

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

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

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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

INTRODUCTION

Gastro-oesophageal reflux disease (GORD) affects 10%–30% of the world population.¹

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.

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 USA² 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 properties¹¹ 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 week²⁰ 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/alginate 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) score²² 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 testing²³ 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 Martignucci *et al.*²³ Diagnoses of pathological GORD, functional heartburn and hypersensitive oesophagus were given based on definitions from the Lyon Consensus²⁴ 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

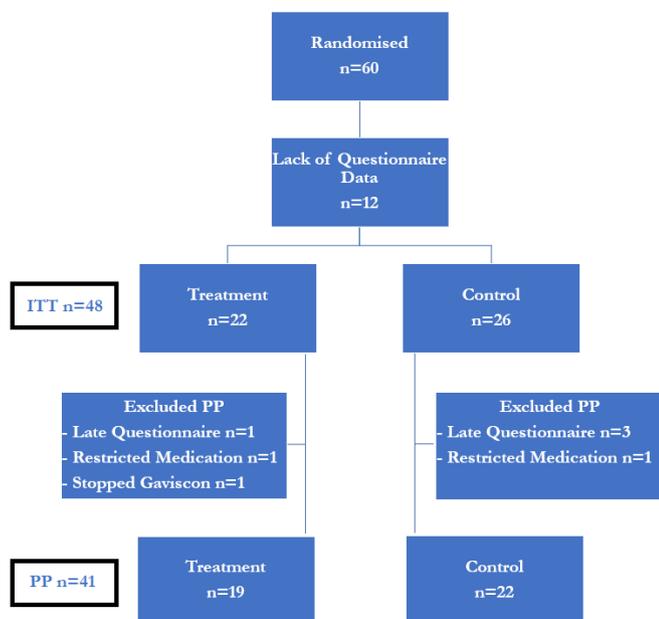


Figure 1 Flow of participants through the study for the primary outcome of Gastro-Oesophageal Reflux Disease Health-Related Quality of Life score. Participants were selected from those established on the ≥ 4 weeks course of proton pump inhibitors who then had to stop them before attending for reflux 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 \pm 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 $p \leq 0.05$ 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.

