A turbulent decade for NSAIDs: update on current concepts of classification, epidemiology, comparative efficacy, and toxicity

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Abstract  Non-steroidal anti-inflammatory drugs (NSAIDs) represent a diverse class of drugs and are among the most commonly used analgesics for arthritic pain worldwide, though long-term use is associated with a spectrum of adverse effects. The introduction of cyclooxygenase-2-selective NSAIDs early in the last decade offered an alternative to traditional NSAIDs with similar efficacy and improved gastrointestinal tolerability; however, emerging concerns about cardiovascular safety resulted in the withdrawal of two agents (rofecoxib and valdecoxib) in the mid-2000s and, subsequently, in an overall reduction in NSAID use. It is now understood that all NSAIDs are associated with some varying degree of gastrointestinal and cardiovascular risk. Guidelines still recommend their use, but little is known of how patients use these agents. While strategies and guidelines aimed at reducing NSAID-associated complications exist, there is a need for evidence-based algorithms combining cardiovascular and gastrointestinal factors that can be used to aid treatment decisions at an individual patient level.

Keywords  Anti-inflammatory agents, non-steroidal · Cyclooxygenase-2 inhibitors · Comparative efficacy · Comparative safety

Introduction
Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs in the world [1, 2]. With demonstrated efficacy in the management of pain [3], they are a recommended therapy for the large population who suffer from osteoarthritis (OA) [4–7] and rheumatoid arthritis (RA) [8]. However, their chronic use is associated with a well-recognized spectrum of side effects, in particular those involving the gastrointestinal system [9] and, as highlighted by the relatively recent withdrawal of certain cyclooxygenase (COX)-2-selective agents (rofecoxib and valdecoxib), the cardiovascular system [10, 11].

There was subsequently a reduction in the prescribing of all NSAIDs [12, 13], re-thinking about the value of classifying drugs on COX selectivity alone, and increasing investigation into the relative toxicity profiles of NSAIDs. At the end of this rather turbulent decade for NSAIDs, it now seems timely to briefly review their classification, recent epidemiology of use, and the comparative efficacy and toxicity of different NSAIDs, with a focus on the gastrointestinal and cardiovascular risks that pose a major concern in practice.

For the purposes of this review, the terms non-selective (ns) and COX-2-selective will be used where appropriate, whereas the generic term NSAID will refer to all agents. Peer-reviewed, English-language articles were identified for inclusion in this review through searches of MEDLINE and selected on the basis of their relevance. Search terms included: NSAIDs, COX-2, efficacy, safety,
tolerability, gastrointestinal, and cardiovascular, alone or in combination.

Mechanism of action of NSAIDs

The principle of NSAID therapy dates back to the use of willow bark more than 5,000 years ago for musculoskeletal pain [14, 15]. The active ingredient of willow bark, salicin, was isolated in 1828 and the industrial production of salicylic acid underway by 1874 [14, 15]. Aspirin (acetylsalicylic acid) was developed in 1897 in an attempt to improve palatability [14, 15]. Indomethacin and ibuprofen were among the first non-aspirin NSAIDs to be introduced in 1964 and 1969, respectively [14, 15]. Subsequently, many new classes of NSAIDs have followed, including diclofenac in 1974 and naproxen in 1976 [14, 15].

NSAIDs are a diverse group of drugs with common analgesic, anti-inflammatory, and anti-pyretic therapeutic properties [16]. The action of NSAIDs was first described in 1971 when Vane and Piper demonstrated that NSAIDs inhibit the biosynthesis of prostaglandins by preventing the substrate arachidonic acid from binding to the COX enzyme active site [17]. The COX enzyme was subsequently found to exist in two isoforms—COX-1 was characterized in 1976, and the gene for the COX-2 isoenzyme was later discovered in 1991 [17]. COX-1 is constitutively expressed and catalyzes the production of prostaglandins that are involved in numerous physiological functions, including maintenance of normal renal function in the kidneys, mucosal protection in the gastrointestinal tract, and pro-aggregatory thromboxane A₂ in the platelets [17, 18]. By contrast, COX-2 expression can be induced by cytokines and other inflammatory mediators in a number of tissues, including endothelial cells, and is believed to have a role in the mediation of pain, inflammation, and fever [16, 17]. There has been speculation on the existence of a third isoform, COX-3, which would explain the mechanism of action of acetaminophen, a poor inhibitor of COX-1 and COX-2. Splice variants of COX-1 and COX-2 have emerged that have been referred to as COX-3 but have transpired to have little relevance in humans [19].

