Bulletin 92 | May 2015

PrescQIPP Community Interest Company

Safety of long term proton pump inhibitors (PPIs)

Over £116 million is spent annually on all proton pump inhibitors (PPIs) in England (ePACT Dec 14). QIPP projects in this area focus on reducing prescribing of PPIs for cost and safety reasons by adhering to current guidance including stepping-down therapy where appropriate.

Recommendations

- Offer lifestyle advice to manage dyspepsia, e.g. healthy eating, weight reduction and smoking cessation, and managing symptoms by avoiding causes and using treatment only when needed at the lowest effective dose for the shortest duration. Community pharmacists should offer initial and ongoing help for people with symptoms of dyspepsia.[1]
- Review medication for possible causes of dyspepsia. These include calcium channel blockers, nitrates, theophyllines, bisphosphonates, corticosteroids, or non-steroidal anti-inflammatory drugs (NSAIDs). In people needing referral for endoscopy, suspend NSAID use.[1]
- Prescribe low acquisition cost PPIs in preference to high acquisition cost PPIs, for the shortest duration (and clearly documented indications). There is no evidence that any PPI is more effective than another.[2] Offer histamine H2-receptor antagonist (H_2RA) therapy (e.g. ranitidine) if the response to the PPI is inadequate.
- Offer an annual review to people needing long term management of dyspepsia. Encourage them to try stepping down to the lowest effective dose needed to control symptoms, or 'as needed'/'on demand' to manage their own symptoms, or stopping treatment completely where appropriate. Advise returning to self-treatment with antacid and/or alginate therapy where required, either prescribed or purchased over-the-counter (OTC),[1] especially if rebound symptoms occur.
- Avoid long term, frequent dose, continuous antacid therapy in functional dyspepsia (it only relieves symptoms in the short term rather than preventing them).[1]
- Review long term PPI prescribing to reduce the potential risk of *Clostridium difficile*, bone fractures[3] and to a lesser extent the risk of higher mortality in older patients,[4] acute interstitial nephritis, community acquired pneumonia, hypomagnesaemia, vitamin B_{12} deficiency and rebound acid hypersecretion.[5] There may be indications where the benefits of long term PPI use outweigh the risks (e.g. Barrett's Oesophagus, oesophageal stricture dilation, and gastroprotection for NSAID treatment). Assess on an individual basis and review regularly.

Background

Five PPIs are currently available in the UK. Differences between the PPIs in terms of clinical efficacy and safety are minimal. Lansoprazole, omeprazole, pantoprazole, rabeprazole and esomeprazole are available generically (see Chart 1 for cost comparison.)[6] Multiconstituent products (which can also contain an NSAID) are also available (Vimovo®, Axorid®).[7,8]

Some of the costs associated with treating dyspepsia are decreasing, but overall the use of treatments are increasing. As a result the management of dyspepsia continues to have potentially significant costs to the NHS.[1]

There are growing concerns about long term treatment with PPIs. In recent years, observational studies have indicated associations with a variety of serious adverse effects from long term PPI use. The best evidence is for *Clostridium difficile* infection and increased risk of bone fractures in susceptible populations. The data for the risk of pneumonia is inconsistent. There is no strong evidence yet for an association between the other adverse effects and long term use of PPIs. However they are biologically plausible. They include acute interstitial nephritis, hypomagnesaemia, vitamin B_{12} deficiency, rebound acid hypersecretion syndrome[9] and increased mortality in older patients.[4] There may be indications where the benefits of long term PPI use outweigh the risks – assess on an individual basis. However, reviewing and reducing therapy will not only reduce prescribing costs but will potentially increase patient safety.

Dyspepsia and Gastro-oesophageal reflux disease (GORD)

Dyspepsia has no universally accepted definition but is any symptom of the upper GI tract present for 4 weeks or more, including upper abdominal pain or discomfort heartburn, acid reflux, nausea or vomiting.[1] It is often related to eating and may be accompanied by belching.[6] GORD is a chronic condition where gastric juices from the stomach (usually acidic) flow back up into the oesophagus. It can be severe or frequent enough to cause symptoms or damage to the oesophagus (for example oesophagitis) or both. It can lead to abnormality of the cells in the lining of the oesophagus (Barrett's oesophagus) which is itself considered the most important risk factor for oesophageal adenocarcinoma, the incidence for this has increased considerably in the past decade.[1]

