BMJ Open Gastroenterology

Randomised clinical trial: the use of alginates during preinvestigation proton pump inhibitor wash-out and their impact on compliance and symptom burden

Andres Vales ,[1] Cathal Coyle,[2] Kate Plehhova,[2] Anthony Hobson,[1] Philip Woodland[3]

To cite: Vales A, Coyle C, Plehhova K, *et al*. Randomised clinical trial: the use of alginates during preinvestigation proton pump inhibitor wash-out and their impact on compliance and symptom burden. *BMJ Open Gastro* 2023;**10**:e001026. doi:10.1136/bmjgast-2022-001026

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjgast-2022-001026).

Please note a brief abstract of this study has been accepted for e-poster presentation at the Digestive Disease Week 2022 meeting.

Received 17 September 2022
Accepted 18 November 2022

[1]The Functional Gut Clinic, London, UK
[2]Reckitt Benckiser Plc, Slough, UK
[3]Barts Health NHS Trust, London, UK

Correspondence to
Andres Vales;
andres@thefunctionalgutclinic.com

ABSTRACT

Background/aims Investigation of gastro-oesophageal reflux disease is usually performed off proton pump inhibitors (PPIs). This can exacerbate symptoms, potentially impacting investigation accuracy if patients circumvent the preinvestigation instructions. There are no standard recommendations on how to manage PPI withdrawal. We aimed to assess the impact of structured alginate use on symptom burden.

Methods Participants were already established on ≥4 weeks of PPI therapy and being referred for manometry and 24-hour pH/impedance testing. Preinvestigation instructions involved stopping PPIs and H2 receptor antagonists for 1 week, but antacids and alginates were allowed until the night before. Participants were randomised to follow these standard instructions (control group), or the same instructions with the provision of Gaviscon Advance to be taken four times daily (treatment group). The primary outcome assessed change in Gastro-Oesophageal Reflux Disease Health-Related Quality of Life Score.

Key results Data for 48 patients were available for primary outcome assessment. While patients in the control group had a significant increase in symptoms (median difference 6.5, 95% CI (1 to 7), p=0.04), no change occurred in the treatment arm (median difference -1.5, 95% CI (-2, 3.5), p=0.54). There were no serious adverse events.

Conclusions Structured alginate use prevents symptom exacerbation during preinvestigation PPI wash-out. These findings are limited to the 1-week wash-out period but can benefit thousands of patients undergoing investigation for gastro-oesophageal reflux each year. Further research is required to assess this effect in other settings, such as sustained PPI deprescription. The trial was funded by Reckitt Benckiser.

Trial registration number EudraCT registration 2019-004561-41

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Proton pump inhibitor (PPI) cessation is difficult due to symptom exacerbation.
⇒ There are no randomised controlled trials to assess if alginates can reduce rebound symptoms during PPI cessation.

WHAT THIS STUDY ADDS

⇒ Regular alginate use can maintain reflux symptom suppression during preinvestigation PPI wash-out.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This improves the quality of life of the many thousands of patients that stop PPIs before upper gastrointestinal investigation each year.
⇒ Further research is required to assess if this benefit can help in PPI deprescription.

INTRODUCTION

Gastro-oesophageal reflux disease (GORD) affects 10%–30% of the world population.[1] Proton pump inhibitors (PPIs) are effective at reducing gastric acid secretion and improving symptoms but contribute to significant healthcare costs. US$10–US$20 billion is spent on GORD per year in the USA[2] and in 2018 over 60 million PPI prescriptions were written in England costing nearly £90 million.[3] The National Institute for Health and Care Excellence guidelines on reflux therapy advocate PPI use without further investigation;[4] however, they have only moderate sensitivity (78%) and specificity (54%) for the diagnosis of GORD.[5]

Attempts at PPI cessation frequently fail due to exacerbation of symptoms.[6] This can be due to resumption of acid reflux, but in other patients the symptom exacerbation occurs even in the absence of pathological exposure.[7] It has even been shown that, after a 4–8 weeks course of PPIs, abrupt cessation can result in reflux symptoms in healthy

individuals.[8 9] Consequently, many patients may take PPIs unnecessarily.[10]

