



*National Institute for
Clinical Excellence*

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**Guidance on the
Use of Proton
Pump Inhibitors
in the Treatment
of Dyspepsia**

This document has been circulated to the following:

- Health Authority Chief Executives in England and Wales
- NHS Trust Chief Executives in England and Wales
- PCG Chief Executives
- Local Health Group General Managers
- All GPs in England and Wales
- Consultant Gastroenterologists in England and Wales
- NHS Director for Wales
- Chief Executive of the NHS in England
- NHS Executive Regional Directors
- Special Health Authority Chief Executives
- Community Health Councils in England and Wales
- Patient advocacy groups
- Commission for Health Improvement
- NHS Clinical Governance Support Team
- Chief Medical and Nursing Officers in England and Wales
- Medical Director & Head of NHS Quality – National Assembly for Wales
- Clinical Effectiveness Support Unit - Wales
- Representative bodies for health services, professional organisations and statutory bodies, Royal Colleges

This Guidance is written in the following context:

This Guidance represents the view of the Institute's Appraisal Committee, the membership of which is set out in Appendix A, which was arrived at after careful consideration of the available evidence. Health professionals are expected to take it fully into account when exercising their clinical judgement about the use of proton pump inhibitors to treat dyspepsia. This guidance does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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Guidance on the Use of Proton Pump Inhibitors in the Treatment of Dyspepsia

Technology Appraisal Guidance No. 7

Issue Date July 2000
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1. Guidance

- 1.1 In patients with documented duodenal or gastric ulcers, a treatment strategy of testing for *Helicobacter pylori* and, where positive, eradicating the infection is recommended. Long-term acid-suppressing therapy should not be used. Those patients who are *H. pylori* negative or remain symptomatic after eradication therapy should be treated as described in 1.6.
- 1.2 For patients with a documented non steroidal anti-inflammatory drug (NSAID)-induced ulcer, who must unavoidably continue with NSAID therapy (e.g. those with severe rheumatoid arthritis), an acid suppressor, usually a proton pump inhibitor (PPI), should be prescribed. After the ulcer has healed, the patient, where possible, should be stepped down to a maintenance dose of the acid suppressor.
- 1.3 Patients who have severe gastro-oesophageal reflux disorder (GORD) symptoms or who have a proven pathology (e.g. oesophageal ulceration, Barrett's oesophagus) should be treated with a healing dose of a PPI until symptoms have been controlled. After that has been achieved, the dose should be stepped down to the lowest dose that maintains control of symptoms. A regular maintenance low dose of most PPIs will prevent recurrent GORD symptoms in 70-80% of patients and should be used in preference to the higher healing dose. Where necessary, should symptoms re-appear, the higher dose should be recommenced. In complicated oesophagitis (stricture, ulcer, haemorrhage), the full dose should be maintained. Patients with mild GORD symptoms and/or those who do not have a proven pathology can frequently be managed by alternative therapies (at least in the first instance) including antacids, alginates, or H₂RAs (H₂ receptor antagonists).
- 1.4 Patients diagnosed with non-ulcer dyspepsia (NUD) may have symptoms caused by different aetiologies and should not be routinely treated with PPIs. Should the symptoms appear to be acid-related, an antacid or the lowest dose of an acid suppressor to control symptoms should be prescribed. If they do not appear to be acid-related, an alternative therapeutic strategy should be employed.
- 1.5 Patients presenting in general practice with mild symptoms of dyspepsia may be treated on either a "step-up" or a "step-down" basis. Neither group should normally be treated with PPIs on a long-term basis without a confirmed clinical diagnosis being made.
- 1.6 In circumstances where it is appropriate to use a PPI and where healing is required, the optimal dose to achieve this should be prescribed initially. Once healing has been achieved, or for conditions where it is not required, the lowest dose of the PPI that provides effective symptom relief should be used.

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- 1.7 The least expensive appropriate PPI should be used.
 - 1.8 The use of PPIs in paragraphs 1.1 to 1.7 refers for each indication only to those PPIs which have been licensed for that use.
 - 1.9 On present evidence, PPIs do not have any serious contraindications for the vast majority of users, and have been in common use for some eight or nine years. While their use in sufficient dosage to cure, or to control symptoms, is well warranted in terms of their clear benefits, any additional use cannot be recommended.