PPIs are effective short term treatments for gastric and duodenal ulcers. They are also used in combination with antibacterials for the eradication of *Helicobacter pylori*. Following endoscopic treatment of severe peptic ulcer bleeding, high dose PPIs reduce the risk of rebleeding and the need for surgery. PPIs are also used for prevention (gastroprotection) and treatment of NSAID-associated ulcers. In patients who need to continue NSAID treatment after an ulcer has healed, the dose of PPI should not normally be reduced because asymptomatic ulcer deterioration may occur.[7] The prescriber should carry out a risk assessment of using the NSAID plus a PPI in individual patients with the option of using another form of regular analgesia, e.g. regular full dose paracetamol, if the use of an NSAID is contra-indicated. NSAID treatment should be regularly reviewed and the PPI stopped when the NSAID is stopped if being used for gastroprotection.

A PPI can be used to reduce the degradation of pancreatic enzyme supplements in patients with cystic fibrosis. They can also be used to control excessive secretion of gastric acid in Zollinger-Ellison syndrome, where high doses are often required.[7]

National guidance

The current National Institute for Health and Care Excellence (NICE) clinical guideline (CG) on dyspepsia and GORD was published in 2014.[1] It should be consulted for detailed guidance, particularly on peptic ulcer disease and on surveillance for people with Barrett's oesophagus as this is outside the scope of this bulletin. A summary of key recommendations from NICE CG184 for dyspepsia and GORD are given below.[1]

Offer simple lifestyle advice, including advice on healthy eating, weight reduction, smoking cessation and avoiding factors associated with dyspepsia such as alcohol, coffee, chocolate and fatty food. Having the main meal well before bedtime (3-4 hours beforehand) and raising the head of the bed may help some people. Provide people with educational materials to support their care, or access to them.

Review medications for possible causes of dyspepsia, e.g. calcium antagonists, nitrates, theophyllines, bisphosphonates, corticosteroids, NSAIDs.[1]

Particular care is needed in those presenting with 'gastric alarm features'. These include bleeding, dysphagia (difficulty swallowing), recurrent vomiting or unintended weight loss. Urgent endoscopic investigation is required in these instances.[7] Refer patients immediately (same day) to a specialist, suspending NSAID use where appropriate.[1] Do not initiate PPIs at least 14 days before endoscopy as

they may mask the symptoms of gastric cancer. For pre-existing treatment, stop PPIs 14 days before endoscopy (as a washout period).[6]

When initiating treatment, offer people with dyspepsia a PPI for 4 weeks and for GORD a full-dose PPI for 4 or 8 weeks, considering the acquisition cost of the PPI. For severe oesophagitis, offer a PPI for 8 weeks taking into account the person's preference and clinical circumstances (for example, tolerability of the PPI, underlying health conditions and possible interactions with other medicines). If symptoms recur after initial treatment, offer a PPI at the lowest effective dose for the shortest duration. Discuss with people how they can manage their own symptoms by using treatment only when they need it. Offer H_2RA therapy (e.g. ranitidine) if the response to the PPI is inadequate.[1]

Offer people who need long term management of dyspepsia an annual review of their condition. Encourage such people to try stepping down or stopping treatment. This involves reducing their use of prescribed medication: by using the lowest effective dose, by trying 'as needed' use when appropriate and by returning to self-treatment with antacid and/or alginate therapy (unless there is an underlying condition or co-medication that needs continuing treatment).[1] This may be for gastroprotection when prescribed with an NSAID, in conditions such as osteoporosis for example (see NICE CG177 and PrescQIPP bulletin on NSAID risks and choices).

Alternatively if a person's severe oesophagitis fails to respond to maintenance therapy carry out a clinical review. People who have had dilatation of an oesophageal stricture should remain on full-dose PPI therapy long term.[1]

Evidence base

There is an overall lack of randomised, controlled trials (RCTs) on the long term use of PPIs and adverse effects. Observational studies form the majority of available data. This type of study has limitations as they can only suggest an association, not establish a cause and are prone to confounding. For example treatment plans may be changed depending on the individual patient's risk factors, tolerability or treatment response. Therefore observed differences in outcomes may be due to heterogeneity (differences) among the patients, not only the different treatments.[4]

Adverse effects of PPIs are usually mild and reversible and include headache, diarrhoea, nausea, abdominal pain, constipation, dizziness and skin rashes. However long term PPI treatment may be associated with uncommon, serious adverse effects such as:[6,9]

1. *Clostridium difficile* infection.
2. Increased risk of bone fractures.
3. Acute interstitial nephritis (AIN).
4. Increased mortality in older patients.
5. Community acquired pneumonia.
6. Hypomagnesaemia.
7. Vitamin B12 deficiency.
8. Rebound acid hypersecretion syndrome.

