Welcome to Reducing Upper Gastrointestinal Risks and Increasing Gastroprotection in Patients Requiring Chronic NSAID Therapy.

This program is presented by Dr. Byron Cryer. Dr. Cryer is an Associate Professor in Internal Medicine, Digestive and Liver Diseases at the University of Texas Southwestern Medical School and the Dallas VA Medical School.
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Welcome to our program on NSAIDs. Our learning objectives for this program are three.

First, to discuss the impact and risks of chronic NSAID therapy on the upper gastrointestinal tract, including the spectrum of pathologic conditions that may occur.

Two, to describe the different gastroprotective benefits of the currently available therapies in patients requiring chronic NSAID use.

And three, state treatment and management strategies to risk stratify patients who require chronic NSAIDs, and to consequently reduce upper gastrointestinal risks in these patients.
### List of NSAIDs Available by Prescription

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*a Also available as over-the-counter preparations in the US
*b Combination tablet of NSAID/synthetic prostaglandin E₁
*c Parenterally administered

Shown here is the list of NSAIDs available by prescription in the United States. NSAIDs are divided by those which are COX-2 Inhibitors and those which are non-selective NSAIDs and among the non-selective NSAIDs there are the aspirin-based products titled salicylates and the non-salicylate NSAIDs. Among the COX-2 Inhibitors currently there is only one available in the United States, which is Celecoxib. As seen by the list there were two previously available in the United States, Rofecoxib and Valdecoxib, which have since been withdrawn from the market.
Spectrum of NSAID-induced GI Mucosal Injury

Upper GI
- GERD
- Subepithelial petechial hemorrhages
- Erosions
- Ulcers
  - Stomach > duodenum
- Bleeding
  - Stomach > duodenum
- Perforations/obstruction

Small Intestine
- Ulcers
- Strictures
- Diaphragms
- Enteropathy

Colon
- Colitis
- Ulcers
- Strictures
- Diverticular bleed or perforation
- Collagenous colitis
- Relapse of IBD

While NSAIDS are very effective therapies for treating pain and arthritis, they have a principal adverse effect of gastrointestinal injury. Most of us are familiar with their effects in the upper gastrointestinal tract, however, NSAIDs have well established effects in the small intestine and colon. This program does not allow us to go into great detail on their small intestinal and colonic effects and most of the discussion will be in the upper gastrointestinal tract where most of the effects occur.
The ambiguous use of NSAIDs by patients in the United States has led to considerable morbidity and mortality. There are over 100,000 hospitalizations per year in the U.S. related to a consequence of NSAID use and there are also greater than 16,000 deaths per year which are derived from a complication of NSAID use, primarily in the gastrointestinal tract.
All of the following statements are true regarding the prevalence of NSAID use EXCEPT:

A. It is estimated that between 1 and 5% of the US population take NSAIDs regularly.
B. Among elderly patients, the prevalence of chronic NSAID use is approximately 10-15%.
C. In 2000, there were approximately 111.4 million prescriptions written for NSAIDs at a cost of $4.8 billion.
D. Among the elderly, the prevalence of at least once-weekly use of NSAIDs has been reported to be as high as 90%.
E. The true prevalence of NSAID use is difficult to accurately ascertain, as the use of over-the-counter NSAIDs is difficult to measure.
Fortunately, mortality associated with NSAIDs and aspirin has been declining worldwide. Shown here are different rates over time in various countries across the world. In 1999, on the figure on the right, was the rate per million of people for mortality associated with NSAID use. This number is comparable to the 16,500 deaths previously shown on the earlier slide. As can be seen when moving forward in time into 2003 and 2005, mortality related to NSAID use has been declining. This decline is attributable to three principal features: 1) the eradication of the bacteria H. pylori, the principal cause of ulcer disease; 2) the introduction of proton pump inhibitors, also known as PPIs; and 3) attributable to the introduction of the COX-2 specific inhibitors.
It is important to review that the salient differences in mechanisms of action between nonspecific NSAIDs and COX-2 inhibitors is that COX-2 inhibitors, at their clinical doses, do not inhibit the COX-1 enzyme, and therefore, do not reduce the prostaglandins in the stomach that protect against injury. Also, in the platelet, COX-2 inhibitors do not inhibit prostaglandins that provide hemostasis and which are important for cardiovascular effects.