Classification of NSAIDs

NSAIDs can be classified according to numerous characteristics, including COX selectivity, and chemical and pharmacological properties (Table 1). NSAIDs generally have chemical similarity in that they are relatively lipid-soluble, weak acids. There are, however, some clinically relevant differences in pharmacokinetic properties [20].

NSAIDs generally have high bioavailability after oral administration. As a result of their chemical properties, they are well absorbed from the gastrointestinal tract and hepatic clearance is low [20]. However, the rate of absorption varies between NSAIDs, which can impact upon the suitability of different NSAIDs for particular indications [20]. NSAIDs can also be categorized by half-life into two groups: those with a short half-life (<6 h) and

| NSAID    | COX-2 selectivity (SI) | Chemical structure | Bioavailability (%) | Half-life (h) | Volume of distribution | Clearance | Peak (h) | Protein binding (%) | Renal elimination (%) | Clinical dose (mg/d)a |
|----------|------------------------|--------------------|---------------------|---------------|------------------------|----------|----------|---------------------|-----------------------|----------------------|
| Ibuprofen | Non-selective (1.05)   | Propionic acid     | >80                 | 2             | 0.15 L/kg              | 3.0–3.5 L/h | 1–2      | 99                  | 45–79                 | 1,200–3,200          |
| Diclofenac| Non-selective (1.97)   | Acetic acid        | 50–60               | 2             | 0.1–0.2 L/kg           | 21.0 L/h  | 2        | >99                 | 65                    | 100–150              |
| Naproxen  | Non-selective (0.33)   | Propionic acid     | 95                  | 12–17        | 0.16 L/kg              | 0.13 mL/min/kg | 2–4      | >99                 | 95                    | 500–1,000            |
| Meloxicam | Selective (>2.04)      | Oxicam             | 89                  | 15–20        | 10 L                   | 0.4–0.5 L/h | 4–5      | 99                  | 50                    | 7.5–15.0             |
| Celecoxib | Selective (7.70)       | Pyrazole           | NS                  | 11           | 400 L                  | 27.7 L/h  | 3        | 97                  | 27                    | 200                  |
| Ketoprofen| Non-selective (0.02)   | Propionic acid     | 90                  | 2.1          | 0.1 L/kg               | 6.9 L/h   | ≤2       | >99                 | 80                    | 200–300              |
| Etoricoxib| Selective (105.40)     | Bipyridine         | 100%                | 22           | 120 L                  | 50 mL/min | 1        | 92                  | 75                    | 60                   |

SI/ COX-2-selectivity index (SI = ratio of COX-1 half maximal inhibitory concentration [IC₅₀]/COX-2 IC₅₀), COX-2 cyclooxygenase-2, NS not specified, NSAID non-steroidal anti-inflammatory drug

a Standard clinical dose for OA

b Non-enteric coated
those with a long half-life (Table 1). This provides a guide to dosing with short half-life NSAIDs (e.g., ibuprofen) generally administered every 6–8 h and longer half-life NSAIDs (e.g., naproxen and celecoxib) administered once or twice daily [20–23]. Rapid absorption is a desirable feature for patients using NSAIDs for immediate analgesic relief, but may not always be most appropriate for patients with chronic pain.

**Epidemiology of NSAID prescribing**

NSAIDs are among the most commonly used drugs worldwide, used by more than 30 million people every day [2]. More than 111 million prescriptions are written for NSAIDs in the USA annually, and they account for approximately 60% of the USA over-the-counter (OTC) analgesic market [1]. The most commonly used NSAIDs are diclofenac and ibuprofen, which account for almost 40% of global NSAID sales for OA [24] (Fig. 1). Excluding OTC use, ibuprofen and naproxen are the most commonly prescribed NSAIDs in the USA, while diclofenac prescription is more common in the UK [24]. Reasons for regional variation may not just relate to drug properties but may also include which NSAID was first to market in a particular region.

The introduction of COX-2-selective agents with improved gastrointestinal safety led to an overall increase in the use of NSAIDs. Using prescription claims data, a Canadian study observed that the overall number of NSAID prescriptions among patients aged over 65 years increased by 68% between March and November 2000 following the introduction of celecoxib and rofecoxib. This increase was almost entirely attributable to COX-2-selective agents as the level of nsNSAID prescribing remained relatively stable [25].

