

# Nonsteroidal anti-inflammatory drugs: prostaglandins, indications, and side effects

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**Abstract:** For centuries, nonsteroidal anti-inflammatory drugs (NSAIDs) have been part of our clinical practice. They started out as drugs with anti-inflammatory and analgesic action, and gradually their use has been expanded to new therapeutic targets, some of which are unrelated to their primary mode of action. Today, our armamentarium includes a large range of compounds, attesting to their utility in the treatment of clinical pathologies ranging from pain and inflammation to prevention and treatment of cancer. On the other hand, although NSAIDs share many common properties, their use poses risks, and physicians should be cognizant of their subtle differences and potential complications. In this context, this review article presents insight into NSAIDs' pathophysiology and mode of action in the clinical setting, their indications, and their potential side effects.

**Keywords:** nonsteroidal anti-inflammatory drugs, prostaglandins, COX

## Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) have their origin in the extracts of salicylate-containing plants initially described in ancient Roman and Greek literature.<sup>1</sup> In particular, the extracts of willow tree were known for their antipyretic, analgesic, and anti-inflammatory properties.<sup>2</sup> For many centuries, there was no real progress until advances made in chemistry over a century ago that enabled the synthesis of salicylic and acetylsalicylic acids.<sup>1</sup> In the early 1960s, indomethacin and ibuprofen were developed, and their use increased as a result of their being approved for over-the-counter sale.<sup>1</sup> Several other molecules were discovered; however, their mechanism of action eluded scientists until 1971 (Table 1). In the same year, Sir John Vane demonstrated the inhibition of the enzymatic production of prostaglandins by NSAIDs.<sup>3</sup> A major setback occurred in 2004 with the worldwide withdrawal of rofecoxib and valdecoxib due to the apparent high risk of myocardial infarction.<sup>1</sup> Nevertheless, NSAIDs today are one of the most commonly used medications. Approximately 70% of people aged 65 years or older are reported to use NSAIDs at least once per week.<sup>4</sup> In the US alone, more than 111 million prescriptions are issued annually, at an approximate cost of \$4.8 billion.<sup>5</sup>

## Mechanism of action of NSAIDs

### Biosynthesis of prostaglandins and leukotriene pathway

It is more than 80 years since prostaglandins were identified in the human body.<sup>6</sup> They were first described by Goldblatt as substances produced by the prostate gland and contained in the seminal fluid, with antihypertensive properties.<sup>6</sup> Later, it was

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**Table I** Nonsteroidal anti-inflammatory drugs by class<sup>1,18,88</sup>

Class	Drug
Salicylates	<ul style="list-style-type: none"> <li>• Aspirin (acetylsalicylic acid)</li> <li>• Salsalate</li> </ul>
Nonacetylated salicylates	<ul style="list-style-type: none"> <li>• Diflunisal</li> <li>• Magnesium salicylate</li> <li>• Choline magnesium trisalicylate</li> </ul>
Propionic acid derivatives	<ul style="list-style-type: none"> <li>• Ibuprofen</li> <li>• Ketoprofen</li> <li>• Naproxen</li> <li>• Fenoprofen</li> <li>• Flurbiprofen</li> <li>• Oxaprofen</li> </ul>
Fenamates	<ul style="list-style-type: none"> <li>• Mefenamic acid</li> <li>• Meclofenamate sodium</li> </ul>
Indoles	<ul style="list-style-type: none"> <li>• Indomethacin</li> <li>• Sulindac</li> <li>• Tometin sodium</li> </ul>
Oxicams	<ul style="list-style-type: none"> <li>• Piroxicam</li> <li>• Meloxicam</li> </ul>
Phenylacetic acids	<ul style="list-style-type: none"> <li>• Diclofenac sodium</li> <li>• Diclofenac potassium</li> </ul>
Pyrazole derivatives	<ul style="list-style-type: none"> <li>• Phenylbutazone</li> </ul>
Pyrrolo-pyrrole	<ul style="list-style-type: none"> <li>• Ketorolac</li> </ul>
Pyranocarboxyl acid	<ul style="list-style-type: none"> <li>• Etodolac</li> </ul>

shown that prostaglandins are formed by a great variety of cells within the human body.<sup>2</sup> Their effect is complex and depends on the type of target cell.<sup>2</sup> The exact role of every individual prostaglandin is still unclear, as in time the same compound could exert different or even opposite responses to the target cells.<sup>2</sup>

