A Clinician’s Guide to the Selection of NSAID Therapy

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Introduction

The comprehensive review on nonsteroidal anti-inflammatory drug (NSAID)—associated gastrointestinal risk by Ruffalo and colleagues raises several points that clinicians must consider when treating individuals who require NSAID therapy:

- In many instances, patients who experience NSAID-related gastrointestinal complications do not have previous gastrointestinal symptoms. Thus, clinicians should not wait for symptoms to develop before instituting risk-reducing measures.
- Clinicians should familiarize themselves with all risk factors for adverse gastrointestinal events and should assess patients with these points in mind.
- The current literature suggests that aspirin, especially in combination with another NSAID, significantly increases a patient’s risk for adverse gastrointestinal events.
- Although COX-2 selective inhibitors, in the absence of aspirin, lead to lower rates of clinically meaningful gastrointestinal adverse events than do traditional NSAIDs, this advantage is likely to diminish in the presence of aspirin.
- Proton pump inhibitors (PPIs) and misoprostol (Cytotec®, Pharmacia) effectively heal NSAID-induced ulcers and prevent their recurrence, even with continued NSAID use.
- Antisecretory agents (e.g., PPIs and gastroprotectant agents such as misoprostol) should be prescribed when aspirin and any NSAID (e.g., a COX-2 or a traditional agent) are used concomitantly in patients at risk for adverse gastrointestinal events.

In light of these points, the table on the following page presents a matrix based on two key clinical parameters—gastrointestinal risk and aspirin use (based on cardiovascular risk)—and is designed to guide clinicians in selecting a treatment strategy that (1) emphasizes therapeutic benefit, (2) minimizes the risk of NSAID-related gastrointestinal events, and (3) addresses the pharmacoeconomics of available treatment options.

To determine the ideal treatment strategy, clinicians should first assess the patient’s risk factors for NSAID-related gastrointestinal events. In the table, choose the left column in patients at no/low gastrointestinal risk or the right column in patients at gastrointestinal risk. Then determine, according to cardiovascular risk, whether the patient is currently taking aspirin; choose the top row for patients not receiving aspirin or the bottom row for patients receiving aspirin. Clinicians should remember the patient’s need for aspirin prophylaxis and should consider initiating therapy in patients at risk for cardiovascular events.

Rationale for Therapy

Upper Left Quadrant

The patient is at no or low risk for gastrointestinal complications and does not use or require aspirin prophylaxis for cardioprotection.

In this case, monotherapy with a traditional nonselective NSAID appears to be a reasonable initial approach to anti-inflammatory therapy. COX-2 selective inhibitors (coxibs) are an option in these individuals; subgroup analyses of the large COX-2 outcomes trials demonstrate that coxibs significantly reduce the relative rate of gastrointestinal complications compared with traditional NSAIDs in this low-risk cohort. Thus, the only reason to withhold a safer strategy is simply one of pharmacoeconomics.

The incremental cost-effectiveness of using a coxib (or of adding gastroprotective therapy to the traditional NSAID) is closely linked to the patient’s risk for developing an ulcer; cost-effectiveness analyses report that the use of safer, more expensive regimens is a relatively poor “value” in this low-risk patient group. If gastrointestinal symptoms develop while the patient is receiving a traditional NSAID, an antacid or an antisecretory agent (e.g., a PPI or a histamine H2 receptor agonist) should be added. Although these antisecretory agents can be used effectively to treat dyspepsia, only PPIs and misoprostol have been documented as effective in healing and preventing recurrence of ulcers brought on by NSAIDs.

Upper Right Quadrant

The patient is at risk for NSAID-induced gastrointestinal complications and does not use or require aspirin prophylaxis for cardioprotection.

In this case, monotherapy with a COX-2 selective inhibitor represents a reasonable initial treatment option. The gastrointestinal safety benefits of coxibs—approximately a 50% reduction in clinically important gastrointestinal events when compared to traditional NSAIDs—has been rigorously confirmed in these patients at risk. Moreover, economic analysis suggests that the unrestricted use of coxibs for individuals with gastrointestinal risk factors is a worthwhile added expenditure.
An alternative strategy may be recommended for at-risk individuals who need NSAID therapy but are already taking a PPI for other indications.