Nonspecific NSAIDS, because they inhibit COX-1 and COX-2 have effects in the stomach as well as in the platelet.
In addition to COX-inhibition, NSAIDs cause gastrointestinal injury through other mechanisms. In normal stomach physiology, gastric epithelial cells function at a pH of around 7 and are protected from the acidic gastric juice which has a pH of about 2. By a layer of mucous and bicarbonate desacrated by gastric epithelial cells, NSAIDs inhibit mucous and bicarbonate secretion from the gastric epithelial cells and therefore reduce this barrier that protects against injury effects of gastric acid. Therefore therapies that inhibit gastric acid secretion and raise the pH of gastric juice would allow the gastric epithelial cells to not be exposed to the acid related injury that typically occurs with NSAIDs. Despite the gastrointestinal injury associated with NSAIDs these agents remain a cornerstone of therapy for management of patients with arthritis.
Assessment of NSAID GI Injury

- **Healthy Volunteers**
  - Intermediate markers of injury (prostaglandins)
  - Fecal red blood cell loss
  - Short-term endoscopy study

- **Arthritis Patients**
  - Long-term Endoscopy studies:
    - Endoscopic ulcers, mostly asymptomatic
  - Clinical events:
    - Symptomatic ulcers
    - GI Bleeding
    - Perforation
    - Obstruction

The quantitative effects of NSAID damage will vary by the type of patient being evaluated and the type of study used to assess NSAID gastrointestinal damage. The types of studies can vary from short-term studies in healthy volunteers to longer-term endoscopic studies in patients with arthritis. Most important are the types of studies which evaluate clinical events. That is, events which are apparent to the patient such as symptomatic ulcers or gastrointestinal bleeding, perforation or obstruction. Unfortunately, studies evaluating clinical events are fewer than studies evaluating other types of gastrointestinal injury with NSAIDs. Over the next several slides we will go over some of the results of these various manifestations of NSAID related gastrointestinal injury.
Shown here is an endoscopic photograph of the stomach of an inset user. We are looking at the antrum of the stomach with the pyloris shown in the middle. The characteristic features are endoscopic hemorrhages and erosions which are scattered throughout the stomach, primarily concentrated in the antrum of the stomach. And aspirin users, these features are seen in over 90% of individuals who take aspirin. Fortunately, most of these lesions are asymptomatic and are never appreciated by the patients who are taking the NSAIDs.
On this slide is a more concerning consequence of NSAID use. An NSAID related gastric ulcer shown in the middle of the endoscopy. Also associated with this ulcer are other features characteristic of NSAID use such as erosions and hemorrhage. This feature is seen in up to 40% of NSAID users.
The prevalence of ulceration attributable to NSAIDs will vary by whether one is assessing that ulceration endoscopically or whether this is a patient who presents with pain or complication of NSAID use. In endoscopic studies, in which the endoscopy is performed on a scheduled basis as part of a clinical research trial, ulcers related to NSAID use are seen in up to 40% of patients, with gastric ulcers seen in approximately 30% of patients, and duodenal ulcers seen in up to 10% of patients. Clearly 40% of patients who take NSAIDs are not returning with complaints of NSAID related ulceration. Which means that most of NSAID related ulceration is asymptomatic. A more important characteristic of NSAID use would be the clinically significant ulceration which occurs in the gastrointestinal tract. That would be ulcers that would be associated with pain or bleeding. Clinically significant ulceration occurs in about 2% of NSAID users.
Reducing the Risk of GI Complications with NSAIDS