Following the withdrawal of rofecoxib and valdecoxib in the mid-2000s, there was a reduction in prescribing of all NSAIDs, primarily driven by marked decreases in the use of COX-2-selective agents that were not compensated by increases in nsNSAID use of the same magnitude. A prospective cohort study using American registry data found that the use of COX-2-selective agents decreased from 55.1 to 29.2% among patients with RA or psoriatic arthritis between 2003 and 2005. In contrast, use of nsNSAIDs increased from 50.2 to 73.9% [12]. Similarly, in Germany, COX-2-selective agent prescriptions decreased by 37.1 million defined daily doses (DDDs) between 2004 and 2005, and nsNSAID prescriptions increased by 19.0 million DDDs [13]. This study reported an overall decrease in NSAID use of 8.4% [13]. It could be speculated that availability of generic COX-2-selective inhibitors in coming years following patent expiration will result in a resurgence in their use, although this remains to be seen.

**Use of NSAIDs by patients**

Use of NSAIDs, and in particular chronic use, increases with age, with an estimated 10–40% of people aged over 65 years using prescribed or OTC NSAIDs daily [26, 27]. In a survey of patients aged over 55 years with knee OA in two general practices in the UK, NSAIDs were used more commonly among patients from an affluent rural area compared with those from a deprived urban area [28]. There is also evidence to suggest that many patients use NSAIDs intermittently, as less than half receive prescriptions with enough medication to sustain longer-term daily use [29].

Use of OTC NSAIDs, generally available without prescription at lower doses, is also very common. A USA poll of more than 2,000 adults found that approximately 30% use OTC analgesics on a regular basis for arthritis or some other form of chronic pain [30]. Based on the findings of the 1997 Roper survey commissioned by the American Gastroenterological Association and the 2002 National Consumer League study, with a combined total of 9,062 respondents, ibuprofen-based NSAIDs are the most widely used OTC NSAIDs, with the majority of patients using them on an as-needed basis [31]. The Roper study found that among prescription NSAID users, approximately 40% also use OTC NSAIDs at the same time [31].

Approximately one half of NSAID users in the Roper survey were not aware of the potential side effects. Among all NSAID users, 33% perceived prescription NSAIDs to be safer and 32% perceived OTC NSAIDs to be safer. Consumption of more than the recommended dose was
Comparative analgesic efficacy of NSAIDs

NSAIDs have demonstrated short-term efficacy compared with placebo in the treatment of OA [3] (Fig. 2). The efficacy of NSAIDs has been further evaluated in a comparative effectiveness review for the Agency for Healthcare Research and Quality (AHRQ) Effective Healthcare Program [32], a drug effectiveness review project by the Oregon Health and Science University (OHSU), funded by the Center for Evidence-based Policy [33] and a UK National Health Service (NHS) health technology assessment [34].

Comparisons and meta-analyses of published studies have found that there are no clear differences in efficacy among nsNSAIDs at standard doses in the treatment of knee, back, or hip pain [32, 33]. Similarly, based on more than 20 randomized controlled trials and systematic reviews, the AHRQ review found that there are no significant differences in efficacy between COX-2-selective agents and nsNSAIDs [32]. In a review of previous systematic reviews of randomized controlled trials, the NHS health technology assessment found that COX-2-selective agents had equivalent efficacy to nsNSAIDs for the treatment of RA and OA [34]. Although sometimes based on data using supratherapeutic doses, celecoxib 200–800 mg/day has efficacy equivalent to naproxen 1,000 mg/day, diclofenac 100–150 mg/day, and ibuprofen 2,400 mg/day. Etoricoxib 60–120 mg/day also has efficacy similar to naproxen 1,000 mg/day, diclofenac 150 mg/day, and ibuprofen 2,400 mg/day [34].

In randomized trials, celecoxib and nsNSAIDs have been found to be associated with similar levels of pain reduction in patients with OA, ankylosing spondylitis, and RA [33]. In the Successive Celecoxib Efficacy and Safety Study (SUCCESS), celecoxib 200–400 mg/day was found to have efficacy comparable to naproxen 1,000 mg/day and diclofenac 100 mg/day for the treatment of more than 13,000 patients with OA over 12 weeks [35].

