

## Managing NSAID Risks

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### Background

NSAIDs (nonsteroidal anti-inflammatory drugs) are useful in the treatment of several different types of pain. Unfortunately, NSAIDs can cause gastrointestinal ulceration and bleeding, and cardiovascular events. Although the chance of a serious adverse event is relatively small, the consequences can be devastating. Certain NSAIDs may have more of a propensity to cause gastrointestinal or cardiovascular events. Although no single NSAID is free of both gastrointestinal and cardiovascular risks, an NSAID can be selected based on whether the patient is more at risk for a cardiovascular event or a gastrointestinal event. In addition, gastroprotective agents such as proton pump inhibitors can be used to decrease gastrointestinal risk. This article provides information to help health care professionals manage NSAID gastrointestinal and cardiovascular risk, and avoid aspirin/NSAID interactions.

### Gastrointestinal Risk

NSAIDs inhibit production of prostaglandins by inhibiting the enzymes COX (cyclooxygenase)-1 and COX-2. Prostaglandins produced by COX-2 mediate inflammation, pain, and fever. This enzyme is the main target of therapeutic importance with NSAID therapy. NSAIDs also inhibit the COX-1 pathway to varying degrees. Prostaglandins produced by the COX-1 pathway increase gastrointestinal mucosal blood flow, mucus and bicarbonate production, and epithelial growth. NSAIDs harm the gastrointestinal mucosa by direct irritation and by inhibition of production of protective prostaglandins via inhibition of the COX-1 pathway. Inhibition of COX-1 by NSAIDs deprives the gastroduodenal mucosa of prostaglandins' protections against acid, enzymes, and bile salts, thus increasing the risk of ulcers.<sup>1</sup>

The risk for a gastrointestinal bleed or perforation increases about four-fold in patients

who use NSAIDs compared to those who don't.<sup>2,3</sup> Risk factors for an NSAID-associated gastrointestinal event includes male gender, history of peptic ulcer (especially bleeding ulcer), dyspepsia, and cardiovascular disease.<sup>1,4</sup> Age is a significant risk factor; increased risk begins at age 60 years and rises thereafter.<sup>1</sup> Risk is also increased by use of antiplatelets (e.g., aspirin), anticoagulants (e.g., warfarin), corticosteroids, or high NSAID doses.<sup>1,4</sup> Risk decreases after the first few months of NSAID use, but never goes away.<sup>4</sup>

Different NSAIDs confer different degrees of gastrointestinal risk. Risk is high with some of the longer acting NSAIDs (e.g., piroxicam [57 hours], ketorolac [up to ten hours], and sustained-release formulations), perhaps due to longer mucosal exposure.<sup>4,5,6</sup> Ibuprofen seems to have the lowest risk of gastrointestinal events.<sup>5</sup> This might be because low doses are typically used, possibly owing to nonprescription availability, or because it has a short half-life (two hours).<sup>4,6</sup>

A systematic review of observational studies revealed that risk of upper gastrointestinal bleeding or perforation was not increased by celecoxib. Risk was low with ibuprofen (RR 2.69), followed by diclofenac (RR 3.98), meloxicam (RR 4.15), indomethacin (RR 4.15), ketoprofen (RR 5.4), naproxen (RR 5.57), piroxicam (RR 9.94), and ketorolac (RR 14.54).<sup>2</sup> Risk in one case-control study, from lowest to highest, was ranked: ibuprofen (twice the risk of non-use), meloxicam and celecoxib (RR 2.7), diclofenac (RR 3.7), ketoprofen (RR 5.4), indomethacin (RR 7.2), and naproxen (RR 8.1).<sup>5</sup> A meta-analysis of case-control studies ranked risk, from lowest to highest, as follows: ibuprofen, followed by diclofenac, sulindac, diflunisal, naproxen, and indomethacin with around twice the risk of ibuprofen, and highest with piroxicam and ketoprofen, with around four times the risk of ibuprofen.<sup>7</sup> A cohort study found a lower risk with nabumetone, and surprisingly

