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Efficacy and safety of alginate formulations in patients with gastroesophageal reflux disease: a systematic review and meta-analysis of randomized controlled trials

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Abstract. – OBJECTIVE: Alginate formulations are increasingly being used for treating gastroesophageal reflux disease (GERD). However, the benefits of alginate versus control or proton pump inhibitors (PPIs) are somewhat unclear. We performed a systematic review and meta-analysis to summarize data from recent randomized controlled trials (RCTs) comparing the efficacy and safety of alginate-based formulation with PPIs or control for the treatment of GERD.

MATERIALS AND METHODS: PubMed, Embase, Scopus, BioMed Central, CENTRAL, and Google scholar databases were searched from 1st January 2000 to 15th June 2020. Primary outcome was a reduction of symptoms while secondary outcomes were adverse events and treatment withdrawals. Ten articles with 11 RCTs were included.

RESULTS: Qualitative analysis of four trials indicated better outcomes with alginates *vs.* placebo/antacids. Our pooled analysis, however, indicated no statistically significant difference between alginates and placebo/antacids for relief of heartburn, regurgitation, or dyspepsia. Similarly, no difference was seen between a combination of alginate and PPI vs. PPI alone for reduction of heartburn, regurgitation, or dyspepsia symptoms. The risk of adverse events and treatment withdrawal did not differ between the two groups in either comparison. Descriptive analysis of studies comparing alginate vs. PPI indicated no difference between the two drugs.

CONCLUSIONS: Our study indicates that alginates may have greater efficacy than placebo/antacids in improving outcomes of GERD. However, current evidence on the efficacy of alginate-based formulations vs. PPI or the role of added alginates with PPI is questionable, and suggests no difference between the two drugs. The risk of adverse events with alginates is no greater than that of placebo or PPIs.

Key Words:
Alginate, Proton pump inhibitors, Gastroesophageal reflux disease, Meta-analysis.

Introduction

Gastroesophageal reflux disease (GERD) is a common gastrointestinal (GI) ailment that affects around 18.1%-27.8% of population in North America[1]. Classical symptoms of the disease include distressing heartburn and acid regurgitations, especially after meals. Patients may also experience other symptoms such as epigastric pain, bloating, dysphagia, laryngitis, and cough[2,3]. These symptoms have adverse effects on the patients' quality of life by affecting sleep, routine functioning, social interactions as well as mental well-being[4,5]. Despite being a benign disease, a high prevalence of GERD can have important socio-economic repercussions[6].

Traditionally, GERD has been classified into two major groups, based on diagnostic endoscopy: erosive GERD and non-erosive reflux disease (NERD)[2]. Proton pump inhibitors (PPIs) are usually the first-line of therapy for erosive GERD. However, there have been concerns over the response to PPIs in NERD patients[7]. Acid pocket, a reservoir of unbuffered highly acidic gastric secretions located in the proximal stomach, can enter the esophagus after the opening of the esophagogastric junction[8] . Targeting this acid pocket therefore can lead to the effective management of the condition. Alginate-based formulations react with the gastric acid and form a gel "raft" that floats over the gastric contents. The formation of this raft over the acid pocket acts as a physical barrier for the reflux of gastric contents[9].

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To date, several trials have investigated the efficacy of alginate-based formulations and compared them with PPIs with mixed results[10-13]. In 2017, Leiman et al[14] assessed the efficacy of alginate-based formulations in a systematic review and meta-analysis, and reported that alginate may be effective for the treatment of GERD. However, in that review, only odds ratios (OR) of treatment effectiveness were pooled from the included studies, with varied definitions of treatment response. There was no analysis of patient-reported tools such as Heartburn Reflux Dyspepsia Questionnaire (HRDQ) and Reflux Disease Questionnaire (RDQ), as well as no analysis of adverse events. Furthermore, the majority of the studies in their review were published before 2000. In light of these limitations and recent publications of additional RCTs[10,12] , there is a need for an updated review of current data to generate high-quality evidence. The main goal of his systematic review and meta-analysis is to summarise data from recent studies comparing the efficacy and safety of alginate-based formulation with PPIs or control for the treatment of GERD.

