NICE National Institute for Health and Care Excellence

2019 surveillance of gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management (NICE guideline CG184)

Surveillance report

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Contents

Surveillance decision

We will not update the guideline on gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management.

Overview of 2019 surveillance methods

The surveillance process consisted of:

- Initial feedback from topic experts via a questionnaire.
- Input from stakeholders on known variations in practice and policy priorities.
- Literature searches to identify relevant evidence.
- Assessing the new evidence against current recommendations and deciding whether or not to update sections of the guideline, or the whole guideline.
- Consulting on the decision with stakeholders, except if we propose to update and replace the whole guideline.
- Considering comments received during consultation and making any necessary changes to the decision.

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Evidence considered in surveillance

Search and selection strategy

When considering the options for surveillance of this guideline, we noted that the existing evidence base showing the effectiveness of proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H_2RAs) was robust at the time the guideline was developed.

Additionally, in our initial evidence-gathering processes, we did not identify any new interventions for dyspepsia or gastro-oesophageal reflux disease (GORD) that were likely to impact on current recommendations. This included checking Cochrane reviews, ongoing research, and seeking feedback from topic experts.

Evidence searching focused on 2 areas:

- Long-term safety of PPIs
  - We searched for new evidence related to the long-term safety of PPIs. We found 44 studies in a search for systematic reviews published before 22 August 2018.
- *H pylori* eradication regimens
  - For *H pylori* eradication regimens we checked a total of 4 annual reports from the English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR).

We also searched for new Cochrane reviews related to the whole guideline. We found 5 relevant Cochrane reviews published before 2 May 2018.

Overall we included 51 studies.

Literature searching was not conducted for other sections of the guideline: the community pharmacist, common elements of care, referral guidance for endoscopy, reviewing patient care, laparoscopic fundoplication, referral to a specialist service, and surveillance for people with Barrett's oesophagus. We did not identify any information relevant to these areas in the initial evidence gathering, including checking Cochrane reviews, ongoing research, and seeking feedback from topic experts. We asked stakeholders to indicate any information suggesting a need to update a section of the guideline that was not a focus of this surveillance.

See appendix A for details of all evidence considered in this surveillance review, and references.

Effectiveness of PPIs and H_2RAs

The findings of 2 systematic reviews supported the view that evidence of effectiveness for these drugs is robust. One of these studies was identified in the PPI safety search, and 1 was identified in the Cochrane review search.

A recent systematic review (Scally et al. 2018) assessed PPIs, H_2RAs, and prostaglandins in a range of indications. These drug classes were considered together as 'gastroprotectant drugs'. Overall, 849 trials were included, 580 of which assessed prevention of ulcers; 233 assessed healing; and 36 assessed treatment of acute upper gastrointestinal bleeding. The median duration of treatment was 1.4 months. In prevention

trials, gastroprotectants reduced development of endoscopic and symptomatic ulcers and upper gastrointestinal bleeding. There was no significant reduction in mortality. Reductions in upper gastrointestinal bleeding had a larger effect size with PPIs than prostaglandin analogues or H_2RAs. Prevention of gastrointestinal bleeding was not affected by use of non-steroidal anti-inflammatory drugs. In healing trials, gastroprotectants increased endoscopic ulcer healing and PPIs were more effective than prostaglandin analogues or H_2RAs. The authors noted that the results may have overestimated the size of the effect because of small study bias (median n=78). This study shows that PPIs and H_2RAs are effective for a range of indications.

A Cochrane review (Pinto-Sanchez et al. 2017), concluded that PPIs are effective for the treatment of functional dyspepsia, independent of the dose and duration of treatment compared with placebo. Additionally, PPIs may be slightly more effective than prokinetics. There appeared to be no benefit of adding prokinetics to PPI treatment. The findings support current guidance on PPI use for functional dyspepsia. If symptoms continue or recur after initial treatment, a PPI or H_2RA should be taken at the lowest dose possible to control symptoms.

