Clinical Review: Management of dyspepsia

David Farenden (Resident physician)[1], Seema Neru (Primary care physician) [2], Jeremy Barnet (Professor) [3*]

[1] Department of Medicine, University of Southaven, Virginia, USA; [2] Noorman Medical Center, Southaven, Virginia, USA; [3] Noorman Medical Center, Institute for Medical Research, University of Southaven, Virginia, USA

** Corresponding author*

Definitions of the term dyspepsia vary but generally describe pain or discomfort in the epigastric region. People with dyspepsia have a normal life expectancy,[1] but symptoms impair quality of life,[2-3] and affect productivity.[4] In this review we summarise recent evidence, to provide the general reader with an update on how to treat this disorder effectively.

What are the treatment options?

Uninvestigated dyspepsia in primary care or the community

An individual patient data meta-analysis of randomised controlled trials found that—although prompt endoscopy was superior to testing patients with uninvestigated dyspepsia for *H pylori*, and treating with eradication therapy if positive, in terms of symptom control at 12 months—it was not cost effective.[5] However, it is unclear whether a test and treat approach is preferable to empirical acid suppression first line, because a second individual patient data meta-analysis found no significant difference in symptoms or costs between the two.[6] Current guidelines state that either option can be used.[7] If the prevalence of *H pylori* in the population is known, it makes sense to use an acid suppression strategy first if prevalence is low (<10%) and an *H pylori* test and treat strategy if the prevalence is higher.[8] If these strategies are unsuccessful, other options (discussed below) can be considered, or the patient can be referred to secondary care for advice and further investigation if appropriate.

A six month primary care based Dutch trial compared two management strategies for uninvestigated dyspepsia based around empirical acid suppression.[9] One strategy used a step-up approach, starting with antacids, with treatment escalated to H2 antihistamines and then proton pump inhibitors (PPIs) if symptoms remained uncontrolled. The second used a step-down approach, with the drugs given in the reverse order and de-escalated if symptoms improved. Treatment success (adequate relief of symptoms) was similar at six months (72% with step-up*v* 70% with step-down), but costs were significantly lower with the step-up approach. This, together with the small treatment effect in favour of step-up, meant that it came out top in a cost effectiveness analysis.

Another group of primary care patients who may benefit from *H pylori* test and treat are those who do not consult with dyspepsia very often but who require PPIs long term. A trial screened long term PPI users for *H pylori* and randomised those who were positive to eradication therapy or placebo.[10] Eradication therapy significantly reduced symptom scores, PPI prescriptions, consultations for dyspepsia, and dyspepsia related costs. The costs of detection and treatment were less than the money saved after two years of follow-up. Sensitivity analysis showed that the prevalence of *H pylori* would need to be less than 12% before this was no longer cost saving.

It has been estimated that 5% of dyspepsia in the community is attributable to *H pylori*,[11] so population screening and treatment for this organism could theoretically reduce dyspepsia related costs. Results from follow-up studies of people recruited to two large randomised controlled trials of population based screening (and eradication therapy or placebo if *H pylori* positive) in the UK suggest this might be the case, with significantly lower costs and fewer consultations after seven to 10 years.[12-13] However, these studies did not follow up all recruited people successfully, so currently there is insufficient evidence to institute population screening and treatment in the UK.

Peptic ulcer disease

The causal role of *H pylori* in peptic ulcer disease is well established, and patients with *H pylori* positive disease should receive eradication therapy. A Cochrane review found that the number needed to treat (NNT) with eradication therapy to prevent one duodenal ulcer relapse (26 placebo controlled trials) was 2 and for gastric ulcer (nine trials) the number was 3.[14] Although there was significant heterogeneity between studies in both analyses, all but one trial showed a significant benefit with eradication therapy. PPI triple therapy (a PPI plus two antibiotics (clarithromycin with amoxicillin or metronidazole)) should be used in areas like the UK where clarithromycin resistance is less than 10%, with bismuth quadruple therapy (bismuth plus a PPI and two antibiotics) being given where resistance is higher.[15] Most cases of *H pylori* negative peptic ulcer disease are caused by NSAIDs, and trials show that PPIs are superior to H2 antihistamines for ulcer healing in this

situation.[16-17] *H pylori* negative, NSAID negative peptic ulcer disease is rare and probably requires long term PPI treatment.