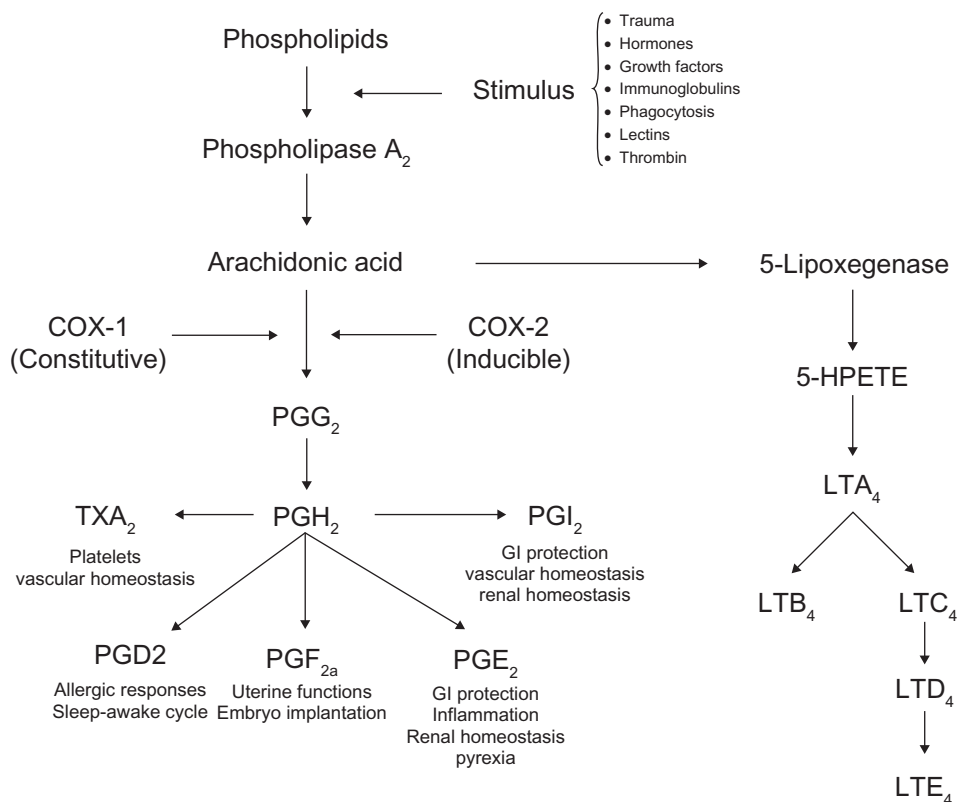
During the biosynthesis of prostaglandins, cyclooxygenase (COX or prostaglandin H synthase) catalyses the conversion of arachidonic acid to the prostaglandin endoperoxidases, prostaglandin G<sub>2</sub> (PGG<sub>2</sub>), and then PGH<sub>2</sub> (Figure 1).<sup>7,8</sup> PGH<sub>2</sub> is the precursor of the biologically active prostaglandins and thromboxanes. PGH<sub>2</sub> is then isomerized into various prostanoids such as thromboxane A<sub>2</sub> (TXA<sub>2</sub>), prostacyclin (PGI<sub>2</sub>), PGD<sub>2</sub>, PGE<sub>2</sub>, and PGF<sub>2a</sub>.<sup>7,8</sup>