- Identify risk factors
- Use of gastroprotective drugs
- Safer NSAIDS


After having discussed the principle manifestations of adverse consequences of NSAID use in the gastrointestinal tract, I would now like to turn the discussion to review how we can reduce the risk of gastrointestinal complications with NSAIDs. This strategy is fairly straightforward. First, we should identify individuals who take NSAIDs who are at risk for NSAID related ulceration. After identifying the susceptible population, that is those at risk, we would next follow one of two strategies. Either the use of gastroprotective drugs along with the NSAID or the use of safer NSAIDs.
All of the following are factors which place patients at high risk of NSAID-induced gastrointestinal complications EXCEPT:

A. Age > 60
B. Concomitant anticoagulant use
C. Concomitant corticosteroid use
D. Prior gastrointestinal event
E. Use of a nonselective NSAID

All of the following are factors which place patients at high risk of NSAID-induced gastrointestinal complications EXCEPT:

A. Age > 60
B. Concomitant anticoagulant use
C. Concomitant corticosteroid use
D. Prior gastrointestinal event
E. Use of a nonselective NSAID
The first step in NSAID risk reduction is to identify the individuals at risk for having a complication on a NSAID. There are several well established risk factors for NSAID associated gastrointestinal complications, which are shown on this slide. While many of us have assumed that these risk factors are qualitatively similar, these risks actually differ in their quantitative extent of risk. The risk factor which is associated with the greatest amount of risk is to have had a past history of complicated ulcer, as shown on this slide. These individuals who previously had a bleeding ulcer are 13.5 times as likely to have a gastrointestinal complication on an NSAID as someone who does not take an NSAID. Other risk factors include taking an anticoagulant, such as Coumadin, having a previous history of a non-complicated ulcer, having older age, or concurrently taking a corticosteroid.
After having identified which NSAID taking patients might be at greater risk, the next step would be to employ strategies which would reduce the risk to the patient. One strategy would be to use gastroprotection, that is, to give another agent along with the NSAID which reduces the risk of NSAID related injury. The two prevailing strategies for gastroprotection are the use of Misoprostol or the use of proton pump inhibitors. Shown on the next two slides will be examples of studies that have supported the use of each of these strategies.
The most important trial, which supported the use of Misoprostol as a risk of reducing strategy, was called the MUCOSA Trial, which was a trial of 8,000 NSAID taking patients who, along with their NSAID were either given placebo or misoprostol, and were followed for six months for the development of serious upper gastrointestinal complications. At the end of six months, the individuals who were taking misoprostol along with their NSAID had a 40% reduction in gastrointestinal complications compared to the individuals who were taking NSAIDs alone.
One of the better trials, which supported the use of proton pump inhibitors as a gastroprotective strategy, is shown here. This was not a trial which is designed to answer the question of whether co-therapy with a proton pump inhibitor would reduce NSAID related gastrointestinal bleeding. The question being asked in this trial was whether eradication of \textit{H. pylori} prior to NSAID exposure would be associated with the subsequent reduction in NSAID related bleeding. Therefore a group of 150 \textit{H. pylori} positive patients were enrolled in this trial. Half of the patients were eradicated of their \textit{H. pylori} infection prior to being given an NSAID. The other half of the patients persisted with their \textit{H. pylori} infection and were given, as a control, a proton pump inhibitor, Omeprazole, along with their chronic NSAIDs. Each group was followed for six months. The surprising observation was that, at the end of six months, the group which received proton pump inhibitors along with their NSAID experienced a 76\% reduction in the rate of upper gastrointestinal bleeding, one of the strongest pieces of evidence to support the proton pump inhibitor as a strategy associated with the reduction and risk of NSAID related bleeding.
Reducing the Risk of GI Complications with NSAIDS

- Identify risk factors
- Use of gastroprotective drugs
- Safer NSAIDS


The other prevailing strategy which reduces the risk of gastrointestinal complications with NSAIDs would be the use of safer NSAIDs, primarily the COX-2 specific inhibitors.
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\(^a\) Also available as over-the-counter preparations in the US
\(^b\) Combination tablet of NSAID/synthetic prostaglandin E\(_1\)
\(^c\) Parenterally administered