The following sections give further details about each of the specific adverse effects.

1. *Clostridium difficile* infection (CDI)

A National Prescribing Centre (NPC) Rapid Review in 2010 highlighted two US studies investigating PPI use and CDI. The Rapid Review stated PPIs have undoubted benefits in certain GI conditions. However gastric acid suppression has been a suggested risk factor for CDI, since gastric juices that have a greater acidity are more effective at killing the bacterium and neutralising its toxin then less acidic gastric juices.[10]

A study published in 2005 based on the UK General Practice Research Database (GPRD), found that people with CDI were about three times more likely to have been prescribed a PPI in the previous 3 months than people without CDI.[11] Other studies found that hospital inpatients taking daily PPIs were over 70% more likely to develop CDI than non-users. Patients who received more frequent PPIs had more than a doubling of this risk.[10,12] The results may have important public health implications, as they suggest that compared with no acid suppression at least one additional case of nosocomial CDI should be expected for every 533 patients who receive a daily PPI, after controlling for other risk factors. Although this seems a relatively large Number-Needed-to-Harm (NNH), the magnitude of exposure is large. They found, similar to others' estimates, 60% of patients received acid-suppressive therapy. In the absence of an RCT several important steps are recommended. Firstly ensure patients receive the least intense acid-suppressive therapy appropriate for their clinical condition, secondly minimise exposure in low risk, non-critically ill patients for stress ulcer prophylaxis and thirdly ensure prophylactic medications are not continued beyond discharge.[12] PPIs are often prescribed without a clear indication and CDI is more common in those exposed to PPIs than those who are not exposed. PPI use concurrent with treatment for CDI was associated with a 42% increased relative risk of recurrent infection 15 to 90 days afterwards. Risks were highest among those older than 80 years and those receiving antibiotics not targeted to CDI. Although C. difficile spores are acid-resistant, vegetative forms are susceptible to acidity. Elevated gastric pH levels may allow or facilitate conversion from spore to vegetative forms of C. difficile in the upper GI tract. Other mechanisms include impairment of leukocytes and other immune responses and antimicrobial properties of PPIs.[13] Older age, antibiotics after diagnosis of CDI and use of PPIs are the most frequent risk factors for recurrence.[14]

2. Increased risk of bone fractures

The NPC Rapid Review highlighted one RCT which did not show an increased risk of fractures. However, trials assessing fracture risk have generally only lasted for 6 months. Even a modest increase in risks mean a substantial amount of patient harm at a population level when the risk factor is widely experienced. The data suggest the choice of PPI (lower cost versus higher cost) and use of any PPIs in individual patients should be carefully reviewed. Benefits of PPIs may not justify the risks for many users.[10]

Two meta-analyses suggest the risk of fractures increased by 10-40% above baseline, especially if PPIs are used in high doses and over long durations (>1 year). This was observed mainly in elderly patients, other factors may contribute to the increase in fracture risk.[3,15,16] PPIs have been shown to inhibit gastric proton pumps at physiologic concentrations, but the inhibition of osteoclast proton pumps is much less pronounced. It is not necessary to treat patients to the point of neutralising acid to resolve reflux symptoms, so the recommendation is to choose drug doses thoughtfully with consideration of the desired therapeutic outcome.[15] The evidence for a modest association between PPI use and risk of fractures, is not seen with H_2RA exposure. The association is most consistent for spine fractures. Clinicians who are concerned about patients with high fracture risk may wish to consider the option of H_2RAs instead of PPIs.[16]