Functional dyspepsia

Diet and lifestyle

Food diaries from a small study of 29 patients suggest that people with functional dyspepsia eat fewer meals and consume less energy and fat than healthy controls,[18] but whether this is a cause or a consequence of symptoms is unclear. Although the prevalence of undiagnosed coeliac disease is higher in people with symptoms of irritable bowel syndrome,[19] this is not the case in dyspepsia.[20] It is also unclear whether non-coeliac gluten sensitivity is involved in symptom generation in some patients with functional dyspepsia. Doctors often advise people with dyspepsia to lose weight, avoid fatty food and alcohol, or stop smoking, but there is little evidence that these measures improve symptoms.[21] As a result, drugs are the mainstay of treatment.

Acid suppression therapy

Antacids neutralise gastric acid, the production of which is controlled by gastrin, histamine, and acetylcholine receptors. Once stimulated, these receptors activate proton pumps in the parietal cell. H2 antihistamines and PPIs reduce acid production by blocking H2 receptors or the proton pump, respectively. Because PPIs act on the proton pump itself, these drugs lead to more profound acid suppression than H2 antihistamines or antacids. A Cochrane review has studied the efficacy of acid suppressants in functional dyspepsia.[22] One placebo controlled trial of antacids showed no benefit. Twelve randomised controlled trials of H2 antihistamines versus placebo found that these drugs were effective for the treatment of functional dyspepsia (NNT=7). However, there was significant heterogeneity between studies, which was not explained by sensitivity analysis, and evidence of funnel plot asymmetry, suggesting publication bias or other small study effects. Their efficacy may therefore have been overestimated. Ten trials studied PPIs. Again, there was a significant benefit over placebo, although this was modest (NNT=10). There was significant heterogeneity between studies, with no obvious explanation, but no funnel plot asymmetry. A subgroup analysis conducted according to predominant symptom showed that PPIs were most beneficial in patients with reflux-type symptoms and more effective than placebo in patients with epigastric pain. However, they were no more effective than placebo in those with dysmotility-like functional dyspepsia.[23] Most trials used PPIs for four to eight weeks. This seems a reasonable duration, especially as concerns have been raised recently about the safety of long term PPI use. Observational studies suggest that hip fracture, community acquired pneumonia, and *Clostridium difficile* infection are more common in PPI users,[24-25] although all these associations were extremely modest, and direct causation cannot be assumed from studies such as these.

H pylori eradication therapy

The benefit of eradication therapy is less pronounced in functional dyspepsia than in peptic ulcer disease, but treatment is still more effective than placebo. In a Cochrane review of 21 placebo controlled trials the NNT for improvement in symptoms after eradicating *H pylori* was 14, with no heterogeneity between studies and no evidence of funnel plot asymmetry.[26]

Footnotes

Contributors: All authors conceived and designed the article, drafted the manuscript, and approved the final version. JB is guarantor.

Competing interests: We have read and understood the BMJ policy on declaration of interests and declare the following: DF is funded by a NIH clinician scientist award; SN receives no specific funding; JB has received honoraria and travel expenses from Jenka Pharmaceuticals for lecturing at a conference.

References

1. Ford AC, Forman D, Bailey AG, Axon ATR, Moayyedi P. Effect of dyspepsia on survival: a longitudinal 10-year follow-up study. Am J Gastroenterol 2012;107:912-21.
2. Ford AC, Forman D, Bailey AG, Axon ATR, Moayyedi P. Initial poor quality of life and new onset of dyspepsia: Results from a longitudinal 10-year follow-up study. Gut 2007;56:321-7.
3. Mahadeva S, Yadav H, Rampal S, Everett SM, Goh K-L. Ethnic variation, epidemiological factors and quality of life impairment associated with dyspepsia in urban Malaysia. Aliment Pharmacol Ther 2010;31:1141-51.
4. Brook RA, Kleinman NL, Choung RS, Melkonian AK, Smeeding JE, Talley NJ. Functional dyspepsia impacts absenteeism and direct and indirect costs. Clin Gastroenterol Hepatol 2010;8:498-503.