Cessation difficulty can be observed in patients stopping PPIs before undergoing upper gastrointestinal investigations. In one study, 80% of patients attending for reflux studies suffered worse symptoms in the PPI-free week preceding the test. When asked anonymously, 15% admitted to surreptitiously taking PPIs during the abstinent period, potentially impacting test accuracy.[7]

Reducing this difficulty would improve the patient experience before testing. Alginate preparations, such as Gaviscon Advance (Reckitt Benckiser, Slough, UK) may help achieve this given their raft-forming properties[11] and topical protectant effects,[12 13] which reduce reflux symptoms.[14 15] Furthermore, alginate and antacid use does not reduce the sensitivity or specificity of *Helicobacter pylori* testing or gastroscopy.[16] Research on whether alginates can reduce rebound symptoms during PPI cessation is scant. Some studies used alginates as part of PPI deprescription initiatives, but none were randomised control trials.[17–19]

We; therefore, decided to assess whether structured alginate use during the preinvestigation PPI wash-out period reduces symptom burden.

METHODS

Patients

The study proposal can be found as online supplemental file 1 submitted with this article. Participants ≥18 years old were selected from those referred for oesophageal manometry and 24-hour pH/impedance monitoring at The Functional Gut Clinic which is a tertiary healthcare, outpatients' clinic in central London. Typically reflux monitoring is performed having stopped PPIs for 1 week[20] to allow for parietal cell turnover.

When booking in, patients already established on the ≥4 weeks course of standard or double dose PPI therapy were given information about the study. Prospective participants were screened over the phone and those with red flag symptoms, known Barrett's oesophagus, grade C/D oesophagitis, peptic ulcer disease, upper gastrointestinal malignancy or those with previous oesophageal or gastric surgery were excluded. Those with allergies to alginates/antacids or on a low salt diet were also excluded.

Study design

This was a single-centre, randomised, open-label study to assess the effects of Gaviscon Advance on patients stopping their PPIs before reflux testing. Registration was made with EudraCT number 2019-004561-41 and recruitment occurred between August 2020 and June 2021.

Participants were randomly assigned using Sealed Envelope to one of two parallel groups in a 1:1 fashion. Randomisation occurred in randomly permuted blocks of sizes 2, 4 or 6. Participants were asked to complete questionnaires the day before stopping their PPIs. Everyone was given the usual information regarding the wash-out period, namely stopping PPIs and H2 Receptor Antagonists (H2RAs) for 7 days and advised that antacids/alginates could be taken up to the night before the test. The treatment group only were given a bottle of Gaviscon Advance (oral suspension, containing 1000 mg sodium alginate and 200 mg potassium bicarbonate per 10 mL dose). They were asked to take 10 mL of suspension, four times a day (after breakfast, lunch, dinner and before bed) from when PPIs were stopped until the night before testing. Participants attended 1 week later and completed repeat questionnaires before their manometry and 24-hour pH/impedance test.

Study measurements

The primary outcome was change in Gastro-Oesophageal Reflux Disease Health-Related Quality of Life (GERD-HRQL) questionnaire score.[21] This validated questionnaire assesses reflux symptoms using 10 questions on a 0–5 scale giving a maximum score of 50 which indicates the worst possible symptoms.

A secondary outcome was change in Gastrointestinal Symptom Rating Scale (GSRS) score[22] consisting of 15 gastrointestinal questions each scored 0–6 with higher scores indicating worse symptoms. Additional measurements were the Mean Nocturnal Baseline Impedance (MNBI) on 24-hour pH/impedance testing[23] and an anonymous end of study questionnaire asking participants if they surreptitiously took any restricted medications (ie, PPIs or H2RAs).