The results of a small-scale RCT suggest that even taking a PPI for 8 weeks might alter calcium and bone metabolism, in the elderly especially the obese and males.[17] A systematic review found a significant association between regular use of PPIs and risk of hip fractures. This risk increases with a longer duration of PPI use in post-menopausal women with a history of smoking, which is known to inhibit calcium absorption. So smoking and PPI use may have a synergistic effect on fracture risk mediated by impaired calcium absorption. The estimated absolute risk associated with PPI use is 5 hip fractures per 10,000 person years. This suggests potential for a high burden of fractures across the population attributable to PPIs. The increased risk of hip fracture was no longer evident after PPI use had stopped for two years. This highlights the importance of carefully evaluating the need for long term, continuous use of PPIs particularly among individuals with a history of smoking.[18]

3. Acute interstitial nephritis (AIN)

AIN is a rare complication of PPI use.[5] Medications account for 60% of cases of AIN, including antibiotics, NSAIDs, diuretics and PPIs. All of the PPIs have been implicated.[9] The main limitation is that data is restricted to case reports. The standard treatment involves early diagnosis of AIN, withdrawing the causative drug, administering steroids depending on the degree of acute kidney injury and clinical assessment.[9,19] This avoids the development of chronic kidney disease and its consequences. PPIs can often be replaced with lifestyle measures, antacids and ranitidine (which is very rarely associated with AIN).[19]

4. Higher mortality in older patients

A study in 2013 found that long term PPI use may be associated with higher mortality in older patients. The risk appears to increase with higher doses, but RCTs including frail, older patients are needed. PPIs may interfere with absorption of nutrients, exacerbating the risk of malnutrition common in older people. Recent findings suggest that PPIs may be inappropriately prescribed in 50% to 80% of patients admitted to geriatric and internal medicine wards. In the meantime physicians need to use caution and balance benefit and harm in long term prescribing of high-dose PPIs.[20]

5. Community Acquired Pneumonia (CAP)

A small but significant increase in hospitalisation from pneumonia due to PPI exposure has been found. The estimated 30-day fatality rate among older people hospitalised with CAP was 18%. The widespread use of PPIs means that many people could be affected.[21]

It has been suggested that the greatest risk of pneumonia is within 48 hours of starting PPI therapy. This is inconsistent with bacterial overgrowth as a mechanism of colonisation. PPIs take 5 days to reach steady state but bacterial overgrowth due to PPI use would require substantially longer periods of exposure. GORD may itself be a risk factor for pneumonia (from stomach content aspiration) and is a confounding factor. No specific interventions are recommended in clinical practice.[5]

6. Hypomagnesaemia

A literature search for hypomagnesaemia with long term PPI use found only case reports, no systematic reviews or observational studies. A case report of 2 patients, concludes that long term PPI users who are highly adherent to treatment can eventually deplete the total body magnesium stores and present with severe complications of hypomagnesaemia.[22] In another case report the authors suggest that PPIs should be considered in the differential diagnosis of hypomagnesaemia and this side effect may not be as rare as initially thought.[23]

A Drug Safety Update states that severe hypomagnesaemia has been infrequently reported in patients treated with PPIs – the exact incidence is unknown. Some cases occurred after 3 months of PPI therapy, but most occurred after 1 year of treatment. Hypomagnesaemia can result in serious conditions: fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia. Initially they can be subtle and overlooked as a result. In most cases hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI. Consider measuring magnesium levels before starting PPI treatment and repeat measurements periodically during prolonged treatment, especially in those taking PPIs with digoxin or diuretics.[3]

7. Vitamin B_{12} deficiency

At present there is little evidence to suggest vitamin B_{12} monitoring is required routinely in all patients on PPIs. However the effects of long term treatment should be monitored.[24]

A review of PPI side effects found mixed results from studies of PPI use and vitamin B12 deficiency. Data supporting an association are from small, non-randomised retrospective studies or case reports with

varying methods of B_{12} level measurements. Prospective studies demonstrated B_{12} levels within normal range. This suggests any risk of decreased vitamin B_{12} levels is clinically insignificant and a normal diet will safeguard against a clinically relevant deficiency when taking a PPI. The elderly and malnourished may be at a higher risk, as they are more likely to have borderline baseline levels.[9]

