Guidance for Safe and Effective use of Proton Pump Inhibitors (PPIs)

Background and RISKS associated with PPIs

- PPIs are one of the most frequently prescribed drugs, but are often prescribed without an appropriate indication and continued indefinitely without review.
- Overprescribing of PPIs has financial and potentially adverse clinical consequences.[1]
- **Long term use of PPIs** has been linked to **serious adverse effects** such as:[2]
    - ***Clostridium difficile* infection**[3]
    - **Increased risk of bone fractures**[4]
    - **Increased mortality in older patients**
    - **Acute interstitial nephritis**
    - **Hypomagnesaemia**[5]
    - **Vitamin B_{12} deficiency**
    - **Rebound acid hypersecretion syndrome**
    - **Community acquired pneumonia**
    - **Hyponatraemia**
- **PPIs should be initiated ONLY where clearly indicated and for the shortest duration that is appropriate, in order to minimise adverse effects**.[2] By stopping or reducing treatment when appropriate, the risk of serious adverse effects will be reduced.

PPIs and *Clostridium difficile* infection

- Evidence suggests that PPI use is associated with an increased risk of *Clostridium difficile* infection,[3] so stop or review PPIs in patients with or at high risk of *Clostridium difficile* infection.[6]
- **Risk factors** for *Clostridium difficile* infection include advanced age, antibiotic use (most commonly the broad spectrum antibiotics: clindamycin, cephalosporins, quinolones and co-amoxiclav), underlying morbidity, inflammatory bowel disease and hospitalisation.[7] Other medication considered as risk factors for *Clostridium difficile* infection are laxatives, enemas, enteral nutrition, anti-motility drugs, anti-emetics, corticosteroids and chemotherapy.
- Also take into account current incidence of *Clostridium difficile* infection in the community.

PPIs and increased risk of bone fractures – MHRA 2012

- There is evidence of a modest increased risk of fracture with PPIs especially if used in high doses and over long durations (>1year). Two meta-analyses suggest the risk of fracture is increased by 10-40% above baseline.[4] PPIs should be used with caution in patients with other risk factors for bone fractures.
- Treat patients at risk of osteoporosis according to the current clinical guidelines and ensure they have an adequate intake of vitamin D and calcium.[4]

PPIs and hypomagnesaemia – MHRA 2012

- Severe hypomagnesaemia has been reported infrequently in patients treated with PPIs, although the exact incidence is unknown.[5]

- For patients expected to be on prolonged treatment, and especially for those who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and repeat measurements periodically during treatment.[5]

PPIs and Clopidogrel: interaction – MHRA 2010

- In 2009, the MHRA advised that concomitant use of a PPI with clopidogrel should be avoided unless considered essential. In 2010, the MHRA updated guidance advised against the use of clopidogrel and omeprazole or esomeprazole to avoid an interaction but did not support extending this advice to other PPIs.[8]
- Concomitant use of clopidogrel and omeprazole or esomeprazole should be discouraged unless considered essential. The potential risk of a slight reduction in efficacy of clopidogrel should be weighed against the potential gastrointestinal benefit of the PPI.[8]

PPIs and very low risk of Subacute cutaneous lupus erythematosus (SCLE) - MHRA 2015[9]

- SCLE can occur weeks, months, or years after exposure to a PPI.
- If a patient treated with a PPI develops lesions, especially in sun-exposed areas of the skin and it is accompanied by arthralgia:
    - Advise them to avoid exposing the skin to sunlight
    - Consider SCLE as a possible diagnosis
    - If SCLE is suspected discontinue the PPI and seek specialist advice if needed[10]

Guidance for safe and effective prescribing

Diagnosis, referral and management should follow NICE CG184 2014 Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management:[11] https://www.nice.org.uk/guidance/cg184

On first presentation with dyspepsia symptoms:

- Offer lifestyle advice, e.g. healthy eating, weight reduction and smoking cessation. (ALL patients should be given this advice)
    - Advise the patient to avoid alcohol, coffee, chocolate and fatty foods, or food/drink which exacerbates symptoms. Having the main meal 3-4 hours before bedtime, avoiding large meals and raising the head of the bed may also help.
    - Address psychosocial triggers, such as stress.
- Review medication for possible causes of dyspepsia. These include calcium channel blockers, nitrates, theophyllines, bisphosphonates, corticosteroids, or NSAIDs.[11]
- Manage dyspepsia with antacid and/or alginate therapy. H2- receptor antagonists (e.g. ranitidine) can be tried if antacids have failed.
- Community pharmacists should offer initial and ongoing help for people with symptoms of dyspepsia.[11]
- Patients undergoing endoscopy should be free from medication with either a PPI or an H2-receptor antagonist for a minimum of 2 weeks. [10]
- If patient needs endoscopy stop NSAID use.[11]