The investigation involved high-resolution manometry and 24-hour ambulatory pH/impedance studies (both Diversatek Healthcare, Highlands Ranch, Colorado, USA). The manometry was used to detect the lower oesophageal sphincter (LOS) position and assess any hiatus hernia. The pH/impedance catheter (six impedance, two pH sensors) was placed with the oesophageal pH sensor 5 cm above the proximal margin of the LOS. MNBI was calculated using the method reported by Martinucci *et al*.[23] Diagnoses of pathological GORD, functional heartburn and hypersensitive oesophagus were given based on definitions from the Lyon Consensus[24] and Rome IV criteria.[25]

Statistics

We could find no study designed similarly to ours, however, a previous study adding Gaviscon Advance to participants already taking PPIs showed a reduction in symptoms of approximately half.[26] We assumed a similar medium effect size of 0.5, which meant 23 participants in each arm would identify a difference in symptoms with an 80% power. Assuming a 30% drop-out rate, we aimed to recruit 30 participants in each arm.

Disruption from COVID-19 meant participants could not be assessed face to face initially and were asked to complete the baseline questionnaires online before commencing the wash-out period. This led to some participants forgetting to complete the questionnaire before the day of stopping their PPIs. The date of completion

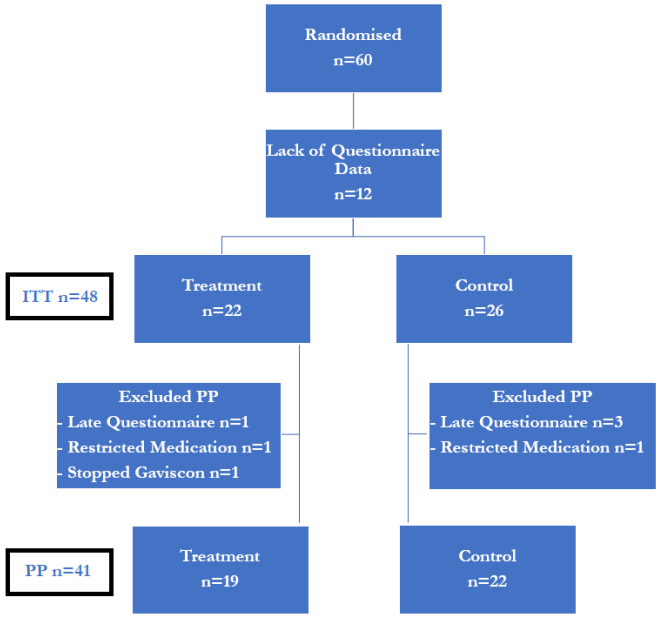

Figure 1 Flow of participants through the study for the primary outcome of Gastro-Oesophageal Reflux Disease Health-Related Quality of Life score. Participants were selected from those established on the ≥4 weeks course of proton pump inhibitors who then had to stop them before attending for reflux investigation. ITT, intention to treat; PP, per protocol.

of the questionnaires was tracked by computer time-stamp and those missing the baseline date by more than 1 day (n=4) were removed from the per-protocol analysis. However, the only participants excluded from the intention-to-treat (ITT) analysis were those who did not complete the questionnaires (n=12) such that there was no data available.

Statistical analysis was performed using IBM SPSS Statistics V.26. Continuous data are described as mean±SD or median and IQR as appropriate. Categorical data are described as numbers and percentages. Changes from the baseline measurements were assessed using Wilcoxon signed-rank tests for paired samples, and Mann-Whitney U or χ^2 tests for independent samples. Statistical significance was defined as a p≤0.05 and were presented along with 95% CIs.

RESULTS

The study flow chart is displayed in figure 1. Sixty patients met the screening criteria and agreed to participate in the study. The median age of all participants enrolled was 48 (range 18–76) and 29 (48.3%) were female.

Twelve participants were removed from analysis for the primary outcome due to a lack of questionnaire data. Therefore, 48 were included in the final ITT analysis and were randomised to either follow the usual information (n=26) or to take Gaviscon Advance (n=22). Participant baseline demographics and clinical data are shown in table 1.