8. Rebound acid hypersecretion syndrome (RAHS)

A 2013 systematic review by Lødrup et al included 3 patient studies and 2 studies with asymptomatic volunteers. They concluded that RAHS following PPI therapy induces reflux-like symptoms in asymptomatic volunteers, but the significance of this in patient populations is unclear. The studies in patients with reflux disease found no evidence of symptomatic RAHS, but these studies were hampered by methodological weaknesses such as retrospective or uncontrolled designs and inadequate run-in, treatment or follow-up periods. Therefore it cannot be concluded if symptoms related to RAHS are clinically important in patients or lead to reuptake of acid-suppressive medication. Well-designed studies should include patients without acid-related disorders, such as functional dyspepsia. They should investigate the direct association between RAHS, symptom generation and risk of restarting acid-suppressive therapy after withdrawal.[25]

An earlier systematic review found no strong evidence for a clinically relevant increase in acid production after withdrawal from PPI therapy. This review included 2 patient studies and 6 studies with healthy volunteers. However RAH needs to be considered in patients treated with a PPI for a longer duration, who previously experienced rapid recurrence of symptoms after PPI withdrawal. Clinicians may wish to consider a gradual step-down of PPI treatment in these patients.[26] Otherwise switching to alternate day therapy for 1-2 weeks before discontinuation is another option. RAH does not appear to be a clinical problem in patients taking PPIs on demand.[5]

Minimising adverse effects

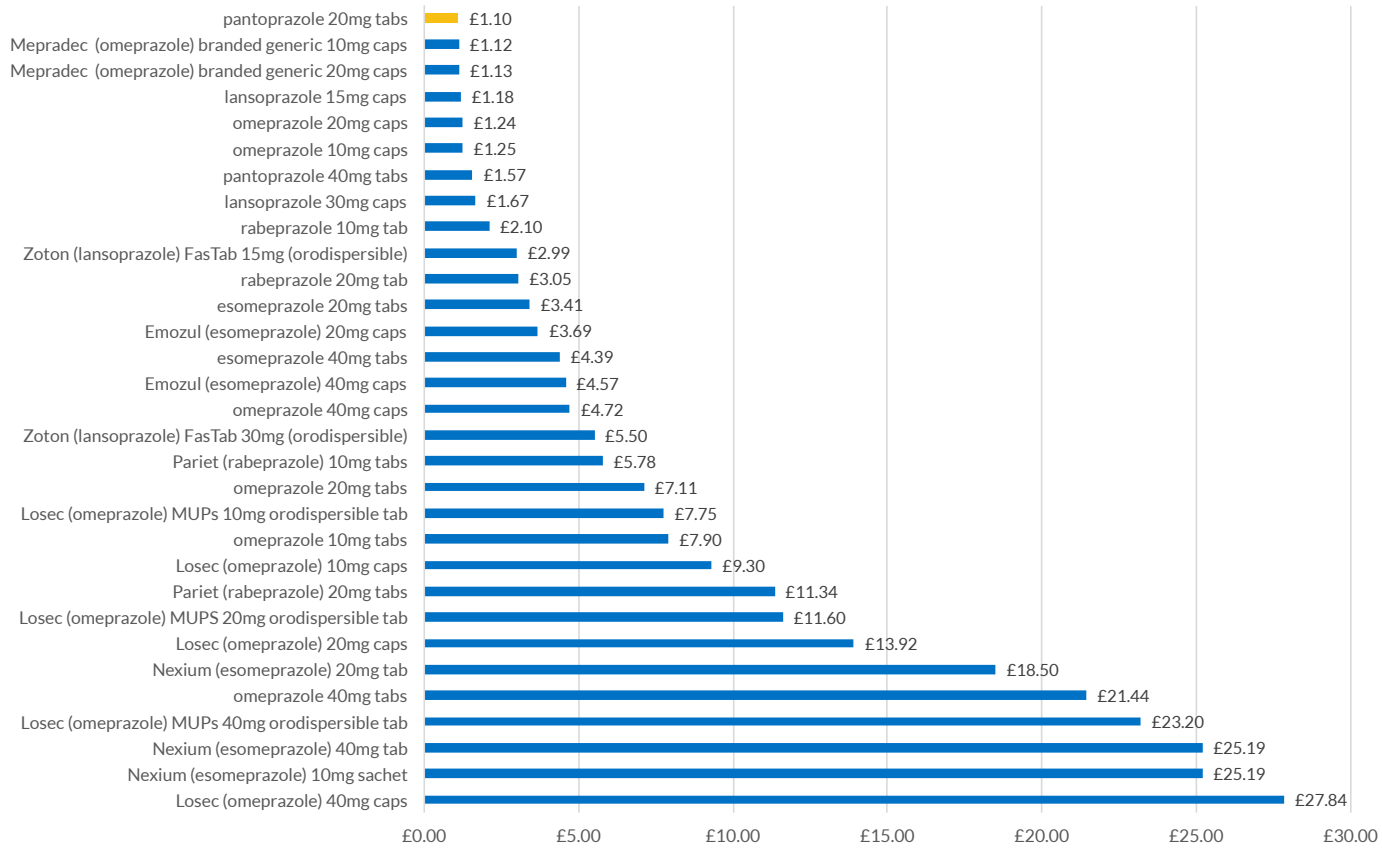
In summary, to minimise all potential adverse effects, prescribe PPIs for clearly documented indications only and for the shortest duration. Strong data are lacking to support the risk of most of the adverse effects described above. However, it is advisable to exercise caution in the elderly and in patients with other risk factors for *C. difficile* infection or bone fractures,[9] which have the strongest association with PPI use.