Coming back to our list of prescribed NSAIDs available in the United States. Among the COX-2 inhibitors we currently have one which remains Celecoxib. However, there were two that were previously available in the United States, Rofecoxib and Valdecoxib. And currently in development are Etoricoxib, Parecoxib and Lumiracoxib, which are still undergoing evaluation in clinical trials.
Shown here is a comparison of in vitro selectivity of COX-1 versus COX-2 for various NSAIDs. Going in the positive direction, towards the right, is increasing COX-1 selectivity. Going in the negative direction, towards the left, is increasing COX-2 selectivity. In general the more COX-1 selective a drug is, the greater its ulceragenic effects are in clinical practice. And conversely, the more COX-2 selective a drug is, the more gastrointenstinally safe it is in clinical practice.
Which of the following statements is true regarding Meloxicam (Mobic™)?

A. Meloxicam’s COX-2 selectivity decreases as the dose is increased (ie, above 15 mg).
B. Meloxicam causes decreased platelet aggregation when used at approved dosages.
C. Meloxicam has been associated with an equivalent risk of gastrointestinal adverse events compared to diclofenac and piroxicam.
D. Higher doses of meloxicam (ie, 30 mg daily) have not been associated with increased adverse GI effects.
E. Cardiovascular risks associated with meloxicam are decreased when compared to other NSAIDs.
Shown here is a recent comparison of risk of upper gastrointestinal bleeding with NSAIDs, COX-2 inhibitors, and aspirin. Another important feature of the gastrointestinal effects of COX-2 inhibitors, is that if low dose aspirin is concurrently taken, the risk of gastrointestinal complications markedly increases. In this recent observational study, in patients not taking aspirin, COX-2 inhibitors had less risk of gastrointestinal bleeding compared with other NSAIDs. However, in patients taking low dose aspirin with either NSAIDs and COX-2 inhibitors, their risk of upper gastrointestinal bleeding markedly increased. It should also be noted, that aspirin taken alone at a dose of 100 mg per day is associated with considerable risk of gastrointestinal bleeding.
Aspirin appears to negate some of the beneficial effects of COX-2 inhibitors is shown here. In this 12-week endoscopic evaluation of aspirin, the COX-2 inhibitor Rofecoxib, and Ibuprofen, or a COX-2 inhibitor plus aspirin, than those receiving aspirin alone or placebo. Interestingly, the ulcer rate in the Rofecoxib plus aspirin group was similar to the ulcer rate in the Ibuprofen group.
Risk Factors for NSAID-associated GI Complications