The efficacy of etoricoxib and nsNSAIDs has also been compared in seven relatively small studies [34]. These studies found that etoricoxib 30–120 mg/day had comparable efficacy to naproxen, diclofenac, and ibuprofen at standard doses in patients with OA and RA [36–42]. In a more recent long-term study, etoricoxib 90–120 mg/day was found to have greater efficacy compared with naproxen 1,000 mg/day over 12 weeks, but similar efficacy over 121 weeks [43].

Among COX-2-selective agents, the efficacy of rofecoxib 25 mg/day, etoricoxib 30 mg/day, and lumiracoxib 200 or 400 mg/day has been compared with celecoxib 200 mg/day. No significant differences for pain relief at these doses have been found [32, 44, 45].

![Fig. 2 Efficacy of NSAIDs compared with placebo for the treatment of OA of the knee [3]. Knee OA studies 2–13 weeks in length. Adapted by permission from BMJ Publishing Group Limited (Bjordal JM et al. BMJ; 329: 1317, copyright 2004)](image-url)

| NSAID               | Number of patients | P-value |
|---------------------|--------------------|---------|
| Celecoxib           | 800                | 0.006   |
| Acetaminophen       | 53                 | 0.002   |
| Etodolac/naproxen   | 254                | 0.006   |
| Rofecoxib           | 219                | <0.001  |
| Naproxen/nabumetone | 279                | 0.733   |
| Etoricoxib          | 386                | <0.001  |
| Valdecoxib/naproxen | 613                | 0.002   |
| Meloxicam           | 271                | 0.034   |
| Nabumetone          | 347                | 0.080   |
| Celecoxib/diclofenac| 600                | <0.001  |
| Etodolac/nabumetone | 270                | 0.002   |
| Lumiracoxib         | 1,702              | 0.003   |
| Flurbiprofen        | 39                 | 0.119   |
| Nabumetone          | 328                | 0.351   |
| Celecoxib           | 104                | 0.053   |
| Etodolac            | 715                | 0.015   |
| Celecoxib           | 801                | <0.001  |
| **Combined**        | 10,845             | <0.001  |

Favors placebo Favors NSAID
How effective are NSAIDs in clinical practice?

The majority of clinical trials evaluating the analgesic efficacy of NSAIDs typically report outcomes as mean population changes. Such results can be difficult to translate for individual patients in clinical practice. In a recent study, data from seven randomized, controlled OA trials (≥6 weeks’ duration) assessing the efficacy of etoricoxib compared with other NSAIDs or placebo, using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), investigated this NSAID’s effects on different levels of pain relief [46]. While 60–80% of patients experienced minimal pain relief (≥15% improvement from baseline), only 20–30% experienced extensive pain relief (≥70% improvement from baseline).

Comparative toxicity of NSAIDs

Like many drugs, NSAIDs are associated with a broad range of side effects, including renal toxicity, exacerbation of hypertension, fluid retention, gastrointestinal complications, and cardiovascular events [15]. Furthermore, the presence of chronic co-morbidities in many, particularly elderly, patients with arthritis who require NSAIDs can be associated with increased risks of complications resulting in complex treatment decisions to balance risks and benefits [47].

Gastrointestinal toxicity

NSAIDs are associated with a spectrum of upper gastrointestinal complications, ranging from endoscopic ulcers in 10–30% of patients, to serious ulcer complications in 1–2% of patients [48, 49], although the exact incidence is changing [50]. In recent years, the effect of NSAIDs on the lower gastrointestinal tract has begun to receive greater attention with opinion moving toward a focus on the complications affecting the whole gastrointestinal tract. At present, lower gastrointestinal complications are less well characterized but thought to be increasingly common [50–52]. One systematic review reported the overall risk (OR) of lower gastrointestinal bleeding to be 1.9–18.4 in case–control studies [53].

In 1998, it was estimated that approximately 100,000 people were hospitalized annually in the USA as a result of NSAID-related gastrointestinal complications [54], and mortality is reported as approximately 5% [55], which highlights the clinical importance of such events. Perhaps more importantly for people with arthritis who have few analgesic options, minor side effects (including symptoms of dyspepsia) occur in up to 60% of patients [49] and poor tolerability results in many patients discontinuing therapy [56]. Management of gastrointestinal complications and dyspepsia adds significantly to the economic burden of arthritis [57].