Table 1 Demographics and baseline clinical data (intention to treat population)

	Treatment Group, n=22	Control Group, n=26
Female	9 (40.9)	15 (57.7)
Age in years, median (IQR)	46 (18)	52 (13)
Heartburn	22 (100)	24 (92.3)
Regurgitation	20 (90.9)	22 (84.6)
Chest pain	6 (27.3)	4 (15.4)
LPR symptoms	8 (36.4)	14 (53.8)
Dysphagia	15 (68.2)	15 (57.7)
PPI standard dose/once daily	6 (27.3)	4 (15.4)
PPI standard dose/twice daily	3 (13.6)	2 (7.7)
PPI max dose/once daily	8 (36.4)	12 (46.2)
PPI max dose/twice daily	5 (22.7)	8 (30.8)
PPI response—good	10 (45.5)	6 (23.1)
PPI response—partial	7 (31.8)	11 (42.3)
PPI response—poor	5 (22.7)	9 (34.6)
Manometric hiatus hernia	8 (36.4)	7 (26.9)
Oesophagitis grade A/B	5 (22.7)	7 (26.9)

Values are expressed as numbers (percentages) unless stated otherwise.
LPR, laryngopharyngeal reflux; PPI, proton pump inhibitor.

Efficacy analysis

The change in overall GERD-HRQL scores before and after the PPI wash-out are shown in figure 2. There was no overall reduction in score on stopping PPIs in the treatment group (median difference −1.5, 95% CI (−2 to 3.5), p=0.54). Conversely, the control group showed a significant increase in symptoms after stopping PPIs (median difference 6.5, 95% CI (1 to 7), p=0.04).

The GSRS score reduced for the treatment group however the difference was not significant (median difference −3, 95% CI (−7 to 1), p=0.10). The control group showed an increase in GSRS-recorded symptoms but again the difference was not significant (median difference 1, 95% CI (−3 to 4), p=0.84).

Only 2/48 (4.2%) participants admitted to surreptitiously taking restricted medicines during the wash-out period. One participant from the treatment group took PPIs on 3 days of the wash-out period and one participant from the control group took H2RAs on 2 days. There were 14/26 (53.8%) participants in the control group who took antacids/alginates during the study. Five of those said they used them on all 7 days, four used them on at least four or more days, the remainder took them on only 1 or 2 days.

For the 24-hour pH/impedance test, from the 60 patients initially randomised, 5 (8.3%) cancelled their appointment and 3 (5%) did not tolerate intubation.