Long-term safety of PPIs

The Medicines and Healthcare Products Regulatory Agency (MHRA) has issued several drug safety updates covering the following risks:

- interaction of omeprazole or esomeprazole with clopidogrel (April 2010)
- hypomagnesaemia (April 2012)
- fracture (April 2012) and
- subacute cutaneous lupus erythematosus (September 2015).

Topic expert feedback indicated ongoing concerns about the long-term safety of PPIs.

We searched for new evidence in this area. We restricted the search to systematic reviews to improve the robustness of the data and to obtain a manageable set of highly relevant search results. We discussed this approach with the MHRA, and shared our findings for its consideration.

The summary of product characteristics (SPC) was checked for each PPI to determine

whether the identified adverse events were already recognised. Appendix A summarises the findings.

Overall, we identified 43 systematic reviews of adverse events with use of PPIs or H_2RAs. Studies identified in searches were summarised from the information presented in their abstracts. This approach allowed consideration of the overall direction of effect observed in studies, and whether the effect was consistent across studies.

Cardiovascular adverse events

Several of the SPCs for PPIs licensed in the UK (esomeprazole, lansoprazole and omeprazole) recognise an interaction with clopidogrel whereas the SPCs for pantoprazole and rabeprazole do not. None of the SPCs recognises a risk of cardiovascular events in people not on clopidogrel. We identified 14 systematic reviews reporting on cardiovascular outcomes in people taking PPIs. There was a consistent association between the combination of clopidogrel plus a PPI and adverse cardiovascular events and a possible association between PPIs and cardiovascular events in people who are not taking clopidogrel. More limited evidence suggested there may be no adverse cardiovascular risk when PPIs are taken in combination with aspirin.

Infection

The SPCs recognise an increased risk of gastrointestinal infections with PPI treatment. We found 12 systematic reviews addressing infection. The evidence consistently suggests increased occurrence of community-acquired pneumonia and infection with *Clostridium difficile* in people taking PPIs. One review indicated that PPIs may also increase the occurrence of spontaneous bacterial peritonitis in people with cirrhosis. One review suggested an association between H_2RAs and spontaneous bacterial peritonitis in people with cirrhosis. One study suggested an association between PPI use and small intestinal bacterial overgrowth.

Kidney disease

Kidney disease, particularly interstitial nephritis is recognised in all SPCs as a very rare adverse event associated with PPI treatment. We found 7 systematic reviews that consistently suggested that PPIs are associated with adverse effects on the kidney. Studies reporting on H_2RAs suggested that there may be no association with adverse effects on the kidney.

Cancer and precancerous conditions

All SPCs for PPIs recognise an associated risk of developing benign fundic gland polyps. We found 5 systematic reviews in this area. The evidence confirms there may be an association between taking PPIs and fundic gland polyps, enterochromaffin-like hyperplasia and gastric cancer. However, there is evidence to suggest that *H pylori* infection has a role in these conditions, which may be a confounding factor. No association was seen between PPIs and colorectal cancer (in 1 review) or with corporal atrophy or metaplasia (in 2 reviews).

Fracture

Risk of fracture is recognised in SPCs for all PPIs. Four systematic reviews consistently found an association between PPI treatment and fractures, including spine and hip fractures.

Other adverse effects

Gastric atrophy was identified as an adverse event associated with PPIs in 1 systematic review. The SPC for rabeprazole notes no increase in atrophic gastritis with up to 8 weeks of treatment. However, the SPC for omeprazole notes that atrophic gastritis is also associated with *H pylori* infection; the presence of *H pylori* infection may therefore be an important confounding factor to consider against the finding of increased gastric atrophy.

All SPCs recognise that dose adjustment is necessary for people with severe liver disease, which is consistent with the finding in 1 systematic review of hepatic encephalopathy in people with liver dysfunction who were taking a PPI. SPCs for PPIs also already recognise the risk of hypomagnesaemia, which was reported in 2 systematic reviews.

Impact on the guideline – long term safety of PPIs

The guideline recommends PPIs in several sections:

- interventions for uninvestigated dyspepsia
- interventions for GORD
- interventions for peptic ulcer disease

- interventions for functional dyspepsia
- *H pylori* testing and eradication.

