

# Peptic ulcer disease

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## Purpose of review

This review attempts to contextualize some of the clinically important publications of the last 2 years as they relate to the broad topic of dyspepsia and peptic ulcer disease, both *Helicobacter pylori* and nonsteroidal anti-inflammatory drug-related.

## Recent findings

This review includes findings which provide insight with regard to the triaging of dyspeptic subjects, information on new proton pump inhibitor drugs and *H. pylori* eradication 'rescue regimens'. The 'COX-2 debacle' is discussed and new data relating to the efficacy of co-therapy strategies for the prevention of nonsteroidal anti-inflammatory drug gastropathy are presented, while the use of antiplatelet agents as 'safe' substitutes for aspirin cardioprophylaxis is questioned. The important issue of proton pump inhibitor safety and nonsteroidal anti-inflammatory drug enteropathy are addressed.

## Summary

The review provides a summary and interpretation of literature pertaining to the above issues, and should provide a point of departure for clinical decision-making relevant to these issues.

## Keywords

*Helicobacter pylori*, nonsteroidal anti-inflammatory drugs, NSAIDs, PPIs, proton pump inhibitors

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## Abbreviations

<b>COX-2</b>	cyclo-oxygenase-2
<b>FDA</b>	Food and Drug Administration
<b>NSAID</b>	nonsteroidal anti-inflammatory drugs
<b>PPI</b>	proton pump inhibitor

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## Introduction

This review focuses on papers of clinical significance published during the period 2005–2006. Primary topics addressed are dyspepsia, the treatment of peptic ulcer disease, *Helicobacter pylori* and the broad topic of nonsteroidal anti-inflammatory drug (NSAID)/aspirin gastroenteropathy. The principal aim is to highlight and introduce new data published in this period and to contextualize some of the important developments in this period, based on relevant publications.

## Dyspepsia

In managing the dyspeptic patient, the clinician faces a number of challenges, not least of which is to decide who requires further investigation. Traditionally, the patient's age and an assessment of symptoms impact this decision. Two papers address this problem. The first, a Scottish study, utilizing an extensive database, identified 3293 patients diagnosed with foregut malignancy over a two-year period [1]. Of these, 290 patients were younger than 55 years of age; the authors state that only 21 of these did not manifest alarm features at presentation, nine of the 'non-alarm' patients being younger than 45 years of age. As usual, treatment with curative intent was unusual. The authors interpret their findings as supporting an increase in the threshold for age-triggered investigation to 55 years.

The systematic review by Moayyedi *et al.* [2] offers little encouragement for the clinical triage of dyspeptic patients. This group found that neither clinical impression nor suitably designed computer models distinguished between organic and functional dyspepsia. Alas, while clinical assessment fared better than chance, the advantage was not as great as we would like to think.

The issue of 'predominant symptom' as an aid to identify pathophysiological mechanisms, and, by inference, guide treatment was addressed in a reasonably sized study [3]. Not surprisingly, although weak associations were identified, the predominant symptom approach did not predictably identify pathophysiological subgroups. It seems that, with the exception of predominant heartburn, symptom assessment is not helpful in categorizing and managing patients with nonorganic dyspepsia. Longstreth [4] makes a point worth noting: functional dyspepsia represents more than just abnormal gastrointestinal function, it also involves the interaction of the stomach and intestine with the central nervous system. That is probably why management is more about coping than curing.

Those readers still interested in the 'test and treat' versus endoscopy for dyspepsia debate will be reassured to know that little has changed – prompt endoscopy has again been found to offer a small benefit in terms of 'cure', but it is less cost effective than a test and treat strategy for the initial management of dyspepsia [5]. We should clearly do what we think is best for the individual patient.

### Treatment of peptic ulcer disease

We apparently have not reached the end of acid suppressive drug development with the introduction of esomeprazole. The focus has shifted to the development of a drug with a longer circulating half-life which, in turn, would provide more sustained availability for blocking proton pumps. In this regard, Hunt *et al.* [6] report their comparison of tenatoprazole with esomeprazole, both taken once daily, and conclude that tenatoprazole has a longer serum half-life, which translates to a prolonged period of gastric acid suppression, with a beneficial effect on nocturnal pH control. Time and marketing, and perhaps clinical need, will once again determine the eventual success of this new variation on the theme.

