All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Safe Use of Proton Pump Inhibitors

February 2018

This document has been prepared by a multiprofessional collaborative group, with support from the All Wales Prescribing Advisory Group (AWPAG) and the All Wales Therapeutics and Toxicology Centre (AWTTC), and has been endorsed by the All Wales Medicines Strategy Group (AWMSG).

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KEY MESSAGES

- Proton pump inhibitor (PPI) use in Wales has continued to increase (by nearly 25% over the last 6 years), with PPI prescribing 14% higher than in England.
- The evidence base around the adverse effects from long-term use of PPIs is increasing.
- Prescribers should only use PPIs for recognised indications and appropriate durations to minimise PPI overuse and the associated increased risk of harm.
- Adverse effects include a greater risk of fractures, hypomagnesaemia and infections, including *Clostridium difficile* infection.
- Older people may be more susceptible to the adverse effects of long-term PPI use.

CONTENTS

1.0 PROTON PUMP INHIBITOR PRESCRIBING

In Wales the prescribing of proton pump inhibitors (PPIs) has risen by nearly 25% over the last six years. Wales has a 14% higher prescribing rate than England, with an estimated 11% of the population receiving monthly PPI prescriptions[1]. In 2016, over £6.5 million was spent on PPIs in primary care in Wales[2]. The PPIs currently available are: esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole[3]. PPIs are generally used to treat common gastrointestinal symptoms, such as dyspepsia, as well as to prevent harm from other medicines, for example, peptic ulcers caused by non-steroidal anti-inflammatory drugs (NSAIDs)[3].

PPIs are generally well tolerated, with a low incidence of adverse effects associated with short-term use. However, there is increasing evidence that long-term PPI use is associated with an increased risk of adverse effects[4]. Some of these adverse effects, such as fractures and *Clostridium difficile* infection, are themselves associated with considerable morbidity and mortality, as well as high treatment costs.

1.1 Managing dyspepsia symptoms before starting PPI therapy

Before starting PPI therapy, people should be given lifestyle advice (Table 1) and encouraged to self-treat with an antacid and/or alginate[4]. This approach is effective in controlling symptoms for many people. A flow diagram detailing the management of dyspepsia is provided within Appendix 1.

Table 1. Lifestyle advice for people with dyspepsia [4]

Advise people with dyspepsia that symptoms may be improved if they:
Lose weight (if the person is overweight)
Stop smoking
Stop or reduce alcohol consumption
Stop or reduce intake of any food or drink associated with worsening symptoms (e.g. fatty foods, coffee, chocolate)
Eat meals at regular times, avoiding large or late meals
Avoid bending over or lying down immediately after eating
Use antacid and/or alginate when necessary for immediate symptom relief after meals and at bedtime
Advise people with reflux symptoms when lying down to:
Avoid meals within 3 to 4 hours of going to bed
Raise the head of their bed by 10 to 20 cm (4 to 8 inches) using blocks under the legs of the bed
Use antacid when necessary and/or alginate for immediate symptom relief at bedtime

1.2 Medicines that cause or increase risk of dyspepsia, gastrointestinal bleeding or ulceration

Certain medicines can cause or increase the risk of dyspepsia, gastrointestinal bleeding or ulceration; these include[4]:

- Antiplatelets e.g. aspirin (including 75 mg)
- Anticoagulants
- Corticosteroids
- NSAIDs
- Antibiotics
- Selective serotonin reuptake inhibitors (SSRIs)
- Bisphosphonates
- Calcium-channel blockers
- Iron
- Nitrates e.g. isosorbide mononitrate
- Nicorandil
- Theophylline and aminophylline
- Others: colchicine, levodopa, digoxin, potassium chloride

Each medicine or medicine group offers a different risk factor for dyspepsia, gastrointestinal bleeding or ulceration. These risks will additionally be influenced by medicine dosage, frequency and co-prescribing, as well as patient factors such as age, lifestyle and co-morbidities. For estimated upper gastrointestinal bleeding risk of different medicines and medicine groups, please see Table 2.

1.3 Short-term PPI prescribing

When defined short-term courses are prescribed, the person's symptoms should be reviewed on course completion and the PPI discontinued as appropriate. Some people may need to have repeated short courses of PPI treatment (2 to 3 times a year) to control their symptoms. Alternatively, others may benefit from taking PPIs on an "as-needed" basis[5].

PPIs can be prescribed in short-term use for indications including[3]:

- treating peptic ulcers (usually a 4 to 8 week course)
- eradicating *Helicobacter pylori* (*H. pylori)* infection (1 to 2 week course in combination with antibiotics)
- treating dyspepsia and gastro-oesophageal reflux disease (GORD) (4 to 6 week course if medication review and lifestyle advice are ineffective):
    - for uninvestigated dyspepsia (continuously for 4 weeks or intermittently to control symptoms)
    - for symptomatic functional dyspepsia, after *H. pylori* eradication (for 4 weeks)
    - for severe GORD (for 4 to 6 weeks before titrating down).

1.4 *Helicobacter pylori* eradication

In adults with dyspeptic symptoms that are persistent or recurrent despite treatment, one option is to test for the presence of *H. pylori,* and eradicate if present[6]. PPIs are an integral part of *H. pylori* eradication regimens[3] and are typically given in combination with antibiotics. Prescribers should refer to local guidance to be informed of the recommended PPIs for their locality. Prescribers should seek further advice from a gastroenterologist if eradication of *H. pylori* is not successful after first- and second-line treatment regimens[6].

1.5 Long-term PPI prescribing

Long-term PPI exposure may lead to adverse effects and should only be used if people have an established clinical need. In people receiving long-term courses the prescriber should clearly document the indication, and the person should be regularly reviewed to assess and check for adverse effects.

PPIs can be prescribed in long-term use for indications including[3]:

- control of excessive acid secretion in people with Zollinger-Ellison syndrome
- prevention and treatment of NSAID-associated ulcers, and/or NSAID-related dyspeptic symptoms
- maintaining remission in severe GORD
- gastroprotection in people with a history of dyspepsia who require aspirin after a cardiovascular or cerebrovascular event
- preventing relapse in people with gastric and duodenal ulcers
- GORD that is refractory to other treatments
- acid reflux disease.

The 2015 WeMeReC bulletin "Proton pump inhibitors" states:
"*the NICE recommendations for using PPIs as maintenance, longer-term, are relatively selective and include severe oesophageal stricture, Barrett's oesophagus, and those requiring gastroprotection when considered at high-risk of GI complications with regular NSAID use*"[4].

1.6 Risk of gastrointestinal bleeding from medicines use

NSAIDs, anticoagulants and antiplatelets cause over a third of hospital admissions due to avoidable adverse drug reactions (ADRs). Gastrointestinal bleeds are implicated in half of the deaths from primary care ADRs[7]. A case series analysis has estimated the incidence rate ratio (IRR) of upper gastrointestinal bleeding in relation to specific medication groups. These medicines, as monotherapies with their associated IRRs, are listed in Table 2[8]. Appendix 2 provides the associated IRRs of these medicines when used in specific combinations.

Table 2. Relative risk of diagnosed upper gastrointestinal bleeding during exposure to specific medicine groups (with corresponding 95% confidence intervals) as monotherapy[8]

Medication group	IRR (95% confidence interval)
Non-selective NSAIDs	4.27 (4.11-4.44)
Corticosteroids	4.07 (3.83-4.32)
Aldosterone antagonists	3.27 (3.06-3.50)
Low-dose aspirin	3.05 (2.94-3.17)
Anticoagulants	3.01 (2.85-3.19)
Cyclooxygenase-2 selective inhibitors	2.90 (2.67-3.15)
Nitrates	2.55 (2.43-2.68)
Selective serotonin reuptake inhibitors	2.06 (1.94-2.18)
Antiplatelet (excluding low-dose aspirin)	1.74 (1.61-1.87)
Gastroprotective agents	1.61 (1.56-1.66)
Calcium channel blockers	1.57 (1.51-1.63)

1.7 Antiplatelets and PPI use

A study of long-term antiplatelet therapy in secondary prevention of vascular disease showed that the severity, case fatality and poor functional outcome of bleeds increase with age. In people aged 75 years and over, most major upper gastrointestinal bleeds are disabling or fatal[9]. PPIs are recommended in older people who are receiving aspirin-based antiplatelet treatment[10].