A nested case–control study found that, compared with non-use, nsNSAIDs increased the risk of developing serious upper gastrointestinal complications by a factor of 3.7 (95% confidence interval [CI] 3.1, 4.3), and COX-2-selective agents by a factor of 2.6 (95% CI 1.9, 3.6) [9]. Among individual NSAIDs, the relative risk (RR) of developing serious upper gastrointestinal complications compared with non-use ranged from 2.0 with ibuprofen to 12.0 with etoricoxib, though this was based on retrospective analyses that probably had an element of confounding by indication for the COX-2-selective agents. It has previously been reported that, based on meta-analyses from 1991 to 2004, the RR of serious gastrointestinal complications is 3–4-fold higher in nsNSAID users compared with non-users [58]. A more recent systematic review of observational studies reported that the RR for upper gastrointestinal bleeding or perforation varies between individual NSAIDs, ranging from 1.42 (95% CI 0.85, 2.37) with celecoxib to 14.54 (95% CI 5.87, 36.04) with ketorolac (Fig. 3), and is influenced by NSAID half-life [59].

The majority of studies evaluating the gastrointestinal safety of NSAIDs have found that COX-2-selective inhibitors are associated with a lower risk of ulcers and complications than nsNSAIDs [35, 60–63]. However, in some studies, the difference in rate of all upper gastrointestinal clinical events and complicated events is not significant [61, 63]. A 2008 review of randomized controlled trials and meta-analyses estimated that COX-2-selective agents are associated with 61% RR reduction for ulcer

![Fig. 3 Risk of upper gastrointestinal bleeding/perforation with individual NSAIDs from published studies since 1990 [59]. *Studies published after 2000. P-values derived from heterogeneity test and n (number of studies). Adapted by permission from John Wiley & Sons, Inc (Massó González EL et al. Arthritis Rheum; 62: 1592, copyright 2010)
complications compared with nsNSAIDs [64] and a separate systematic review of observational studies calculated that the RR for upper gastrointestinal bleeding or perforation was greater with nsNSAIDs (RR 4.50; 95% CI 3.82, 5.31) than COX-2-selective agents (RR 1.88; 95% CI 0.96, 3.71) as a class, though it was noted that risk varied between individual NSAIDs [59].

There are a number of risk factors for NSAID-associated gastrointestinal injury, including high NSAID dose, older age, Helicobacter pylori infection, a history of ulcer or ulcer complications, and concomitant use of OTC NSAIDs, low-dose aspirin, anticoagulants, or corticosteroids [65–67]. Concomitant use of low-dose aspirin for cardiovascular prophylaxis is common among NSAID users (approximately 20–25% in clinical trials [62, 63, 68]) but increases the risk for mucosal damage [69, 70] and eliminates the gastrointestinal benefits of COX-2-selective agents [9, 62, 63]. For example, in a nested case–control study, García Rodríguez and Barreales Tolosa found that the RR of upper gastrointestinal complications was higher among patients using aspirin plus COX-2-selective agents (RR 1.9; 95% CI 1.0, 3.6) compared with COX-2-selective agents alone (RR 0.6; 95% CI 0.4, 0.9) [9].

NSAIDs, particularly diclofenac, nimesulide, and sulindac, are also associated with drug-related hepatotoxicity, as indicated by liver function test abnormalities in clinical trials and reports of fatal liver injury among NSAID users [71, 72]. Lumiracoxib, an analog of diclofenac, is a COX-2-selective inhibitor that was never approved in the USA and was withdrawn from the European market in 2007 as a result of concerns about potential liver toxicity [73].

**Cardiovascular toxicity**

NSAIDs are associated with an increased risk of cardiovascular adverse events such as myocardial infarction, heart failure, and hypertension [74], and this increase in risk appears to be dependent on duration of exposure [33]. It has been suggested that the mechanism for this may be the impact of COX inhibition on the balance between COX-2-mediated production of pro-aggregatory thromboxane in platelets and anti-aggregatory prostaglandin I2 in endothelial cells [18, 75, 76].

Previously, increasing COX-1 selectivity has been associated with an increased risk of gastrointestinal toxicity, while increasing COX-2 selectivity has been associated with an increased risk of cardiovascular toxicity [77]. It has since been suggested that this concept is flawed, as while COX-2-selective agents have varying but little effect on COX-1, COX-2-selective agents and nsNSAIDs both inhibit COX-2 at traditional therapeutic doses and have potential for cardiovascular toxicity. Therefore, COX selectivity alone is not sufficient to define the risk of NSAID-associated complications. Based on clinical evidence and an increased understanding of differences between individual NSAIDs, an alternative concept has been proposed that incorporates the association between increasing dose and NSAID-associated gastrointestinal and cardiovascular risk [77].