Materials and Methods

Search Strategy

The review was designed and implemented based on the guidelines of the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses)[15] and the Cochrane Handbook for Systematic Reviews of Intervention[16], except for protocol registration. The electronic databases of PubMed, Embase, Scopus, BioMed Central, CENTRAL, and Google scholar were searched by two reviewers independently. Search limits were from 1st January 2000 to 15th June 2020. For the search, we used a combination of MeSH terms and free-text keywords. Two sets of key-words (one for the drug and other for the disease) were searched in different combinations. The first set of key-words were: "alginate", "sodium alginate", "alginic acid", "alginic acid-polyethyl methacrylate", "Gaviscon", and "algicon". For the disease, the following terms were used: "gastro-oesophageal reflux", "gastroesophageal reflux", "non-erosive reflux disease", "GERD", "NERD" AND "endoscopy negative reflux disease". After removing the duplicates, screening

of titles and abstracts was performed as a first step, followed by the review of the full text of the potential studies. Both reviewers assessed individual articles based on the inclusion and exclusion criteria. Any disagreements were resolved by discussion. After screening, the bibliography of included studies and review articles on the subject were hand searched for any missed references.

Inclusion Criteria

Only randomized controlled trials (RCTs) were eligible to be included in the review. We further defined the inclusion criteria based on the PICO (Population, Intervention, Comparison, Outcome) framework as follows: *Population*: studies conducted on adult patients (>18 years) with GERD; *Intervention*: any kind of alginate formulations with or without other drugs like PPI; *Comparison*: placebo, antacids, or PPI; *Outcomes*: reduction of symptoms and adverse events. Only English language studies were included. Studies on erosive esophagitis, non-RCTs, retrospective studies, single-arm studies, and studies not reporting relevant data were also excluded.

Data Extraction

After mutual agreement on the inclusion of studies, data were extracted by two reviewers independently. Data regarding authors, publication year, study type, diagnosis, sample size, demographic details, intervention and control drugs, study outcomes, and treatment period were extracted. The primary outcome of the interest of our analysis was the reduction in GERD symptoms. The secondary outcome was the risk of adverse events and adverse event-related treatment withdrawal. Any other outcomes reported by the included studies were reported descriptively.

Risk of Bias Assessment

The Cochrane Collaboration risk assessment tool was used for assessing the quality of included RCTs[16]. Two reviewers independently assessed each study. The following seven domains were used for quality assessment: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. The study was judged to have "high", "unclear", or "low" risk of bias for each domain. Any disagreements were resolved by discussion.

Statistical Analysis

Studies were grouped studies based on the similarity of intervention and controls into alginate *vs.* placebo/antacids; alginate + PPI *vs.* PPI, and alginate *vs.* PPI groups. Meta-analysis was conducted if at least three trials reported similar outcomes, otherwise, a descriptive analysis was

conducted. "Review Manager" (RevMan, version 5.3; Nordic Cochrane Centre [Cochrane Collaboration], Copenhagen, Denmark; 2014) was used for the meta-analysis. Outcome data was entered into the meta-analysis software and cross-checked for correctness. Since GERD symptoms were recorded by patient-reported questionnaires and as continuous outcomes, they were summarized using the mean difference (MD) with 95% confidence intervals (CI). Where different questionnaires or scales were used, the Standardized Mean Difference (SMD) was used. We used "change from baseline scores" in the meta-analysis of symptom severity. Risk ratios (RR) were calculated for adverse events and treatment withdrawals. We used a random-effects model to calculate the pooled effect size for all our analyses. Heterogeneity was assessed using the I^2 statistic. I^2 values of 25-50% represented low, values of 50-75% medium, and more than 75% represented substantial heterogeneity. Due to the inclusion of fewer than 10 studies per meta-analysis, funnel plots were not used to assess publication bias.

Results

PRISMA flow-chart of the study is presented in Figure 1. After full text-review of the selected studies, two articles were excluded. One study[17] did not report relevant outcomes, while another study[18] compared alginate with domperidone. A total of ten RCTs were included[10-13,19-24]. Details of these trials are presented in Table I.