Because of a probable interaction, the Medicines and Healthcare products Regulatory Agency (MHRA) has advised that the combination of clopidogrel with omeprazole or esomeprazole should be avoided, unless considered essential. Current evidence does not extend this advice to other PPIs[11]. For further details of this interaction and others involving PPIs, refer to the British National Formulary[3] and appropriate summaries of product characteristics.

1.8 Non-steroidal anti-inflammatory drugs and PPI use

Gastrointestinal bleeding and ulceration can occur with NSAID treatment. The risk of serious gastrointestinal side effects varies between individual NSAIDs: piroxicam, ketoprofen and ketorolac are associated with the highest risk, and ibuprofen (up to 1.2 g daily) is associated with the lowest risk[3].

Not all people who are prescribed an NSAID will need gastroprotection to prevent adverse effects[4]. People at high risk of NSAID-induced ulcers, when the NSAID cannot be discontinued, should be prescribed a PPI (at a dose licensed for gastroprotection) to protect against peptic ulceration. The PPI will need to be continued for the duration of the NSAID treatment, and reviewed for discontinuation when the NSAID is stopped[12].

1.9 Other medicines requiring possible PPI use

Some medicines can cause or increase the risk of dyspepsia, gastrointestinal bleeding, or ulceration[4,5]. Any medicine identified to be causing gastrointestinal symptoms of clinical significance should be reviewed. Where appropriate this medicine can be considered for discontinuation and a suitable alternative prescribed. In those circumstances where this is not preferable and it is clinically justified gastroprotection can be considered in the form of a PPI[4].

1.10 PPI choice

Differences between PPIs in terms of clinical efficacy and safety are minimal[12]. No PPI is more effective than another at equivalent doses, and so the National Institute for Health and Care Excellence (NICE) recommends using the least expensive PPI[6]. Branded preparations and alternative formulations, such as dispersible tablets, are less cost effective than standard generic formulations. Unlicensed liquid formulations (specials) are considerably more expensive and should be reserved for hospital specialist initiation. If treatment with one PPI is ineffective, switching to an alternative PPI is a cost-effective therapeutic strategy[13].

2.0 PPI SAFETY

As PPIs have become more widely used, evidence continues to emerge about their safety and the potential for adverse effects. Most of these adverse effects appear to be associated with long-term PPI use. Suspected adverse effects to PPIs should be reported to the MHRA through the Yellow Card reporting scheme.

Most of the evidence for the possible long-term harmful effects of PPIs comes from case reports and observational data. Some studies have calculated the numbers needed to harm (NNH); however, this is not always possible because much of the data around PPI adverse effects are from observational studies[4]. Randomised controlled trials would have a reduced risk of bias, but those conducted to date often have small numbers of patients and are too short to detect rarer events[14]. Therefore, the findings of well-designed observational studies should be considered and are described in this section, including appropriate statistical calculations. It may be that in these studies, patients who need long-term PPIs have worse health overall than the patients with whom they are being compared. Therefore, some information is provided for consideration when prescribing on an individual patient basis rather than stating wide prescribing recommendations.

2.1 Higher mortality

A recent observational study of people taking PPIs showed that their all-cause mortality increased the longer they took them. People who received PPIs for between one and two years had a 50% increased risk of death compared with those who took them for less than a month[15]. An increased risk of death was also associated with the lack of a documented gastrointestinal indication for PPI use[15].

The higher risk of death with PPI use is likely to be mediated by the occurrence of one or more of the adverse events associated with PPI use, for example, osteoporotic fracture, chronic kidney disease, hypomagnesaemia, and *Clostridium difficile* infection. Long-term PPI use should be limited to people who have a clear medical indication and in whom the benefits will outweigh any potential risks[15].

2.2 Fractures

In 2012 the MHRA said there was an increased risk of bone fractures associated with long-term use of PPIs[16]. This was largely based on observational studies suggesting that PPIs may cause a modest increase in the risk of hip, wrist or spine fracture, especially if used in high doses over durations of more than one year. The increased risk was seen mainly in older people[16]. A more recent meta-analysis of 18 observational studies concluded that PPI use modestly increased the risk of any-site fracture (relative risk [RR] 1.33, 95% confidence interval [CI] 1.15 to 1.54). However, there was no determinable difference between short- or long-term use[17].

The possible mechanism for PPI-induced increased fracture risk remains largely unexplained; one proposed theory is the decreased absorption of calcium due to increased pH in the small intestine[18]. However, a causal relationship is yet to be established so other factors could be contributing to the increased risk.

No association between PPI use and osteoporosis has been demonstrated[19]. However, the MHRA recommends that people at risk of osteoporosis who need PPIs should be treated according to current clinical guidelines to ensure they have an adequate intake of vitamin D and calcium[16]. If necessary, they should also receive other preventative therapy, such as bisphosphonates[3].

2.3 *Clostridium difficile* infection

The weight of evidence appears to support an association between PPI use and an increased risk of *Clostridium difficile* infection (CDI)[4]. A MeReC Rapid Review highlighted a large observational study showing that hospitalised patients taking daily PPIs were

over 70% more likely to develop CDI than those not taking PPIs[20,21]. People who already had CDI and were treated with PPIs had a more than 40% increased relative risk of infection recurrence[22].

Although a causal link has not yet been proven, because gastric acid is thought to play a principal role in sterilising the stomach contents entering the digestive tract, it is plausible that raising the pH of the stomach with a PPI may increase the load of pathogenic microbes. However, it is possible that these associations are confounded by other CDI risk factors[4]. These include older age, antibiotic treatment, underlying morbidity, hospitalisation, and history of CDI[23]. Prescribers should consider reviewing the need for, and stopping, PPIs in people with CDI or at high risk of CDI[4,24].

A speculative estimate of the number needed to harm with PPI use has been stated at around 4,000 people at 1 year. For hospitalised patients receiving antibiotics this reduced significantly to 50 people at 1 year after two weeks of admission[25].

2.4 Pneumonia

There is conflicting evidence for an increased risk of community-acquired pneumonia (CAP) with PPI treatment. A meta-analysis from 2010 found an association between PPI use and CAP[26]. A separate study found that this association was particularly strong during the first seven days of PPI treatment[27]. However, a more recent population-based study concluded that any association between the use of PPIs and risk of CAP is likely to be due entirely to confounding factors[28].

Further research is needed into a link between PPI and CAP before the impact on clinical practice can be determined[4]. However, it seems that caution is warranted when prescribing PPIs for older people who are at increased risk of infection and for whom pneumonia may be an important cause of morbidity and mortality, and for people with asthma or chronic obstructive pulmonary disease[29,30].

2.5 Acute interstitial nephritis

Acute kidney injury is a common cause for admission to hospital[31] and acute interstitial nephritis is a common cause of acute kidney injury. An association has been reported between acute interstitial nephritis and PPIs[32,33]. A population-based, cohort, observational study investigated PPIs and the risk of acute interstitial nephritis and acute kidney injury in older people. It showed a higher rate of acute interstitial nephritis (0.32 vs. 0.11 per 1,000 person-years; hazard ratio [HR] 3.00; 95% CI 1.47 to 6.14), and acute kidney injury (13.49 vs. 5.46 per 1,000 person-years; HR 2.52; 95% CI 2.27 to 2.79) in people taking PPIs than among the control group[34].