**COX-2-selective agents**

A meta-analysis comparing the effects of different COX-2-selective agents found that there was a significant increase in the incidence of serious vascular events with COX-2-selective agents compared with placebo (rate ratio 1.42; 95% CI 1.13, 1.78; $P = 0.003$) that was primarily as a result of increased risk of myocardial infarction [78].

In the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, it was observed that rofecoxib 50 mg/day was associated with a fourfold increase in the incidence of myocardial infarction compared with naproxen 1,000 mg/day in patients with RA [60]. The Adenomatous Polyp Prevention On Vioxx (APPROVe) study found that rofecoxib 25 mg/day was associated with an increased RR of thrombotic events compared with placebo in patients with a history of colorectal adenomas after 18 months of treatment and an increased risk of myocardial infarction after 15 months of treatment [79]. Based on these findings, rofecoxib was withdrawn from the market in 2004. Valdecoxib was subsequently withdrawn in 2005 [80].

Cardiovascular safety data for celecoxib are available from three long-term trials: the Alzheimer’s Disease Anti-inflammatory Prevention Trial (ADAPT) [81], the Adenoma Prevention with Celecoxib (APC) study [82], and the Prevention of colorectal Sporadic Adenomatous Polyps (PreSAP) study [83]. Celecoxib 200–400 mg/day was associated with a significant and dose-related increase in death from cardiovascular causes in APC, but not in PreSAP or ADAPT [84]. However, based on an analysis of cardiovascular events in APC, all three studies were subsequently suspended [84]. In one systematic review, celecoxib was associated with a greater risk of myocardial infarction compared with placebo and nsNSAIDs [34], but another two concluded that the cardiovascular risk of celecoxib is generally similar to that with placebo or nsNSAIDs [84, 85].

The cardiovascular safety of etoricoxib 60 or 90 mg/day was compared with diclofenac 150 mg/day in a pooled analysis of data from three trials in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) program. The risk for thrombotic cardiovascular events with long-term therapy was found to be similar to nsNSAID treatment (hazard ratio 0.95; 95% CI 0.81, 1.11) [86].
nsNSAIDs

The cardiovascular safety of nsNSAIDs has been a highly contentious issue during the latter half of the last decade. A meta-analysis of randomized trials found that high-dose ibuprofen (rate ratio 1.51; 95% CI 0.96, 2.37) and high-dose diclofenac (rate ratio 1.63; 95% CI 1.12, 2.37) were associated with a moderately increased risk of any vascular events compared with placebo, similar to that observed with COX-2-selective agents, but the risks associated with naproxen, though they cannot be completely excluded, were substantially lower (rate ratio 0.92; 95% CI 0.67, 1.26) (Fig. 4) [78]. Another systematic review and meta-analysis of controlled observational studies comparing the risks of cardiovascular events with individual NSAIDs found that diclofenac was associated with a higher risk of cardiovascular events (RR 1.40; 95% CI 1.16, 1.70) than ibuprofen (RR 1.07; 95% CI 0.97, 1.18) and naproxen (RR 0.97; 95% CI 0.87, 1.07) [87]. This issue has been further complicated by evidence from pharmacokinetic studies suggesting an interaction between ibuprofen and aspirin that results in reduced platelet inhibition by aspirin [88]. However, overall, there is a lack of long-term studies that have evaluated both gastrointestinal and cardiovascular events, particularly for nsNSAIDs, which may limit our understanding of the true benefits and risks of NSAIDs [33].

Modern recommendations aimed at reducing NSAID toxicity

It is important that both individual NSAID and patient risk factors should be considered in prescribing decisions.

Current treatment guidelines recommend that NSAIDs should be used at their lowest effective dose [5, 6, 89] and that long-term use should be avoided where possible [6, 7].

Reducing gastrointestinal risk

It is generally recommended that patients with gastrointestinal risk factors should be treated with COX-2-selective agents or nsNSAIDs plus gastroprotective co-therapy [5–7, 90, 91]. Available gastroprotective agents include H2 receptor antagonists, misoprostol, and proton pump inhibitors (PPIs). PPIs have superior efficacy to H2 receptor antagonists [92, 93], which do not provide sufficient acid suppression at traditional doses to prevent most ulcers [94–96]. Compared with misoprostol, PPIs have not demonstrated superior efficacy in ulcer prevention, but they are deemed to be clinically equivalent when the safety and poor compliance issues of misoprostol are considered [97].