The data shown on the previous two slides, indicating that aspirin increases the gastrointestinal risk of NSAIDs, brings us back to a consideration of the risk factors for gastrointestinal complications and NSAID users and points out that individuals who take multiple NSAIDs, specifically the person who takes aspirin plus an NSAID or a prescribed NSAID plus an over-the-counter NSAID, is considered a multiple NSAID user and this individual is at the second greatest risk of developing a complication of NSAIDs.
The use of low dose aspirin along with a COX-2 inhibitor is not a trivial issue and is in fact quite a common practice in clinical practice. Shown here are data from a managed care organization of utilization of aspirin along with COX-2 inhibitors. In the group of patients who are being prescribed long-term COX-2 inhibitors, if one looks at patients who are 55 years of age or greater, about 50% of those patients, those users of COX-2 inhibitors, were also taking low dose aspirin.
Although the initial studies of COX-2 inhibitors focused on their gastrointestinal complications and potential for reduction of gastrointestinal risk. Over the last several years, the majority of the focus of the discussion of the COX-2 inhibitors, has turned to their cardiovascular risk. Considerations of cardiovascular risk with COX-2 inhibitors first appeared in the VIGOR trial, which was a large scale outcomes trial evaluating gastrointestinal complications in patients who were taking Rofecoxib compared to arthritis patients who were taking Naproxen. Although initially designed as a gastrointestinal trial, the surprise observation was a four-fold increase risk of myocardial infarction in individuals who had taken Rofecoxib compared to individuals who had taken Naproxen. At the time, it was unclear as to whether this four-fold difference in myocardial infarctions was a result of an increase of myocardial infarctions associated with Rofecoxib or a decrease of myocardial infarctions associated with Naproxen. It was unclear because there was not a placebo group in this trial and there clearly is going to be a background rate of myocardial infarctions occurring in a patient population with rheumatoid arthritis not attributable to the effects of any drug. So this debate ensued for several years as to whether or not COX-2 specific inhibitors would be associated with an increase in myocardial infarctions or not. And the absolute definitive of this discussion was not reached until the results of the placebo control trials became available.
In 2005, the results of prospective placebo controlled trial reporting cardiovascular events with a COX-2 specific inhibitor, Rofecoxib, became available. This was a trial called the APPROVE trial, which was initially designed to evaluate whether a COX-2 specific inhibitor would be associated with a reduction in adanoamous polyps in the colon. And this placebo controlled comparison, which extended three years, although initially designed to evaluate the potential polyp reducing effects of a COX-2 specific inhibitor, there once again was a surprise observation of an increase in confirmed thrombotic cardiovascular events in the group which had received Rofecoxib 25 mg. In fact, the rate of cardiovascular events in the Rofecoxib group was twice that seen in the placebo group. The results of this trial led the manufacturer of Rofecoxib to withdraw Rofecoxib from the market because of a definitive conclusion of an increase of cardiovascular events when compared to placebo.
Following the results of the cardiovascular observation with Rofecoxib it was unclear as to whether this cardiovascular manifestation would be specific to Rofecoxib or whether this was a manifestation of all the COX-2 specific inhibitors. Also in 2005, the results of another polyp trial became available. In this instance, the polyp trial was with Celecoxib. This was similarly a study that was designed comparing Celecoxib to placebo to assess whether the use of a COX-2 specific inhibitor, Celecoxib, would be associated with a reduction in adenomous polyps in the colon. Once again, the surprise observation was that there was a statistically significant increase in myocardial infarctions in the group that had received high doses of Celecoxib compared to the group that received placebo.
Cardiovascular events have also been observed with valdecoxib and parecoxib (the intravenous formulation of valdecoxib). In patients recently undergoing coronary artery bypass grafting, 3 days of therapy with IV parecoxib followed by oral valdecoxib through day ten was associated with a statistically significant increase in cardiovascular events at six weeks post-surgery compared to patients who received placebo.

This was one of the critical studies which led the US Food and Drug Administration to conclude that the overall risk vs. benefit profile of valdecoxib is unfavorable and to recommend its withdrawal from the market.
Recent Trials Provide Mounting Evidence That CV Risks Are a Class Effect

<table>
<thead>
<tr>
<th>Jeffrey M. Drazen, MD</th>
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<td>New England Journal of Medicine, Editor in Chief</td>
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- “Since three different COX-2 inhibitors were all found to be associated with cardiovascular complications, it appears that this is a class effect.”

- “Because there are well-established options for treatment of all the approved indications for these drugs, it is reasonable to ask whether the use of the drugs can now be justified.”


The group of trials that we recently reviewed regarding the cardiovascular effects of COX-2 inhibitors led the Editor in Chief of the New England Journal of Medicine to conclude in his editorial that since three different COX-2 inhibitors were all found to be associated with cardiovascular complications, it appears that this is a class effect. He went on to state that, because there are well-established options for treatment of all the approved indications for these drugs, it is reasonable to ask whether the use of the drugs can now be justified.
### Concomitant Aspirin Does Not Decrease CV Risk of COX-2 Inhibitors