Along with the prostaglandin pathway, the leukotrienes pathway is a strong mediator of inflammation. It involves the conversion of arachidonic acid to 5-hydroperoxyeicosatetraenoic acid (5-HPETE) (Figure 1).<sup>9</sup> 5-HPETE is then catalyzed, forming an unstable epoxide, the leukotriene A<sub>4</sub> (LTA<sub>4</sub>). The latter is further catalyzed to either leukotrienes B<sub>4</sub> or C<sub>4</sub>. LTC<sub>4</sub> might be converted to LTD<sub>4</sub>, which can be further converted to LTE<sub>4</sub>. The LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub> are called peptidoleukotrienes or cysteinyl leukotrienes. Involvement of the leukotriene pathway contributing to the unwanted effect of NSAIDs has also been postulated. Diverted arachidonic acid to this pathway after

inhibition of COX by NSAIDs causes increased formation of leukotrienes, which are also mediators of inflammation.<sup>1</sup> Among these, LTB<sub>4</sub> is involved in inflammatory processes causing neutrophil, monocyte, and eosinophil chemotaxis, neutrophil degranulation, and lysosomal enzyme release, as well as modulation of pain and immune responses.<sup>1</sup> LTB<sub>4</sub> levels have been found to be elevated in patients with rheumatoid arthritis and have been implicated in chronic inflammation and joint destruction.<sup>10</sup> In addition, the cysteinyl leukotrienes have powerful spasmogenic action, especially in airway smooth muscles and vasculature, and are released during asthmatic attacks, inflammation, hypersensitivity reactions, and rheumatoid arthritis.<sup>9</sup> Leukotrienes can also cause vasoconstriction of the gastric mucosa and increase formation of reactive radicals, which can cause gastrointestinal (GI) mucosal lesions.<sup>9,10</sup> This suggests that the blockage of the protective prostaglandins by the NSAIDs could result in further toxicity by the products of leukotriene pathway.

## NSAIDs as inhibitors of COX-1 and COX-2

There are two COX enzymes: COX-1 and COX-2.<sup>11</sup> These proteins are structurally distinct, have the same molecular weight, and show 60% homology of their DNA.<sup>12</sup> Their difference resides in their substrate binding sites, which are smaller in COX-1 than in COX-2.<sup>12</sup> The active site of COX lies in a narrow hydrophilic tunnel composed of an active inner site and protected by an outer area that is made up of three  $\alpha$  helices. NSAIDs attach to these outer helices and temporarily prevent the passage of arachidonic acid from reaching the active site and triggering the production of prostaglandins.<sup>13</sup> COX-1 is constitutively expressed in most cells and is involved in physiological processes. In the GI tract, prostacyclin and PGE<sub>2</sub> exert a protective effect by reducing acid secretion, vasodilatation of blood vessels of gastric mucosa, and stimulation of mucus production, which acts as a barrier.<sup>14</sup> In the kidneys, prostaglandins play a key role in regulating blood flow and enhancing organ perfusion.<sup>14</sup> COX-1 expression is also found in fetal and amniotic cells, uterine epithelium in early pregnancy, and the central nervous system and is believed to exert complex integrative functions.<sup>15</sup> On the other hand, COX-2 was considered to be induced by inflammation and the presence of proinflammatory cytokines and mitogens.<sup>16</sup> It has been suggested that the anti-inflammatory action of NSAIDs is due to the inhibition of COX-2, whereas COX-1 inhibition is associated with unwanted effects related to interference of the regulatory and protective mechanisms.<sup>16,17</sup> However, recent studies have indicated that COX-2 is also constitutively



**Figure 1** The arachidonic acid cascade.

expressed in the brain and, in particular, in the hippocampus and cortical glutaminergic neurons, as well as in the kidneys, uterus, and prostate.<sup>18,19</sup> Similarly, COX-1, despite its constitutive expression, is shown to participate in inflammation (eg, lipopolysaccharide-induced inflammation) where it might be inducible.<sup>20</sup>