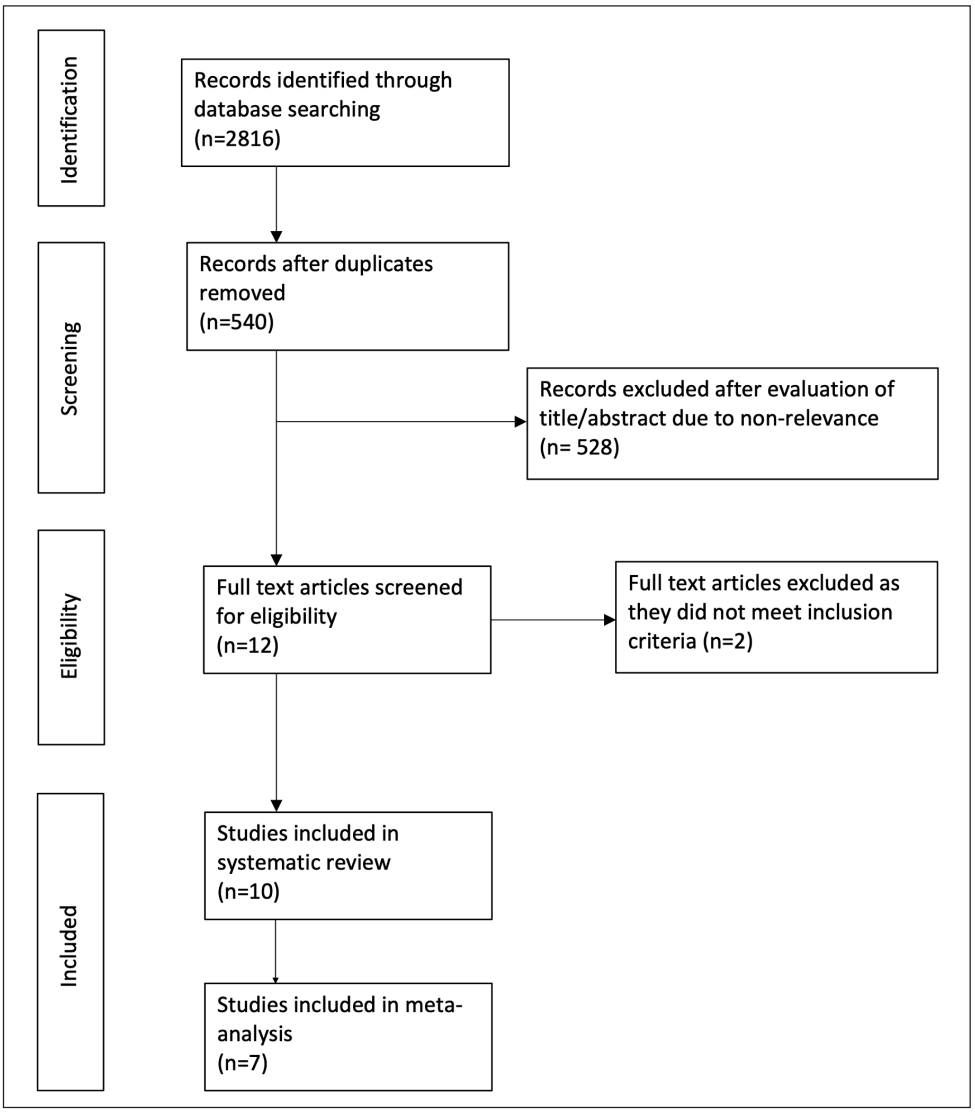

Figure 1. Study flow chart.

Table I. Details of included studies.