If a PPI is indicated:

- **Short term treatment** (usually 4-8 weeks depending on the indication, but see NICE Guideline CG184[11]) should be prescribed.
- Clearly document the indication in the patient record.
- Prescribe **low acquisition cost PPIs** in preference to high acquisition cost PPIs:
    - **Omeprazole capsules are first line choice** in the Barnsley Joint Formulary (omeprazole tablets have a significantly higher cost), **lansoprazole capsules are the second line choice** and pantoprazole tablets can be used if the patient is on medication which interacts with either of the above.[12]

- Lansoprazole orodispersible tablets should be used **only** for patients with swallowing difficulties or enteral tubes.[12]
- Rabeprazole is non-formulary in Barnsley.[12]
- The use of **esomeprazole is restricted**. It can be used for patients who remain symptomatic on omeprazole 40mg, but the patient must be reviewed regularly. It is restricted for use in Savary-Miller Grade IV oesophagitis (Los Angeles Grade D) or above, or when complicated by GI bleeding. There is no evidence that one PPI is more effective than another at equivalent doses.[13] Newer PPIs offer no advantage in terms of clinical efficacy.[13] Over the last 3 years the total esomeprazole items in Barnsley has increased from 900 items a month to over 1400 items a month (ePACT October 2017).
- There are slight variations in licensed indications, drug interactions and cautions for individual PPIs. Please consult the product SPC for further information at https://www.medicines.org.uk/emc/

- Offer H2-receptor antagonist therapy if the response to the PPI is inadequate.[11] Some patients will be prescribed a PPI without having tried a H2-receptor antagonist previously.

- **REVIEW PPI TREATMENT on completion of the course, where 'stepping down' to the lowest effective dose required to control symptoms, using PPIs 'as required' or discontinuation of treatment, should be considered.**
  - Note: some patients with severe oesophagitis won't respond to the first choice PPI so it may be necessary to trial a different PPI.[11]

Review long term PPIs:

- Offer an **annual review** to people needing PPIs for long term management of dyspepsia. Consider 'stepping down' to the lowest effective dose required to control symptoms, using PPIs 'as required' or stopping treatment where appropriate.[11]
  - **Step-down**: Options include reducing the daily PPI dose, giving doses on alternate days or using PPIs 'as required'.[14]
  - **Stop-PPI**: Gradual dose reduction of PPI treatment can help prevent rebound acid hypersecretion. Alternate day therapy for 1-2 weeks before discontinuation is another option.[2]
  - Advise returning to **self-treatment with antacid and/or alginate therapy** where required, either prescribed or purchased over-the-counter.[2] These can be used first-line to control symptoms with 'as required' PPI use.[14] They can also help reduce rebound acid hypersecretion when reducing PPI therapy.
  - Patients should be counselled on managing **rebound acid hypersecretion** on reducing PPI use.
- Document the decision in the patient's notes.
- There are data to support stopping PPIs in patients who have been taking them long term. A trial published in 2006 showed that discontinuation of PPIs was successful in 27% of long term PPI users.[15] However GORD patients had more difficulty discontinuing PPIs than non-GORD patients.
- Avoid long term, frequent dose, continuous antacid therapy in functional dyspepsia (it only relieves symptoms in the short term rather than preventing them). [11]

Indication for long term PPI use:

There are indications where the benefits of long term PPI use outweigh the risks:[2,11,14]

- Barrett's Oesophagus
- Oesophageal stricture dilation
- Severe oesophagitis complicated by past strictures, ulcers or haemorrhage
- Previous peptic ulcer with major haemorrhage
- Zollinger- Ellison Syndrome
- Gastroprotection for NSAID treatment in high risk patients:[16]
  - Aged 65 years or older
  - History of gastroduodenal ulcer, GI bleeding, or gastroduodenal perforation

- Co-medication that increases the likelihood of upper GI adverse events e.g. aspirin (even low- dose), anticoagulants, corticosteroids and antidepressants (SSRIs, venlafaxine or duloxetine)
- Serious comorbidity, such as cardiovascular disease, hepatic or renal impairment (including dehydration), diabetes, or hypertension
- Using the maximum recommended dose of an NSAID
- Requirement for prolonged NSAID use (including people with osteoarthritis or rheumatoid arthritis of any age, and those with chronic low back pain who are 45 years of age or older)

This list is not exhaustive. Assess patients on an individual basis and review regularly. Always review PPI therapy when NSAIDs stopped.

Development Process

This guidance has been subject to consultation and endorsement by the Gastroenterologists in Barnsley and was ratified by the Area Prescribing committee on 11th April 2018

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