# Protecting against ulceration

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## If a patient requires NSAIDs long-term, should a PPI be routinely co-prescribed?

### CLINICAL SCENARIO

Josef, a 68-year-old retiree, saw me recently with knee osteoarthritis, and commenced a therapeutic trial of naproxen.

Afterwards, a discussion on a GP online forum made me wonder whether I should have co-prescribed a proton pump inhibitor (PPI) for prophylactic gastro-protection.

This has not been my usual practice for individuals with no specific risks or history of peptic ulcers. What is the evidence?

### CLINICAL QUESTION

When commencing NSAIDs, what is the effect of using PPIs as prophylaxis on the risk of gastrointestinal toxicity?

### THE RESEARCH EVIDENCE

**Step 1: The Cochrane Library**

The Cochrane Library has a systematic review, published in 2002, on the prevention of NSAID-induced gastroduodenal ulcers.[1] It was edited in 2011, and content was assessed as up-to-date to May 2009. I investigated whether there was a more recent review.

**Step 2: TripDatabase**

I conducted a search using the TripDatabase PICO search tool (Participant: "NSAID", Intervention: "PPI", Comparator: "placebo", Outcomes: blank).

No newer systematic review was identified. A useful clinical review article on the topic from 2013 still cited the Cochrane systematic review as the primary evidence.[2]

Let's look at the Cochrane systematic review by Rostom et al. (2002) in detail.[1]

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### CRITICAL APPRAISAL

I will use the systematic reviews critical appraisal sheet from the Centre for Evidence Based Medicine.[3]

### PICO

**What PICO question does the systematic review ask?**

In people who had taken NSAIDs for longer than three weeks (Participants); what is the effect of PPIs (and also H2-antagonists or misoprostol), used as prophylaxis (Intervention); compared with placebo (Comparator); on the primary outcome of endoscopic ulcers, and clinical ulcer complications (Outcome)?

**Is it clearly stated?**

Yes.

**Is it unlikely that important studies were missed?**

Probably. Like most Cochrane systematic reviews, the search strategy was exhaustive, involving multiple electronic databases, and is well documented.

**JADAD SCALE**

This instrument is commonly used to assess the methodological quality of randomised trials.[4] It rates three domains, randomisation, blinding, and patient withdrawals/dropouts, producing a score from 0 (worst) to 5 (best). A Jadad score of 3 is often used as a threshold of "reasonable" quality, though whether 3 is included or excluded varies between publications.

Stat Facts

The systematic review was assessed as up-to-date to 2009 — it is possible that there may be newer primary research not included. It should be noted that a funnel plot comparing PPI vs placebo (figure 2, p. 8)[1] possibly indicates some publication bias favouring PPIs.

**Were appropriate criteria used to select articles for inclusion?**

Yes. The authors only included randomised trials.

**Were the included studies sufficiently valid for the question?**

Probably/possibly. The authors formally assessed the risk of bias of the included studies using Jadad's scale (see Stat Facts).[4]

Of the six studies in the systematic review that looked at PPIs, all but one had a score less than three. Only one had a score greater than three.

**Were the results similar between studies?**

Yes. There was minimal heterogeneity measured ($I^2$ = 0% for multiple outcome comparisons) between the studies for PPI vs placebo on total endoscopic ulcers. All studies demonstrated uniform benefit from the PPIs.

**What were the results?**

Comparing PPI vs placebo on total endoscopic ulcers for patients taking NSAIDs:

- Eight weeks or longer: risk ratio 0.34 (95% CI 0.28 to 0.42), P < 0.00001

Other results:

- PPIs might cause more diarrhoea: risk ratio 1.66 (95% CI 0.85 to 3.22), P = 0.13
- PPIs probably reduce dyspepsia: risk ratio 0.50 (95% CI 0.30 to 0.82), P = 0.0059

One small study looked at "clinical ulcers". Although a statistically significant result wasn't found, clinical ulcers were observed only in the placebo group, with none in the PPI group (4 vs 0).[5]

## DISCUSSION AND CONCLUSION

The clinical evidence points clearly towards PPIs having a gastro-protective effect in individuals taking long-term NSAIDs, insofar as endoscopic ulcers are concerned.

My rough calculation based on the data in this paper is that there is a number needed to treat (NNT) value of five, to prevent one endoscopic ulcer in patients treated with NSAIDs for eight weeks or longer.

However, it is crucial to recognise that endoscopic ulcers are common in long-term NSAID use (up to 40%)[6] and the majority of these will never present clinically[1].

Guidelines around the topic are a little vague. NICE guidance documents are relatively assertive in recommending co-prescribing of PPIs with NSAIDs, especially for people with arthritis.[7]

eTG Complete recommends that prophylaxis be considered for patients with "risk factors for increased gastrointestinal toxicity".[8]

In the absence of large randomised trials using clinical outcomes,[2] this may be a pragmatic recommendation.

Josef had low gastrointestinal risk so I opted not to start a PPI.

References available on request