Study	Year	Diagnosis of GERD	Study drug	Control drug	Sample size		Male Gender (%)		BMI		Treatment duration
					Study	Control	Study	Control	Study	Control	
Wilkinson et al[12]	2019	As per Montreal definition. Frequent troublesome heartburn and/ or regurgitation (with or without dyspepsia symptoms) of at least moderate intensity during the previous 3 months and on at least 5 days during the week before the start of screening.	Gaviscon Double Action®	Placebo	212	212	48.1	45.8	28± 5.93	27.7± 5.43	7 days
Kim et al[10]	2019	Episodes of heartburn or regurgitation symptoms for at least 3 months without evidence of reflux esophagitis in a screening endoscopy; symptoms of heartburn or regurgitation during the 1-week screening period (either ≥4 days of mild symptom or ≥ 2days of moderate to severe symptoms).	A: Lamina G® + PPI B: Lamina G® only	PPI	A: 46 B: 24	48	A: 17.4 B: 16.7	23.4	A: 22.2 ± 2.3 B: 22 ± 3.2	22.3± 3.8	4 weeks
Coyle et al A*[11]	2017	Symptomatic GERD as per Montreal definition despite compliance with once-daily standard dose of PPI for at least the previous 4 weeks.	Gaviscon Double Action® + PPI	PPI	26	26	69.2	46.2	30.1± 6.1	30.4± 6.2	7-9 days
Coyle et al B*[11]	2017	Symptomatic GERD as per Montreal definition despite compliance with once-daily standard dose of PPI for at least the previous 4 weeks.	Gaviscon Double Action® + PPI	PPI	131	131	37.4	42.7	29.4± 5.3	29.2± 6.2	7-9 days
Reimer et al[19]	2016	Symptomatic GERD as per Montreal definition despite compliance with once-daily standard dose of PPI for at least the previous 4 weeks.	Gaviscon Advance® + PPI	PPI	66	70	34.9	48.6	28.1± 4.9	28± 6.5	7 days
Thomas et al[13]	2014	GERD symptoms for at least 3 months and on at least 5 of the preceding 7 days.	Gaviscon Double Action®	Placebo	56	54	57.1	51.9	29.2± 5.5	30.5± 6.3	7 days
Chiu et al[20]	2013	Heartburn or regurgitation (either one) as main symptom at least 2 days a week and had been present for ≥1 month before screening; heartburn or regurgitation (either one) during the 7 days screening period, either with frequency for ≥4 days of mild symptom or ≥2 days of moderate to severe symptom	Sodium alginate	PPI	92	91	19.6	23.1	23.9± 4	23.5± 2.9	4 weeks
Pouchain et al[21]	2012	2 to 6 days of GERD episodes per week, with heartburn, with or without regurgitation	Gaviscon®	PPI	120	121	38.2	46.3	26± 5.2	26.2± 4.7	14 days
Manabe et al[22]	2012	Moderate or severe heartburn episodes on more than 2 days per week for at least 1 month before screening	Sodium alginate (Alloid G®) + PPI	PPI	36	40	50	42.9	NR	NR	4 weeks
Lai et al[23]	2006	Classic symptoms including heartburn and/or regurgitation	Alginate (Topaal®)	Antacid	69	65	36.2	16.9	23.4± 3.8	22.8± 3.8	6 weeks
Giannini et al[24]	2006	Symptoms heartburn and/or acid regurgitation for at least 3 days in the week prior to study entry	Gaviscon Advance®	Antacid	93	98	NR	NR	NR	NR	2 weeks

BMI, Body mass index; GERD, Gastro-esophageal reflux disease; PPI, Proton-pump inhibitors; NR, Not reported
*two studies described in the same article

In one publication[11], two trials were reported. Data from both trials are presented separately. The sample size of the trials varied from 26 to 212 patients per group. Treatment duration also varied from 7 days to up to 6 weeks.

We grouped the studies with similar intervention and control drugs. Four studies compared treatment with alginate vs placebo/antacid[12,13,23,24]. In four publications[10,11,19,22], a combination of alginate and PPI was compared with PPI only, while in three studies[10,20,21] singular alginate therapy was compared with PPI. Details of outcomes reported by the included studies are presented in Table II.