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indomethacin, compared to ibuprofen. There was a 30% to 40% higher risk with ketoprofen, naproxen, and immediate-release diclofenac compared to ibuprofen; and a 63% higher risk with sustained-release diclofenac. Piroxicam had over three times the risk of ibuprofen.<sup>8</sup>

A selective COX-2 inhibitor should provide pain relief with lower gastrointestinal risk.<sup>1</sup> Among “traditional” NSAIDs, meloxicam, nabumetone, and etodolac have some COX-2 selectivity and seem to be less likely than less selective NSAIDs to cause gastrointestinal events.<sup>4,8,10</sup> The selective COX-2 inhibitor celecoxib (*Celebrex*) is associated with about a 20% lower risk of bleeding compared to traditional NSAIDs.<sup>5</sup> However, celecoxib does not seem to be safer than non-selective NSAIDs past six months of use.<sup>11</sup> But at least short term, celecoxib appears safer from a gastrointestinal standpoint than other NSAIDs, even in low-dose aspirin users.<sup>24</sup>

In summary, the bulk of evidence suggests that ibuprofen and the agents with relatively more COX-2 selectivity have the lowest gastrointestinal risk, and piroxicam and ketorolac have the highest risk [Evidence level B; case-control and cohort studies].<sup>2,5,7,8</sup>

Gastroprotective agents that are available to reduce NSAID gastrointestinal risk include misoprostol and proton pump inhibitors.<sup>11</sup> Misoprostol reduces the risk of gastroduodenal complications by about 40% among patients at higher than average risk.<sup>12</sup> The recommended dose is 200 mcg four times daily, but adverse effects (e.g., diarrhea cramping) may require dose reduction.<sup>11</sup> However, lower doses may also cause gastrointestinal symptoms and have not been shown to reduce ulcer complications.<sup>9</sup> Proton pump inhibitors are well-tolerated and have been shown to reduce the risk of bleeding ulcers associated with celecoxib in high-risk patients (NNT=11).<sup>13</sup> Furthermore, PPIs can reduce the risk of NSAID-associated ulcer bleeding in patients with *H. pylori* and a history of ulcer bleeding. They also seem protective against NSAID-associated ulcer bleeding in epidemiologic studies and in secondary analysis of prospective studies.<sup>4</sup> Standard dose H<sub>2</sub>-blockers reduce the risk of NSAID-associated duodenal ulcers.<sup>9,11</sup> But high dose H<sub>2</sub>-blockers (e.g., 80 mg/day famotidine) reduce the risk of both duodenal and gastric ulcers.<sup>9,11,33</sup> Benefit is

highest in patients with *H. pylori*.<sup>11</sup> It should be noted that H<sub>2</sub>-blockers have not been shown to reduce the risk of serious gastrointestinal events in NSAID users.

### Cardiovascular Risk

In addition to the hypertension and heart failure concerns with all NSAIDs, NSAIDs seem to increase the risk of cardiovascular events (heart attack, stroke, death) to varying degrees, even in healthy people.<sup>14</sup> Adverse cardiovascular events associated with NSAIDs are thought to be caused by NSAIDs upsetting the balance between vasoconstricting, platelet aggregating thromboxane A<sub>2</sub> (produced by COX-1) and opposing vasodilating prostacyclin (produced by COX-2). This may lead to vasoconstriction, platelet aggregation, and thrombosis.<sup>15</sup> NSAIDs that tend to be more COX-2 selective could therefore be assumed to have more cardiovascular risk. In fact, the COX-2 selective agents rofecoxib (*Vioxx*), valdecoxib (*Bextra*), and lumiracoxib (*Prexige*, Canada only) were withdrawn from the market due to cardiovascular risk.<sup>16</sup>