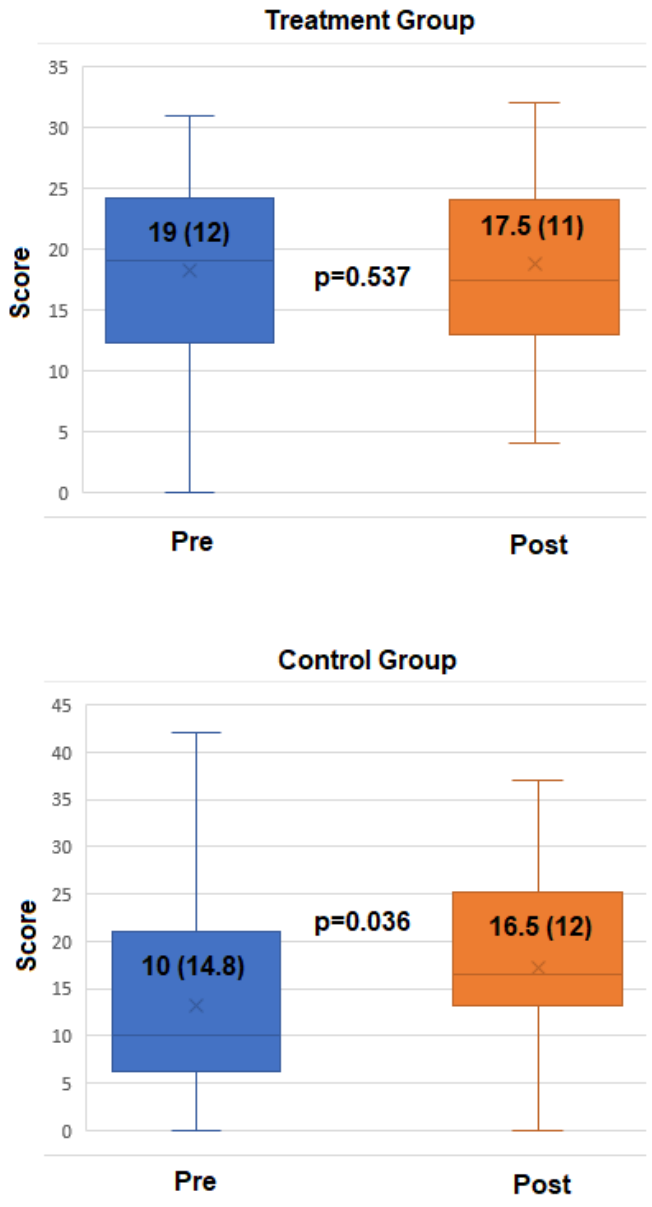

Figure 2 Box plot of Gastro-Oesophageal Reflux Disease Health-Related Quality of Life scores before and after the PPI wash-out period (intention to treat population). No change was seen in the treatment group, but the control group experienced worse symptoms 1 week later. Data are expressed as median (IQR). PPI, proton pump inhibitor.

Therefore 52 completed the reflux investigation, of which n=24 were in the treatment group and n=28 in the control group. The only significant difference in the pH/impedance study data was with hypersensitive oesophagus, where all five patients identified were in the control group, p=0.029 (table 2).

Safety

There were no serious adverse events reported. Minor events were reported in keeping with reflux-type rebound symptoms. One participant decided to stop taking Gaviscon after only a few doses due to a severe dislike of the taste, however, they confirmed that this was not an adverse reaction but personal preference. They adhered to the remaining study criteria and were kept in the ITT analysis.

Table 2 24 hour pH/impedance data between groups

	Treatment n=24	Control n=28	P value
MNBI, Ω, mean (SD)	1751 (1104)	2131 (1095)	0.219
AET, %, mean (SD)	8.7 (10)	4 (4.1)	0.108
RE, median (IQR)	64 (33.5)	55 (32.5)	0.373
Pathological GORD	13 (54.2)	8 (28.6)	0.061
FH	3 (12.5)	2 (7.1)	0.514
HO	0	5 (17.9)	0.029

Values are expressed as numbers (percentages) unless stated otherwise.
AET, acid exposure time; FH, functional heartburn; GORD, gastro-oesophageal reflux disease; HO, hypersensitive oesophagus; MNBI, mean nocturnal baseline impedance; RE, reflux events.

DISCUSSION

This study shows that structured alginate use significantly reduces reflux symptom deterioration in the week after stopping long-term PPIs. No change in the GERD-HRQL score was seen when regular alginate was given after stopping PPIs. Conversely, the control group saw a significant increase in symptoms.

The GSRS is a more generalised gastrointestinal questionnaire, our intention being to assess if Gaviscon Advance would cause irritable bowel type symptoms. Instead there was a slight improvement in GSRS score for the treatment group, however, the change was not significant.

MNBI, percentage acid exposure time and reflux events all showed a tendency towards worse values in the treatment group, although the changes were not significant. There were a greater number of participants diagnosed with GORD in the treatment group, which was close to significance (p=0.06).

A previous study showed that 15% of patients surreptitiously took restricted medications before attending investigation, however, only 4.2% did this in ours. This may be due to the information given or patient selection.

These findings can benefit other investigations. The sensitivity and specificity of *H. pylori* stool antigen or carbon-13 breath testing when off PPI are excellent (both over 95%).[27] However, if performed on PPI therapy, sensitivity is significantly reduced, with over 30% false negative results.[16 28]

During gastroscopy, diagnosis of *H. pylori* using the rapid urease test has a sensitivity of 90%–95%. Again, the use of PPIs results in a significant false negative rate[29] such that immunohistochemical assessment of gastric biopsies is required, at significant time and financial expense. When investigating GORD, up to 40% of patients have erosive oesophagitis.[30] PPIs are effective

in healing oesophagitis (~90% healing at 8 weeks)[31] such that an on PPI gastroscopy is likely to reduce the diagnostic yield. It also may prevent identification of patients with more severe oesophagitis who will need long-term reflux management rather than 'as-required' therapy. For the diagnosis of eosinophilic oesophagitis, PPIs have been shown to supress eosinophilia such that recent consensus guidelines recommend stopping PPIs for at least 3 weeks prior to biopsy to ensure accurate diagnosis.[32] Finally, although unusual, there are reports of PPIs masking early gastric and oesophageal adenocarcinoma.[33]

Census data showed that over 800 000 gastroscopies were performed in 2019 in England.[34] Instructions for stopping medications for gastroscopy are usually very similar such that the findings of our study could potentially improve outcomes for many patients nationwide.