There has been much speculation and interest in the possibility that other COX enzymes exist in addition to COX-1 and COX-2.<sup>21,22</sup> COX-3 was investigated by researchers who mainly studied the enigmatic mode of action of weak COX-1 and COX-2 inhibitors like acetaminophen, which exerts reduction of pain and fever with virtually no anti-inflammatory effects but with good penetration into the central nervous system.<sup>21,22</sup>

NSAIDs also affect processes other than prostaglandin inhibition. Within the cell membrane, they are involved in the oxidation of nicotinamide adenine dinucleotide phosphate in neutrophils.<sup>23</sup> This action results in direct inhibition of neutrophil functions. High doses of NSAIDs have also been found to inhibit proteoglycan synthesis, cell-to-cell binding, and transmembrane ion fluxes. Furthermore, NSAIDs have been found to unmask T-cell suppressor activity, leading to a reduction in rheumatoid factor.<sup>23</sup>

Several ranking systems have been developed in categorizing NSAIDs according to their selectivity.  $IC_{80}$  (ie, the

concentration required to inhibit 80% of COX activity) ranking assay is based on the drug concentration needed to inhibit 80% of COX-1 or COX-2.<sup>24</sup> In this system, the drugs are ranked based on the ratio between the amounts of drug needed to inhibit COX-2 compared with COX-1. Other assays measure the  $IC_{50}$  or the thromboxane  $B_2$  to  $PGI_2$  ratio.<sup>24,25</sup> Brooks et al compared these different assays and found a high degree of variability, suggesting that the reported COX-2/COX-1 ratios, although indicative, are in many cases misleading.<sup>25</sup> For instance, they found that the reported range of COX-2 selectivity varied between 0.067 and 4 for diclofenac, 1.3 and 107.1 for indomethacin, 9.4 and 600 for piroxicam, 0.67 and 53.3 for ibuprofen, and 2 and 167 for aspirin. According to the results of various studies on the ranking scheme in terms of COX-2 selectivity, one can consider rofecoxib, celecoxib, and meloxicam as posing the higher COX-2 selectivity, followed by ibuprofen, diclofenac, and piroxicam.<sup>24,25</sup> Aspirin, indomethacin, and ketorolac have the lowest COX-2 selectivity.<sup>24,25</sup>

## Uses of NSAIDs

### NSAIDs in acute and chronic pain

NSAIDs have a wide range of indications, especially in cases where pain and inflammation are present (Table 2)

Their effectiveness is well proven by their everyday use in such settings, with pronounced analgesic potency and fewer side effects compared with other agents.<sup>26,27</sup> However, it is worthwhile mentioning that this effect is indirect and is exerted by the increase of the sensitivity of nociceptors to stimuli derived from traumatized or inflamed tissue.<sup>2</sup> They switch normally nonexcitable polymodal receptors into a state in which they can be easily excitable.<sup>2</sup>

In an acute and postoperative pain setting, NSAIDs are widely used, primarily to target mild and moderate pain.<sup>28</sup> Several authors suggest that NSAIDs should be used as the first line of treatment in pain therapy and recommend that opioids should be added only if pain is not controlled adequately with NSAIDs alone.<sup>28</sup> There is insufficient evidence that a specific type of NSAID is more effective than others in this setting.<sup>28</sup> Studies comparing opiates with NSAIDs show that NSAIDs are at least as effective as opiates, with some studies suggesting that NSAIDs can achieve greater reductions in pain scores.<sup>29–32</sup> These patients are less likely to require further analgesia in the short term than those receiving opioids.<sup>29</sup> Furthermore, it should be mentioned that the side effects of narcotic analgesics, such as respiratory depression, sedation, and cognitive effects, as well as constipation, can be avoided or minimized.<sup>33</sup> For postoperative patients, this can be translated into decreased hospital stay, allowing early mobilization and weight bearing.<sup>29,34</sup>