This section, Section 1, constitutes the Institute's Guidance on the Use of Proton Pump Inhibitors in the Treatment of Dyspepsia. The remainder of the document is structured in the following way:

- 2 Clinical Need
 - 3 The Technology
 - 4 Evidence
 - 5 Implications for the NHS
 - 6 Related Guidance
 - 7 Further Research
 - 8 Implementation
 - 9 Clinical Audit Advice
 - 10 Review of Guidance
- Appendix A: Appraisal Committee
Appendix B: Sources of Evidence
Appendix C: Information for Patients.

The full document and a summary of evidence will be available from our web site at www.nice.org.uk or by contacting 0541 555 455 and quoting reference number 21942.

Mae'r adran hon (adran 1) hefyd ar gael yn Gymraeg ar ein gwefan neu drwy gysylltu â 0541 555 455, rhif cyfeirnod, 21944.

2

Clinical Need and Practice

- 2.1 Dyspepsia refers to a broad range of symptoms related to dysfunction of the upper gastrointestinal (GI) tract from the oesophagus to the duodenum, including retrosternal or epigastric pain, fullness, bloating, wind, heartburn, nausea and vomiting. Pain may vary from mild to severe, may be intermittent and may often resolve itself without medication. Large numbers of people suffer from dyspepsia, estimated to be up to 40% of the adult population in any one year. Of these, the main causes are gastro-oesophageal reflux disease (GORD) (15 to 25%), gastric and duodenal ulcers (15 to 25%) and stomach cancer (2%). The remaining 60% are classified as non-ulcer dyspepsia (NUD), also called "functional" dyspepsia.
- 2.2 The bacterium *H. pylori* is the major cause of gastric and duodenal ulceration in the UK, and eradication of this infection of the stomach lining leads to healing of the ulcers in the majority of cases. Non-steroidal anti-inflammatory drugs (NSAIDs) often cause dyspeptic symptoms and are a potential cause of ulcers. Co-prescription of drugs to relieve dyspepsia, or to try to reduce the risk of an ulcer caused by the NSAID, is common practice.
- 2.3 About 10% of the population seek their General Practitioner's advice for dyspeptic symptoms each year, and about 10% of these are referred on for a specialist opinion.
- 2.4 Although, for the majority, dyspepsia is not a serious condition, a number of serious causes may nevertheless underlie it. It is important to identify those patients who may have a serious underlying cause for their dyspepsia (especially those with gastric cancer, but also those with ulcers or severe GORD). For that reason, all patients over the age of 55 newly presenting with dyspepsia, and younger patients with so-called "alarm" symptoms (in particular, unexplained weight loss, dysphagia, anaemia and/or progressively worsening symptoms) should be thoroughly investigated. Investigation is usually by upper gastrointestinal endoscopy, which is invasive and costly. Since serious disease is rare in younger patients, endoscopy is therefore not recommended immediately for new patients in the under 45 age group without alarm symptoms. The issue of whether newly presenting patients in the 45-55 age group without alarm symptoms should undergo immediate endoscopy is still a matter of debate.

3

The Technology

- 3.1 A number of drugs are available for the treatment of dyspepsia: antacids neutralise acids in the stomach; alginates form a protective layer on the contents of the stomach and thus reduce acid contact with the oesophagus; prokinetics enhance the motility of the GI tract; histamine receptor antagonists (H₂RAs) and PPIs suppress acid. PPIs act within the cell at a site known as the proton pump. Acid suppression is substantially greater and more prolonged than for H₂RAs, as they block the final common pathway of acid production in

the stomach. There are four proton pump inhibitors: lansoprazole, omeprazole, rabeprazole and pantoprazole. In 1998, the NHS in England spent £291 million on PPIs, £139 million on H₂RAs and £52 million on other dyspepsia drugs. In Wales, the corresponding amounts spent were £23 million (PPIs), £11 million (H₂RAs) and £5 million (others).

4.1 UNDIAGNOSED CAUSE OF DYSPEPSIA.

This is the category in which most patients will present to their general practitioner.