Alginate vs. Placebo/Antacid

Four RCTs[12,13,23,24] were included in the Alginate vs. Placebo/Antacid sub-group: Gaviscon Double Action (Gaviscon DA®), Gaviscon advance®, and Topaal® were compared with placebo/antacid. Descriptive analysis of the results from Table II indicates that all four trials reported significantly better outcomes with alginates as compared to the control group. The severity of symptoms was assessed using the RDQ, Visual analog scale (VAS), or a 4-point Likert scale. Symptom-wise data from these questionnaires were available for a meta-analysis from three trials[12,13,23]. Our pooled analysis indicated no statistically significant difference between alginates and placebo for relief of heartburn (SMD: -1.77 95% CI -3.58, 0.04 p=0.06 I^2=99%), regurgitation (SMD: -1.83 95% CI -3.74, 0.07 p=0.06 I^2=99%) or dyspepsia (SMD: -1.00 95% CI -2.13, 0.13 p=0.08 I^2=97%) (Figure 2). Analysis of the adverse events indicated no statistically significant differences between the two groups (RR: 1.06 95% CI 0.82, 1.37 p=0.66 I^2=0%) (Figure 3). Similarly, there was no difference between the two groups for adverse event-related withdrawals (RR: 1.02 95% CI 0.43, 2.43 p=0.97 I^2=0%) (Figure 4).

Alginate + PPI vs. PPI

Four publications[10,11,19,22] with five trials were available for review in the Alginate + PPI vs. PPI sub-group. Gaviscon DA®, Gaviscon advance®, and pure sodium alginate formulations were used in the intervention group. The results from the included studies were not consistent (Table II). The trial of Reimer et al[19] reported no statistically significant reduction of reflux and heartburn score, and no difference in regurgitation and dyspepsia scores. The exploratory trial of Coyle et al[11] reported a significant decrease in all variables of the HRDQ except for dyspepsia. However, in their confirmatory trial in the same publication, the authors reported no difference between the two treatment groups. Similarly, Kim et al[10] and Manabe et al[22] did not find any significant differences in the reduction of symptoms with the addition of alginate to PPI therapy. Manabe et al[22], however, found a higher number of responders (no symptoms on day 7) in the alginate + PPI group, with patients reporting a higher number of heartburn-free days.

Pooled analysis of total RDQ/HRDQ scores from four trials showed no statistically significant difference between the two treatment groups (SMD: -0.15 95% CI -0.39, 0.08 p=0.20 I^2=41%) (Figure 5). There was also no significant differences in the incidences of heartburn (SMD: -0.40 95% CI -1.08, 0.28 p=0.25 I^2=55%), regurgitation (SMD: -0.39 95% CI -1.01, 0.22 p=0.20 I^2=59%) or dyspepsia (SMD: -0.08 95% CI -0.17, 0.01 p=0.07 I^2=0%) between alginate + PPI and PPI groups (Figure 6). Similarly, we found no statistically significant difference in frequency of adverse events (RR: 1.01 95% CI 0.74, 1.37 p=0.96 I^2=0%) (Figure 7) or treatment withdrawals (RR: 1.57 95% CI 0.40, 6.23 p=0.52 I^2=0%) between two groups (Figure 8).

Alginate vs. PPI

Three studies[10,20,21] compared alginates with PPI. Data from these trials were not consistent enough for a meta-analysis. Descriptive analysis of the results from these studies did not detect significant differences in treatment outcomes between the two groups (Table II). Only one study by Pouchain et al[21] reported a significantly greater number of heartburn-free days with alginate after day 7. However, all trials reported no difference in RDQ scores, pain scores, adequate/complete response, or reduction of nights with symptoms.

Risk of Bias

The authors' judgment of the risk of bias in the included studies is presented in Figure 9. The overall quality of the trials was high. Methods of randomization were not clearly described in two trials[10,24]. Three trials were open-label[22-24]. Eight trials were funded by their respective pharmaceutical companies[10-13,19-21].

Table II. Outcomes and results in the included studies.