In acute interstitial nephritis a first option is to immediately discontinue the PPI; spontaneous recovery occurs after withdrawal in most cases[33]. PPIs can often be replaced with lifestyle measures, an antacid and/or alginate treatment, and/or ranitidine (which is very rarely associated with acute interstitial nephritis)[35].

Because PPIs are often co-prescribed with NSAIDs, there is a possibility that the PPI could be overlooked as the causative agent of the acute kidney injury. Any patient presenting with deteriorating renal function who has been prescribed both a PPI and an NSAID should have both medicines reviewed.

2.6 Chronic kidney disease

The results of a cohort analysis suggest an association between PPI use and chronic kidney disease (CKD) without an intervening acute kidney injury[36]. The association of PPI use with CKD suggests that monitoring for acute kidney injury or acute interstitial nephritis in people taking PPIs may not be sufficient to guard against developing CKD and end-stage renal disease[36].

In early 2017, the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency concluded that there is insufficient evidence for a causal relationship between PPIs and incident CKD and progression to end-stage renal disease to warrant an update of the product information or any additional risk minimisation measure. However, future periodic safety update reports should consider any further evidence as it emerges[37].

The possible mechanisms of PPI-related renal injury are poorly evidenced at present and there is a need for a greater understanding of the effects of PPIs on the kidney before any definite recommendations can be made[36]. However, prescribers should be vigilant to these adverse effects and periodically monitor renal function in people taking PPIs long-term.

2.7 Hypomagnesaemia

The MHRA has warned of the risk of hypomagnesaemia with PPI use[38]. Hypomagnesaemia occurs most commonly after one year of PPI treatment. Serious manifestations of hypomagnesaemia – fatigue, tetany, delirium, convulsions, dizziness, and ventricular arrhythmia – can occur, but they may begin insidiously and may be overlooked[38,39].

Routinely monitoring serum magnesium levels in all people taking a PPI is not recommended. However, measuring serum magnesium levels should be considered before prescribing PPIs to people who will be taking them on a long-term basis and particularly to people who will also be receiving digoxin, diuretics or other treatments associated with hypomagnesaemia. Measurements should be repeated periodically during long-term PPI treatment[38]. Magnesium supplementation is the standard treatment for hypomagnesaemia, but in approximately 25% of cases reviewed, supplementation alone did not improve low serum magnesium levels and PPI treatment had to be discontinued[39].

2.8 Vitamin B_{12} deficiency

Gastric acid is needed to cleave vitamin B_{12} from ingested dietary proteins and enable it to be absorbed. Therefore, PPIs, which suppress gastric acid production, may lead to malabsorption of vitamin B_{12}[4,40].

A large case-control study of more than 200,000 people found a significantly (65%) increased risk of vitamin B_{12} deficiency associated with taking PPIs for two or more years[40]. The same study found a 25% increased risk with the use of H_2 receptor antagonists e.g. ranitidine. Further studies are needed to clarify the clinical significance of these associations[4].

Routinely monitoring vitamin B_{12} in all people taking a PPI is not recommended. However, people at particular risk of vitamin B_{12} deficiency include older or malnourished people taking PPIs for more than one year and people taking other medicines that can affect vitamin B_{12} levels, such as metformin[14].

2.9 Cardiovascular events

An association has been observed between PPI use and adverse cardiovascular outcomes in people at high cardiovascular risk[41]. Among patients with GORD, taking a PPI was associated with a 16% increased risk of myocardial infarction[42,43]. This association does not in itself provide proof of causation, and further studies are needed[4]. When appropriate, prescribers should consider reducing PPI doses, or stopping PPI treatment if possible, in people with existing cardiovascular disease and no strong indication for PPI therapy[4,44].

2.10 Subacute cutaneous lupus erythematosus

The MHRA has advised that PPIs are associated with infrequent cases of subacute cutaneous lupus erythematosus which can occur weeks, months or even years after exposure[45]. In most cases, symptoms resolve on stopping PPI treatment[45].

2.11 Cancer

PPI use is associated with increased serum gastrin levels and bacterial overgrowth, resulting in an increased formation of toxic bile salts[46]. Concerns that this may increase the risk of developing gastric cancer have been raised. A recent population-based study considered the risk of developing gastric cancer with long-term PPI use after *H. pylori* eradication treatment. It reported an association of PPIs with an increased gastric cancer risk even after *H. pylori* eradication therapy. The stated adjusted absolute risk difference for excess gastric cancer in PPI use versus non-PPI use was 4.29 per 10,000 person-years (95% CI 1.25 to 9.54). The study identified a dose-response and time-response trend of PPI use and gastric cancer risk[47].

3.0 OPTIMISING PPI USE

In view of the increased evidence about the adverse effects of PPIs, particularly from long-term use, prescribers are encouraged to use PPIs judiciously. Treatment should be given at the lowest effective dose that controls symptoms, and for the minimum period of time. The use of short courses, as-needed doses, and encouraging people to self-treat with antacid and/or alginate therapy should be commonplace unless there is a recognised indication for long-term PPI treatment[14].

3.1 PPI review

After people have completed defined courses, PPIs should be reviewed and discontinued as appropriate. PPIs should be reviewed between 4 and 8 weeks after starting treatment[4]. For people prescribed long-term PPI therapy, NICE recommends that a medicines review of the PPI is done at least annually[6]. A suggested methodology for a PPI review is shown schematically in Appendix 3. A PPI review toolkit is available in Appendix 4, including an algorithm for deprescribing PPI therapy.

Up to 30% of people may be able to stop PPI therapy immediately after the first course without experiencing symptoms[48]. However, rebound hypersecretion (a rise in acid secretion after discontinuing PPI treatment) can occur after courses as short as 8 weeks' duration[49]. This can often lead to an increase in gastrointestinal symptoms, which may be mistaken for disease relapse. The duration of rebound hypersecretion is unknown, but some studies show reflux-like symptoms within 2 weeks, and for at least 4 weeks after withdrawal from PPI therapy[4].

To help limit the occurrence of rebound hypersecretion, the dose of PPI could be reduced gradually and an antacid and/or alginate could be prescribed for at least 2 weeks[4]. If a step-down approach does not adequately control symptoms, treatment could be resumed with the lowest effective dose of PPI, with consideration to future step-down when appropriate. Prescribers should talk with the patient about the options available for stepping down therapy, considering their preferences in developing the step-down plan[48].

General PPI prescribing recommendations
The following points may help to ensure appropriate prescribing of a PPI:

- before a PPI is started, prescribers should consider lifestyle changes and review other medications where possible
- PPIs should only be prescribed in line with clinical guidelines and the reason for starting should be clearly documented
- intermittent courses should be used, typically for 4 to 8 weeks
- all newly initiated PPIs should be reviewed after the first 4 to 8 week course
- a PPI should not be continued as a repeat prescription unless there is a clear indication
- long-term PPI prescriptions should be reviewed at least annually
- long-term care should emphasise patient empowerment by encouraging lifestyle changes and by promoting symptomatic use of antacids and/or alginates and when appropriate using the lowest effective dose of a PPI, ideally in short courses or on an 'as needed' basis
- during PPI withdrawal, a regular antacid and/or alginate therapy should be prescribed for a minimum of 2 weeks to stop rebound acid hypersecretion.

3.2 Healthcare professionals' role in managing PPI use

All healthcare professionals can offer advice and support to people who are prescribed PPIs.

This involvement could include:

- providing people with the patient information leaflet on PPIs (see Appendix 5)
- advising people that PPIs should be taken between 30 minutes and 60 minutes before breakfast
- providing lifestyle advice, for example, on healthy eating, weight loss or stopping smoking
- referring people to their GP if they present with symptoms needing further investigation, or when prescribed medication has not provided adequate symptom relief
- participating in a multidisciplinary audit of PPI prescribing
- community pharmacists advising on over-the-counter medications for relief of gastrointestinal symptoms, including managing the symptoms of indigestion and reflux through the Common Ailments Service
- community pharmacists undertaking medicines use reviews working with local GP practices to focus on patients who have been prescribed long-term PPIs.