4.1.1 PPIs are often effective because some of the patients have GORD or peptic ulceration. However, prolonged use is only optimal within this group for the small percentage of patients with severe GORD.

4.1.2 Early confirmation of diagnosis by endoscopy in people under the age of 45 years is not, in general, cost-effective, while between 45 and 55, the cost-effectiveness evidence is more equivocal. For these groups of patients, the present evidence on cost-effectiveness is unable to distinguish between starting with high doses of more powerful drugs and stepping down to lower doses or less powerful drugs, or conversely, starting low and stepping up.

4.2 CONFIRMED DIAGNOSIS OF CAUSE OF DYSPEPSIA

4.2.1 In the presence of gastric and/or duodenal ulcers, PPI use will alleviate symptoms. PPIs will also heal the ulcers, but if PPI use is stopped, the ulcers will frequently recur. Thus, evidence strongly supports the importance of the eradication of *H pylori* infection which usually eliminates the need for continuing maintenance PPIs.

4.2.2 For those with an NSAID-induced ulcer and an unavoidable need to continue with the NSAID, PPIs are the most effective in long-term use for both symptom control and ulcer prevention.

4.2.3 PPIs are the most clinically and cost effective drug to heal severe GORD and to prevent its recurrence. In addition, once healing has occurred, evidence indicates that many patients can be maintained on lower doses than are required for initial treatment or on intermittent usage of PPIs. For mild GORD, however, while PPIs are the most effective drug, they may not be the most cost-effective, so it may be prudent to start such patients on less expensive alternatives.

4.2.4 Drugs are of limited effectiveness for NUD. Prokinetics, H2RAs and bismuth salts are all somewhat more beneficial than placebo. The available evidence shows that PPIs are marginally, if at all, more beneficial than placebo in the treatment of NUD.

4.3 The documentation and opinion available to the Appraisal Committee is set out in Appendix B.

5

Implications for the NHS

5.1 All doctors prescribing PPIs will need to review the indications for their use (including licensed indications and safety/side effect profile), and assess the dose used, with the aim of reducing it where appropriate.

5.2 This advice, if implemented fully, could lead to a reduction in the usage of PPIs of at least 15%, and therefore save the NHS some £40 to £50 million per year in drug costs in England and Wales. The full savings are likely to be offset, however, by increased costs of diagnostic testing and by monitoring of long-term PPI usage.

6

Related Guidance

6.1 The Institute has been commissioned to prepare a clinical guideline on the management of dyspepsia. It is anticipated that this will be published in mid 2001.

7

Further Research

7.1 The Institute has no recommendations for further research into the proton pump inhibitors.

8

Implementation

8.1 Primary care groups, local health groups and NHS trusts should review their current practice in the use of proton pump inhibitors against the Guidance.

8.2 As they reach the appropriate stage in their treatment, patients should be offered the therapies set out in section 1 of this Guidance.

9

Clinical Audit Advice

9.1 To enable clinicians to audit their own compliance with this Guidance, it is recommended that treatment plans be recorded for each patient with dyspepsia.

9.2 This information should be incorporated into local clinical audit data recording systems, and consideration given (if not already in place) to the establishment of appropriate categories in routine electronic record keeping systems used in primary care groups and hospitals.

10

Review

9.3 Prospective clinical audit programmes should record the proportion of treatments adhering to the guidance. Such programmes are likely to be more effective in improving patient care when they form part of the organisation's formal clinical governance arrangements and where they are linked to specific post-graduate activities.

10.1 This advice will be reviewed in the light of new evidence in June 2003.

Andrew Dillon
Chief Executive

July 2000

APPENDIX A

Appraisal Committee Members

Professor R. L. Akehurst
Dean, School of Health Related
Research
Sheffield University

**Professor David Barnett
(Chairman)**
Professor of Clinical Pharmacology
University of Leicester

Professor Sir Colin Berry
Professor of Morbid Anatomy
St Bartholomew's and Royal London
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Professor Martin Buxton
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Dr Karl Claxton
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Ms Jean Gaffin
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Mrs Sue Gallagher
Chief Executive
Merton, Sutton and Wandsworth
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Dr Trevor Gibbs
International Medical Operations
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Mr John Goulston
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Mr M Mughal
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Mr James Partridge
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Dr L.J. Patterson
Consultant Physician and Medical
Director
Burnley General Hospital