A recently published Danish cohort study examined risk of specific cardiovascular events in healthy users vs nonusers of NSAIDs.<sup>14</sup> These same investigators had previously examined risk of myocardial infarction and death in this same cohort.<sup>17</sup> All NSAIDs were used for a short period (about a week to a month), mostly in low doses.<sup>14,17</sup> In this study, diclofenac (e.g., *Voltaren*) at doses of 100 mg or more daily increased the risk of cardiovascular death (OR 2.04), coronary death or non-fatal myocardial infarction (OR 2.01), and fatal or nonfatal stroke (OR 1.70) in a case-crossover analysis, a method that minimized the effect of unmeasured confounders. For comparison, with rofecoxib the odds ratio for risk of cardiovascular death was 1.66. For coronary death or nonfatal myocardial infarction, the odds ratio was 1.6 at doses ≤25 mg daily and 3.02 at doses >25 mg daily. Celecoxib about doubled the odds of coronary death or nonfatal myocardial infarction, but interestingly, only at doses of 200 mg daily or lower.<sup>14</sup> Previous studies indicate that celecoxib increases the risk of cardiovascular events in a dose-dependent manner.<sup>16</sup> In a case-control study (n=486,378), an increased risk for MI was reported with celecoxib (RR 1.56, 95% CI, 1.22-

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2.00; at  $\leq 200$  mg/day, RR 1.44, 95% CI 1.12-1.87; and at  $>200$  mg/day, RR 2.45, 95% CI 2.41-3.25).<sup>18</sup> And in a randomized study of celecoxib for prevention of colorectal adenomas, celecoxib 400 mg per day doubled the risk of a composite endpoint of cardiovascular death, myocardial infarction, stroke, or heart failure compared to placebo (HR 2.3, 95% CI 0.9 to 5.5).<sup>19</sup> Be aware that few patients in the Danish cohort study received celecoxib or rofecoxib (1.5% and 1.6% of patients, respectively). Also, this was not a randomized study, so confounding by indication may have played a role in the results (i.e., patients at high cardiovascular risk may have been more likely to receive diclofenac). In addition, patients who received celecoxib and rofecoxib tended to be older.<sup>14</sup> However, the increased risk with diclofenac has a pharmacologic basis; it has COX-2 selectivity similar to that of rofecoxib *in vitro*.<sup>16</sup> Also, diclofenac has previously been associated with increased cardiovascular events (observational trials analysis RR 1.40, 95% CI 1.16-1.70; randomized trials analysis RR 1.63, 95% CI 1.12-2.37).<sup>20,21</sup>

In the Danish cohort study, ibuprofen was associated with an increased odds ratio of coronary death or nonfatal myocardial infarction (OR 1.52) and fatal or nonfatal stroke (OR 1.29). A dose-dependent effect was not apparent in this study.<sup>14</sup> In a randomized trial analysis there was an increase in cardiovascular risk with high-dose ibuprofen which was almost statistically significant (RR 1.51; 95% CI 0.96-2.37).<sup>20</sup> In another analysis in patients following hospitalization for a first MI, the risk of death with ibuprofen was increased 2.2-fold at doses higher than 1200 mg/day and re-infarction was increased at doses below and above 1200 mg/day.<sup>22</sup>

Naproxen increased the risk of fatal and non-fatal stroke in the Danish cohort study (OR 1.91).<sup>14</sup> But naproxen was previously found to have a neutral cardiovascular effect in meta-analyses of observational and randomized trials.<sup>20,21</sup>

### **Aspirin/NSAID Interaction**

Many NSAID users take aspirin for its cardiovascular benefit. However, some NSAIDs may interfere with aspirin's antiplatelet effect. Aspirin exerts its antiplatelet effect by irreversibly acetylating platelet COX-1. This prevents

formation of thromboxane A2 for the life of the platelet.<sup>25</sup> Although NSAIDs have antiplatelet effects, the effect is reversible and variable, and therefore cannot be relied upon for cardiovascular protection.<sup>26</sup> If an NSAID is present in the COX-1 channel, it can block aspirin's access to its site of action. An NSAID's ability to block aspirin's action depends on its COX-1 affinity.<sup>25</sup> Immediate-release aspirin can take one hour to cause complete platelet inhibition.<sup>26</sup> So taking the NSAID after aspirin has exerted its antiplatelet effect or allowing the NSAID to clear the system before aspirin is taken will minimize or avoid the interaction.