4.0 USEFUL RESOURCES

Welsh Medicines Resource Centre:
Bulletin: Proton pump inhibitors

National Institute for Health and Care Excellence:
Clinical Guideline CG184: Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management

Medicines and Healthcare products Regulatory Agency:
Proton pump inhibitors: very low risk of subacute cutaneous lupus erythematosus

Drug Safety Update: Proton pump inhibitors in long-term use: increased risk of fracture

Drug Safety Update: Clopidogrel and proton pump inhibitors: interaction – updated advice

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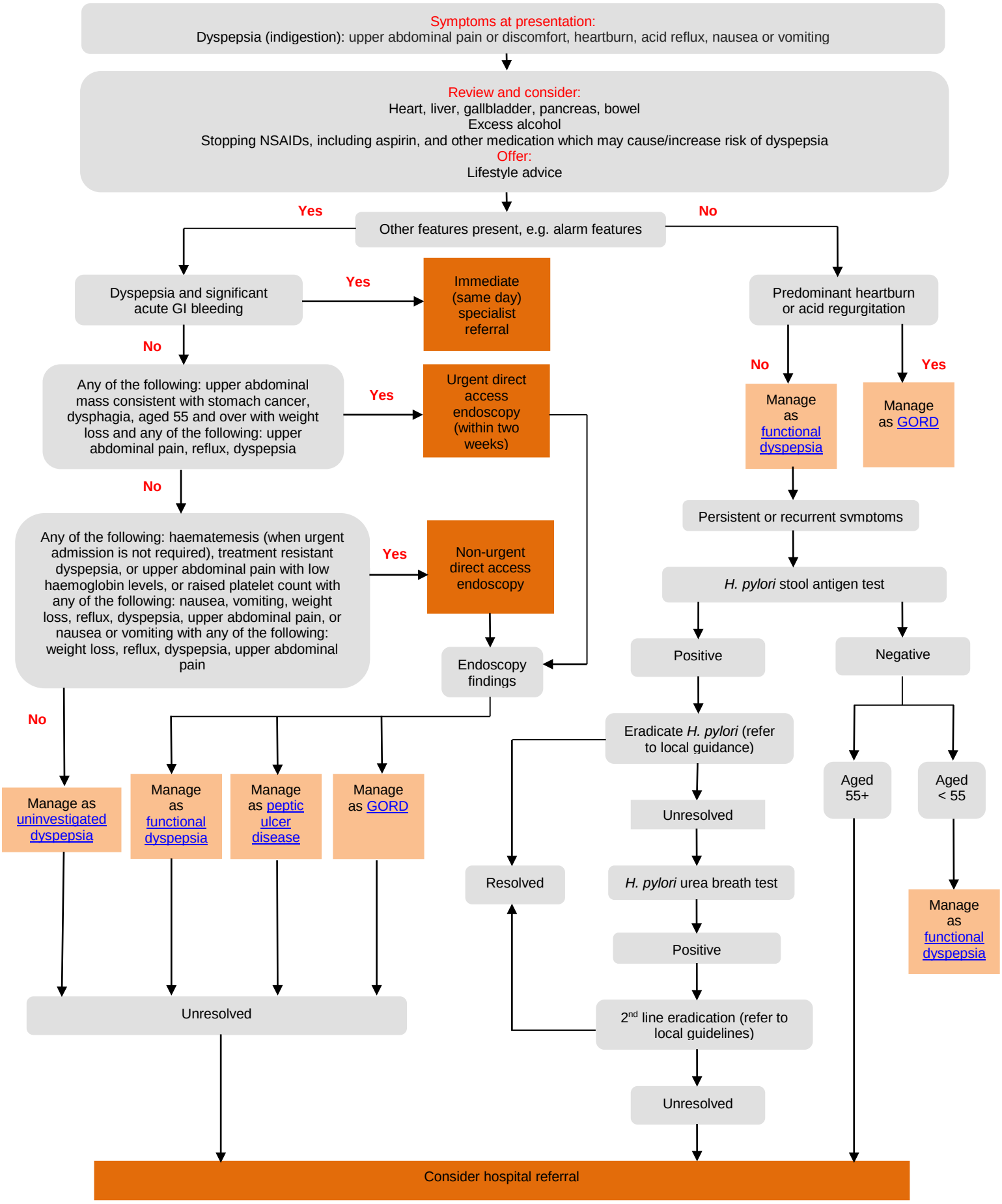
APPENDIX 1: MANAGEMENT OF DYSPEPSIA

(Adapted from NICE Clinical Guideline 184 and original All Wales guidance produced by Dr Miles Allison while working with National Leadership and Innovation Agency for Healthcare, 2008)



APPENDIX 2: RELATIVE RISK OF DIAGNOSED UPPER GASTROINTESTINAL BLEEDING DURING EXPOSURE TO SPECIFIC MEDICINE GROUPS IN MONOTHERAPY AND COMBINATION THERAPY

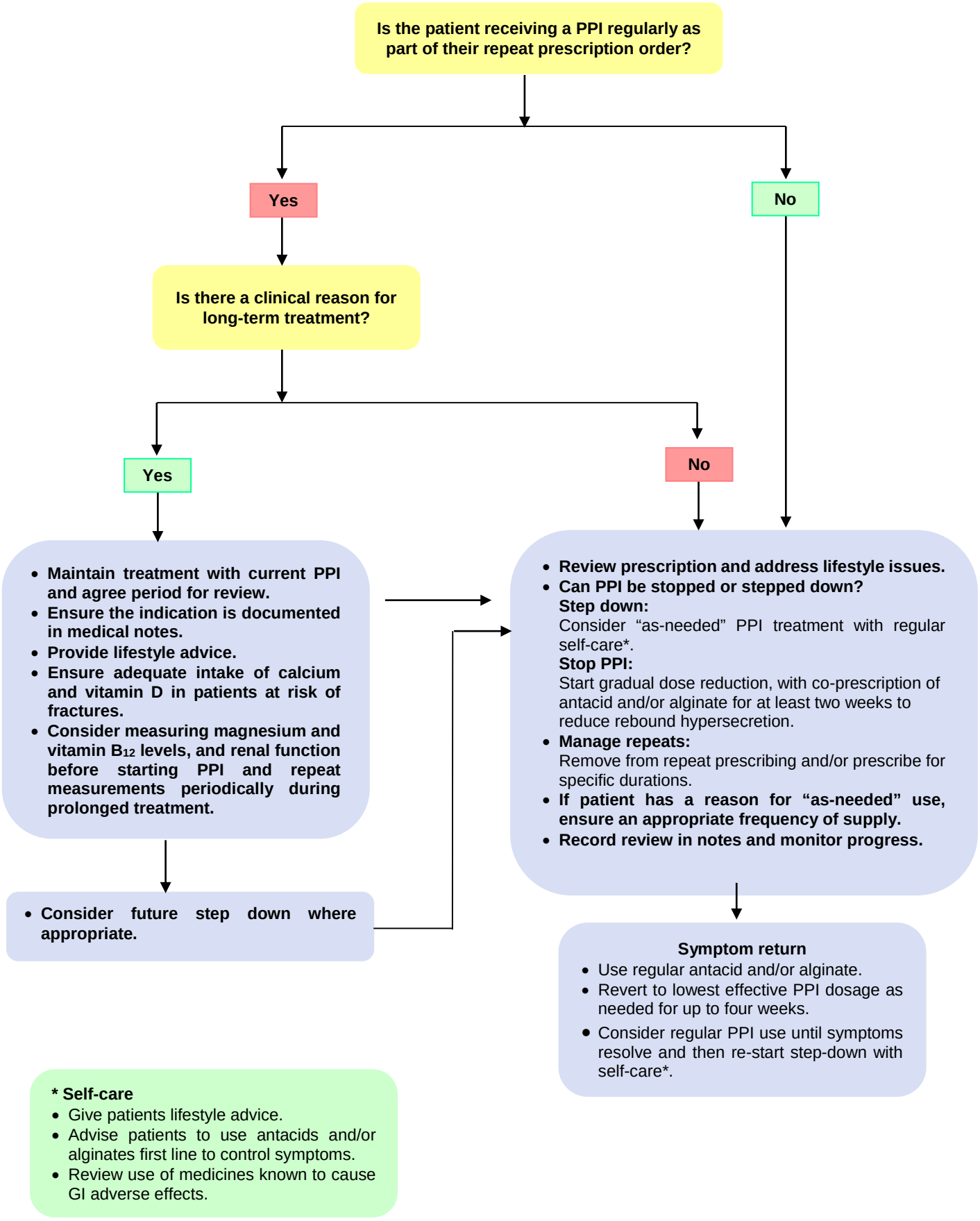
(Taken from Masclee G, Valkhoff V, Coloma P et al. Risk of Upper Gastrointestinal Bleeding from Different Drug Combinations. *Gastroenterology.* 2014;147:784-792.)