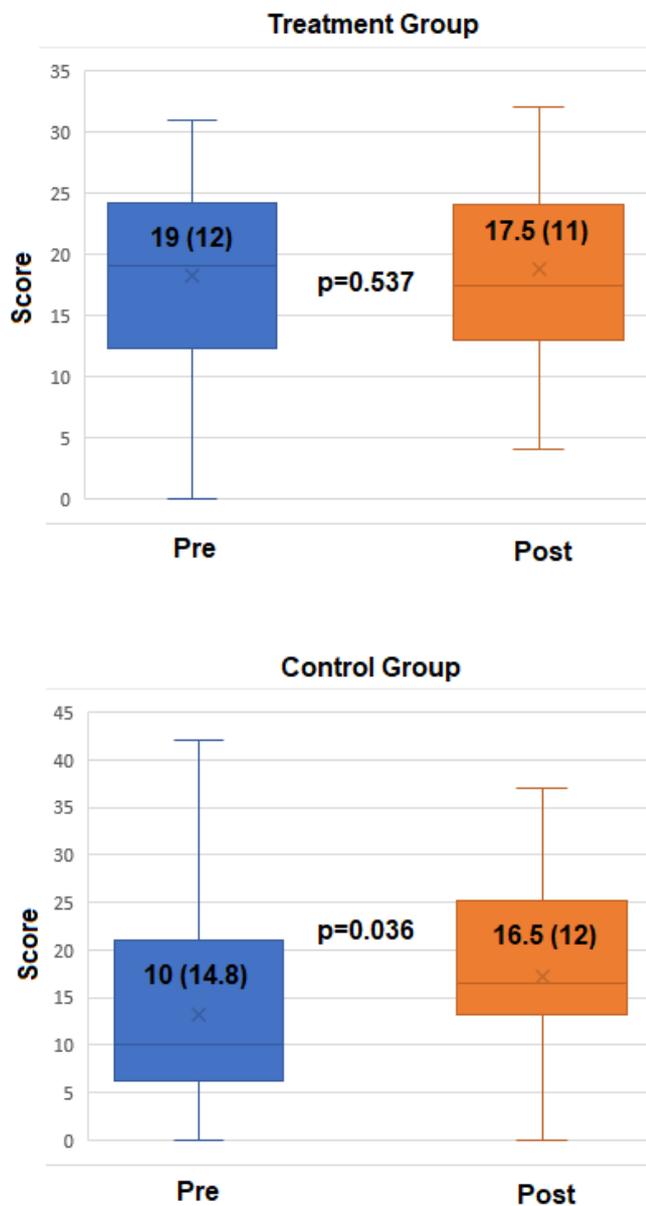


Figure 2 Box plot of Gastro-Oesophageal Reflux Disease Health-Related Quality of Life scores before and after the PPI wash-out period (intention to treat population). No change was seen in the treatment group, but the control group experienced worse symptoms 1 week later. Data are expressed as median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

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.

adverse reaction but personal preference. They adhered to the remaining study criteria and were kept in the ITT analysis.

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 rate²⁹ 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 suppress 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/alginate 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.

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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.

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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 Committee REC 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.

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PPI-Washout Study – Proposal - V.1.6 – 01/02/2020

The use of antacids and alginates during pre-investigation PPI washout: impact on compliance and symptom burden.

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Introduction

Gastroesophageal reflux disease (GORD) affects 10-30% of the world population and cost more than \$9-10 billion per year in the US, mainly due to use of proton pump inhibitors (PPIs) ^{1,2}. PPIs are currently the most efficacious pharmacological therapy for GORD and peptic ulcer disease, and are very effective at suppressing gastric acid secretion. Although there are reports of important adverse effects (most reliably increased risk of enteric infection and reduced bone density), PPIs are safe drugs with few side effects.

The tolerability and safety of PPIs has led to widespread (often empirical) prescription, and indeed NICE guidelines on reflux and dyspepsia therapy advocate PPI therapy without further investigation. As such, there are extremely high levels of PPI prescription in the UK. In 2017 there were nearly 60 million PPI prescriptions written in England, at a drug cost of nearly £100 million (*Prescribing and Medicines Team ND. Prescription Cost Analysis: England 2017 2018 [Available from: <http://digital.nhs.uk/pubs/prescostanalysiseng2017>].*) Although PPIs are often used for initial management of reflux symptoms as a “PPI trial”, it has only moderate sensitivity of 62% and specificity of 67% for the diagnosis of GORD³. Thus, many patients may continue PPI unnecessarily^{4,5,6}.

Often attempts to stop PPIs are made, because of patient preference, concern about their safety, and/or cost⁷. Unfortunately, PPI cessation can be challenging because of exacerbation of reflux symptoms, and attempts frequently fail⁸. This leads to PPI re-prescribing and perpetuation of long term use.

This problem can be encapsulated by observing patients who need to stop PPIs in order to undergo upper gastrointestinal testing such as gastroscopy or reflux studies. We recently demonstrated that, in patients attending our unit for reflux studies (for which they need to stop PPI for 1 week), exacerbation of symptoms is common after PPI cessation (submitted for publication 2019). Over 80% of patients suffered distressing worsening of symptoms in the week preceding the test when stopping PPIs and, when asked anonymously, 15%

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admitted to surreptitiously taking PPIs during the abstinent period (with potential impact on test accuracy).

The phenomenon of post-PPI cessation symptoms is not limited to symptomatic patients. After cessation of an 8 week course of esomeprazole, even previously asymptomatic healthy volunteers developed heartburn and dyspeptic symptoms^{9,10}. This highlights the difficulty faced when trying to stop PPIs, and shows that mitigating clinical strategies are required.