#### Deaths from CV Causes in Celecoxib Polyp Trial

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Celecoxib</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-ASA users</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=1421)</td>
<td>1.1%</td>
<td>2.6%</td>
<td>2.4 (0.9-6.4)</td>
</tr>
<tr>
<td># deaths/ total pts</td>
<td>5/466</td>
<td>25/955</td>
<td></td>
</tr>
<tr>
<td>ASA users</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=614)</td>
<td>0.9%</td>
<td>3.5%</td>
<td>3.8 (0.9-16.6)</td>
</tr>
<tr>
<td># deaths/ total pts</td>
<td>2/213</td>
<td>14/401</td>
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</tbody>
</table>


Given the three previous studies indicating that COX-2 specific inhibitors are associated with an increase in cardiovascular risk and given that aspirin at low dose is a known effective of therapy for reducing cardiovascular events. An important question is whether or not concomitant administration of aspirin along with a COX-2 specific inhibitor would be associated with a reduction in myocardial infarctions. This question was assessed into two polyp trials. In the Celecoxib trial we just reviewed, Celecoxib users were divided into those who used aspirin compared to those who did not take aspirin. In the middle column of the table shown in this slide are the results of deaths from cardiovascular causes in Celecoxib users. Clearly in the Celecoxib users who took aspirin along with Celecoxib there was not a reduction in deaths from cardiovascular causes indicating that the concurrent use of lotus aspirin along with the COX-2 specific inhibitor will not reduce the cardiovascular effects of a COX-2 specific inhibitor.
### Are Coxibs the Only Approach for GI Safety?

**Other possible alternatives:**

- “Second-generation” Coxibs
- Nonspecific NSAID + Co-therapy
- Older “Safer” NSAIDs
  - Non-Acetylated Salicylates
  - Nabumetone
  - Diclofenac
  - Etodolac
- NSAIDs in development:
  - NO-NSAIDs
  - PC-NSAIDs

Given the limitations of COX-2 specific inhibitors which we just reviewed both in the gastrointestinal tract with regard to their concomitant use of aspirin, as well as the cardiovascular effects. This leads us to ask whether there are other approaches to achieve gastrointestinal safety. Shown in this slide are several other possible alternatives to achieve gastrointestinal safety in patients who take NSAIDs. The other prevailing strategy which is commonly used is the use of a non-specific NSAID plus co-therapy.
All of the following are acceptable methods with which to prevent gastrointestinal adverse events in patients requiring NSAID therapy EXCEPT:

<table>
<thead>
<tr>
<th>Option</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.</td>
<td>Use of a COX-2 inhibitor (ie, celecoxib) in place of a traditional nonselective NSAID (ie, piroxicam)</td>
</tr>
<tr>
<td>B.</td>
<td>Concomitant administration of misoprostol</td>
</tr>
<tr>
<td>C.</td>
<td>Concomitant administration of lansoprazole</td>
</tr>
<tr>
<td>D.</td>
<td>Concomitant administration of famotidine</td>
</tr>
<tr>
<td>E.</td>
<td>Concomitant administration of esomeprazole</td>
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All of the following are acceptable methods with which to prevent gastrointestinal adverse events in patients requiring NSAID therapy EXCEPT:

- A. Use of a COX-2 inhibitor (ie, celecoxib) in place of a traditional nonselective NSAID (ie, piroxicam)
- B. Concomitant administration of misoprostol
- C. Concomitant administration of lansoprazole
- D. Concomitant administration of famotidine
- E. Concomitant administration of esomeprazole
Proton pump inhibitors can be an effective therapy to reduce NSAID-associated gastric and duodenal ulcers

In this secondary prevention study of more than 400 patients with NSAID-associated ulcers, after healing of their ulcers, patients were then randomized to either the proton pump inhibitor, omeprazole 20 mg once daily, or to the H₂-receptor antagonist, ranitidine 150 mg twice daily, for 6 months. At the end of 6 months, omeprazole was significantly superior to ranitidine in preventing the development of both NSAID-associated gastric and duodenal ulcer. All patients continued taking NSAIDs during the study.
This is a study of another proton pump inhibitor, lansoprazole, in the prevention of NSAID-associated ulcers.

