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Review

Executive summary

The management of dyspepsia: a systematic review

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Background

Managing dyspepsia costs the NHS in excess of £500 million per year; 2% of the population consult their general practitioner (GP) with dyspepsia each year, and 450,000 endoscopies are performed at a cost of £90 million. Most patients undergoing endoscopy have no significant abnormality and are termed as having non-ulcer dyspepsia (NUD). The initial management of uninvestigated dyspepsia in primary care is considered in this review together with treatments for proven NUD. The study linked systematic reviews with simulation modelling to provide the best available evidence for managing patients with dyspepsia.

Questions addressed

The management of uninvestigated dyspepsia in primary care

1. How effective is initial pharmacological therapy?
2. How effective is early endoscopy?
3. How effective is *Helicobacter pylori* screening before endoscopy in patients with dyspepsia?
4. How effective is *H. pylori* screening before eradication therapy in patients with dyspepsia?
5. Does subdividing dyspepsia on the basis of symptom patterns predict response to particular therapies?
6. What are the most cost-effective combinations of initial investigation strategy and prescribing for patients?
7. What are the most important strategies to compare in future trials?

Therapy for proven NUD

1. How effective is pharmacological therapy?
2. How effective is *H. pylori* eradication?
3. What is the most cost-effective therapy?
4. What are the most important therapies to compare in the treatment of NUD?

Methods

Data sources

The Cochrane Collaboration Controlled Trials Register and Database of Systematic Reviews, MEDLINE, EMBASE, CINAHL, SIGLE and ISCI were searched up until January 1999. Experts in the field of dyspepsia, major pharmaceutical companies and journal editors were also contacted. Authors of publications only available as abstracts were contacted for full trial results.

Study selection

Dyspepsia was defined following the 1988 Rome Working Party definition as any symptom referable to the upper gastrointestinal tract lasting for more than 4 weeks. Two reviewers independently selected eligible trials, according to the following criteria.

Dyspepsia in primary care

- Population: patients presenting to primary care with dyspeptic symptoms but not selected on the basis of any previous investigative results.
- Intervention: empirical acid suppression therapy; early endoscopy (with or without a screening questionnaire); *H. pylori* screening followed by endoscopy of patients with positive results; *H. pylori* screening followed by eradication therapy for patients with positive results.
- Comparison: placebo/antacid; other medication; other strategy.
- Outcomes: quality of life; individual dyspepsia symptoms or symptom scores; patient acceptability; consultation and referral rates for upper gastrointestinal symptoms; prescribing; diagnostic findings; costs.

Pharmacological treatment for NUD

Patients with NUD were defined as those with dyspepsia and insignificant findings at endoscopy or barium meal, who were not required to have had 24-hour oesophageal pH studies, upper abdominal ultrasound or computed tomography scans. Patients with hiatus hernia, less than five gastric erosions or mild duodenitis were included, as these lesions correlate poorly with dyspepsia symptoms.

- Population: adult patients (aged 16–80 years) presenting in secondary care with diagnosis of NUD; all patients to have had either an endoscopic or barium meal examination to exclude peptic ulcer disease.

- Intervention: antacids; H_2-receptor antagonists, including cimetidine, famotidine, nizatidine and ranitidine; proton pump inhibitors (PPIs); prokinetics, including cisapride, domperidone and metoclopramide; mucosal protecting agents, including colloidal bismuth compounds, misoprostol, and sucralfate; antimuscarinics, including pirenzepine; pre-defined effective *H. pylori* eradication therapy versus placebo or acid suppression.
- Outcomes: individual dyspepsia symptom scores; global symptom scores expressed in dichotomous format; quality of life.

Data extraction
Data from eligible trials were collected for analysis.

Data synthesis
Data from ordinal outcomes, such as dyspepsia rating scales, were combined by transforming to a binary scale. Fixed effect models (Mantel–Haenszel) were used for pooling data to obtain a pooled relative risk (RR) unless significant heterogeneity was present, when the random effects model (DerSimonian and Laird) was adopted. For continuous outcomes, the inverse variance (Woolf's method) model was used as the fixed effect method and the DerSimonian and Laird method for random effects. Egger's test of asymmetry was used to detect publication bias. Numbers-needed-to-treat (NNTs) and their confidence intervals (CIs) were calculated. For continuous measures, Hedges' adjusted *g* was used to calculate standardised mean differences, expressing the treatment effect in units of standard deviation.

