A Cost-Effective Disease Management Approach to Minimizing NSAID-Related GI Mucosal Injury

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Summary
Nonsteroidal anti-inflammatory drugs (NSAIDs) are prescribed often in the U.S., particularly among older adults. Although the drugs are effective for pain relief, their widespread usage in tandem with over-the-counter generic NSAIDS, such as aspirin, is leading to increasing numbers of complications including gastrointestinal bleeding.

Key Points
• COX-2 inhibitors have been in use four years and have an outstanding safety record in clinical trials.
• Multiple NSAID use is the second-highest risk factor for GI bleeding.
• The use of over-the-counter NSAIDS effectively negates the protective benefits of COX-2 inhibitors.
• If aspirin use continues, as it will for many patients with comorbidities, the addition of a proton-pump inhibitor (PPI) should be considered.

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“ACHES AND PAINS” ARE CITED AMONG the most common reasons that patients visit their primary care providers. If over-the-counter anti-inflammatories do not effectively decrease symptoms, and there are no risk factors to contraindicate their use, nonsteroidal anti-inflammatory drugs (NSAIDs) are often prescribed. In the U.S., 13 million people regularly use NSAIDs.1 Among older adults, NSAID use increases. Seventy percent of adults older than 65 take NSAIDs at least once a week; 34 percent take at least one dose of an NSAID every day.2 However, NSAID-related complications, including gastrointestinal bleeding, are prevalent. Studies conducted several years ago, before COX-2 inhibitors were in use, concluded that these complications accounted for approximately 107,000 hospitalizations and as many as 16,500 deaths annually.3

COX-2 inhibitors have been in use for four years. In terms of efficacy, COX-2 inhibitors (rofecoxib, celecoxib, and valdecoxib) are equal to generic NSAIDs. Their outstanding safety record, at least in clinical trials, is what has set them apart from traditional NSAIDs.4 Generic NSAIDs, such as ibuprofen and naproxyn, block enzymes that are responsible for the production of prostaglandins. Prostaglandins have a wide variety of functions in the body, including involvement in mediating inflammation and the production of mucus that lines the GI tract. The COX-1 enzyme aids in the production of prostaglandins that are involved in protecting the gastric mucosa. The COX-2 enzyme leads to the production of prostaglandins that are important mediators in inflammation. Because generic NSAIDs block both COX-1 and COX-2 enzymes, there is a significant risk of GI bleeding and ulceration when they are used, especially in patients at high risk of complications. COX-2 inhibitors, by contrast, block only the COX-2 enzyme involved in inflammation, and clinical trials have shown that they have the potential to reduce the risk of ulcers and other gastric complications by roughly half.4

Well-Informed Treatment Decisions
Despite the superiority of COX-2 inhibitors with respect to safety, clinicians’ decisions regarding NSAID
therapy remain difficult. COX-2 inhibitors are more expensive than generic NSAIDs. The U.S. healthcare delivery system spends billions on NSAIDs every year. Because managed care is pressured to regulate pharmacy costs, clinical guidelines for NSAID therapy recommend the use of COX-2 inhibitors be limited to people with risk factors for GI bleeding or other gastric complications. Exhibit 1 ranks risk factors for NSAID-related GI injury, including past GI bleeding, multiple NSAID use, high NSAID dose, anti-coagulant use, steroid use, and age.5,6,7

Even with high-risk patients receiving the safer COX-2 inhibitors, hospitalizations for NSAID-related gastric injury are increasing. A recently released study appearing in the British Medical Journal cited that hospitalizations resulting from NSAID-related complications have increased 10 percent since COX-2 inhibitors were introduced in 2000. One reason is simply that more people are receiving NSAID therapy. Within the last four years, there has been a 41 percent increase in total NSAID use.8 Exhibit 2 illustrates these results.
The second reason for an increase in hospitalizations, despite safer treatment options for NSAID therapy, has often been—and continues to be—overlooked. Multiple NSAID use is the second highest risk factor for GI bleeding; people on multiple NSAIDs are nine times more likely to experience GI problems than people receiving only one NSAID (see Exhibit 1).\textsuperscript{5,6,7} Because of the pharmacology of NSAIDs, described earlier and illustrated in Exhibit 3, the use of over-the-counter NSAIDS effectively negates the protective benefits of COX-2 inhibitors. Essentially, patients taking OTC NSAIDS, including aspirin, plus COX-2 inhibitors, are multiple NSAID users, and thus are at high-risk of developing an NSAID-related GI injury.