The main limitation of our study is that, despite randomisation, the GERD-HRQL scores between the groups differ at baseline. After investigation, a subversion of the allocation procedure could not be found. Possible causes could be the small sample size, the use of a single centre, or a lack of diversity in the group. It may also reflect the trend towards higher oesophageal acid exposure seen in the treatment arm. Nevertheless, the differences in change from baseline were clear, with significant deterioration seen in the control group that was not seen in the treatment arm.

Despite the treatment group having a higher baseline, measurement of deterioration remained possible. The GERD-HRQL score has a maximum value of 50, such that the score could have increased were the trend to have been in that direction.

More patients were found with true GORD in the treatment arm with a trend towards lower MNBI and increased acid exposure. This may be due to chance, or that better control of symptoms from Gaviscon use allows for a behaviourally more 'normal'" day, making the reflux study more reflective of their natural GORD severity. Conversely, if patients do not take Gaviscon proactively during the wash-out period, worsening symptoms may restrict their activities during the reflux study, leading to a higher false negative rate through inactivity. Ultimately, the difference in 24-hour reflux data in our study was not significant, however, this hypothesis could be a target for further research.

The fact that more GORD patients (and higher mean acid exposure) were found in the treatment group adds to the validity of our findings. Patients with true GORD are more likely to become symptomatic during PPI withdrawal, yet the symptom deterioration was seen in the control group (where more patients had physiological acid exposure).

Other limitations were that H2RAs were restricted throughout the wash-out period, where some centres allow them until 48 hours before investigation. This was primarily so the focus of the study could be on alginate use. Given the current recall of ranitidine,[35] and remaining H2RAs being in short supply, we believe this to have a limited effect on our findings.

In a previous study, we used an anonymised questionnaire to assess PPI cessation compliance, however, it appears the same method was not effective during this trial. Further thought will be made on how to better capture this issue in future.

Finally, the open-label nature of the study may contribute bias, however, many patients can identify Gaviscon Advance by taste. This effect is lessened since the control group were allowed to take antacids/alginates and in fact over half of the control group took them ad hoc during the wash-out period. Thus, this represents a real-world comparator group and is a main strength of the study. The difference for the treatment group is they were given specific instructions on how and when to use them.

CONCLUSION

This study supports the use of regular alginate use (in a proactive rather than reactive fashion) to ease symptoms during PPIs cessation before diagnostic testing such as reflux studies, *H. pylori* testing or gastroscopy.

This finding could be beneficial when PPIs are stopped in other situations. Previous uncontrolled studies suggest a role of alginates in PPI deprescribing. This would be of great benefit considering the volume of PPI prescriptions globally and is especially true with the current global recall of ranitidine, as well as growing patient reticence about taking long-term PPI therapy. A future randomised, controlled study to assess the effectiveness of alginates in this setting is required.

Acknowledgements Many thanks to the wider Functional Gut Clinic team who helped with technical and general support.

Contributors The guarantor of the article is PW. AV helped with performing the research, data collection/analysis and writing the paper. CC helped with study design, project administration and writing the paper. KP helped with project administration and writing the paper. AH helped with study design and project administration. PW helped with study design, project administration and writing the paper. All authors approved the final version of the paper.

Funding This study was funded by Reckitt Benckiser Plc, Slough, UK.