The guideline additionally recommends an annual review for people who need long-term management of dyspepsia symptoms, and encouraging them to try stepping down or stopping treatment (unless there is an underlying condition or comedication that needs continuing treatment).

The data on PPI safety are from retrospective observational studies and so the observed effects may be influenced by both recognised and unrecognised confounding factors that are often not completely accounted for in analyses. Recognised confounding factors include adherence to the drug being studied, concomitant use of other drugs, smoking status, and presence of obesity or diabetes. These studies may also be affected by indication bias, in which the adverse event may be associated with the underlying condition, and by protopathic bias, in which treatments are taken for an early manifestation of an undiagnosed condition. Overall, the evidence was considered to be insufficient to affect current recommendations to use PPIs, which are an effective treatment for conditions needing gastric acid suppression.

We have shared these findings with the MHRA, which will consider this evidence in their ongoing monitoring of the safety of medicines, alongside data from other sources such as case reports, non-clinical studies, data from clinical trials, and other published and unpublished data. If any SPCs are updated, we will again consider the impact on the guideline.

H pylori eradication

The guideline currently recommends first-and second-line regimens for *H pylori* eradication. To reduce the development of antibiotic resistance, different regimens are recommended depending on the person's previous exposure to antibiotics. Changes in resistance patterns have an important role in determining whether these antimicrobial agents remain appropriate. However, we found no information on *H pylori* resistance patterns in the UK.

We checked reports from ESPAUR for any information that could impact on the currently recommended antimicrobial regimens for *H pylori* eradication. The 2018 report covered data for the years 2013 to 2017 and the 2017 report covered 2012 to 2016, but neither mentioned treatment of *H pylori*.

The 2016 report had no information on *H pylori* resistance; however, it highlighted a UK-based study that surveyed clinical pathology accreditation laboratories in England. This indicated that few laboratories routinely perform culture and antibiotic sensitivity testing for *H pylori*. The 2015 report, which covered 2010 to 2014 also had no information on *H pylori* resistance.

Public Health England (PHE) has indicated that there is increasing anecdotal evidence of difficult-to-treat *H pylori* infections. However, without laboratory evidence of emerging resistance patterns, it is not possible to update the guideline in this area at this time. PHE will amend their guidance on first-and second-line eradication regimens so that NICE and PHE have consistent recommendations.

We agreed to amend wording so that we specify levofloxacin as the recommended quinolone in our guidance on second-line eradication of *H pylori*. This change is consistent with the European Medicine Agency's opinion on the suspension or restrictions of quinolone and fluoroquinolone antibiotics. In the guideline, levofloxacin is recommended when other antibacterial treatments cannot be used:

- as a second-choice option for first-line treatment in people who are allergic to penicillin **and** have previous exposure to **both** clarithromycin and metronidazole
- for second-line treatment in people who have previous exposure to **both** clarithromycin and metronidazole
- for second-line treatment in people who are allergic to penicillin **and** have not had previous exposure to a quinolone.

We are also aware that a preparation of tri-potassium di-citrato bismuth suitable for use in the *H pylori* eradication regimen recommended in the guideline is no longer available in the UK. Several preparations of bismuth subsalicylate remain available for treating symptoms of dyspepsia, although none are specifically licensed for *H pylori* eradication.

Impact on the guideline – H pylori eradication

Overall, we identified no need to update current recommendations on *H pylori* eradication.

Other sections of the guideline

One Cochrane review (Pinto-Sanchez et al. 2017) was considered alongside the evidence

on PPI effectiveness. One Cochrane review (Song et al. 2014) was considered alongside the evidence on PPI safety (see appendix A).

Lan et al. (2014) assessed acupuncture in dyspepsia, concluding: 'The body of evidence identified cannot yet permit a robust conclusion regarding the efficacy and safety of acupuncture for functional dyspepsia'. The guideline does not cover acupuncture for treating dyspepsia, and evidence is currently insufficient to support recommendation development in this area.