The Celecoxib Long Term Arthritis Safety Study, or CLASS Trial, illustrated this point. The CLASS Trial sought to determine if the use of celecoxib versus the traditional NSAID significantly reduced the risk of ulcer-related complications. Amid some controversy surrounding a flawed trial design, the CLASS Trial
instead provided unanticipated evidence that the risk of developing ulcers and other gastric complications is not diminished among patients taking aspirin and celecoxib versus those taking a traditional NSAID. Indeed, the incidence of ulcer-related complications over six months increased four-fold among patients who used aspirin and celecoxib concurrently versus those who used celecoxib alone (see Exhibit 4). The data suggest that these results can be generalized to the concurrent use of other COX-2 inhibitors and aspirin.

The use of over-the-counter NSAIDs, particularly aspirin, is profoundly common, even among people who have been prescribed an NSAID. Most people believe that aspirin is benign, even protective. Indeed, both the U.S. Preventive Services Task Force and the American Heart Association recommend the daily use of aspirin in apparently healthy men and women for its heart-protective properties, as outlined in Figure 5. However, for those receiving NSAID therapy, even with a COX-2 inhibitor, the regular use of aspirin can cause GI injury. Nonetheless, COX-2 inhibitor use while taking aspirin is commonplace. In a survey that appeared in the Archives of Internal Medicine, 50 percent of people who took a COX-2 inhibitor reported that they also regularly took aspirin. Another 10 to 20 percent reported taking another NSAID in addition to their COX-2 inhibitor.

Before a provider prescribes a generic NSAID or a COX-2 inhibitor, the patient’s use of over-the-counter NSAIDS, particularly aspirin, must be assessed. NSAID therapy for the patient who does not take aspirin is straightforward: A patient who has a low risk of developing an NSAID-related GI injury should receive a traditional NSAID; a patient who has a high risk of developing an NSAID-related GI injury should receive either a COX-2 inhibitor or a generic NSAID if already taking a proton-pump inhibitor (PPI).

Balancing Patient Treatment Needs

For those who take aspirin, the risk of experiencing an NSAID-related GI event must be balanced with the cardio-protective benefits that aspirin provides. If aspirin use continues, as it will for many patients with comorbidities, the addition of a proton-pump inhibitor (PPI) should be considered. PPIs are commonly used to reduce GI bleeding in high-risk traditional NSAID users. PPIs should also be prescribed for patients who take aspirin and a COX-2 inhibitor.

Exhibit 5: Recommendations for Aspirin Use Among the General Population

**WHO NEEDS ASPIRIN?**

**U.S. Preventive Services Task Force Guidelines**
Aspirin should be considered for all apparently healthy men and women whose 10-year risk of CVD event is ≥ 6%

**American Heart Association Guidelines**
Aspirin should be considered for all apparently healthy men and women whose 10-year risk of CVD event is ≥ 10%

Exhibit 6: Algorithm for Determining NSAID Therapy

<table>
<thead>
<tr>
<th>No/low NSAID GI risk</th>
<th>NSAID GI risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No ASA</strong></td>
<td><strong>Use a COX-2 selective inhibitor, or if already taking PPI, add a traditional NSAID</strong></td>
</tr>
<tr>
<td><strong>ASA</strong></td>
<td><strong>If absolute risk requires a risk-reducing intervention, use a traditional NSAID plus gastro-protective agent</strong></td>
</tr>
<tr>
<td><strong>If absolute risk requires a risk-reducing intervention, use a traditional NSAID plus gastro-protective agent</strong></td>
<td><strong>A gastro-protective agent must be added, irrespective of type of NSAID prescribed</strong></td>
</tr>
</tbody>
</table>
Finally, the increased costs of a COX-2 inhibitor must be weighed against its negligible protective benefits when used in conjunction with aspirin. No clinical trials have specifically investigated the potential benefits of a COX-2 inhibitor plus a PPI when aspirin is used, versus a traditional NSAID plus a PPI when aspirin is used. Data has shown, however, no statistically significant benefit of a COX-2 inhibitor, when used alone, over a NSAID plus PPI in patients at high-risk of recurring ulcers and bleeding. Because COX-2 inhibitors are considerably more expensive than traditional NSAIDs, many guidelines indicate that NSAID therapy consists of a generic NSAID if a patient is at high-risk for gastric injury and is already on a PPI.14

A useful tool for determining the safest and most cost-effective NSAID therapy for individual patients appears in Exhibit 6.13 This 2x2 algorithm is a surprisingly simple, commonsense, disease management approach to NSAID therapy. It can be easily distributed and implemented and could yield demonstrable results. By making providers aware of the potential dangers of the concomitant use of aspirin and COX-2 inhibitors and the need for an additive PPI in those instances, unnecessary GI-bleeding and other NSAID-related gastric complications may be prevented and the costs of hospitalization contained. Curbing the use of COX-2 inhibitors and substituting traditional NSAIDs where appropriate could also control costs, while at the same time safely and effectively treating those “aches and pains.”

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References