It has become common practice, one daresay 'the standard of care', for patients with upper gastrointestinal bleeding to receive acid suppression in the form of proton pump inhibitor (PPI) therapy, whether oral or intravenous. In their Cochrane-based review, Leontiadis *et al.* [7] find that, although the use of PPIs (a mix of oral and intravenous studies) reduce the re-bleeding rates and need for surgery, it has no benefit when it comes to all cause mortality. In case we have missed it, they tell us again that it reduces transfusion requirements and hospital stay [8].

During the period under review, one became aware of a concern regarding the use of the PPIs and the risk for developing infection. Williams and McColl [9] address this issue in their review on the subject of PPI use and bacterial overgrowth, concluding that there is evidence of a predisposition to enteric bacterial overgrowth, but suggest that it is only rarely a clinical problem. The real concerns are raised, however, by a couple of papers looking at the risk of developing *Clostridium difficile* colitis when exposed to PPIs. It seems that the incidence and severity of *C. difficile* colitis is increasing [10,11\*].

Perhaps not surprisingly, Dial *et al.* [10,12\*] report evidence that hospitalized patients receiving PPI therapy are at increased risk of developing *C. difficile* colitis.

### *Helicobacter pylori*

The '*H. pylori* literature' continues to wane as once radical ideas become firmly entrenched as self-evident fact. Some would say that the most noteworthy event in this field has been the awarding of the Nobel Prize for

Medicine to Marshall and Warren in 2005. The press release accompanying the announcement is succinct [13]. It summarizes the original observations by Warren, comments on the tenacity of both Warren and Marshall in challenging the dogma of the time and points out that the mechanism of disease is still being unravelled. In making the award, the committee stated, 'Thanks to the pioneering discovery by Marshall and Warren, peptic ulcer disease is no longer a chronic, frequently disabling condition, but a disease that can be cured by a short regimen of antibiotics and acid secretion inhibitors.'

Readers of this review will appreciate, however, that the subset of patients with apparently idiopathic, *H. pylori* negative peptic ulcer disease is not small and may be increasing [14], while the duration of the 'short course' of antibiotic treatment is still being debated [15].

The announcement touches on a couple of issues that deserve emphasis: antibiotics can cure the infection but indiscriminate use can lead to resistance, and treatment should be for a valid indication (peptic ulcer disease being cited). The issue of resistance is real, leading to a number of so-called 'rescue regimens', to be used once more traditional treatments fail. In this regard, levofloxacin-based therapies seem to be in vogue, with reports from especially Europe suggesting clinical efficacy [16,17]. Rifabutin also comes up as a component of 'rescue therapy', but one would be reluctant to advise use of this potentially valuable drug for *H. pylori* eradication [18].

The Nobel press release also alludes to the association of chronic inflammation with 'other' conditions, and *H. pylori* has been implicated in yet another disease of altered immunity: chronic idiopathic thrombocytopenic purpura (ITP). Suzuki *et al.* [19] report their observations following eradication of the infection in patients with ITP, and report a statistically significant improved platelet response in patients eradicated of the infection.

### Nonsteroidal anti-inflammatory drugs

If the awarding of the Nobel Prize to the *H. pylori* pioneers was the story with regard to *H. pylori* in the period under review, the 'COX-2 debacle' dominated the NSAID literature. Hindsight being the exact science that it is, this has been a boom time for editorial writers.

In a nutshell, the study by Bombardier *et al.* [20], the pivotal rofecoxib clinical outcomes study, found an increased incidence of cardiovascular events in patients treated with rofecoxib. This was not a predefined outcome measure, the study was not powered to investigate this finding and explanations were postulated (naproxen being cardioprotective was a view seemingly espoused at the time even by those who are now quite critical [21]).

We tended to ignore the fact that, based on our understanding of normal physiology, unopposed cyclo-oxygenase-2 (COX-2) inhibition should be pro-thrombotic [22].

The chickens came home to roost in 2005, when no less than three studies reported adverse cardiovascular outcomes in patients taking rofecoxib for colorectal adenoma prevention [23], celecoxib for the same indication [24] and parecoxib and valdecoxib for postoperative pain prevention [25]. These studies deserve some comment: they were all large,  $\pm 2500$ ,  $\pm 2000$  and  $\pm 1700$  patients; the risk of myocardial events with rofecoxib use only became evident after 18 months of usage (keep in mind the short follow-up of the Bombardier study); mortality was similar in the rofecoxib treated and placebo groups [23]; celecoxib use was associated with an increased mortality due to a composite endpoint including cardiovascular and cerebrovascular causes [24]; and the parecoxib/valdecoxib endpoints included myocardial, cerebrovascular and pulmonary vascular events [25].