One Cochrane review (Boghossian et al. 2017) concluded that in people with mild GORD, on-demand deprescribing may lead to an increase in symptoms such as dyspepsia or regurgitation as well as a reduction in pill burden. Participant satisfaction was lower with on-demand PPIs. This study highlights the difficulties that may be faced when following recommendations to encourage patients on long-term treatment to try stepping down or stopping treatment (unless there is an underlying condition or comedication that needs continuing treatment). However, the guideline committee noted that periodic medication review is an important component of good patient care. Additionally, dyspepsia was considered to have a relapsing and remitting nature, so taking medication would not be necessary during periods of remission. Thus, the current recommendations remain valid despite the apparently conflicting evidence from this Cochrane review.

The final identified Cochrane review (Garg et al. 2015) found 'considerable uncertainty' in the balance of benefits versus harms of laparoscopic fundoplication compared with long-term treatment with PPIs. Because of a lack of alternative options, this finding is unlikely to impact on current guidance to offer fundoplication to people with confirmed reflux who do not want or cannot tolerate long-term treatment with PPIs.

Ongoing research

We checked for relevant ongoing research; of the ongoing studies identified, 1 study was assessed as having the potential to change recommendations; therefore we plan to check the publication status regularly, and evaluate the impact of the results on current recommendations as quickly as possible. This study is:

- Helicobacter Eradication Aspirin Trial (HEAT).

Intelligence gathered during surveillance

Views of topic experts

Topic expert feedback indicated ongoing concerns about the long-term safety of PPIs, which led to the focused search in this area, as discussed in the previous sections.

Related NICE guidance

The issue of PPI safety is also relevant to other NICE guidelines. However, there is no immediate impact on these other guidelines:

- Gastro-oesophageal reflux disease in children and young people: diagnosis and management (NICE guideline NG1)
- Acute upper gastrointestinal bleeding in over 16s: management (NICE guideline CG141)
- Barrett's oesophagus: ablative therapy (NICE guideline CG106).

Other sources of information

We considered all other correspondence received since the guideline was published. We received notification that a preparation of bismuth used for *H pylori* eradication was no longer available in the UK, as noted in the section on H pylori eradication.

Views of stakeholders

We consulted on this surveillance decision because we propose to not update this guideline.

In this consultation, in addition to expressing views on the proposal we requested that stakeholders highlight:

- any large observational studies of PPI safety that would be missed by the searches, for example:
  - studies published after the search dates for the included systematic reviews
  - studies addressing adverse events that were not the focus of existing systematic reviews
- any information on *H pylori* resistance patterns in the UK
- any information suggesting a need to update a section of the guideline that was not a focus of this surveillance.

Overall, 5 stakeholders commented. Two stakeholders represented government organisations, 1 represented a medical society, and 2 represented the healthcare industry.

Three stakeholders provided a general response that they had no comments. Two stakeholders disagreed with the decision to not update the guideline and provided feedback on the question seeking additional information on PPI safety, *H pylori* resistance, or sections of the guideline that were not a focus of this surveillance.

The issues raised by stakeholders were use of a medical device for people whose dyspepsia is inadequately treated by PPIs and use of serum assays for diagnosing *H pylori* infection.

Evidence provided in support of the medical device was not eligible for consideration in surveillance (reviews not using systematic reviewing methods). Evidence provided in support of serum assays for *H pylori* was either ineligible for consideration in surveillance (not providing statistical data for diagnostic accuracy) or was consistent with current recommendations.

See appendix B for full details of stakeholders' comments and our responses.

Equalities

No equalities issues were identified during the surveillance process.

Editorial amendments

During surveillance of the guideline we identified the following points in the guideline that

should be amended.

In recommendation 1.9.9, where 'a quinolone' is recommended, this will be amended to 'levofloxacin', which more accurately reflects the guideline committee's considerations and clinical practice.

In recommendation 1.9.11, information on duration and frequency of treatment will be added for consistency with other recommendations in this section.

Overall decision

After considering all evidence and other intelligence and the impact on current recommendations, we propose that no update is necessary.

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