One could say that NSAIDs' superiority over other painkilling approaches lies in the multiple ways that they can be used. Besides the traditional approach, NSAIDs can be used pre-emptively, ie, before prostaglandin release or topically, providing higher concentrations locally at the area of inflammation. A pre-emptive, multimodal, perioperative analgesic regimen is based on the principle that two or more agents acting at different levels are used before surgery to

improve pain levels after surgery.<sup>35,36</sup> In fact, this model has been studied in patients undergoing major orthopedic procedures, and results showed decreased postoperative narcotic requirements with decreased hospital stay and earlier rehabilitation.<sup>35,36</sup> Topical NSAIDs penetrate the skin and distribute to the target tissues that lie underneath the application site.<sup>37</sup> The pharmacologically effective dose is delivered at the inflamed site, and there is minimal systemic absorption; therefore, the risk of related adverse events is low.<sup>37,38</sup> They represent a convenient, effective, and safer form of pain relief, and they are an attractive option, particularly considering current concerns about the safety of traditional NSAIDs and COX-2 inhibitors.<sup>37,38</sup>

Chronic pain derived from joint destruction continues to be one of the biggest causes of disability and loss of function worldwide. In this setting, NSAIDs relieve pain and reduce swelling and stiffness.<sup>23,39,40</sup> As a result, these patients have improved mobility with increased joint function and grip strength.<sup>39,40</sup> This effect is only palliative and has not shown to permanently arrest or reverse the underlying disease process. In such cases, disease-modifying antirheumatic drugs like azathioprine, infliximab, and methotrexate may be considered.<sup>23</sup> Although COX-2 selective NSAIDs have been developed to target the management of chronic pain, it became clear that these drugs have the same symptomatic relief as the non-selective NSAIDs, but COX-2 provides better GI tolerability and fewer GI-related side effects.<sup>41,42</sup> The Celecoxib versus Omeprazole and Diclofenac in patients with Osteoarthritis and Rheumatoid Arthritis (CONDOR) trial has shown that COX-2 NSAIDs pose less risk for GI events than a nonspecific NSAID plus a proton pump inhibitor (PPI) (omeprazole).<sup>41</sup> In ankylosing spondylitis, continuous NSAIDs seem to prevent progression of structural damage possibly due to retardation of osteoproliferation and have a high symptomatic efficacy.<sup>43,44</sup>

**Table 2** Most common indications for nonsteroidal anti-inflammatory drug use<sup>89</sup>

- Mild-to-moderate pain due to inflammation and tissue injury
- Sprains, strains, and rheumatism
- Back pain and sciatica
- Osteoarthritis and rheumatoid arthritis
- Acute gout
- Inflammatory arthropathies (eg, ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome)
- Dysmenorrhea, headache, and migraine
- Postoperative pain
- Renal and biliary colic
- Antipyretic
- Other inflammatory conditions

## NSAIDs usage not related to analgesia and arthritis

Over the last three or four decades, observations have suggested that NSAIDs can be involved in the treatment of conditions unrelated to chronic inflammation or painful states. The first observation suggested that aspirin, but not salicylate, inhibited the activation and aggregation of platelets.<sup>45</sup> Later, it became clear that, unlike other NSAIDs, aspirin induces a long-lasting covalent and irreversible inhibition of COX enzyme and thus inhibits platelet TXA<sub>2</sub> biosynthesis.<sup>45,46</sup> The activation and aggregation of platelets are the nidus for thrombus formation; therefore, aspirin's unique effect has

been exploited in the prevention of thromboembolic and vascular diseases.<sup>46</sup>

The NSAID properties related to tumor inhibitions and prevention of metastasis are less clear. Several studies have suggested that the abundant production of prostaglandins and cytokines produced by the tumors is a key factor for their metabolism and proliferation, as well as the angiogenesis, tumor invasion, resistance to apoptosis, and suppression of antitumor immunity.<sup>47–49</sup> Therefore, their inhibition by NSAIDs has favorable results.<sup>47</sup> More difficult to explain is the protective effect of NSAIDs against tumors. NSAIDs were reported to reduce the incidence of tumors, including gastric, lung, brain, breast, and biliary tract tumors.<sup>50</sup> This mode of action is still poorly understood and is regarded as a non-COX effect of NSAIDs.