Two further studies deserve mention. Graham *et al.* [26] reported a nested case-control study, which suggested that rofecoxib was more likely than celecoxib to increase the risk of serious coronary artery disease. Interestingly, cardiovascular events in current users of celecoxib were diminished and rofecoxib's increased risk became apparent at a relatively early stage of treatment. Hippisley-Cox [27], using a nested case-control analysis with its inherent flaws, also reported an increased myocardial infarction rate associated with rofecoxib use, but also found increased risk with the use of diclofenac and ibuprofen. So, muddy waters indeed, but the bottom-line seems to be that cardiovascular events are increased with highly selective COX-2 inhibitors.

Retribution was swift and is ongoing. A number of issues are worthy of discussion.

Oberholzer-Gee [28] provides an insightful perspective on the pressures driving a pharmaceutical company's decision-making process when it comes to drug marketing; the stakes are enormous. Most concerning are the allegations that data considered unfavourable by the drug companies were suppressed. Psaty and Furberg [29] state that Pfizer completed a trial of celecoxib use in Alzheimer's disease patients in 2000, but never published the unfavourable cardiovascular results, only making them available to the public in January of 2005, after the bubble had burst, while Merck is accused of systematic disinformation in relation to the cardiovascular effects of rofecoxib [30,31]. Both the US Food and Drug Administration (FDA) and the pharmaceutical companies can be faulted for not demanding (FDA) and conducting clinical trials, which would have settled this issue. It is suggested that, cynically, the industry diverted resources

to investigate a broadening of drug indications rather than clarifying the cardiovascular issues [32].

The editors of the *New England Journal of Medicine* accused the authors of the pivotal Bombardier study of selective reporting, claiming that three cases of myocardial infarction, all in the rofecoxib group, were not included in the publication [33]. They claim that this omission resulted in an understatement of the difference in the risk of myocardial infarction between the rofecoxib and naproxen treated groups. To their credit, the 'non-Merck' authors of the study offer a well reasoned and nonemotional rebuttal, which to this reader at least seems convincing enough [34].

The post-mortems and litigation will continue. The fact is that a significant side effect of a blockbuster class of drugs was missed in prelaunch studies and important pointers were missed. It will happen again. The pressures of bringing a new drug to market are enormous, and the postmarketing surveillance system is poor at identifying an increased incidence of a relatively common event [32]. It is going to be interesting to see, given the perception of poor FDA vigilance in this debacle, what hoops the FDA will put in place for drug developers to jump through in future.

#### *The rest*

With the bad press surrounding the COX-2 inhibitors, old fashioned co-therapy will be in vogue again. Scheiman *et al.* [35] report on two studies (in a single publication) which investigated the prevention of ulcer development, by esomeprazole, in 'at-risk' individuals using nonselective NSAIDs. They report that both the 20 and 40 mg formulation of esomeprazole significantly reduced the rate of ulcer development in patients taking nonselective NSAIDs. Interestingly, this study included COX-2 selective agents: the proportion of placebo treated (co-therapy) patients developing ulcers were no different in the NSAID and COX-2 specific treatment groups (and esomeprazole provided protection in both). Goldstein *et al.* [36] report that esomeprazole, in dosages of 20 and 40 mg per day, is effective in healing gastric ulcers in subjects who need to continue taking their NSAIDs, with 8-week healing rates of 92% and 88%, and 4-week rates of 78% and 79%.