A Drug Safety Update in 2010 advised against use of clopidogrel and omeprazole or esomeprazole to avoid an interaction, unless considered essential. This was in light of new evidence, which did have some methodological limitations but cast some doubt on the clinical relevance of interactions between clopidogrel and all PPIs. There is a possibility of reduced inhibition of platelet aggregation whether the two medicines are given simultaneously or 12 hours apart.[27]

Cost

Chart 1, on the following page, shows costs for 28 days treatment (one daily dose) for generic and brands of PPIs. Generic pantoprazole 20mg tablets are the preferred option at £1.10 for 28 tablets. Nexium® products (esomeprazole) and Losec® MUPS (omeprazole) are the non-preferred options, due to their comparatively high cost.

Chart 1. Cost comparison of generic PPIs with brands for 28 days[7,8]



If prescribing of PPIs reduced by 30%, this would **save £35 million in England over 12 months** (ePACT Oct- Dec 2014). **This equates to £61,468 per 100,000 patients.**

Summary

- Only prescribe PPIs for clearly documented indications. Strong data supporting the risk of adverse effects are lacking. However, exercise caution in the elderly and in patients with other risk factors for C. difficile infection or bone fractures.[10]
- PPIs should be initiated for a short duration depending on the indication and careful consideration should be given before prescribing long term PPIs.
- People taking long term PPI treatment should be maintained on the lowest dose necessary to control symptoms and reviewed periodically to assess symptom resolution and treatment tolerability.
- Careful consideration should be given to stepping-down therapy in line with NICE guidance.[1]
- If prescribing of PPIs reduced by 30%, this would save more than £35 million over 12 months.