Table 2. Relative Risk of Diagnosed UGIB During Exposure to Specific Drug Groups (With Corresponding 95% CIs) in Monotherapy and in Combination With Other Drugs

	Monotherapy		Combination with					
			nsNSAIDs		COX-2 inhibitors		Low-dose aspirin	
Drug groups	n	IRR (95% CI)	n	IRR (95% CI)	n	IRR (95% CI)	n	IRR (95% CI)
No drug[a]	69,664	1.00 (reference)	NA		NA		NA	
nsNSAIDs	3327	4.27 (4.11–4.44)	NA		NA		416	6.77 (6.09–7.53)
COX-2 inhibitors	635	2.90 (2.67–3.15)	NA		NA		131	7.49 (6.22–9.02)
Low-dose aspirin	4733	3.05 (2.94–3.17)	416	6.77 (6.09–7.53)	131	7.49 (6.22–9.02)	NA	
Corticosteroids	1378	4.07 (3.83–4.32)	244	12.82 (11.17–14.72)	40	5.95 (4.25–8.33)	190	8.37 (7.14–9.81)
SSRIs	1793	2.06 (1.94–2.18)	210	6.95 (5.97–8.08)	65	5.82 (4.45–7.62)	401	4.60 (4.09–5.17)
GPAs	5279	1.61 (1.56–1.66)	678	3.90 (3.59–4.24)	95	2.37 (1.92–2.93)	607	2.54 (2.32–2.78)
Aldosterone antagonists	1211	3.27 (3.06–3.50)	76	11.00 (8.63–14.03)	10	4.02 (2.07–7.81)	131	5.01 (4.13–6.08)
Calcium channel blockers	3546	1.57 (1.51–1.63)	363	4.45 (3.98–4.98)	77	3.11 (2.46–3.93)	1123	3.07 (2.86–3.29)
Anticoagulants	1760	3.01 (2.85–3.19)	143	8.69 (7.30–10.35)	21	5.01 (3.21–7.82)	168	6.94 (5.86–8.22)
Antiplatelets (excluding low-dose aspirin)	994	1.74 (1.61–1.87)	87	6.50 (5.19–8.15)	9	1.73 (0.87–3.44)	246	5.49 (4.71–6.41)
Nitrates	2572	2.55 (2.43–2.68)	172	5.82 (4.97–6.82)	49	5.09 (3.79–6.82)	859	3.79 (3.51–4.10)

NOTE. n refers to the number of UGIB events during exposure to specific drug groups (the total number does not add up to 114,835 because of diagnoses of UGIB in "other drug category").
NA, not applicable.
[a]No use of the predefined drugs of interest.

APPENDIX 3: PPI REVIEW: MAIN ACTION POINTS



APPENDIX 4: PPI REVIEW TOOLKIT

Purpose of document

This audit and review has been developed by the Welsh Analytical Prescribing Support Unit (WAPSU). The document is for use in primary care to highlight prescribing and possible patient safety issues with PPIs. It will be available on the AWMSG website.

Background

Quality improvement toolkits have been developed to assist in collating and auditing information. These are produced with reference to evidence-based practice and priorities in Wales. They should be seen as good practice and are intended to improve data quality and help development within the practice.

Improvements in practice will be optimised by multidisciplinary involvement in the audit and team discussion of the results. It is recommended that action plans implemented after this audit are reviewed within six months and that a re-audit is done if possible in 6 to 12 months.

Aims

- To ensure adequate, timely review of all patients receiving a PPI, in line with NICE guidance.
- To minimise the use of high acquisition cost (HAC) PPIs.
- To ensure all patients on long-term PPIs are receiving these for appropriate indications and are being monitored regularly for potential adverse effects.
- To ensure all patients on long-term PPIs have their magnesium and vitamin B_{12} levels, and renal function, monitored.
- To ensure all patients on long-term PPIs have an adequate intake of calcium and vitamin D.

Objectives

- To identify all patients over the age of 18 years receiving long-term PPI and where appropriate, discontinue treatment, reduce the dose or move to ‘as-needed’ administration.
- To identify all patients requiring continued long-term PPI treatment and investigate for adverse effects.
- To identify all patients prescribed HAC PPIs and, where appropriate, stop or switch to a low acquisition cost (LAC) alternative.

Inclusion criteria

- All patients over the age of 18 years receiving:
  - four or more prescriptions (acute or repeat) for a PPI in the last six months.

Exclusion criteria

- Other medical situations where changes to medication would be inappropriate, e.g. chemotherapy, palliative care or a mental health condition.
- Under 18 years of age.
- Patients who need a medicine that has potential to cause gastrointestinal symptoms e.g. NSAID.
- Patients for whom “as-needed” treatment or self-care is not appropriate including those with a history of benign oesophageal stricture, Zollinger–Ellison syndrome or Barrett’s oesophagus.

Prioritisation

All patients prescribed PPIs should be reviewed. However, it may not be appropriate to consider changes to PPI treatment in some patients. In patients where a previous PPI switch has been attempted and was not successful, consider why it was unsuccessful; do these factors still apply?

Preparation

- The auditor should brief practice staff about the review.
- Local community pharmacists should be informed of the review to enable them to provide supporting advice.

The review process

1.0 Identify patients receiving a prescription for a PPI who meet the inclusion criteria

Use the GP clinical database system to search for all patients over the age of 18 years who have:

- been prescribed a HAC PPI in the last six months (acute or repeat prescription)
- a PPI on their repeat prescription (for 28 days or equivalent)
- collected four or more prescriptions for a PPI in the last six months.

Include the generic name and brand name for each medicine in the search. Some computer systems will allow a search on the action group for PPIs to avoid having to enter the medicine names individually.

Table 1. PPIs currently available for prescribing in Wales.

Generic name	Brand name
Esomeprazole	Nexium®
Lansoprazole	Zoton®
Omeprazole	Losec®
Pantoprazole	Protium®
Rabeprazole	Pariet®
Note: remember to include all formulations of PPIs including dispersible tablets and liquid specials	

2.0 Complete the data collection sheet

A sample data collection form for PPI review is included. This can be adapted for local use. Use the patients' medical records to complete these forms.

3.0 Identify patients suitable for review or discontinuation of treatment

Review patients for their continuing need for a PPI, or their suitability for a reducing the dose, "as-needed" use or a switch to a cost-effective alternative (e.g. change from a HAC to a LAC PPI; change to a more cost-effective formulation). Use the flow diagram in Appendix 3.

4.0 Authorise the change

If the review is completed by a non-GP, make sure that each dose reduction, move to "as-needed" management or discontinuation of use is authorised by the patient's own GP or as agreed within the practice.