Study	Outcomes	Results
Alginate vs. Placebo/Antacid		
Wilkinson et al[12]	1. ≥ 1.5 points reduction of RDQ score 2. Change in RDQ score 3. Nights with symptoms 4. OTE questionnaire	1. Significantly higher number of patients treated with Gaviscon Double Action responded to treatment 2. Significantly greater decrease in RDQ score with Gaviscon Double Action 3. No significant difference between the two groups 4. Significantly higher change of symptoms reported by patients taking Gavison Double Action
Thomas et al[13]	1. Change in RDQ scores 2. OTE questionnaire	1. Significantly greater reduction of RDQ scores with Gaviscon Double Action 2. Treatment response significantly higher with Gavison Double Action
Lai et al[23]	1. Severity of symptoms on VAS scale at 3 weeks 2. Frequency of heartburn, regurgitation and sleep disturbances	1. Significantly greater reduction of heartburn, regurgitation, vomiting and belching with alginate but no difference in nausea, epigastric pain, and dysphagia 2. Significantly reduced frequency of heartburn with alginate but no difference in regurgitation and sleep disturbances
Giannini et al[24]	1. Severity of symptoms on Likert scale 2. Complete resolution of symptoms	1. Greater reduction of severity of symptoms in the alginate group 2. Higher number of patients reported complete resolution in the alginate group
Alginate + PPI* vs. *PPI		
Kim et al[10]	1. Patients with complete resolution of symptoms 2. Change in RDQ, PAGI-QoL, PAGI-SYM scores 3. Symptom-free days during treatment period 4. Nights with symptoms	1. No significant difference between the two groups 2. No significant difference between the two groups 3. No significant difference between the two groups 4. No significant difference between the two groups
Coyle et al A*[11]	1. Change in HRQD scores 2. Number of responders [Defined as those patients with a reduction of at least 3 days with HRDQ score (heartburn and regurgitation combined) >0.7] 3. Patient satisfaction scores 4. Number of symptom free days 5. Nights with symptoms	1. Significantly greater decrease in HRDQ score with Gaviscon Double Action + PPI for all except dyspepsia 2. Significantly greater number of responders with Gaviscon Double Action + PPI 3. Significantly improved patient satisfaction with Gaviscon Double Action + PPI 4. No significant difference between the two groups 5. No significant difference between the two groups
Coyle et al B*[11]	1. Change in HRQD scores 2. Number of responders [Defined as those patients with a reduction of at least 3 days with HRDQ score (heartburn and regurgitation combined) >0.7] 3. Patient satisfaction scores 4. Number of symptom free days 5. Night time symptoms	1. No significant difference between the two groups 2. No significant difference between the two groups 3. No significant difference between the two groups 4. No significant difference between the two groups 5. No significant difference between the two groups

Continued

Table II (continued). Outcomes and results in the included studies.

Study	Outcomes	Results
Alginate + PPI* vs. *PPI		
Reimer et al[19]	1. Change in HRQD scores	1. Significantly greater reduction of reflux and heartburn score with Gaviscon Advance + PPI but no difference in regurgitation and dyspepsia scores
	2. Nights with symptoms	2. Significantly greater reduction of nights with symptoms with Gaviscon Advance + PPI
	3. Number of symptom free days	3. No significant difference between the two groups
	4. Patient satisfaction scores	4. Significantly higher patient satisfaction with Gaviscon Advance + PPI
Manabe et al[22]	1. Responders (Defined as no symptoms of heartburn by day 7)	1. Significantly more responders with Sodium alginate + PPI
	2. Reduction of each symptom	2. No significant difference between the two groups
	3. Heartburn-free days	3. Significantly higher with Sodium alginate + PPI
Alginate vs. PPI		
Kim et al[10]	5. Patients with complete resolution of symptoms	5. No significant difference between the two groups
	6. Change in RDQ, PAGI-QoL, PAGI-SYM scores	6. No significant difference between the two groups
	7. Symptom-free days during treatment period	7. No significant difference between the two groups
	8. Nights with symptoms	8. No significant difference between the two groups
Chiu et al[20]	1. Adequate heartburn or regurgitation relief (Defined as no more than 1 day of mild heartburn or regurgitation episodes in the last 7 days before day 28)	1. No significant difference between the two groups
	2. Change in RDQ scores	2. No significant difference between the two groups
	3. Patient satisfaction scores	3. No significant difference between the two groups
Pouchain et al[21]	1. Time to onset of first 24 hour heartburn-free period	1. No significant difference between the two groups
	2. Number of heartburn-free days by day 7	2. Significantly greater in PPI group
	3. Pain intensity	3. No significant difference between the two groups

HRDQ, Heartburn Reflux Dyspepsia Questionnaire; RDQ, Reflux Disease Questionnaire; OTE, overall treatment evaluation; PAGI, Patient Assessment of Upper Gastrointestinal Disorders; QoL, Quality of life; SYM, Symptom severity index; VAS, visual analog scale.
*two studies described in the same article