RRs, mean differences and standardised mean differences were pooled. Additional analyses investigating heterogeneity and publication bias were undertaken.

Modelling
All health economics modelling adopted an NHS perspective. Effects of treatment were obtained from the systematic reviews where possible; other necessary data, including test performance, prevalence and outcome data were obtained systematically from papers collected alongside the reviews, but not relating directly to the study questions. Cost data were obtained from the Drug Tariff and NHS 1998 Reference Costs. Markov cost-effectiveness models of therapy for proven NUD were constructed. The discrete event simulation model of the management of dyspepsia in primary care was programmed directly in Visual Basic©. Costs were discounted at 6% and benefits at 3%. Cost-effectiveness ratios and incremental cost-effectiveness ratios (ICERs) for comparisons of strategies were obtained and a wide sensitivity analysis of variation in both costs and effectiveness was performed.

Results

Interventions for uninvestigated dyspepsia in primary care
In all, 12 papers reporting 14 comparisons were found, with a further four trials being available as abstracts. Meta-analysis of trials comparing PPIs with antacids and H_2-receptor antagonists, and of early endoscopy compared with initial acid suppression was possible. PPIs were very significantly more effective than both H_2-receptor antagonists and antacids. RR reductions with 95% CIs were: for PPIs versus antacids, 29% (36 to 21); for PPIs versus H_2-receptor antagonists 37% (53 to 15). Results for other drug comparisons were either absent or inconclusive. Early endoscopy may be more effective than initial prescribing but the effect size was small and non-significant (RR reduction, 11% (1 to 22)). Although economic data are not yet available, cost-effectiveness is likely to be low. *H. pylori* test-and-endoscope was associated with no significant difference in effectiveness compared with selective endoscopy at the GP's discretion, and no reduction in costs. *H. pylori* test-and-treat has been shown to be as effective as early endoscopy and to reduce costs in patients referred for investigation, but uncertainty remains as to its cost-effectiveness in primary care compared with empirical acid suppression.

The model indicated that strategies involving initial prescribing, or *H. pylori* eradication (test-and-treat) were more cost-effective than strategies involving endoscopy. Prescribing H_2-receptor antagonists was more effective than antacid (ICER, £15.88 per additional month symptom-free over 5 years). PPIs were more effective than antacids (ICER, £21.76 per month) and H_2-receptor antagonists (ICER, £41.64 per month). The results were sensitive to the costs and effectiveness of the medications. A mean saving of 3 weeks' dyspeptic symptoms over 5 years was obtained by *H. pylori* test-and-treat rather than prescribing, with an ICER of £62.77 per month saved. The result was sensitive to the cost of ongoing dyspepsia treatment and the prevalence of *H. pylori*.

Interventions for NUD
The one eligible trial suggested that antacids were no more effective than placebo in NUD.

Meta-analysis was possible for prokinetics, H_2-receptor antagonists, PPIs, bismuth, pirenzepine, sucralfate, and *H. pylori* eradication against placebo. Prokinetics and H_2-receptor antagonists were more effective than placebo (prokinetics: RR reduction, 50% (95% CI, 30 to 70); H_2-receptor antagonists, 29% (47 to 4)) but trials were often of poor quality with significant heterogeneity between studies. A funnel plot revealed that the results of the prokinetic meta-analysis could be due to publication bias or related quality issues. PPIs and bismuth tended to be more effective than placebo but this did not reach statistical significance. There was no evidence that sucralfate was superior to placebo. Pirenzepine showed a significant benefit (RR reduction, 4 (95% CI, 3 to 10) but this was based on only two trials and the drug is no longer available in the UK. *H. pylori* eradication was associated with a 9% RR reduction (95% CI, 14 to 4); an NNT of 15 (10 to 1) was calculated based on a control event rate of 72%.