All reviews and dose changes should be clearly documented in the medical notes. If the change is not authorised, the reason for this should be recorded in the patient's medical notes.

If a patient is to remain on a HAC PPI, record the reason for this in the patient's medical notes.

In every case where the review results in a patient remaining on long-term regular PPIs, record the reason for this in the patient's medical notes. All patients remaining on long-term regular PPI treatment should be counselled on adequate calcium and vitamin D intake, and should have a blood test to monitor serum magnesium levels periodically during treatment, especially patients who will take a PPI concomitantly with digoxin or medicines that may cause hypomagnesaemia (e.g. diuretics).

5.0 Changes to the patient's medical notes
Remove the PPI from repeat prescription for all patients who have not collected a prescription in the last six months. This will prompt a review of symptoms if a request for the PPI is made again.

Add the details of the new medication and changes in dose or directions to the patient's current medication record, ensuring that the non-proprietary (generic) formulation is selected. Document the change in the medical notes.

Remove the medication to be discontinued from the patient's repeat prescribing list on the current medication record.

Document the reasons for all changes in the patient's medical notes, e.g. therapeutic substitution, switch to LAC PPI or removal of high-risk medication such as an NSAID. Ensure the indication for the PPI is documented.

6.0 Notify the patient about changes to their medication
Send an appropriate letter to each patient, informing them of the changes made to their medication.

Alternatively, send a letter inviting a patient to attend for review and discussion, make the changes during a face-to-face consultation.

A Patient Information Leaflet (PIL), "*Stopping Your PPI*" (in English and Welsh), is provided in Appendix 5 and is also available on the AWMSG website.

7.0 Keep a record
Keep a separate record of all patients for whom the PPI dose has been altered or stopped.

8.0 Arrange follow-up monitoring
Arrange a follow-up for some patients, when considered necessary. This could be patients who are particularly concerned.

9.0 At follow-up
Ensure that the patient's symptoms remain controlled, and if they are not discuss an appropriate way forward to regain control.

Record those patients for whom a treatment switch is unsuccessful and all reasons why, to inform future attempts.

10.0 Summary of review
Use the GP practice summary form to review all changes made and to measure the effectiveness of the change programme.

INDIVIDUAL DATA COLLECTION FORM FOR PPI REVIEW

Patient name/ID						
Medicine	**Dose**	**Formulation**	**Last collected**	**What is the dosing schedule?**		
				Regularly	**PRN**	**Unknown**

Who initiated/recommended current PPI? (Tick most appropriate)				
GP	Hospital discharge	Pharmacist	Hospital specialist	Other, please specify
Is the patient on any medication which may interact with the PPIs [most importantly clopidogrel (omeprazole/esomeprazole), warfarin, phenytoin]? Please state				

Indication for PPI? (Tick all that apply)			
Endoscopically confirmed GORD		Uninvestigated dyspepsia	
Endoscopically confirmed peptic ulcer disease		Uninvestigated reflux disease	
Endoscopically negative reflux disease or functional (non-ulcer) dyspepsia		Benign oesophageal stricture	
Zollinger–Ellison syndrome		Barrett's oesophagus	
Uncertain diagnosis, please specify ……		Other, please specify	
Prophylaxis of medicine-induced dyspepsia/ulceration, please specify medicine(s) …… Is there opportunity to review the medicine(s)?			

***H. pylori* testing (if indicated)**			
Has the patient been tested for *H. pylori*?	Yes	No	Unknown
If positive, has this patient had *H. pylori* eradication therapy?	Yes	No	Unknown

Has the patient received lifestyle advice?	Yes	No

Has a previous switch/review been undertaken? If yes, give details	
Has the patient been on another PPI previously? If yes, give details	
Has the dosage of the PPI been changed during the current course of treatment? If yes, give details	

Is the patient on long-term PPIs (> 1 year)?	Yes	No
If yes:		
Has the patient had a PPI review in the last 12 months?	Yes	No
Has the patient had their serum magnesium monitored? (BNF states measurement of serum magnesium concentrations should be considered before and during prolonged treatment with a PPI; important in patients on long-term PPIs who are also receiving digoxin, diuretics or other medicines known to cause hypomagnesaemia)	Yes	No
Has the patient been advised about calcium and vitamin D intake/taking calcium and vitamin D supplements? (Patients at risk of osteoporosis should be treated in line with current guidelines to ensure adequate calcium and vitamin D)	Yes	No
Have the following patient factors been considered: vitamin B_{12} deficiency, renal function, *Clostridium difficile* infection, pneumonia?	Yes	No

Is there a reason for not reviewing PPI in this patient (see possible exclusions)?	
Yes, please specify	No

Has the patient been identified as being able to change from their current PPI/dose to a more suitable alternative?		
Yes	No (continue on current PPI)	Unsure (refer to GP for review)

If yes, what action is the most appropriate for this patient?	
Reduce dose of LAC PPI at regular usage – state dose and directions	
Reduce to LAC PPI at PRN usage with self-care – state dose	
Switch from HAC PPI to LAC PPI – state PPI and dose	

Stop PPI (remove PPI from repeat if not collected for > six months). If long-term PPI, consider reducing PPI dose before stopping or provide acute prescription of an antacid and/or alginate for 2–4 weeks to prevent rebound hypersecretion	
Other, please state	
Proposed action (tick when completed)	
Send letter to patient inviting them to make appointment for review	
Send letter to patient informing them of change, enclose PIL explaining change	
Action to be completed by:	

Completed by ……. **Date.....……**

Reviewed and authorised by (GP sign) …….. **Date.....……**

GP PRACTICE SUMMARY FORM

GP Practice: **Date of Review:**

Pre-review

	Number	Percentage of practice population
PRACTICE LIST SIZE		
Number of patients in the practice identified in step 1		
Number of patients prescribed a LAC PPI		
Number of patients prescribed a HAC PPI		
Number of patients suitable for inclusion in the review		

Documentation

	Quantity	Percentage of patients reviewed
Number of patients with a documented indication for therapy when PPI initially prescribed		
Number of patients with a documented indication for long-term use		
Number of patients who have had lifestyle advice documented in their notes within the last 12 months		
Number of patients who have had a review of their PPI in the last 12 months		
Number of patients on long-term treatment who have had their serum magnesium monitored		
Number of patients with whom calcium and vitamin D intake has been discussed/supplements being taken		