Aspirin and antiplatelet agents generated some interest over this period. A couple of studies documented the ulcer and complication rates of various formulations of aspirin. Yeomans *et al.* [37] report an 11% prevalence of gastroduodenal ulcers in patients taking 75–325 mg of aspirin daily for at least 28 days, only 20% of these being symptomatic, with a calculated 12-month risk of 28%. The study by Laine *et al.* [38], which documents the risk of ulcer development of patients taking a 75 mg dose of

enteric coated aspirin (with or without rofecoxib), indicates that, over a 12-week period, ulcers developed in 7% of aspirin treated subjects. Clearly 'enteric coating' is not the answer, but then we knew this. Taha *et al.* [39] documented the incidence of upper gastrointestinal haemorrhage in patients presenting to a single hospital over a 6-year period. They report that the incidence of haemorrhage in subjects taking low-dose aspirin rose from 15 per 100 000 (of the population) to 27 per 100 000 over this period, with the possible association with other antithrombotic drugs rising from four to 12 per 100 000 over the same period. Cardiovascular mortality dropped over the same period, however; it seems that although the cardioprotective effects are as hoped for, we may need some (gastro)protection.

The prolific Hong Kong group found that it was probably better to treat *H. pylori* negative patients at risk for recurrent ulcer complications (having presented with aspirin associated ulcer bleeding) with a combination of aspirin (80 mg/day) and esomeprazole (40 mg/day) than with clopidogrel (75 mg/day) [40\*\*]. Re-bleeding rates over the 12-month study period were 8.6% in the clopidogrel group and 0.7% in the co-therapy group (statistically significant, number needed to treat, 14). Clearly clopidogrel can not be considered a safe alternative to aspirin, and co-therapy will have to be considered in high-risk subjects. The merit of PPI co-therapy for antiplatelet agents is supported by the case-control study of Ibanez *et al.* [41], who reported that, as a group, antiplatelet agents accounted for 14.5% of all their cases of upper gastrointestinal bleeding, but that the concomitant use of a PPI decreased all risk estimates, with the combination of aspirin and a PPI having a lower risk of upper gastrointestinal bleeding than clopidogrel (and ticlopidine). One's clinical impression will certainly support the fact that the 'antiplatelet' drugs are not a safe alternative to aspirin when it comes to upper gastrointestinal complications.

While much of our attention is focused on gastroduodenal complications of NSAID use, a number of studies remind us that NSAIDs affect the rest of the gut as well, and perhaps more so than we think. Capsule endoscopy is the investigation *du jour*, and studies suggest an unexpectedly high rate of small bowel lesions in patients taking NSAIDs. Maiden *et al.* suggest that 68% of 40 healthy volunteers developed some small bowel lesion after 14 days of treatment with diclofenac [42\*]. This surprisingly high incidence finds some support in the observation of Graham *et al.* [43\*] who claim the presence of visible small bowel injury in 71% of chronic NSAID users, versus 10% of control subjects. Alarming as these findings are, the findings of Goldstein *et al.* [44\*] offer more food for thought. They report on the small bowel lesions associated with the use of celecoxib, naproxen plus omeprazole

and placebo. Theoretically this would be an important observation as, although gastroprotective, the PPIs could hardly be expected to protect the small bowel. Their findings would support this: the mean number of patients developing small bowel lesions was 55% of subjects taking naproxen/omeprazole, 16% in those taking celecoxib and 7% on placebo. Taken together, these findings suggest that small bowel lesions are common in patients on NSAIDs; PPI co-therapy does not protect the small bowel from NSAID injury; and COX-2 selective agents protect both the stomach and small bowel from NSAID injury.

We have been waiting, a long time now it seems, for further clinical details regarding the so-called NO-NSAIDs. Nothing significant seems to have evolved following the report of Fiorucci *et al.* [45], now so long ago. These drugs would theoretically have the anti-inflammatory and antiplatelet effects of the NSAIDs/aspirin, but reduce pro-inflammatory cytokine production and apoptosis by a number of mechanisms. Fiorucci reported their 'proof of concept' study way back in 2003, and showed that their NO-aspirin possesses the desired antiplatelet effect while being essentially devoid of gastroduodenal toxicity (we await the capsule endoscopy data which must surely come). One is tempted to wait for the NO-aspirins before succumbing to the temptation to supplement one's diet with the recommended daily allowance of aspirin. Let's hope for more reports of progress.

## Conclusion

This review includes findings which provide insight with regard to the triaging of dyspeptic subjects, information on new PPI drugs and *H. pylori* eradication 'rescue regimens'. The COX-2 debacle is discussed and new data relating to the efficacy of co-therapy strategies for the prevention of NSAID gastropathy are presented, while the use of antiplatelet agents as 'safe' substitutes for aspirin cardioprophylaxis is questioned. The important issue of PPI safety and NSAID enteropathy are addressed.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 683–684).

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