Competing interests AV is an employee of The Functional Gut Clinic. CC and KP are employees of Reckitt Benckiser. AH is director and shareholder of The Functional Gut Clinic. PW has received research funding from, and is a consultant for, Reckitt Benckiser.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by HRA Surrey Borders Research Ethics CommitteeREC Ref - 20/LO/0042. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Deidentified participant data are available in spreadsheet format on reasonable request. The study proposal has also been made available. Requests can be made to the first author—andres@thefunctionalgutclinic.com—Orcid ID 0000-0001-7774-310X. Reuse is permitted once the authors have approved and ensured any obligations (eg, Ethics committee guidelines etc) have been met and that the study is cited as the original source of the data.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been

ORCID iD

Andres Vales http://orcid.org/0000-0001-7774-310X

REFERENCES

1 El-Serag HB, Sweet S, Winchester CC, *et al*. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2014;63:871–80.
2 Gawron AJ, French DD, Pandolfino JE, *et al*. Economic evaluations of gastroesophageal reflux disease medical management. *Pharmacoeconomics* 2014;32:745–58.
3 NHS Digital. Prescription cost analysis, 2018. Available: https://digital.nhs.uk/data-and-information/publications/statistical/prescription-cost-analysis
4 Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management. *National Institute for health and care excellence: clinical guidelines*. London, 2019.
5 Numans ME, Lau J, de Wit NJ, *et al*. Short-term treatment with proton-pump inhibitors as a test for gastroesophageal reflux disease: a meta-analysis of diagnostic test characteristics. *Ann Intern Med* 2004;140:518–27.
6 Pilotto A, Leandro G, Franceschi M, *et al*. Short- and long-term therapy for reflux oesophagitis in the elderly: a multi-centre, placebo-controlled study with pantoprazole. *Aliment Pharmacol Ther* 2003;17:1399–406.
7 Hoshikawa Y, Nikaki K, Sonmez S, *et al*. Exacerbation of gastroesophageal reflux symptoms after discontinuation of proton pump inhibitors is not associated with increased esophageal acid exposure. *Neurogastroenterol Motil* 2020;32:e13735.
8 Reimer C, Søndergaard B, Hilsted L, *et al*. Proton-pump inhibitor therapy induces acid-related symptoms in healthy volunteers after withdrawal of therapy. *Gastroenterology* 2009;137:80–7.
9 Niklasson A, Lindström L, Simrén M, *et al*. Dyspeptic symptom development after discontinuation of a proton pump inhibitor: a double-blind placebo-controlled trial. *Am J Gastroenterol* 2010;105:1531–7.
10 Lee TJ, Fennerty MB, Howden CW. Systematic review: is there excessive use of proton pump inhibitors in gastro-oesophageal reflux disease? *Aliment Pharmacol Ther* 2004;20:1241–51.
11 Rohof WO, Bennink RJ, Smout AJPM, *et al*. An alginate-antacid formulation localizes to the acid pocket to reduce acid reflux in patients with gastroesophageal reflux disease. *Clin Gastroenterol Hepatol* 2013;11:1585–91.
12 Woodland P, Batista-Lima F, Lee C, *et al*. Topical protection of human esophageal mucosal integrity. *Am J Physiol Gastrointest Liver Physiol* 2015;308:G975–80.
13 Sonmez S, Coyle C, Sifrim D, *et al*. Duration of adhesion of swallowed alginates to distal oesophageal mucosa: implications for topical therapy of oesophageal diseases. *Aliment Pharmacol Ther* 2020;52:442–8.
14 Thomas E, Wade A, Crawford G, *et al*. Randomised clinical trial: relief of upper gastrointestinal symptoms by an acid pocket-targeting alginate-antacid (Gaviscon Double Action) - a double-blind, placebo-controlled, pilot study in gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2014;39:595–602.
15 Vardar R, Keskin M, Valitova E, *et al*. Effect of alginate in patients with GERD hiatal hernia matters. *Dis Esophagus* 2017;30:1–7.