Professor Philip Routledge
Professor of Clinical Pharmacology
University of Wales

Professor Andrew Stevens
Professor of Public Health
University of Birmingham

APPENDIX B

Proton Pump Inhibitors in the Treatment of Dyspepsia

Documentation and Opinion Available to the Committee

1. The following documentation and opinion was made available to the Committee:
 - a. Assessment Report

The Appropriate Use of Proton Pump Inhibitors in the Treatment of Dyspepsia, Prepared by the NICE Appraisals Team, March 2000.
 - b. Manufacturer/Sponsor submissions:
 1. AstraZeneca
 2. BASF Pharma
 3. Eisai Ltd.
 4. Janssen-Cilag Ltd.
 5. Reckitt & Colman
 6. Wyeth Laboratories
 - c. Professional/Specialist Group, Patient/carer Group and Trade Association submissions:
 1. British Medical Association
 2. British Society of Gastroenterology & Royal College of Physicians of London
 3. Faculty of Pharmaceutical Medicine
 4. Oesophageal Patients Association
 5. Royal College of General Practitioners
 6. Royal Pharmaceutical Society
 - d. The following experts were invited to make submissions to the committee:
 1. Professor R. E. Pounder, Professor of Medicine, Royal Free Hospital
 2. Dr. R. P. Walt, Consultant Gastroenterologist, Birmingham Heartlands Hospital

APPENDIX C

Guidance on the Use of Proton Pump Inhibitors in Dyspepsia – Patient Information

The patient information in this appendix has been designed to support the production of your own information leaflets; you can download it from our web site (www.nice.org.uk) where it is available in English and Welsh. A printed version of this text is available in English/Welsh or English alone. If you would like copies of the printed leaflet please contact 0541 555 455, and quote the reference number 21945 for the English/Welsh version and 21943 for the English only version.

What is NICE Guidance?

The National Institute for Clinical Excellence (NICE) is a part of the NHS. It produces guidance for both the NHS and patients on medicines, medical equipment and clinical procedures and where they should be used.

When the Institute evaluates these things it is called an appraisal. Each appraisal takes around 12 months to complete and involves the manufacturers of the drug or device, professional organisations and the groups who represent patients.

NICE was asked to look at the available evidence on a group of drugs called Proton Pump Inhibitors (PPIs) and provide guidance that would help the NHS decide when they should be used for treating a condition called dyspepsia.

What is dyspepsia?

Dyspepsia is a general term used to describe discomfort or pain in the upper abdomen or chest, often after meals. Other symptoms include burning, fullness, bloating, wind, nausea and vomiting. Pain may be mild or severe, it may come and go and it often resolves itself without medication. Dyspepsia is sometimes called indigestion or heartburn. For most people dyspepsia is not serious, however, for some patients dyspepsia may be caused by a more serious underlying condition (e.g. a peptic ulcer).

At any one time it is estimated that 4 out of 10 adults each year may suffer from dyspepsia. Each year about 1 in 10 people will need to seek their GP's advice for dyspepsia symptoms, and about 1 in 10 of those who visit their GP need to be referred for a specialist opinion, or tests, because of continuing or more severe symptoms.

The main causes of this more severe dyspepsia are:

- **Gastro-oesophageal reflux disease (GORD):** this is an irritation and sometimes inflammation (sometimes described as a burning) of the lower end of the oesophagus (gullet) This is usually caused by digestive juices (especially acid) repeatedly moving upward from the stomach into the gullet.
- An **ulcer** is a break in the lining of the stomach or the duodenum (the first part of the small intestine) resembling ulcers that some people get from time to time in their

mouth. Because of a component of digestive juice, called pepsin, they are often described as a 'peptic ulcer'. Infection of the stomach lining by the bacterium *Helicobacter pylori* (*H pylori*) is the major cause of ulcers in the UK, and eradication of this infection leads to healing of the ulcers in the majority of cases.