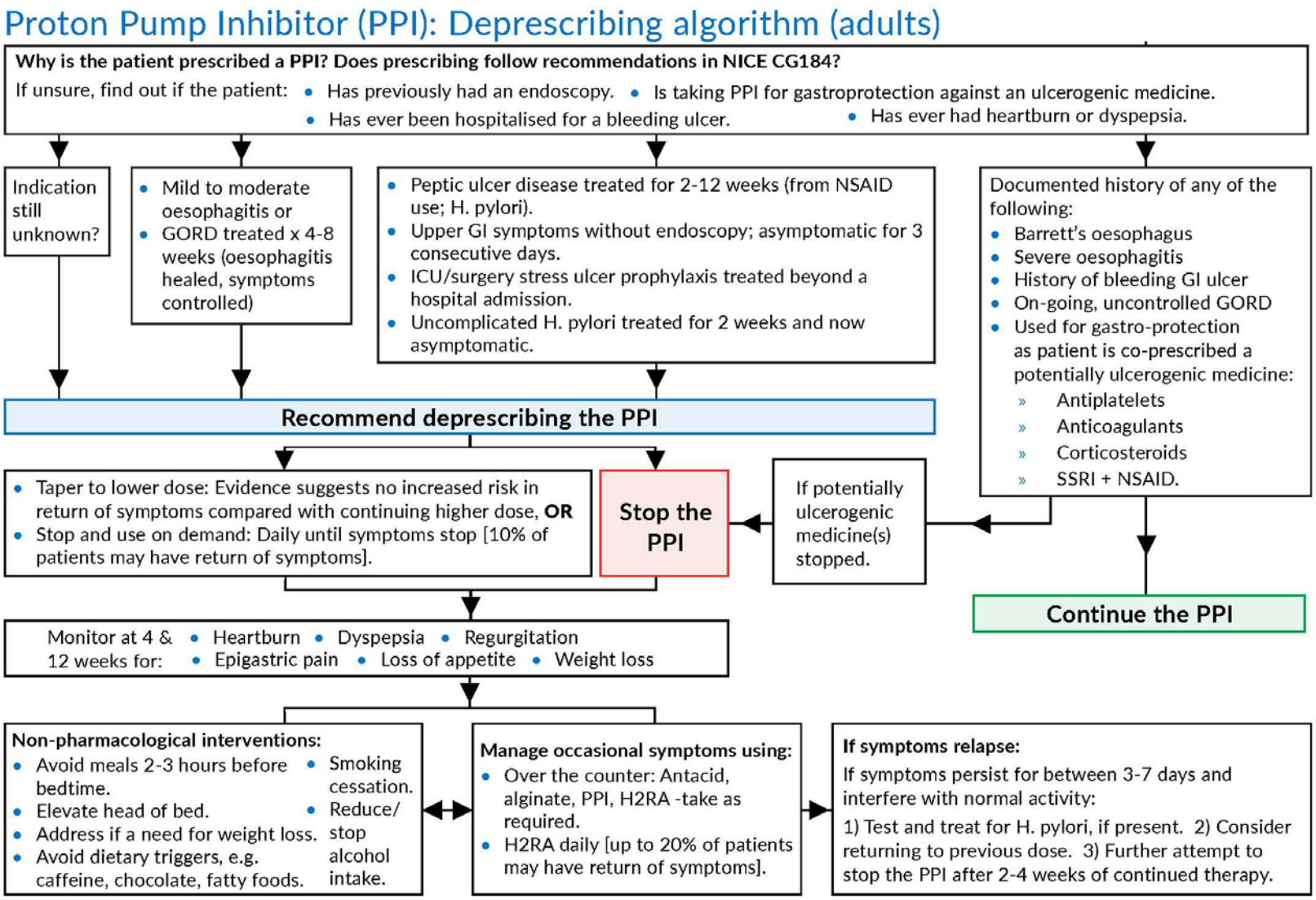
Summary of interventions made

	Quantity	Percentage of patients reviewed
Total number of patients: Dose of LAC PPI reduced		
Total number of patients: LAC PPI reduced to "as-needed" use and self-care		
Total number of patients: Stop PPI (encourage self-care with antacid and/or alginate)		
Total number of patients: Switch from HAC PPI to LAC PPI		

Post review summary

	Number	Percentage of practice population
PRACTICE LIST SIZE		
Number of patients in the practice on a PPI		
Number of patients prescribed a LAC PPI		
Number of patients prescribed a HAC PPI		

PPI DEPRESCRIBING ALGORITHM (TAKEN FROM PRESCQIPP)



APPENDIX 5: PATIENT INFORMATION LEAFLET

(see following page)

- If your symptoms are worse at night, try raising the head of the bed by 10 to 20 cm (4 to 8 inches) using blocks under the legs of the bed.
- Stop or reduce your alcohol consumption. Do not regularly drink more than 14 units per week. If you do drink as much as this, it is best to spread this evenly across 3 days or more. If you feel that you have a problem with alcohol, talk to a healthcare professional.
- Stop smoking. Discuss ways to quit smoking with a healthcare professional or call “Help Me Quit” free on 0800 085 2219.

Q A *What should I do if I develop problems?*

You should talk to a healthcare professional if:

- your symptoms do not get any better, or they get worse
- you experience vomiting, especially if this contains blood or material that looks like coffee grounds
- your bowel movements are dark and sticky
- swallowing is difficult or painful
- you have unexplained weight loss.

Seek urgent medical attention if you experience chest pain that gets worse with or after exercise, or pain that goes into your chin or left shoulder—as this type of pain may be a sign of a heart problem.

To be completed by healthcare professional:

Name of PPI stopped:	
Medicines given to control symptoms (if applicable):	
Name of healthcare professional:	
Contact number:	

PATIENT INFORMATION

STOPPING YOUR PPI

What is a PPI?

PPIs, or proton pump inhibitors, are a group of medicines that are used to reduce the amount of acid that your stomach makes. By lowering the acid level, they can help relieve symptoms and prevent harm.

You will have been given one of the following PPIs:

- esomeprazole
- lansoprazole
- omeprazole
- pantoprazole
- rabeprazole

Q A *Why am I taking a PPI?*

Your healthcare professional will talk with you about why a PPI might be helpful and how long you should take it for. This will depend on why you are taking it, because PPIs can be used for lots of different reasons.

Q A *How long should I take my PPI for?*

To start with, you may be given a PPI for 4 weeks. If your symptoms continue then you may be given another 4-week course.

Many people find that after 4 to 8 weeks of taking a PPI their symptoms are better. After this time you should stop taking the PPI.

Q A *Why should I stop my PPI treatment?*

Your healthcare professional has decided that you no longer need to take a PPI. This will help prevent any side effects that can be caused by long-term PPI treatment. Unwanted side effects of long-term PPI treatment include increased risk of fractures, infections, and low magnesium.

If you are unsure why your PPI is being stopped, or you would like to discuss this further, then ask a healthcare professional. You should only be taking PPIs long-term if there is a definite need, which your healthcare professional has discussed with you.

Q A *How will I stop my PPI?*

Your healthcare professional will usually recommend one of three options for stopping your PPI. These are:

1. Stop taking the PPI

You may be advised to stop taking your PPI, either straightaway or when your current supply is finished, and take an antacid and/or alginate if you still have symptoms. An antacid neutralises the acid in your stomach, and an alginate prevents acid flowing into your oesophagus (food pipe).

2. Take PPI only when needed

You may be advised to take your PPI only when you have symptoms. When the symptoms are relieved (often after a few days) you would then stop taking the PPI.

3. Reduce PPI dose

If you have taken your PPI for several months, and particularly if you have been taking a high dose, your healthcare professional may reduce your PPI dose for a few weeks before stopping it.

Q A *What if my symptoms come back?*

Some people find that when they stop taking their PPI, their symptoms return and may even seem worse than before they started treatment. This is because if you take a PPI for more than a few weeks, your stomach will try to increase its ability to make acid. This means that for a while after you stop taking your PPI, the acid levels in your stomach may be higher than before you started treatment.

Your healthcare professional may give you an antacid and/or alginate. If needed, these can help to control your symptoms until your acid levels return to normal. Alternatively, you may be given a medicine known as an H_2-receptor antagonist, such as ranitidine, which works in a similar way to a PPI but has fewer long-term side effects.

If you have symptoms when you stop taking your PPI and you have not been offered any other medicine, or if you think the medicine you've been given is not working, you should talk to a healthcare professional.

Symptoms can sometimes come back again, possibly after several months. If this happens, you should talk to a healthcare professional.

Q A *What can I do to help?*

Lifestyle advice for helping with symptoms:

- Keep to a healthy weight.
- Avoid food and drink that make your symptoms worse, such as spicy or fatty foods, chocolate, coffee, cola drinks, orange juice.
- Eat meals at regular times.
- Avoid large or late meals and avoid bending over or lying down immediately after eating.
- Avoid medicines that can make symptoms worse, for example, some painkillers. Ask a healthcare professional which medicines are best for you to take.