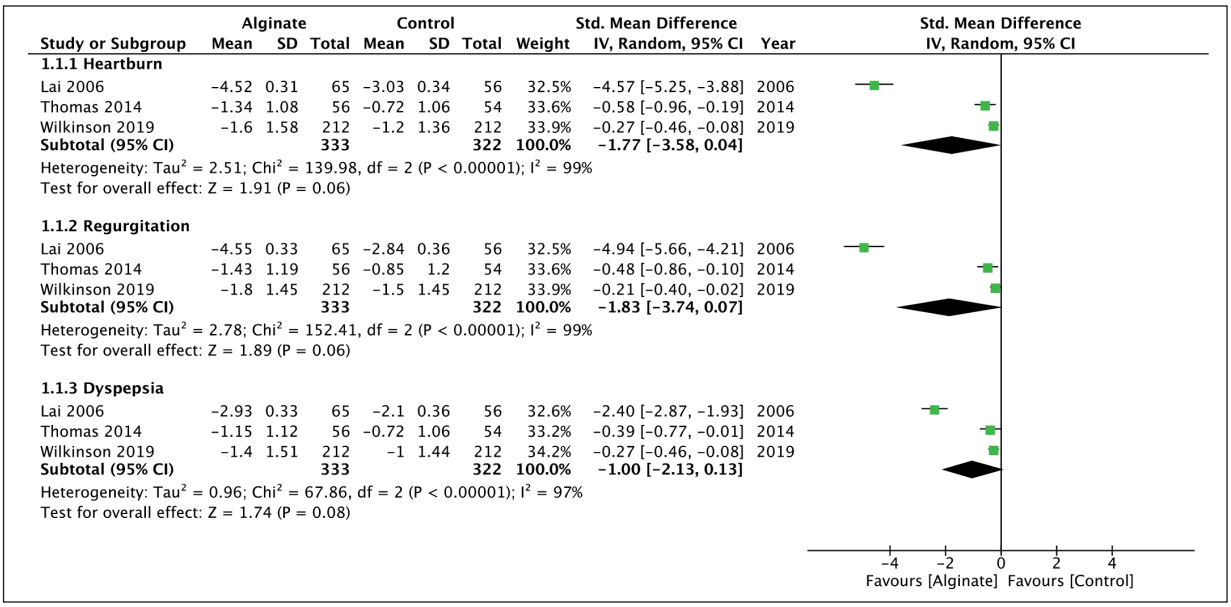

Figure 2. Meta-analysis of heartburn, regurgitation and dyspepsia scores for alginate *vs.* placebo/antacids.

Discussion

Our systematic review and meta-analysis of current literature encompassing 11 RCTs suggest that alginate may be somewhat more effective than placebo/antacids in improving outcomes of GERD. Current evidence on the efficacy of alginate-based formulations *vs.* PPI or the role of added alginates with PPI is, however, questionable with literature suggestive of no difference between the two drugs. The risk of adverse events with alginates is no greater than that of placebo or PPIs.

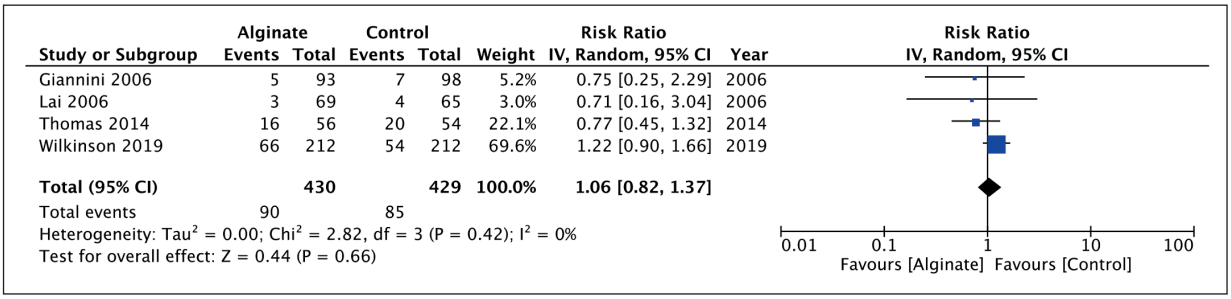

Figure 3. Meta-analysis of adverse events for alginate *vs.* placebo/antacids.