Rationale for PPI washout before investigation

There are several situations where PPI therapy is mandated or recommended to be stopped before investigation.

Prior to H pylori antigen testing:

In patients with dyspepsia, NICE guidance in patients without red flag symptoms includes ‘test and treat’ for *Helicobacter pylori*. It is also recommended that a 2-week washout from PPI therapy is observed before testing for H pylori stool antigen or carbon-13 urea breath testing. This is because PPI use adversely affects the sensitivity of tests. In the absence of PPI therapy, the sensitivity and specificity of these tests is excellent (sensitivity and specificity over 95%)(1). When urea breath test or stool antigen is performed on PPI therapy sensitivity is significantly reduced, with over 30% false negative results(2, 3).

Prior to upper gastrointestinal endoscopy:

Oesophagogastroduodenoscopy (OGD) is a frequently performed test to investigate upper gastrointestinal symptoms, including dyspepsia and gastro-oesophageal reflux symptoms. Gastric biopsies can be tested rapidly and inexpensively with the rapid urease test for H pylori, with a sensitivity of 90-95%. Again, use of PPIs results in a significant false negative rate of the rapid urease test(4). To make an endoscopic diagnosis of H pylori in patients taking PPI requires immunohistochemical assessment of gastric biopsies, at significant time and financial expense.

When the endoscopy is being done for investigation of gastro-oesophageal reflux symptoms, the use of PPIs is likely to reduce the diagnostic yield. Up to 40% of patients with GORD have erosive oesophagitis(5). PPIs are very effective in healing reflux oesophagitis (~90% healing at 8 weeks)(6). Whilst there are clear advantages to PPI therapy in these

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cases, it does mean that definitive diagnosis may not be made at endoscopy where oesophagitis has healed.

Finally, there is a small risk of PPI use masking a serious diagnosis at OGD. Although unusual, there are reports of PPIs masking early gastric and oesophageal adenocarcinoma(7).

Prior to ambulatory oesophageal pH testing:

In most cases, where a diagnosis of gastro-oesophageal reflux is being sought, ambulatory reflux monitoring should be performed off PPIs for at least 1 week(8) to allow adequate time for parietal cell turnover to be complete before testing.

Potential role of routine alginates during PPI washout period

Alginate preparations (such as Gaviscon Advance, Gaviscon Double Action) have raft-forming properties(9) and variable antacid effects that are effective in reducing reflux and dyspeptic symptoms in affected individuals(10, 11). Furthermore, alginate and antacid use does not reduce the sensitivity or specificity of H pylori testing or endoscopy(3). It is unknown whether using regular alginates can reduce rebound symptoms on stopping PPIs.

Hypothesis

Regular alginate use during the pre-investigation PPI washout period reduces patient symptom burden and improves compliance with PPI abstinence.

Aim

To evaluate the effect of regular Gaviscon Advance on dyspepsia and reflux symptom burden in the week after stopping PPI therapy.

Primary Outcome

- Change in GERD-HRQL score

Secondary Outcomes

- Change in gastrointestinal symptom score
- PPI and H2-receptor antagonist use

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- Mean nocturnal baseline impedance measurement (12)

Methods

Study population

Adult patients will be recruited from sites where The Functional Gut Clinic have regular oesophageal physiology clinics.

Patients will be having ambulatory reflux testing off PPI medication as part of their standard clinical investigation for dyspepsia and/or reflux symptoms.

Inclusion criteria:

- Adult patients ≥ 18 years age.
- Clinical investigation for reflux symptoms (heartburn and/or regurgitation) or dyspepsia (nausea, upper abdominal discomfort, early satiety and/or upper abdominal bloating).
- Already established on ≥ 4 weeks of standard or double dose PPI therapy.
- Clinical requirement for pre-investigation PPI washout period.
- Ability to communicate well with the study team and comply with the requirements of the entire study.
- Has the capacity to understand written English.