In a landmark study, Catella-Lawson et al. found that ibuprofen's interference with aspirin's antiplatelet effect could be avoided by taking aspirin two hours before ibuprofen.<sup>27</sup> In another small study, healthy volunteers were given aspirin 81 mg once daily for eight days.<sup>28</sup> Thrice daily ibuprofen 400 mg taken one, seven, and 13 hours after aspirin was added on day nine and continued along with aspirin for ten days. Ibuprofen taken in this manner did not affect platelet function.<sup>28</sup> These investigators assumed nearly complete platelet inhibition if thromboxane B2 (thromboxane A2's more stable metabolite) inhibition was  $>90\%$ .<sup>28</sup> Other investigators have used 95% as the cut-off.<sup>26,29</sup>

Ibuprofen should be avoided with enteric-coated aspirin taken for cardioprotection. One study showed that the antiplatelet effect of enteric-coated low-dose aspirin is attenuated when ibuprofen 400 mg is dosed two, seven, and even 12 hours after aspirin, perhaps because the absorption of enteric-coated aspirin is delayed compared to immediate-release aspirin.<sup>30</sup>

In a small crossover study in healthy volunteers, naproxen 220 mg twice daily plus aspirin 100 mg once daily was taken for five days.<sup>26</sup> In one phase of the study, the morning dose of naproxen was taken two hours before aspirin. After a 14-day washout, patients were crossed over to take naproxen two hours after aspirin. Taking naproxen two hours after immediate-release aspirin did not affect aspirin's antiplatelet effect, but taking naproxen two hours before aspirin did slightly reduce aspirin's antiplatelet effect.<sup>26</sup> In another small study, naproxen 220 mg taken three times daily with daily enteric-coated aspirin 81 mg, mean thromboxane B2 inhibition was 99.7%.<sup>29</sup> This

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study did not specify timing of the naproxen doses relative to the aspirin dose. Furthermore, this study did not rule out a naproxen/aspirin interaction; thromboxane B2 inhibition could have been due to naproxen.

Until more information is available, it is prudent to advise patients that ibuprofen and naproxen should be taken about one hour after aspirin to give aspirin time to bind to platelets. Ibuprofen should be taken no sooner than eight hours before aspirin.<sup>30</sup> Also advise aspirin users to take NSAIDs only occasionally, use immediate-release NSAIDs only, and choose immediate-release (i.e., plain, not enteric coated) aspirin if they plan to take naproxen or ibuprofen.

### Commentary

For patients with cardiovascular disease or risk factors for ischemic heart disease, acetaminophen, aspirin, tramadol, opioids (short-term), or nonacetylated salicylates (e.g., diflunisal; choline magnesium trisalicylate [U.S. only]) are recommended before moving to an NSAID.<sup>23</sup> Keep in mind that aspirin and diflunisal seem to have moderate gastrointestinal risk, although diflunisal has been included in only a few studies.<sup>7</sup> Relative gastrointestinal risk of choline magnesium salicylate is also not well characterized. The American College of Gastroenterology has published guidelines for prevention of NSAID-related ulcer complications that also take into account cardiovascular risk.<sup>4</sup> For purposes of management of gastrointestinal risk, patients are categorized as high, moderate, and low risk. Patients at highest risk are those with a history of complicated ulcer, especially

recent; those using anticoagulants or corticosteroids; and those with more than two risk factors: age over 65, high-dose NSAID, history of uncomplicated ulcer, or use of aspirin or other antiplatelet agent (e.g., clopidogrel [Plavix]). Moderate risk patients have one or two of these risk factors. Low risk patients are those without risk factors.<sup>4</sup> Patients with a history of ulcers should be tested for *H. pylori* and treated if positive.