16 Gatta L, Vakil N, Ricci C, *et al*. Effect of proton pump inhibitors and antacid therapy on 13C urea breath tests and stool test for Helicobacter pylori infection. *Am J Gastroenterol* 2004;99:823–9.
17 Murie J, Allen J, Simmonds R, *et al*. Glad you brought it up: a patient-centred programme to reduce proton-pump inhibitor prescribing in general medical practice. *Qual Prim Care* 2012;20:141–8.
18 Wahking RA, Steele RL, Hanners RE, *et al*. Outcomes From a Pharmacist - led Proton Pump Inhibitor Stewardship Program at a Single Institution. *Hosp Pharm* 2018;53:59–67.
19 Coyle C, Symonds R, Allan J, *et al*. Sustained proton pump inhibitor deprescribing among dyspeptic patients in general practice: a return to self-management through a programme of education and alginate rescue therapy. A prospective interventional study. *BJGP Open* 2019;3:bjgpopen19X101651.
20 Roman S, Gyawali CP, Savarino E, *et al*. Ambulatory reflux monitoring for diagnosis of gastro-esophageal reflux disease: update of the Porto consensus and recommendations from an international consensus group. *Neurogastroenterol Motil* 2017;29:e13067–15.
21 Velanovich V. The development of the GERD-HRQL symptom severity instrument. *Dis Esophagus* 2007;20:130–4.
22 Kulich KR, Madisch A, Pacini F, *et al*. Reliability and validity of the gastrointestinal symptom rating scale (GSRS) and quality of life in reflux and dyspepsia (QOLRAD) questionnaire in dyspepsia: a six-country study. *Health Qual Life Outcomes* 2008;6:12.
23 Martinucci I, de Bortoli N, Savarino E, *et al*. Esophageal baseline impedance levels in patients with pathophysiological characteristics of functional heartburn. *Neurogastroenterol. Motil.* 2014;26:546–55.
24 Gyawali CP, Kahrilas PJ, Savarino E, *et al*. Modern diagnosis of GERD: the Lyon consensus. *Gut* 2018;67:1351–62.
25 Drossman DA, Hasler WL. Rome IV—Functional Gi disorders: disorders of gut-brain interaction. *Gastroenterology* 2016;150:1257–61.
26 Reimer C, Lødrup AB, Smith G, *et al*. Randomised clinical trial: alginate (Gaviscon advance) vs. placebo as add-on therapy in reflux patients with inadequate response to a once daily proton pump inhibitor. *Aliment Pharmacol Ther* 2016;43:899–909.
27 Howden CW, Hunt RH. Guidelines for the management of Helicobacter pylori infection. AD hoc Committee on practice parameters of the American College of gastroenterology. *Am J Gastroenterol* 1998;93:2330–8.
28 Laine L, Estrada R, Trujillo M, *et al*. Effect of proton-pump inhibitor therapy on diagnostic testing for Helicobacter pylori. *Ann Intern Med* 1998;129:547–50.
29 Saniee P, Shahreza S, Siavoshi F. Negative Effect of Proton-pump Inhibitors (PPIs) on Helicobacter pylori Growth, Morphology, and Urease Test and Recovery after PPI Removal--An In vitro Study. *Helicobacter* 2016;21:143–52.
30 Dent J, El-Serag HB, Wallander M-A, *et al*. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2005;54:710–7.
31 Castell DO, Kahrilas PJ, Richter JE, *et al*. Esomeprazole (40 Mg) compared with lansoprazole (30 Mg) in the treatment of erosive esophagitis. *Am J Gastroenterol* 2002;97:575–83.
32 Dhar A, Haboubi HN, Attwood SE, *et al*. British Society of gastroenterology (Bsg) and British Society of paediatric gastroenterology, hepatology and nutrition (BSPGHAN) joint consensus guidelines on the diagnosis and management of eosinophilic oesophagitis in children and adults. *Gut* 2022;71:1459–87.
33 Bramble MG, Suvakovic Z, Hungin AP. Detection of upper gastrointestinal cancer in patients taking antisecretory therapy prior to gastroscopy. *Gut* 2000;46:464–7.
34 Ravindran S, Bassett P, Shaw T, *et al*. National census of UK endoscopy services in 2019. *Frontline Gastroenterol* 2021;12:flgastro-2020-101538.
35 MHRA. Drug alert: recalls for 13 over-the-counter ranitidine medicines, 2019. Available: https://www.gov.uk/government/news/mhra-drug-alert-recalls-for-13-over-the-counter-ranitidine-medicines