

## NSAIDs and GI Effects

### *What Do the Studies Say?*

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#### *Can I prevent ulcers caused by NSAIDs?*

This article is based on the excellent Cochrane systematic review "Prevention of NSAID-induced gastroduodenal ulcers" by Rostom, et al.

#### **Misoprostol, 800 mcg/day, is effective at preventing ulcers**

One large study—the Misoprostol Ulcer Complications Outcomes and Safety Assessment (MUCOSA)—involving 8,843 patients taking non-steroidal anti-inflammatory drugs (NSAIDs) found serious side-effects of NSAIDs (bleeding, perforation, and death) occurred in 1.5% users/year. Misoprostol, 800 mcg/day, reduced the relative risk of these complications; however, to prevent them in one patient, 260 patients had to be treated.

This large number needed to treat must be viewed in light of the fact that common side-effects of NSAIDs (nausea and dyspepsia) correlate poorly with serious, adverse gastrointestinal (GI) events. Therefore, the family physician cannot use common NSAID side-effects as a guide to determine who is developing GI complications from NSAID use.

#### **Josie's case**

Josie, 63, has worked as a chambermaid and short-order cook. She feels stiffness and pain in her knees after standing at the sink or walking for more than 15 minutes. X-rays show marked narrowing of the medial and lateral compartments of both knees.



She has minimal finances, but could afford non-steroidal anti-inflammatory drugs (NSAIDs).

- **Should you put her on NSAIDs?**
- **Can you reduce her risk of gastric and duodenal ulcers by prescribing misoprostol, a H2 receptor antagonist (H2RA), or a proton pump inhibitor?**
- **If you choose misoprostol, should it be 400 mcg/day or 800 mcg/day? If you choose H2RAs, should you prescribe a single or double dose?**

**For a followup on Josie, go to page 74.**

In patients using NSAIDs who are referred for endoscopy, the cumulative incidence of endoscopically diagnosed gastric ulcers is approximately

Table 1

## The relative risk of ulcers for patients taking NSAIDs

	Gastric		Duodenal	
	RR	95% CI	RR	95% CI
Misoprostol, 800 mcg/day	17%	11-24%	21%	9-49%
Misoprostol, 400 mcg/day	39%	30-51%	No benefit compared to placebo	
Double-dose H2RAs	44%	26-74%	26%	11-65%
H2RAs	No benefit compared to placebo		36%	18-74%
Proton pump inhibitors	40%	32-51%	19%	9-37%

NSAIDs: Non-steroidal anti-inflammatory drugs  
RR: Relative risk

CI: Confidence interval  
H2RA: H2 receptor antagonist

For patients taking misoprostol, 800 mcg/day, the risk of diarrhea is 3.25%; the risk for those taking 400 mcg/day is 1.8 times greater.

### H2RAs are effective at preventing ulcers

Five randomized, controlled trials (RCTs) with 1,005 patients taking NSAIDs for three months found that H2 receptor antagonists (H2RAs) did not reduce the risk of gastric ulcers, but reduced the relative risk of

duodenal ulcers to 36% compared to placebo.

*The MUCOSA study found that side-effects of NSAIDs occurred in 1.5% of users/year.*

15%; the incidence of endoscopically diagnosed duodenal ulcers is 6% (but 85% of these ulcers do not become clinically apparent).

In seven studies involving 2,423 patients taking NSAIDs for three months or more, those using misoprostol, 800 mcg/day, had a 17% relative risk of endoscopic gastric ulcers and a 21% risk of duodenal ulcers compared to the placebo rate of 100%.

In six studies with 2,461 patients using NSAIDs, misoprostol, 400 mcg/day, was not as effective, reducing the relative risk of gastric ulcers to 39%.

There is a catch to using misoprostol. In the MUCOSA trial, 732 of 4,404 patients had diarrhea or abdominal pain, compared to 399 of 4,439 on placebo. The relative risk of patients with side-effects stopping misoprostol therapy is 1.5 compared to placebo.