Other uses of NSAIDs include the prevention of Alzheimer's disease, a finding that was based on epidemiological studies but was failed to be reproduced with clinical trials.<sup>51</sup> Furthermore, a potential protective role of aspirin-like analgesics against cataract was suggested, with some studies reporting a 50% reduction in the risk of cataract formation.<sup>52,53</sup>

## NSAIDs adverse effects

### Risk factors

NSAIDs' clinical utility is a fine balance between therapeutic efficacy and toxicity. Several risk factors for increased toxicity have been identified, and a number of clinical characteristics have been associated with a higher risk for complications.<sup>5,12,23,54</sup> The most important risk factor includes a history of pre-existing GI complications, age, concomitant anticoagulation therapy, and high-dose NSAIDs or multiple NSAIDs.<sup>5,12,23,54</sup> Table 3 presents the different risk factors and their relative risk. It is worth mentioning that the presence of *Helicobacter pylori* does not seem to be a risk factor for ulcer in conjunction with NSAID use.<sup>5</sup> When risk factors are present, the indication for NSAID therapy should be scrutinized, and, if appropriate, prophylactic medication and close follow-up should be considered.

### GI

The best-known side effect of NSAID use is GI toxicity, which is the primary limiting factor for their use. It can be categorized into three groups. The first group includes mild GI disturbances including nausea, dyspepsia, heartburn, and abdominal pain or cramps.<sup>5,55</sup> They can occur in 20%–40% of NSAID users, but such symptoms correlate poorly with the development of endoscopic injury or clinical events.<sup>55,56</sup> More severe symptoms are found in the second group derived from

**Table 3** Risk factors for upper gastrointestinal tract (GI) clinical events with nonsteroidal anti-inflammatory drug (NSAID) use criteria for preventive therapies<sup>22,29,49,59</sup>

#### Patient

- Age >65 years
- Alcohol and tobacco

#### Medical history

- Prior peptic ulcer or upper GI event
- Previous NSAID-induced GI side effects
- Severity of underlying disease
- Comorbid conditions
- Poor functional status

#### Medication

- Concomitant use of steroids, ie, prednisolone
- Use of anticoagulants
- Long-term use
- High NSAID dose and use of multiple NSAIDs

**Abbreviations:** GI, gastrointestinal tract; NSAIDs, nonsteroidal anti-inflammatory drugs.

GI mucosal erosions and asymptomatic ulcers, which may heal spontaneously. The third group includes symptomatic ulcers with or without bleeding, which in some cases can be life-threatening.<sup>2,57</sup> The last group occurs in ~1%–2% of NSAID users and has a mortality rate of 10%.<sup>57</sup> It is worth mentioning that this annual incidence of 1% translates into an annual occurrence of ~140,000 NSAID-related complications in the US.<sup>2</sup>

Many gastroprotective strategies have been studied in terms of efficacy to prevent NSAID GI complications.<sup>45</sup> The concomitant use of PPIs or histamine H<sub>2</sub> receptor antagonists has been shown to decrease the incidence of NSAID ulcers but not the severe GI complications.<sup>58</sup> Likewise, concomitant use of prostaglandin E analogs (misoprostol) reverses the gastrototoxic effect of NSAIDs, reducing the asymptomatic lesions by 90%, but it can also reduce ulcer bleeding by 40%.<sup>45,59</sup> Unfortunately, the discontinuation rate of misoprostol is high, as it is frequently poorly tolerated due to symptoms like diarrhea and abdominal pain.<sup>2,45,59</sup>