Exclusion criteria:

- Red flag symptoms or urgent (2 week wait referral).
- Known Barrett's oesophagus, reflux oesophagitis, peptic ulcer disease, or upper gastrointestinal malignancy.
- Other clinical indication for PPI continuation.
- Previous oesophageal or gastric surgery.
- Intolerant of alginate preparations.
- Patients on a low salt diet.
- Unable to tolerate the nasogastric reflux probe for a minimum of 18 hours.

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Patients are typically referred to The Functional Gut Clinic for reflux testing by their upper Gastro-Intestinal (GI) consultants. When patients make contact with the clinic to book their tests, they will be told about the trial and invited to participate.

They will be told that we are investigating symptoms on stopping PPIs for upper GI testing. If they agree, they will be sent the study patient information sheets. The information sheet will include a secure web address for electronic signing of consent (also sent by text message). A face to face meeting will be offered to discuss further if required.

Eligible, consenting patients will be randomised into observation or treatment arms.

Study protocol

After selection, patients will be randomised in a 1:1 fashion into an observation or treatment arm.

All participants will be sent:

- Baseline questionnaires (GERD-HRQL score, gastrointestinal symptom score, perceived symptom response to PPI – see appendix) to be completed just before stopping PPI therapy.
- Clinical questionnaire detailing past medical history

Participants in the control arm will be sent:

- Leaflet explaining the physiology test, and importance of stopping PPIs for accurate testing.

Participants in the intervention arm will additionally be sent:

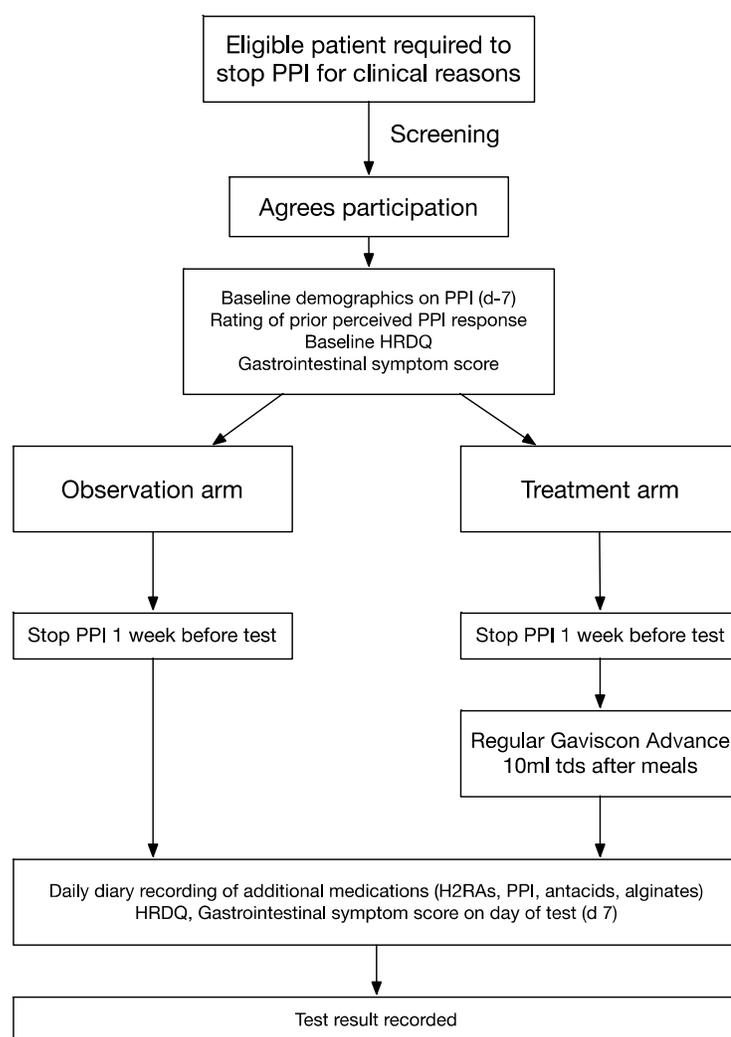
- A supply of Gaviscon Advance
- Instructions to take 10ml Gaviscon Advance 4 times per day (after each meal and at night) from the day of stopping PPI until the day before the procedure.
- Instructions to diary record Gaviscon use.