All patients had a history of NSAID-associated gastric ulcers. After ulcer healing they continued to take an NSAID, with either misoprostol 800 micrograms per day or lansoprazole at a dose of 15 or 30 mg per day. Both doses of lansoprazole (15 mg or 30 mg QD) or misoprostol (200 micrograms QID) were highly effective in preventing ulcer recurrence in these high-risk patients, some of whom also took aspirin in addition to their NSAID. In the placebo group (not shown), 51% of patients were ulcer free after 12 weeks.

While misoprostol was effective, its use was associated with significantly more side effects (primarily diarrhea) than lansoprazole, with 31 percent of patients who took misoprostol reporting a side effect. Ten percent of patients in the placebo group experienced adverse effects (not shown).
An important question from the same study which we just reviewed is whether the proton pump inhibitor maintains gastric protection in patients taking an NSAID plus aspirin.

In this study, concomitant aspirin at a dose of 325 mg per day or less was permitted. Aspirin was used in 15% of patients. In a separate analysis of patients who took NSAIDs plus aspirin, after 12 weeks of therapy, 43% of placebo patients, 83% of misoprostol patients, 83% of lansoprazole 30 mg patients, and 89% of lansoprazole 15 mg patients remained free from gastric ulcers.
We’ve reviewed two prevailing strategies which were associated with a reduction and risk in NSAID users. The use of a COX-2 specific inhibitor alone or the use of co-therapy with a proton pump inhibitor with an NSAID. An important question is how do these two therapies compare to one another for the reduction of the gastrointestinal risk of NSAID related gastrointestinal effects. In this slide, I’ve shown results of a systematic review of 112 randomized controlled trials of gastroprotective agents and COX-2 inhibitors for the prevention of gastrointestinal toxicity in patients taking NSAIDs. There are two important points to take away from this slide. First, H2-receptor antagonists were also evaluated in this study and the H2-receptor antagonists did not lower the risk of gastrointestinal events. More importantly, in accessing the number of patients needed to be treated to prevent 1 symptomatic ulcer the proton pump inhibitor strategy and the COX-2 specific inhibitor strategy were comparable strategies for reducing gastrointestinal risk of NSAIDs.
Risk Factors for NSAID-associated GI Complications

The proton pump inhibitor strategy and the COX-2 specific inhibitor strategy are comparable strategies for most at-risk patients, except for the highest risk group of patients and that is those with past history of complicated ulcers.
Prevention of Recurrent Ulcer Bleeding in High-Risk Patients

COX-2 selective inhibitors have been compared to traditional NSAIDs given along with PPI co-therapy in high risk patients. In this Hong Kong based study on the left, patients hospitalized with NSAID-associated ulcer complications had treatment to heal the ulcer and to eradicate *H. pylori* infection. They were then randomized to receive either celecoxib and placebo or diclofenac and omeprazole. During 6-months of follow-up, both groups had a similar rate of recurrent ulcer bleeding.

A recent update of that study (DDW 2004) reported on the 6 month incidence of ulcers in both study groups. As you can see in high risk patients, neither strategy is ideal. This suggests that some patients – those at high risk to develop ulcers and complications – may be candidates for both a COX-2 specific inhibitor and a proton pump inhibitor.
Other possible approaches to achieve gastrointestinal safety in persons taking NSAIDs would be use of older “safer” NSAIDs, such as the non-acetylated salicylates, for example salsolite, the use of nabumetone, diclofenac or etodolac. Very interestingly, although not yet available in clinical practice there are other NSAIDs in development that are currently being evaluated in clinical trials which may be safer in the gastrointestinal tract. These NSAIDS are called NO-NSAIDs or PC-NSAIDs, but these agents are not yet currently available in the United States.
Our discussion regarding NSAID related gastrointestinal effects thus far have focused on the upper gastrointestinal tract, however, NSAIDs have some very interesting effects on the small intestine and colon.
The small intestine has traditionally not been a site within the gastrointestinal tract that has been accessible to evaluation. Typically because the endoscopes are unable to reach into the small intestine, however, with the advent of newer technology, capsules with cameras that are swallowed which travel throughout the small intestine called videocapsule endoscopy, we have been able to access the effects of NSAIDs within the small intestine. Shown here are the results of a recent trial evaluating small intestinal injury in NSAID users.
Despite the results shown on the previous slide the small intestinal lesions that are being captured by video capsule endoscopy technology is shown on this slide.
What Percent of GI Events Occur in Upper and Lower GI Tracts?