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Three RCTs with 298 patients found that for those who took double-dose H2RAs, the relative risk of gastric ulcers was 44% and the risk of duodenal ulcers was 26% compared to placebo.

Patients taking H2RAs did not complain of side-effects any more than those on placebo. Furthermore, those taking double-dose H2RAs had a lower relative risk of abdominal pain compared to placebo.

### PPIs are effective at preventing ulcers

Eight RCTs with 2,181 patients taking NSAIDs found that patients taking proton pump inhibitors (PPIs) had a relative risk of endoscopically proven gastric ulcers of 40% compared to placebo; duodenal ulcers were reduced to 19% from placebo.

### A followup on Josie

If Josie can afford cyclooxygenase-2-selective NSAIDs, her risk of gastroduodenal ulcers will be 24% relative to what it would be if she took standard NSAIDs.

If she decides to take standard NSAIDs and also takes misoprostol, 800 mcg/day, her relative risk of endoscopic gastric ulcers will be 17% and her relative risk of duodenal ulcers will be 21% compared to the placebo rate.

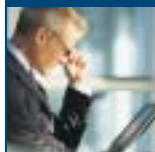
If Josie takes standard NSAIDs and also double-dose H2RAs, her relative risk of gastric ulcers will be 44% and her relative risk of duodenal ulcers will be 26% compared to placebo.

If Josie takes standard NSAIDs while also taking PPIs, her relative risk of endoscopically proven gastric ulcers will be 40% and her relative risk of duodenal ulcers will be 19% compared to placebo.

### Head-to-head comparisons of specific medications for patients taking NSAIDs (Table 1)

- In two RCT's with 600 patients, misoprostol was superior to ranitidine, 150 mg twice daily, in preventing NSAID-induced gastric ulcers, but not in preventing duodenal ulcers.
- In one trial with 425 patients, omeprazole, 20 mg, was superior to ranitidine, 150 mg twice daily, in preventing NSAID-induced gastric ulcers and in preventing duodenal ulcers.
- One study showed that lansoprazole (a PPI), 15 mg/day to 30 mg/day, conferred no benefit for gastric ulcers, but had a lower relative risk of duodenal ulcers compared to misoprostol, 800 mcg/day.

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### Frequently Asked Question

Do patients taking Cox-2 inhibitors have fewer endoscopically proven ulcers than those taking NSAIDs?

Five endoscopic studies with 2,614 patients found that those taking Cox-2-selective NSAIDs have a relative risk of gastroduodenal ulcers of 24% compared to those taking standard NSAIDs.

### What's really important for GPs to know?

The MUCOSA trial was the only clinical trial with enough patients to examine the clinically important ulcer complications of NSAID therapy. It evaluated misoprostol, 800 mcg/day, and showed it to be effective. It also showed that:

- Misoprostol, PPIs, and double-dose H2RAs are all effective at preventing gastric and duodenal ulcers in patients taking NSAIDs, but single-dose H2RAs are only effective at preventing duodenal ulcers.
- Patients on misoprostol, 800 mcg/day, are more likely to stop therapy due to side-effects, whereas those on double-dose H2RAs have less abdominal pain than those on placebo.

Another approach to prescribing NSAIDs is to prescribe cyclooxygenase-2 (COX-2)-selective NSAIDs, which have a far lower risk of GI toxicity. **Dx**

#### Resources

1. Hunt RH, Harper S, Watson DJ, et al: The gastrointestinal safety of the COX-2 selective inhibitor etoricoxib assessed by both endoscopy and analysis of upper gastrointestinal events. *Am J Gastroenterol* 2003; 98(8):1725-33.
2. Rostom A, Dube C, Wells G, et al: Prevention of NSAID-induced gastroduodenal ulcers. *Cochrane Database Syst Rev* 2004 (4):CD002296.