From an economic standpoint, the addition of a traditional NSAID to the prescribed PPI is a reasonable choice. Because there are no data comparing nonselective NSAIDS and COX-2 selective agents in the setting of concomitant PPI therapy, the added expense of a coxib may not be deemed worthwhile in this setting. For patients at the highest risk of an adverse event (e.g., prior gastrointestinal bleeding or use of multiple, high-dose NSAIDs), a coxib should be the NSAID of choice.

**Left Lower Panel**

The patient is at no or low risk for NSAID-induced gastrointestinal complications and requires aspirin prophylaxis for cardioprotection.

For individuals in whom the risk of a combination of aspirin and an NSAID warrants an intervention to reduce the risk of adverse gastrointestinal events, a traditional nonselective NSAID in combination with a gastroprotective agent represents a reasonable initial treatment option. Recall that histamine H₂ receptor antagonists have not been shown to prevent NSAID-induced upper gastrointestinal ulceration. This combination therapy is motivated by two points:

- Aspirin, in the combination with any NSAID (a selective or a nonselective agent) increases the risk of gastrointestinal complications.
- The protective gastrointestinal effect of COX-2 selective agents is diminished in the setting of aspirin.

Although there might be theoretical benefits to using a COX-2 selective agent instead of a traditional NSAID in combination with a gastroprotective agent, these benefits remain unproven. Therefore, economics plays a critical role in the choice of NSAID in patients receiving concomitant gastroprotection; until the added benefits of COX-2 selective agents are established, a traditional NSAID seems reasonable from a cost-effectiveness perspective.

**Right Lower Panel**

The patient is at risk for NSAID-induced gastrointestinal complications and requires aspirin prophylaxis for cardioprotection.

In the case of a patient at risk for gastrointestinal adverse events who also takes low-dose aspirin, a gastroprotective agent must be added, irrespective of the type of NSAID prescribed. It is unknown whether a coxib in addition to a PPI affords superior gastrointestinal safety over a traditional NSAID plus a PPI in the presence of concomitant aspirin in these patients. The

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* Those at risk for gastrointestinal injury include patients older than 60 years of age (risk increases with age), those with a past history of ulcer disease, and those needing high-dose NSAIDs, multiple NSAIDs (including aspirin) and/or those who require concomitant use of corticosteroids and/or warfarin.

** Cardiovascular disease risk factors include men older than 40 years of age, postmenopausal women, a family history of coronary heart disease, and younger individuals with risk factors for coronary heart disease (e.g., dyslipidemia, hypertension, diabetes/metabolic syndrome, or smoking). Consider prescribing aspirin for these individuals.

GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor.


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**Table 1 NSAID Treatment Strategies Based on Gastrointestinal Injury and Cardiovascular Risk**

<table>
<thead>
<tr>
<th>Patients at No or Low GI Risk</th>
<th>Patients at GI Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients not receiving aspirin based on cardiovascular risk</strong>&lt;sup&gt;8,9&lt;/sup&gt;</td>
<td><strong>Patients receiving aspirin based on cardiovascular risk</strong></td>
</tr>
<tr>
<td>Use a traditional NSAID</td>
<td>Use a COX-2 selective inhibitor</td>
</tr>
<tr>
<td>If gastrointestinal symptoms develop, add an antacid or an antisecretory agent (e.g., a PPI or a histamine H₂ receptor agonist) to the regimen.&lt;sup&gt;10&lt;/sup&gt;</td>
<td>If gastrointestinal symptoms develop, add an antisecretory agent (e.g., a PPI or a histamine H₂ receptor agonist) to the regimen, or If patient is already taking a PPI, use a traditional NSAID.&lt;sup&gt;11–13&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Patients receiving aspirin based on cardiovascular risk</strong></td>
<td></td>
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<tr>
<td>Use a traditional NSAID plus a PPI or a gastroprotective agent (misoprostol), or Use a COX-2 selective NSAID plus a PPI or a gastroprotective agent.&lt;sup&gt;13–16&lt;/sup&gt;</td>
<td>Use a PPI or a gastroprotective agent plus either a COX-2 selective inhibitor or a traditional NSAID.&lt;sup&gt;14&lt;/sup&gt;</td>
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choice of NSAID should be determined after one evaluates the tradeoff between the perceived gastrointestinal safety advantages of selective agents over traditional agents and the added cost of the COX-2 selective agent. For those rare individuals who have experienced previous gastrointestinal bleeding, the combination of a COX-2 selective agent and a PPI is recommended at this time, although conclusive evidence is not yet available.

References