### Acute kidney injury and hypertension

Renal vasodilator prostaglandins, among other effects, maintain renal blood flow and glomerular filtration rates. This effect is mainly exerted by them relaxing preglomerular resistance and acting as angiotensin II and norepinephrine antagonists. Therefore, NSAIDs usage can cause a variable degree of renal dysfunction, ranging from a reversible impairment of glomerular filtration rate to irreversible renal damage.<sup>60–63</sup> Following newly initiated NSAIDs therapy, the incidence for renal impairment is higher within the first 4–6 weeks, and it is estimated that in this period of time, 1 in

200 patients aged more than 65 years develop acute renal injury.<sup>60,61</sup> Among NSAIDs, indomethacin posed the highest risk, with ibuprofen, piroxicam, and celecoxib also exhibiting high risk.<sup>63</sup> Celecoxib poses the lowest risk compared with other NSAIDs, suggesting a marked gradient of risk among different NSAIDs.<sup>60,61</sup> NSAID use has also been associated with acute interstitial nephritis, membranous nephropathy, and nephritic syndrome; however, the underlying pathophysiology remains unknown.<sup>62</sup>

Renal prostaglandins also affect the systemic vascular resistance. The result from this effect is an elevation in blood pressure that can be as high as 6 mm Hg.<sup>64</sup> The risk is higher with selective COX-2 NSAIDs compared with nonselective COX-2 NSAIDs and placebo.<sup>64</sup> Among the COX-2 selective NSAIDs, great variability exists with more potent effect obtained by rofecoxib and etoricoxib.<sup>65</sup> Several studies found that the relative risk for developing hypertension with NSAIDs varies from ~two-fold to three-fold compared with nonusers.<sup>64,65</sup>

## Cardiovascular effects

Recently, there has been much focus on NSAIDs, particularly on COX-2 inhibitors, not because of their gastroprotective effect but because of the increasing evidence that their use is associated with cardiovascular (CV) adverse events. Although the exact mechanism is not fully understood, it seems to be linked to the relative imbalance in PGI<sub>2</sub> and TXA<sub>2</sub> production, resulting in a prothrombotic state.<sup>66–68</sup> This has been investigated with a number of studies to date, which showed that the use of COX-2 inhibitors is associated with an elevated risk of CV events in high-risk patients.<sup>67</sup> Graham et al has shown that patients receiving <25 mg/day of rofecoxib had a 1.49-fold risk of developing acute myocardial infarction compared with those receiving celecoxib, and this risk increases to 3.58-fold for patients receiving more than 25 mg daily.<sup>69</sup> It is noteworthy that even short-term exposure was not risk free.<sup>3</sup> Two large-scale trials, the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial and the Adenoma Prevention with Celecoxib (APC) trial, with 2586 and 2035 participants, respectively, are worth mentioning.<sup>67,68</sup> The APPROVe trial showed a 1.9-fold increase in risk of thrombotic events in patients assigned to the rofecoxib group compared with placebo, whereas the APC trial presented a significant increase in the risk of serious CV events, including CV-related death, myocardial infarction, stroke, and heart failure, compared with placebo.<sup>67,68</sup>

## Bone healing

NSAIDs are commonly prescribed in musculoskeletal trauma for relieving pain and inflammation. Several animal studies have indicated that NSAID use was associated with delayed union of fractures and poor outcome.<sup>34,70</sup> However, a considerable number of studies failed to reproduce this effect.<sup>34,70</sup> Controversial data have also been derived from clinical studies, with some authors failing to show an impairment of fracture union, whereas others showed significant risk for delayed union and nonunion.<sup>34,70</sup> In terms of the clinical studies, Davis and Ackroyd studied the effect of 2-week administration of flurbiprofen on Colles' fractures.<sup>71</sup> No impairment on fracture healing union was noted. Similarly, other studies found no effect on osteopenia after Colles' fracture, and aseptic loosening after hip replacement was found.<sup>72,73</sup> However, Giannoudis et al showed a strong association between long-term NSAID administration and nonunion development.<sup>74</sup> In patients undergoing spinal fusion, a time- and dose-dependent effect was found with short-term and low-dose administration to have no effect on the rate of nonunion, whereas long-term postoperative doses of NSAIDs had an increased risk of developing nonunion.<sup>75,76</sup>