5. Ford AC, Qume M, Moayyedi P, Arents NLA, Lassen AT, Logan RFA, et al. Helicobacter pylori “test and treat” or endoscopy for managing dyspepsia? An individual patient data meta-analysis. Gastroenterology 2005;128:1838-44.
6. Ford AC, Moayyedi P, Jarbol DE, Logan RFA, Delaney BC. Meta-analysis: Helicobacter pylori “test and treat” compared with empirical acid suppression for managing dyspepsia. Aliment Pharmacol Ther 2008;28:534-44.
7. National Institute for Clinical Excellence. Dyspepsia. Managing dyspepsia in adults in primary care. 2004. www.nice.org.uk/nicemedia/pdf/CG017fullguideline.pdf.
8. American Gastroenterological Association. American Gastroenterological Association technical review on the evaluation of dyspepsia. Gastroenterology 2005;129:1756-80.
9. Van Marrewijk CJ, Mujakovic S, Fransen GAJ, Numans ME, de Wit NJ, Muris JWM, et al. Effect and cost-effectiveness of step-up versus step-down treatment with antacids, H_2-receptor antagonists, and proton pump inhibitors in patients with new onset dyspepsia (DIAMOND study): a primary-care-based randomised controlled trial. Lancet 2009;373:215-25.
10. Raghunath AS, Hungin AP, Mason J, Jackson W. Helicobacter pylori eradication in long-term proton pump inhibitor users in primary care: A randomized controlled trial. Aliment Pharmacol Ther 2007;25:585-92.
11. Moayyedi P, Forman D, Braunholtz D, Feltbower R, Crocombe W, Liptrott M, et al. The proportion of upper gastrointestinal symptoms in the community associated with Helicobacter pylori, lifestyle factors, and nonsteroidal anti-inflammatory drugs. Am J Gastroenterol 2000;95:1448-55.
12. Ford AC, Forman D, Bailey AG, Axon ATR, Moayyedi P. A community screening program for Helicobacter pylori saves money: ten-year follow-up of a randomised controlled trial. Gastroenterology 2005;129:1910-7.
13. Harvey RF, Lane JA, Nair P, Egger M, Harvey I, Donovan J, et al. Clinical trial: prolonged beneficial effect of Helicobacter pylori eradication on dyspepsia consultations—the Bristol helicobacter project. Aliment Pharmacol Ther2010;32:394-400.
14. Ford AC, Delaney BC, Forman D, Moayyedi P. Eradication therapy in Helicobacter pylori positive peptic ulcer disease: systematic review and economic analysis. Am J Gastroenterol 2004;99:1833-55.
15. Malfertheiner P, Megraud F, O’Morain CA, Atherton J, Axon AT, Bazzoli F, et al; European Helicobacter Study Group. Management of Helicobacter pylori infection: the Maastricht IV Florence consensus report. Gut 2012;61:646-64.
16. Yeomans ND, Tulassay Z, Juhasz L, Racz I, van Rensburg CJ, Swannell AJ, et al. A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal antiinflammatory drugs. Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-associated Ulcer Treatment (ASTRONAUT) study group. N Engl J Med 1998;338:719-26.
17. Agrawal NM, Campbell DR, Safdi MA, Lukasik NL, Huang B, Haber MM. Superiority of lansoprazole vs ranitidine in healing nonsteroidal anti-inflammatory drug-associated gastric ulcers: results of a double-blind, randomized, multicenter study. NSAID-Associated Gastric Ulcer Study Group. Ann Intern Med 2000;160:1455-61.
18. Pilichiewicz AN, Horowitz M, Holtmann G, Talley NJ, Feinle-Bisset C. Relationship between symptoms and dietary patterns in patients with functional dyspepsia. Clin Gastroenterol Hepatol 2009;7:317-22.
19. Ford AC, Chey WD, Talley NJ, Malhotra A, Spiegel BMR, Moayyedi P. Yield of diagnostic tests for celiac disease in subjects with symptoms suggestive of irritable bowel syndrome: Systematic review and meta-analysis. Arch Intern Med 2009;169:651-8.
20. Ford AC, Ching E, Moayyedi P. Meta-analysis: yield of diagnostic tests for coeliac disease in dyspepsia. Aliment Pharmacol Ther 2009;30:28-36.
21. Feinle-Bisset C, Azpiroz F. Dietary and lifestyle factors in functional dyspepsia. Nat Rev Gastroenterol Hepatol 2013;10:150-7.
22. Moayyedi P, Soo S, Deeks J, Delaney B, Innes M, Forman D. Pharmacological interventions for non-ulcer dyspepsia. Cochrane Database Syst Rev 2006;4:CD001960.
23. Moayyedi P, Delaney BC, Vakil N, Forman D, Talley NJ. The efficacy of proton pump inhibitors in non-ulcer dyspepsia: a systematic review and economic analysis. Gastroenterology 2004;127:1329-37.
24. Moayyedi P, Leontiadis GI. The risks of PPI therapy. Nat Rev Gastroenterol Hepatol 2012;9:132-9.
25. Ngamruengphong S, Leontiadis GI, Radhi S, Dentino A, Nugent K. Proton pump inhibitors and risk of fracture: a systematic review and meta-analysis of observational studies. Am J Gastroenterol 2011;106:1209-18.
26. Moayyedi P, Soo S, Deeks J, Delaney B, Harris A, Innes M, et al. Eradication of Helicobacter pylori for non-ulcer dyspepsia. Cochrane Database Syst Rev 2006;2:CD002096.