- Sometimes dyspepsia may be caused by the **medicines commonly taken for arthritis** (Non-steroidal anti-inflammatory drugs - NSAIDs). It is known that these medicines can cause irritation of the stomach lining, possibly leading to ulcers. Therefore patients will often be prescribed another medicine to relieve the dyspepsia symptoms.
- **Non-ulcer dyspepsia (NUD)**: if tests are performed and no medical cause for the dyspepsia is found, the term '**non-ulcer dyspepsia**' is used. This means that no ulcer has been found to account for the symptoms.

What medicines are available to treat dyspepsia?

A number of medicines are available for the treatment of dyspepsia:

- **antacids** – reduce the effect of acids in the stomach
- **alginates** – form a protective layer on the contents of the stomach and therefore reduce acid contact within the oesophagus (gut)
- **prokinetics** – speed up the movement of the gut
- **histamine antagonists** (sometimes called H₂ Antagonists) and **PPIs** – keep in check (suppress) acid production. They are also known as acid-suppressors

In 1998, the NHS in England spent £291 million on PPIs, £139 million on histamine antagonists and £52 million on other dyspepsia drugs. In Wales, £23 million were spent on PPIs, £11 million on H₂RAs and £5 million on other dyspepsia drugs.

What has NICE recommended about the use of Proton Pump Inhibitors in dyspepsia?

It is clear that there are many causes of dyspepsia. The advice NICE has given depends on the cause. Some examples follow:

- Patients presenting in general practice with **mild symptoms of dyspepsia** may be treated on either a "step-up" or a "step-down" basis. These patients should not normally be treated with PPIs on a long-term basis. "Step-up" means that patients would start on perhaps a low dose antacid, gradually trying stronger products until their symptoms are controlled. Once the symptoms are controlled it may then be possible to step down the dose and/or change the type of medicine to the lowest dose that keeps symptoms under control. Sometimes patients need to be treated from the start with a high dose of medicine to control their symptoms and then the dose is reduced to maintain control - this is called the "step-down" approach.
- **Patients with confirmed ulcers** should be tested for *H. pylori*. If the bacterium is present it should be eradicated (wiped out with antibiotics prescribed by your doctor) and long-term acid-suppressors (e.g. PPIs) should not be used.

- For patients with an **ulcer caused by other medicines** (e.g. patients with severe rheumatoid arthritis who are taking non-steroidal anti-inflammatory drugs - NSAIDs), an acid suppressor, usually a PPI, should be prescribed. After healing of the ulcer has occurred, the medicine should be gradually decreased to the lowest dose that maintains control of symptoms.
- Patients with **mild GORD** symptoms and/or those who do not have a proven disease (non-ulcer dyspepsia) can often initially be managed by antacids, alginates, or histamine antagonists and may not need to use PPIs.
- Patients who have **severe GORD** symptoms or a disease such as oesophageal ulceration or Barrett's oesophagus should be treated with a healing dose of a PPI until their symptoms have been controlled. Once the symptoms have been controlled, the medicine should be decreased on a trial basis to see if a lower dose can control the symptoms. A regular low dose (known as maintenance therapy) of most PPIs will prevent the symptoms coming back in 7 or 8 out of 10 of patients. Should symptoms re-appear, your doctor may prescribe the higher dose again.
- NICE has recommended that if your doctor prescribes a PPI then he/she should use the least expensive PPI that is appropriate for your condition.
- All doctors prescribing PPIs have been asked to review the indications for their usage (including licensed indications and safety/side effect profile), and assess the dose used. The aim is to reduce the dose or even stop the medicine where appropriate. Your doctor may discuss this with you at sometime in the future.
- This advice, if implemented fully, will have real benefits to patients because there is no advantage in having more of a drug than is needed. It could also lead to a reduction in the usage of PPIs of at least 15%, and therefore save the NHS in England and Wales £40 to £50 million per year in drug costs. Some of these savings may be used to fund increases in diagnostic testing and the monitoring of long-term PPI use.

What should I do?

If you, or someone you care for, is taking a Proton Pump Inhibitor you should discuss this advice with the doctor or nurse.

Will NICE review its guidance?

Yes. The guidance will be reviewed in June 2003.

Further Information

Further information on NICE, and the full guidance issued to the NHS is available on the NICE web site (www.nice.org.uk). It can also be requested from 0541 555 455, quoting reference 21942.