While it should be remembered that PPIs may not protect the lower gastrointestinal tract [47], a USA cohort study investigating ulcer-related hospitalizations found that the treatment with an nsNSAID plus a PPI was at least as effective as treatment with a COX-2-selective agent. The risk of hospitalization was reduced by 54% in patients using either NSAIDs plus PPI co-therapy or COX-2-selective agents compared with NSAIDs alone [98]. A recent study compared the effects of treatment with celecoxib or diclofenac plus omeprazole for 6 months on gastrointestinal outcomes in patients with OA or RA. While no difference in incidence of hemorrhage, obstruction, or perforation between treatments was observed, a lower incidence of anemia (>20 g/L decrease in hemoglobin or ≥10% decrease in hematocrit; with or without defined gastrointestinal origin) was reported with COX-2-selective agent treatment compared with NSAID plus PPI [51].

A more recent concept is that of further reducing gastrointestinal risk by combining a COX-2-selective agent with a PPI, an approach that has been recommended in the UK based on national-level cost-effectiveness analyses [7, 99]. It has been demonstrated that addition of a PPI to treatment with a COX-2-selective agent significantly reduces the absolute risk of endoscopic gastric ulcers compared with placebo [100].

Although PPIs are generally considered to be well tolerated, the potential for adverse events or interactions with other therapies should be a factor in clinical decision making. For example, in a recent retrospective study, PPI therapy was associated with an increased risk of adverse cardiovascular events in aspirin-treated patients surviving 30 days after a first myocardial infarction, although this would be a population in which NSAID use would be avoided [101].
Despite current recommendations, evidence from observational studies suggests that as many as 60–80% of patients using NSAIDs who have gastrointestinal risk factors, including those using concomitant low-dose aspirin, do not receive appropriate gastroprotection [102, 103]. In addition, of those patients who are prescribed gastroprotective agents, more than 30% may be non-adherent, which increases their risk of gastrointestinal events [100, 104, 105]. Fixed-dose combinations of NSAIDs and gastroprotective agents have emerged as a strategy to improve adherence. For example, Arthrotec® is a combination product containing diclofenac sodium 50–75 mg plus misoprostol 200 μg that is approved for the treatment of osteoarthritis or rheumatoid arthritis in patients at high risk of developing NSAID-associated ulcers and their complications [106, 107]. More recently, a fixed-dose combination of naproxen 500 mg and esomeprazole magnesium 20 mg (VIMOVO®) has been approved for the relief of signs and symptoms of OA, RA, and ankylosing spondylitis, and to decrease the risk of developing ulcers in patients at risk for developing NSAID-associated gastric ulcers [68, 108]. An additional combination therapy in development for this patient population is ibuprofen 800 mg plus famotidine 26.6 mg (DUEXA®) [109].

Reducing cardiovascular risk

The American Heart Association recommends that all NSAIDs should be used at their lowest effective dose. These and other guidelines, including those from the American College of Rheumatology, recommend that all NSAIDs, and particularly COX-2-selective agents, should be avoided where possible in patients with cardiovascular risk factors (such as hypertension, hypercholesterolemia, angina, edema, recent bypass surgery, and a history of myocardial infarction or other cardiovascular events), and should be used only when sufficient pain relief is not achieved with other therapies and the benefit outweighs the increased cardiovascular risk [74, 89–91, 110]. Where NSAID therapy is required for patients at risk of cardiovascular complications, naproxen is recommended as the NSAID of choice [74, 89–91, 110].

Conclusions

The start of the last decade saw a large increase in the use of NSAIDs following the introduction of COX-2-selective agents, which demonstrated improved gastrointestinal tolerability relative to nsNSAIDs, but concerns about their cardiovascular safety emerged and subsequently resulted in reduced use and revised thinking on the classification and safety of all NSAIDs. It is now clear that all NSAIDs are associated with varying degrees of cardiovascular and gastrointestinal risk and that individual drug and patient factors should be considered in treatment decisions.

While strategies exist to prevent complications in patients at risk of NSAID-associated gastrointestinal and cardiovascular injury, they are often underutilized or difficult to apply, particularly in patients with both types of risk factor. There remains a great need for data-driven algorithms combining cardiovascular and gastrointestinal risk that can be applied when assessing an individual patient’s risk.

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