- A nationwide study from Spain of hospital mortality associated with GI complications and NSAID use

<table>
<thead>
<tr>
<th>Percent of GI Events</th>
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<tbody>
<tr>
<td>Upper GI Tract</td>
<td>84.5%</td>
</tr>
<tr>
<td>Lower GI Tract</td>
<td>12.5%</td>
</tr>
<tr>
<td>Perforations (site unspecified)</td>
<td>2.6%</td>
</tr>
</tbody>
</table>


A more important question to answer with respect to the lower gastrointestinal effects of NSAIDs would be what would be the effects of NSAIDs to cause relevant gastrointestinal complications in the lower gastrointestinal tract.
What conclusions can we make from the information that has been reviewed in this program?

First, untoward gastrointestinal effects of NSAIDs are decreasing. Second, most of the significant NSAID gastrointestinal toxicity is upper gastrointestinal (>85%). And third, strategies to reduce risk of gastrointestinal effects of NSAIDs should focus on patients at greatest gastrointestinal risk.
Conclusions

- COX-2 inhibitors were developed to reduce NSAIDs’ GI toxicity:
  - No GI benefit in patients concurrently taking aspirin
  - Patients at highest GI risk have inadequate GI risk reduction
  - CV concerns – not prevented by aspirin

- Other successful strategies available for GI risk reduction
  - Co-Therapy: PPIs or Misoprostol
  - Non-NSAID Analgesics: Acetaminophen

It’s important to remember that the COX-2 specific inhibitors were developed to reduce NSAIDs toxicity. This is a true observation in the clinical trials that have been conducted to access the gastrointestinal effects of COX-2 specific inhibitors.
## Recommendations for NSAID Therapy

<table>
<thead>
<tr>
<th></th>
<th>No/Low NSAID GI Risk</th>
<th>NSAID GI Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No Aspirin</strong></td>
<td>Traditional NSAID</td>
<td>COX-2 Inhibitor or Traditional NSAID + PPI or Consider non-NSAID therapy</td>
</tr>
<tr>
<td><strong>Aspirin</strong></td>
<td>Traditional NSAID + PPI</td>
<td>PPI must be added if a traditional NSAID is prescribed or Consider non-NSAID therapy</td>
</tr>
<tr>
<td></td>
<td>if GI risk warrants gastroprotection or Consider non-NSAID therapy</td>
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**Recommendations for NSAID Therapy**
# Recommendations for NSAID Therapy

<table>
<thead>
<tr>
<th>No Aspirin</th>
<th>NSAID GI Risk</th>
<th>NSAID GI Risk</th>
<th>Highest NSAID GI Risk</th>
</tr>
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<tbody>
<tr>
<td>No Low NSAID GI Risk</td>
<td>Traditional NSAID</td>
<td>COX-2 Inhibitor or Traditional NSAID + PPI or Consider non-NSAID therapy</td>
<td>COX-2 Inhibitor + PPI</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Traditional NSAID + PPI if GI risk warrants gastroprotection or Consider non-NSAID therapy</td>
<td>PPI must be added if a traditional NSAID is prescribed or Consider non-NSAID therapy</td>
<td>No NSAID recommended Continue aspirin + PPI</td>
</tr>
</tbody>
</table>

Thank you for participating in this program. Click Main Menu to go to the Post-test.