- Os yw eich symptomau'n waeth yn y nos, ceisiwch godi pen eich gwely 10 i 20cm (4 i 8 modfedd) gan ddefnyddio blociau o dan goesau'r gwely
- Stopiwch neu lleihewch faint o alcohol rydych yn ei yfed. Peidiwch ag yfed mwy na 14 uned yr wythnos yn rheolaidd. Os ydych chi'n yfed gymaint â hyn, mae'n well ei wasgaru'n gyfartal ar draws 3 neu fwy o ddiwrnodau. Os ydych yn teimlo bod gennych broblem gydag alcohol, siaradwch â gweithiwr gofal iechyd proffesiynol.
- Rhowch y gorau i ysmygu. Trafodwch ffyrdd i roi'r gorau i ysmygu gyda gweithiwr gofal iechyd proffesiynol, neu ffoniwch "Helpa Fi i Stopio" am ddim ar 0800 085 2219.

C
A

Beth ddylwn ei wneud os caf broblemau?

Dylech siarad â gweithiwr gofal iechyd proffesiynol:

- os nad yw eich symptomau'n gwella, neu eu bod yn gwaethygu
- os ydych yn chwydu, yn arbennig os yw'n cynnwys gwaed neu ddeunydd sy'n edrych fel gronynnau coffi
- os yw eich carthion yn dywyll a gludiog
- os yw llyncu'n anodd neu'n boenus
- os byddwch yn colli pwysau heb esboniad

Ceisiwch sylw meddygol ar frys os cewch boen yn y frest sy'n gwaethygu gyda neu wedi ymarfer corff, neu boen sy'n mynd i mewn i'ch gên neu'ch ysgwydd chwith - gan y gall y math hwn o boen fod yn arwydd o broblemau'r galon.

I'w lenwi gan weithiwr gofal iechyd proffesiynol:

Enw'r PPI a stopiwyd:	
Meddyginiaethau a roddwyd i reoli symptomau (os yn berthnasol):	
Enw'r gweithiwr gofal iechyd proffesiynol:	
Rhif cyswllt:	

GWYBODAETH I GLEIFION

STOPIO EICH ATALWYR PWMP PROTON (PPI)

Beth yw PPI?

Grŵp o feddyginiaethau a ddefnyddir i leihau faint o asid y mae eich stumog yn ei greu yw PPI, neu atalwyr pwmp proton. Drwy ostwng lefel yr asid, gallant helpu i liniaru symptomau ac atal niwed.

Byddwch wedi derbyn un o'r PPI canlynol:

- esomeprazole
- lansoprazole
- omeprazole
- pantoprazole
- rabeprazole

C
A

Pam fy mod yn cymryd PPI?

Bydd eich gweithiwr gofal iechyd proffesiynol yn siarad â chi ynglŷn â pham y gallai PPI fod yn ddefnyddiol ac am faint o amser y dylech ei gymryd. Bydd hyn yn dibynnu ar pam eich bod yn ei gymryd, oherwydd gellir defnyddio PPI am lawer o wahanol resymau.

C
A

Am faint ddylwn i gymryd fy PPI?

I ddechrau, efallai y rhoddir PPI i chi am 4 wythnos. Os bydd eich symptomau'n parhau yna efallai y rhoddir cwrs 4 wythnos arall i chi.

Bydd llawer o bobl yn teimlo bod eu symptomau'n well wedi 4 i 8 wythnos o gymryd PPI. Wedi hyn dylech stopio cymryd y PPI.

CA

Pam ddylwn i stopio fy nhriniaeth PPI?

Bydd eich gweithiwr gofal iechyd proffesiynol wedi penderfynu nad oes angen i chi gymryd PPI mwyach. Bydd hyn yn helpu i atal unrhyw sgîl-effeithiau y gellir eu hachosi gyda thriniaeth PPI hirdymor. Mae sgîl-effeithiau nas dymunir triniaeth PPI yn cynnwys perygl cynyddol o doresgyrn, heintiau a lefelau isel o fagnesiwm.

Os nad ydych chi'n siŵr pam fod eich PPI yn cael ei stopio, neu os hoffech drafod hyn ymhellach, yna holwch weithiwr gofal iechyd proffesiynol. Dylech ond bod yn cymryd PPI yn hirdymor os oes angen penodol, y bydd eich gweithiwr gofal iechyd proffesiynol wedi'i drafod gyda chi.

CA

Sut fyddaf yn stopio fy PPI?

Fel arfer bydd eich gweithiwr gofal iechyd proffesiynol yn argymell un o dri opsiwn ar gyfer stopio eich PPI. Y rhain yw:

1. Stopio cymryd y PPI

Efallai y cynghorir chi i stopio cymryd eich PPI, naill ai ar unwaith neu pan fydd eich cyflenwad presennol yn dod i ben, a chymryd gwrthasid a/neu alginad os byddwch yn dal i gael symptomau. Mae gwrthasid yn niwtraleiddio'r asid yn eich stumog, ac mae alginad yn atal asid rhag llifo i'ch oesoffagws (pibell fwyd).

2. Cymryd PPI dim ond pan fo angen

Efallai y cynghorir chi i gymryd eich PPI dim ond pan gewch symptomau. Pan fydd y symptomau'n lleddfu (yn aml ar ôl ychydig ddyddiau) byddwch yn peidio cymryd y PPI.

3. Lleihau dos PPI

Os ydych wedi bod yn cymryd eich PPI am nifer o fisoedd, ac yn enwedig os ydych wedi bod yn cymryd dos uchel, efallai y bydd eich gweithiwr gofal iechyd proffesiynol yn lleihau eich dos PPI am ychydig wythnosau cyn ei stopio'n llwyr.

CA

Beth os bydd fy symptomau'n dychwelyd?

Mae rhai pobl yn gweld bod eu symptomau'n dychwelyd a'u bod hefyd fel petaent yn waeth na chyn iddynt ddechrau ar y driniaeth pan fyddant yn stopio cymryd eu PPI. Mae hyn yn digwydd oherwydd os byddwch yn cymryd PPI am fwy nag ychydig wythnosau bydd eich stumog yn ceisio cynyddu ei gallu i greu asid. Golyga hyn y gallai'r lefelau asid yn eich stumog fod yn uwch na chyn i chi ddechrau eich triniaeth am ychydig amser ar ôl chi stopio cymryd eich PPI.

Efallai y bydd eich gweithiwr gofal iechyd proffesiynol yn rhoi gwrthasid a/neu alginad i chi. Os bydd angen, gall y rhain helpu i reoli eich symptomau hyd nes y bydd eich lefelau asid yn dychwelyd i'r lefel arferol. Neu efallai y cewch feddyginiaeth a elwir yn wrthweithydd derbynnydd H_2, megis ranitidine, sy'n gweithio mewn modd tebyg i PPI ond gyda llai o sgîl-effeithiau hirdymor.

Os cewch symptomau pan fyddwch yn stopio cymryd eich PPI, ac nad ydych wedi cael cynnig unrhyw feddyginiaeth arall, neu eich bod yn meddwl nad yw'r feddyginiaeth a roddwyd i chi yn gweithio, dylech siarad â gweithiwr gofal iechyd proffesiynol.

Weithiau gall symptomau ddychwelyd, o bosibl ar ôl nifer o fisoedd. Os digwydd hyn dylech siarad â gweithiwr gofal iechyd proffesiynol.

CA

Beth allaf i ei wneud i helpu?

Cyngor ffordd o fyw ar gyfer helpu â symptomau:

- Cadwch at bwysau iach.
- Osgowch fwydydd a diodydd sy'n gwaethygu eich symptomau, megis bwydydd sbeislyd neu frasterog, siocled, coffi, diodydd cola, sudd oren.
- Bwytewch brydau ar adegau rheolaidd.
- Osgowch brydau mawr neu hwyr ac osgowch blygu drosodd neu orwedd i lawr yn syth ar ôl bwyta.
- Osgowch feddyginiaethau a allai waethygu eich symptomau, er enghraifft rhai cyffuriau lladd poen. Gofynnwch i weithiwr gofal iechyd proffesiynol pa feddyginiaethau sydd orau i chi eu cymryd.