All participants will hand in questionnaires on arrival for their physiology tests 7 days later, and will complete repeat GERD-HRQL and gastrointestinal symptom score questionnaires.

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They will be invited to record surreptitious taking of PPIs and/or H2-receptor antagonists in an anonymous questionnaire (this will be sealed in an envelope and will only be looked at in final analysis, untraceable to the participant).

GI physiology testing will be performed as per standard clinical practice, and will be reported according to standard practice (13) (14).

**Statistics and analysis**

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The primary outcome will be measured by comparing mean GERD-HRQL scores in the observation and treatment arms. Statistical significance will be tested by a paired t-test. Power calculation: A previous study of Gaviscon in patients with persistent symptoms (the population most likely to be studied in our hospital setting showed a baseline mean HRDQ score of 9.5 (SD 6)(15). Treatment with Gaviscon reduced the mean score to 4.5. If we expect this in the treatment arm, and expect no change in the observation arm, 23 patients in each arm would identify this difference with a power of 90%. To allow for a 30% dropout, we will recruit 30 patients in each arm.

Timeline:

From agreement of the project, ethical approval would be expected to take 2 months.

We would expect to recruit 5 patients per week, and allowing for dropouts would expect to recruit over 16 weeks. We would intend for the first patient to enter the study in December 2019, and the last patient to leave the study in May 2020. Analysis and write up would be predicted to take 2 months, with anticipated submission of results in July 2020.

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Diary record of Gaviscon

Please tick when Gaviscon Advance is taken as instructed

	After breakfast	After lunch	After evening meal	Before bedtime
Day 1	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Day 2	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Day 3	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Day 4	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Day 5	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Day 6	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Day 7	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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Anonymous Questionnaire

Did you take any additional PPI medications (e.g. omeprazole, lansoprazole) over the past 7 days? YES NO

If yes, on how many days in the past week did you take a PPI tablet? _____

Did you take any additional ranitidine/zantac medication over the past 7 days? YES NO

If yes, on how many days in the past week did you take a ranitidine/zantac tablet? _____

Did you take additional Gaviscon medication over the past 7 days? (this was allowable) YES NO

If yes, on how many days in the past week did you take Gaviscon? _____

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If you suffer from heartburn (burning sensation behind the breastbone), how much do you perceive your heartburn symptoms have worsened since stopping your PPI (e.g. omeprazole/lansoprazole) for today's test?

(please circle: 0 = not at all ; 10 = extremely so)

0	1	2	3	4	5	6	7	8	9	10
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If you suffer from regurgitation (unpleasant sensation of material moving up from the stomach behind the breastbone), how much do you perceive your regurgitation symptoms have worsened since stopping your PPI for today's test?

(please circle: 0 = not at all ; 10 = extremely so)

0	1	2	3	4	5	6	7	8	9	10
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If you suffer from epigastric pain (pain at the top of the abdomen, just below the breastbone), how much do you perceive your regurgitation symptoms have worsened since stopping your PPI for today's test?

(please circle: 0 = not at all ; 10 = extremely so)

0	1	2	3	4	5	6	7	8	9	10
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If you suffer from excessive burping, how much do you perceive your burping symptoms have worsened since stopping your PPI for today's test?

(please circle: 0 = not at all ; 10 = extremely so)

0	1	2	3	4	5	6	7	8	9	10
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If you suffer from excessive bloating, how much do you perceive your bloating symptoms have worsened since stopping your PPI for today's test?

(please circle: 0 = not at all ; 10 = extremely so)

0	1	2	3	4	5	6	7	8	9	10
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