Economic modelling based on these data, assuming a threshold ICER of £100 per month, and a wide sensitivity analysis indicated that PPIs and cisapride were unlikely to be cost-effective treatments for NUD. If cheaper prokinetics (domperidone or metoclopramide) were sufficiently effective to give an NNT of at most 55, or H_2-receptor antagonists to give an NNT of 14, these treatments may represent cost-effective choices. *H. pylori* eradication was cost-effective with an ICER against antacid alone of £56 per month.

Conclusions

Implications for healthcare

There is still much uncertainty around the management of dyspepsia, both uninvestigated dyspepsia and proven NUD. This review indicates that the treatment for NUD, for which the evidence is most reliable, is *H. pylori* eradication. The effect is small but cost-effective as the treatment is potentially curative rather than just suppressive. Whether the effect is due to treating latent peptic ulcer disease or some other mechanism, the implication is that patients diagnosed on the basis of a negative endoscopy will benefit from *H. pylori* eradication.

In primary care, the conclusions are much less robust. PPIs are the most effective treatment for undiagnosed dyspepsia and reasonably cost-effective. This is because the case-mix includes patients with peptic ulcer disease and gastro-oesophageal reflux disease, for which PPIs are effective treatments. The relative efficacy of H_2-receptor antagonists is uncertain, because of a lack of trials comparing antacids and H_2-receptor antagonists and a lack of trials in patients without reflux as a dominant symptom. Although management based on early endoscopy may lead to a small reduction in dyspeptic symptoms, the cost-effectiveness of endoscopy is uncertain. Modelling suggests that, for most patients, endoscopy-based management is not cost-effective as there is little gain in symptom relief and considerable additional cost. Of the empirical strategies, *H. pylori* test-and-treat is likely to be more cost-effective than endoscopy but well-designed, primary care based trials are needed to compare cost-effectiveness and effects on quality of life with empirical acid suppression.

Recommendations for research

Primary research

In the treatment of NUD:

(i) long-term effectiveness of H_2-receptor antagonists and 'cheaper' prokinetics compared with placebo in proven NUD
(ii) patient's views on the value of *H. pylori* eradication therapy
(iii) new therapies.

For the initial management of dyspepsia:

(i) cost-effectiveness of *H. pylori* test-and-treat compared with acid suppression for uninvestigated dyspepsia in primary care
(ii) cost-effectiveness of H_2-receptor antagonists compared with PPIs in primary care
(iii) effectiveness of the Rome II criteria for determining therapy in primary care.

Secondary research

These reviews (in their Cochrane format) should be kept up-to-date, as research in this field is extremely fast moving. Given the number of new trials and the potential for important subgroup analysis based on age or symptoms, there is potential for an individual patient data meta-analysis. The Cochrane Upper Gastrointestinal and Pancreatic Disease Review Group is actively planning such a review.

Publication

Delaney B, Moayyedi P, Deeks J, Innes M, Soo S, Barton P, *et al.* The management of dyspepsia: a systematic review. *Health Technol Assess* 2000;**4**(39).

NHS R&D HTA Programme

The NHS R&D Health Technology Assessment (HTA) Programme was set up in 1993 to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS.

Initially, six HTA panels (pharmaceuticals, acute sector, primary and community care, diagnostics and imaging, population screening, methodology) helped to set the research priorities for the HTA Programme. However, during the past few years there have been a number of changes in and around NHS R&D, such as the establishment of the National Institute for Clinical Excellence (NICE) and the creation of three new research programmes: Service Delivery and Organisation (SDO); New and Emerging Applications of Technology (NEAT); and the Methodology Programme.

This has meant that the HTA panels can now focus more explicitly on health technologies ('health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care) rather than settings of care. Therefore the panel structure has been redefined and replaced by three new panels: Pharmaceuticals; Therapeutic Procedures (including devices and operations); and Diagnostic Technologies and Screening.

The HTA Programme will continue to commission both primary and secondary research. The HTA Commissioning Board, supported by the National Coordinating Centre for Health Technology Assessment (NCCHTA), will consider and advise the Programme Director on the best research projects to pursue in order to address the research priorities identified by the three HTA panels.

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Criteria for inclusion in the HTA monograph series
Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The editors and publisher have tried to ensure the accuracy of this report but do not accept liability for damages or losses arising from material published in this report. They would like to thank the referees for their constructive comments on the draft document.

Copies of this report can be obtained from:

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