## Other side effects

Nonaspirin NSAIDs are metabolized in the liver, and small increases in transaminases can occur.<sup>77</sup> As a result, NSAID administration in patients with cirrhotic liver diseases should be avoided; as such, patients are at greater risk of variceal bleeding, worsening of hepatic function, and kidney failure.<sup>77</sup> However, NSAIDs rarely cause hepatic damage, and any hepatic effects are usually reversible.<sup>78</sup> NSAIDs with more potential for hepatic problems include droxicam, clometacin, and sulindac.<sup>79</sup>

Aspirin and other NSAIDs can trigger or exacerbate asthma, resulting in violent attacks. This effect can be attributed to COX-1 inhibition by NSAIDs, which causes alteration of arachidonic acid metabolism, resulting in overproduction of leukotrienes.<sup>80,81</sup> Upper and lower airway eosinophil infiltration is a key feature in this clinical syndrome.<sup>80</sup> The prevalence of aspirin-sensitive asthmatics is ~21%, a figure that doubles in patients with nasal polyps or recurrent sinusitis.<sup>80</sup> Fatal episodes have also been reported; therefore, NSAID and aspirin administration should be avoided in these patients.<sup>77</sup> Recent data suggest that selective COX-2 inhibitors do not elicit bronchospasm and may be a safer option.<sup>80</sup>

In children with acute febrile viral illness, studies have demonstrated an association between aspirin use and Reye's syndrome.<sup>82</sup> Reye's syndrome is an acute metabolic

encephalopathy and liver inflammation triggered by damage to cellular mitochondria.<sup>82,83</sup> The risk of Reye's syndrome is rare and decreases with age; it becomes extremely rare by the late teenage years.<sup>83</sup> Other NSAIDs can trigger Reye's syndrome; therefore, an inborn error of metabolism has been suggested.<sup>82-84</sup> Current advice in many countries, including the US, suggests that aspirin should not be given to those under the age of 16 years, unless specifically indicated in Kawasaki disease or in the prevention of blood clot formation.

NSAID use has also been contraindicated during the last 6–8 weeks of pregnancy.<sup>77,85,86</sup> NSAID administration during this period should be avoided in order to prevent prolonged gestation from inhibition of prostaglandin synthesis, premature closure of the ductus arteriosus, and antiplatelet activity causing maternal and fetal complications.<sup>77,85</sup> Recent data suggest that NSAID use throughout pregnancy increases the risk of miscarriages and birth defects.<sup>86</sup> In breastfeeding women, most NSAIDs can be used safely, although concerns are raised for dipyron and aspirin at a dosage > 100 mg/day.<sup>87</sup> In childhood, parents should be educated regarding correct NSAID dosing and storage in childproof containers to prevent accidental NSAID overdose in children.

## Conclusions

NSAIDs have been used successfully for centuries for the alleviation of pain and inflammation and continue to be used every day by millions of patients worldwide. The recent discovery of the well-praised COX-2 selective inhibitors showed that these agents have a more complex effect not solely bound to analgesia and inflammation. Overall, clinicians should be aware of their potential side effects, and prophylactic treatment should be sought especially in patients with risk factors. Further research in the field will, without question, bring innovative pharmaceutical developments with a considerable spectrum of use.

## Disclosure

The authors report no conflicts of interest in this work.

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