References

1. NICE Clinical Guideline 184. Dyspepsia and gastro-oesophageal reflux disease. September 2014. www.nice.org.uk/guidance/cg184/resources/guidance-dyspepsia-and-gastrooesophageal-reflux-disease-pdf Accessed 05.09.14.
2. All Wales Therapeutics and Toxicology Centre. All Wales Proton Pump Inhibitor and dyspepsia resource pack. Material to support appropriate prescribing of Proton Pump Inhibitors across Wales. April 2013. www.awmsg.org/docs/awmsg/medman/All%20Wales%20Proton%20Pump%20Inhibitor%20and%20Dyspepsia%20Resource%20Pack.pdf Accessed on 27.06.14.
3. Drug Safety Update. Proton pump inhibitors in long term use. 2012; 5 (9): A1-A2. www.mhra.gov.uk/home/groups/dsu/documents/publication/con149785.pdf Accessed 17.06.14.
4. NICE Eyes on Evidence. Use of proton pump inhibitors (PPIs) on discharge from hospital and 1-year mortality in older patients. 2013, Issue 52, p7-9. Available via www.evidence.nhs.uk/ Accessed 27.06.14.
5. Vakil N. Prescribing proton pump inhibitors: is it time to pause and rethink? Drugs 2012; 72 (4): 437- 445.
6. NICE Clinical Knowledge Summaries (CKS). Dyspepsia – unidentified cause. http://cks.nice.org.uk/dyspepsia-unidentified-cause Accessed 17.06.14.
7. Joint Formulary Committee. British National Formulary (app). 67th Edition. London: BMJ Publishing Group and Royal Pharmaceutical Society. November 2014 app update.
8. MIMS app November 2014. Haymarket Publishing, London.
9. Abraham NS. Proton pump inhibitors: potential adverse effects. Current Opinion in Gastroenterology 2012; 28 (6): 615-620.
10. NPC Rapid Review. Increased risk of C. difficile infections and of fractures: two more good reasons to review PPI prescribing. 3 June 2010. http://webarchive.nationalarchives.gov.uk/20110927231944/http://www.npc.nhs.uk/rapidreview/?p=1494 Accessed 26.02.15.
11. Dial S, Delaney JAC, Barkun AN, Suissa S. Use of gastric acid-suppressive agents and the risk of Community-Acquired Clostridium difficile-associated disease. JAMA 2005; 294: 2989-2995.
12. Howell M, Novack V, Grgurich P et al. Iatrogenic gastric acid suppression and the risk of nosocomial Clostridium difficile infection. Arch Intern Med 2010; 170 (9): 784-790.
13. Linsky A, Kalpana G, Lawler EV et al. Proton Pump Inhibitors and risk for recurrent Clostridium difficile infection. Arch Intern Med 2010; 170(9): 772-778.
14. Abou Chakra CN, Pepin J, Sirard S, Valiquette L. Risk factors for recurrence, complications and mortality in Clostridium difficile Infection: a systematic review. PLoS ONE 2014 Jun 4;9(6): e98400.
15. Eom CS, Park Sm, Myung SK et al. Use of acid-suppressive drugs and risk of fracture: a meta-analysis of observational studies. Ann Fam Med 2011; 9: 257-267.
16. Kwok CS, Yeong JK, Loke YK. Meta-analysis: risk of fractures with acid-suppressing medication. Bone 2011; 48(4): 768-776.
17. Jo YK, Cho YK, Ahn SB et al. Effect of proton pump inhibitor on bone metabolism in old age. Gastroenterology 2012; 142 (5) Suppl. 1 S(463).
18. Khalilli H, Huang ES, Jacobson BC et al. Use of proton pump inhibitors and risk of hip fracture in relation to dietary and lifestyle factors: a prospective cohort study. BMJ 2012; 344: e372. www.bmj.com/content/344/bmj.e372.long Accessed 15.08.14.
19. Ray S, Delaney M, Muller AF. Proton pump inhibitors and acute interstitial nephritis. BMJ 2010; 341:c4412. Accessed at http://www.bmj.com/content/341/bmj.c4412 Accessed 15.08.14.
20. Maggio M, Cosonello A, Ceda GP et al. Proton Pump Inhibitors and risks of 1-year mortality and rehospitalisation in older patients discharged from acute care hospitals. JAMA Intern Med 2013; 173(7): 518-523. http://archinte.jamanetwork.com/article.aspx?articleid=1657756 Accessed on 15.07.14.

21. Roughead EE, Ramsay EN, Pratt NL et al. Proton pump inhibitors and the risk of antibiotic use and hospitalisation for pneumonia. MJA 2009; 190: 114-116.
22. Cundy T, Dissanayake A. Severe hypomagnesaemia in long term users of proton-pump inhibitors. Clinical Endocrinology 2008; 69: 338-341.
23. Kuipers MT, Thang HD, Arntzenius AB. Hypomagnesaemia due to use of proton pump inhibitors – a review. The Netherlands Journal of Medicine 2009; 67(5): 169-172.
24. Oh S. Proton Pump Inhibitors uncommon adverse effects. Australian Family Physician 2011; 40(9): 705-708.
25. Lødrup AB, Reimer C, Bytzer P. Systematic review: symptoms of rebound acid hypersecretion following proton pump inhibitor treatment. Scandinavian Journal of Gastroenterology 2013; 48: 515-522.
26. Hunfeld NGM, Geus WP, Kuipers EJ. Systematic review: rebound acid hypersecretion after therapy with proton pump inhibitors. Alimentary Pharmacology & Therapeutics 2007; 25: 39-46.
27. Drug Safety Update. Clopidogrel and proton pump inhibitors: interaction – updated advice. Volume 3, issue 9, April 2010 p4-5.

Additional PrescQIPP resources

Briefing | Data pack | Patient letter, audit

Available here: http://www.prescqipp.info/resources/viewcategory/336-safety-of-long term-ppis

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