any other subspecialist. Across Europe, the proportion of drug prescriptions accounted for by NSAIDs is variable but represents 7.7% of all prescriptions. In the United States, 20 million persons regularly take NSAIDs, and prescription use increases with age to a point prevalence of 10% to 15% in persons older than 65 years. A recent survey of persons aged 65 years and older in Minnesota found that 70% of respondents took NSAIDs, aspirin, or both at least once weekly and 34% at least daily. In 2000, it was estimated that 111.4 million NSAID prescriptions were filled in the United States, at a cost of $4.8 billion. However, these figures might underestimate the actual dimension of NSAID use because they often exclude treatment with over-the-counter (OTC) aspirin and other recently released nonaspirin NSAIDs.

COX-1 inhibition also blocks platelet production of thromboxane and thus increases bleeding when an active GI bleeding site is present. Selective COX-2 inhibitors do not inhibit COX-1 and are therefore less likely to cause bleeding.

**Risk of GI damage:**

NSAID use increases the risk of upper GI bleeding by a factor of 3.8. Recent studies have shown that the cumulative incidence of upper GI complications is between 0.92% and 1.4% after 12 months of NSAID use. Most of these complications are ulcer bleeding events; ulcer perforation and overall gastric outlet obstruction are rare. NSAID use is also associated with lower GI complications. Several studies have found that NSAIDs induce gut inflammation, increase gut permeability, and induce ulceration, stricture, protein malabsorption, bleeding, and perforation.

Autopsy studies have shown that 8.4% of patients who had been taking NSAIDs had ulcers in the small bowel, but only 0.6% of patients who had not been taking NSAIDs had small-bowel ulcers. In a recent trial, naproxen use was associated with a 0.9% incidence of severe lower GI events per year. With the new capsule endoscopy technology, it has been shown that 50% of patients taking NSAIDs have mucosal lesions in the small bowel, although the clinical relevance of these lesions remains to be defined. The worst outcome of NSAID-induced GI complications is death, a result that has not been well studied. In the United States, about 16,000 persons die every year as a consequence of NSAID use, which is a mortality similar to the estimated total deaths due to AIDS during the same period. Recent data from the United Kingdom indicate about 400 deaths yearly from NSAID use in persons aged 60 years and older.

OTC aspirin and NSAID use may be responsible for more than 10% of these GI bleeding events. In some studies, use of OTC rather than prescription NSAIDs was more common in patients with upper GI bleeding. Another, less well-recognized complication of NSAID use is its association with resistant ulcers.

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<th>S.N.</th>
<th>Risk status</th>
<th>Recommended strategy</th>
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<td>1.</td>
<td>Low risk (no risk factors)</td>
<td>Least ulcerogenic NSAID Lowest effective dose</td>
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<tr>
<td>2.</td>
<td>Moderate risk (eg, age &gt;65 yr)</td>
<td>NSAID + PPI or misoprostol COX-2 inhibitor</td>
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<td>3.</td>
<td>History of ulcer complications</td>
<td>COX-2 inhibitor Helicobacter pylori eradication</td>
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Low-dose aspirin is taken worldwide because it is an inexpensive and effective treatment in secondary prevention of both cardiovascular and cerebrovascular disease. Taking into account benefits and risks, the optimal dose is regarded as no more than 100 mg/day. However, even at that dose, patients with GI risk factors also need gastroprotection with a proton pump inhibitor (PPI) 40. Eradication of *H pylori* is of benefit and should always be considered in patients with previous ulcer history. 39

**Recent Advances in NSAID Treatments- Prodrugs of NSAIDs**

NSAID prodrugs are potential agents for enhancing the antioxidant activity, water solubility and dissolution, release of nitric oxide and hydrogen sulfide, site-specific targeting and delivery, and inhibiting anticholinergic and acetylcholinesterase activity.

**Nitric Oxide Releasing NSAIDs**

It has been observed that nitric oxide (NO) imparts gastroprotection by increasing blood flow, mucus production, and bicarbonate secretion in the gastric mucosa 45,46. NO formed by the action of nitric oxide synthase increases mucus and bicarbonate secretion as well as microcirculation and decreases neutrophilendothelial adherence. 47

**Hydrogen Sulfide Releasing NSAID**

Hydrogen sulfide (H2S) also exerts its gastroprotective effects and reverses preexisting ulcers. Derivatives of naproxen, diclofenac, and indomethacin which can release H2S have been reported. 48

**Simultaneous Inhibition of COX and 5-LOX**

NSAID induced inhibition of COX also results in increased production of leukotrienes, one of the potent mediators of inflammation. Recent approach for addressing NSAID-induced GI injury is by development of inhibitors of COX/5-LOX simultaneously. 49,51

**Role of Lactoferrin in Reducing NSAID-Induced Gut Damage**

Some preliminary reports have shown that bovine colostrum has the ability to prevent NSAID-induced gastric ulcers. 49,50. The role of recombinant human lactoferrin in decreasing acute NSAID-induced GI bleeding and reduction of gastric ulcers. 52,53

**Inhibitors of acid secretion**

Acid enhances NSAID induced mucosal damage, and might activate proteolytic pepsin and increase gastric absorption of acidic NSAID. 54. H2-receptor antagonists and PPIs seem to protect gastric mucosa not only by inhibiting acid secretion and thus elevating gastric pH but also by scavenging free radicals. 55,56

**H2-receptor antagonists**

H2-receptor antagonists presented the standard of ulcer treatment up to the development of PPIs. They were the first drugs effectively to heal reflux oesophagitis as well as peptic ulcers.

**Gastroprotective drugs**

Misoprostol is a prostaglandin analogue used to locally replace prostaglandins the formation of which is inhibited by NSAIDs.

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