For patients with low gastrointestinal risk and low cardiovascular risk, choose an NSAID with the least gastrointestinal risk at the lowest effective dose when appropriate (e.g., ibuprofen). For patients with moderate gastrointestinal risk and low cardiovascular risk, use celecoxib or add a proton pump inhibitor or misoprostol to a less COX-2 selective NSAID. For patients with high gastrointestinal risk and low cardiovascular risk, avoid NSAIDs if possible.<sup>4</sup> Alternatively, use celecoxib with a proton pump inhibitor or misoprostol [Evidence level B; lower quality RCT].<sup>4,12,13</sup>

For patients with low or moderate gastrointestinal risk but high cardiovascular risk (e.g., history of cardiovascular event, diabetes, hypertension, hyperlipidemia, obesity), choose naproxen [Evidence level A; high-quality meta-analyses].<sup>4,20,21</sup> Patients with moderate gastrointestinal risk (e.g., those taking aspirin) will also require a proton pump inhibitor or misoprostol.<sup>4</sup> Patients with high risk of both gastrointestinal and cardiovascular risk should not receive an NSAID (including celecoxib).<sup>4</sup> These recommendations are summarized in the following table:

	Low GI risk	Moderate GI risk	High GI risk
Low CV risk	Ibuprofen or other low-GI risk NSAID	1. Celecoxib alone 2. NSAID plus PPI or misoprostol 3. NSAID plus double-dose H2-blocker (second line)	1. Avoid NSAIDs if possible 2. Celecoxib plus PPI or misoprostol
High CV risk	Naproxen	1. Naproxen plus PPI or misoprostol 2. Naproxen plus double-dose H2-blocker (second line)	Avoid NSAIDs

Also consider NSAID alternatives for patients taking low-dose aspirin (e.g., acetaminophen,

tramadol, opioids, topicals) to minimize NSAID interference with aspirin's antiplatelet effects.

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Using NSAIDs safely requires striking a balance between cardiovascular safety and gastrointestinal safety. NSAIDs that are the safest from a cardiovascular standpoint tend to have higher gastrointestinal toxicity and vice versa. But the risk rankings are not absolute, and are based on epidemiologic data. Prospective randomized trials may change what we think we know. Use of proton pump inhibitors or misoprostol can improve gastrointestinal safety of NSAIDs. Choose an agent based on side effects, cost, and adherence. For patients at high cardiovascular risk and low or moderate gastrointestinal risk, *Vimovo* (enteric-coated naproxen 375 mg or 500 mg/esomeprazole 20 mg) is an option in the U.S. and Canada. It's for patients who need a chronic NSAID for osteoarthritis, rheumatoid arthritis, or ankylosing spondylitis.<sup>31,32</sup> Naproxen plus a separate proton pump inhibitor (e.g., omeprazole) can be less expensive for patients in the U.S. However, in Canada *Vimovo* may be the less expensive option.

If a patient with gastrointestinal risk can't take a PPI or misoprostol, a high dose H2-blocker could be used.<sup>9</sup> In the U.S., *Duexis* (ibuprofen 800 mg/famotidine 26.6 mg) is an option for patients with low cardiovascular risk who need gastroprotection. It is for patients with osteoarthritis or rheumatoid arthritis. Taken three times daily, it supplies about 80 mg of famotidine daily, the dose shown to reduce NSAID-associated gastric and duodenal ulcers (NNT=10 vs ibuprofen alone).<sup>33,34</sup> (Note that most patients in the *Duexis* studies were less than 65 years of age and only 6% had a history of ulcer.)<sup>34</sup> But *Duexis* costs about \$150 per month and provides more ibuprofen than many patients need. Consider famotidine 40 mg twice daily plus a generic NSAID "as needed" instead. No matter which NSAID is chosen, or what the patient's risk, use the lowest effective NSAID dose for the shortest time necessary.

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### Levels of Evidence

In accordance with the trend towards Evidence-Based Medicine, we are citing the **LEVEL OF EVIDENCE** for the statements we publish.

Level	Definition
A	High-quality randomized controlled trial (RCT) High-quality meta-analysis (quantitative systematic review)
B	Nonrandomized clinical trial Nonquantitative systematic review Lower quality RCT Clinical cohort study Case-control study Historical control Epidemiologic study
C	Consensus Expert opinion
D	Anecdotal evidence In vitro or animal study

Adapted from Siwek J, et al. How to write an evidence-based clinical review article. *Am Fam Physician* 2002;65:251-8.

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