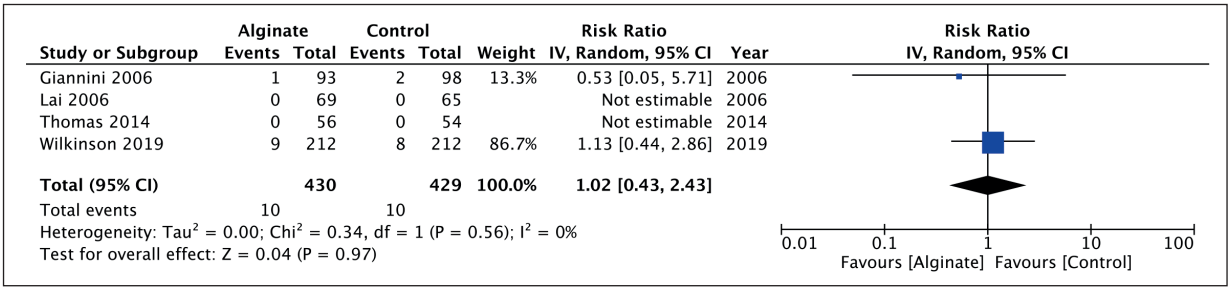

Figure 4. Meta-analysis of treatment withdrawals for alginate vs placebo/antacids.

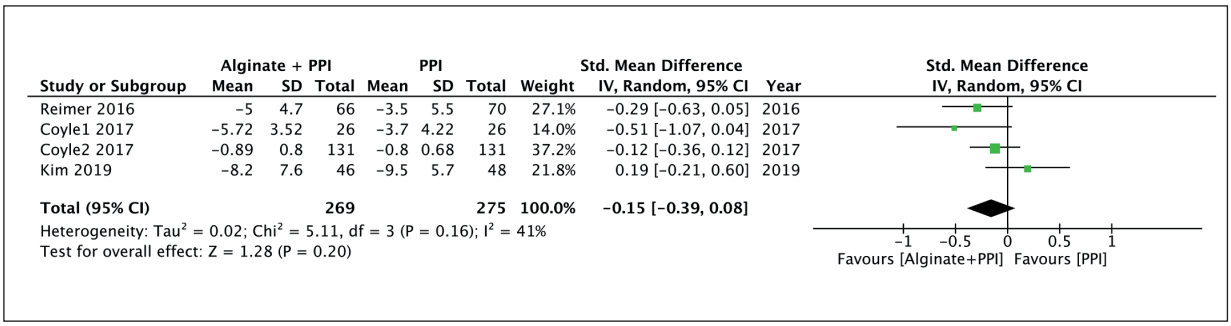

Figure 5. Meta-analysis of total RDQ/HRDQ scores for alginate + PPI *vs.* PPI.

Alginate is a naturally occurring polysaccharide polymer that has been used for the management of GERD symptoms for many decades[9]. The drug acts by rapidly interacting with gastric acid forming a raft-like structure over the gastric contents. During reflux, this gel form preferentially moves into the esophagus thereby reducing symptoms and also preventing mucosal damage[9]. Alginates are capable of eliminating or displacing the acid pocket away from the esophagogastric junction in GERD patients[25]. Nevertheless, a similar effect has also been reported with PPIs[26]. Therefore,, it is important to know if alginates are superior to placebo or PPIs for managing GERD. First clinical trials of the efficiency of alginates are dating back to 1970s[27,28]. However, over the last two decades, there has been renewed interest in the role of alginates for managing GERD patients, with several studies analyzing its efficacy in a randomized setting. This review analyzes data from trials published in the last 20 years.

Descriptive analysis of all four trials comparing alginates with placebo/antacids in our review have indicated significantly better outcomes with alginate-based formulations. Due to the heterogeneity of outcomes, a meta-analysis was only possible for patient-reported symptom reduction scores, the results of which did not favor alginates. Nevertheless, on close examination of the forest plot, it can be seen that the MD of symptom scores for the three trials was statistically significant for all three symptoms, although with the upper end

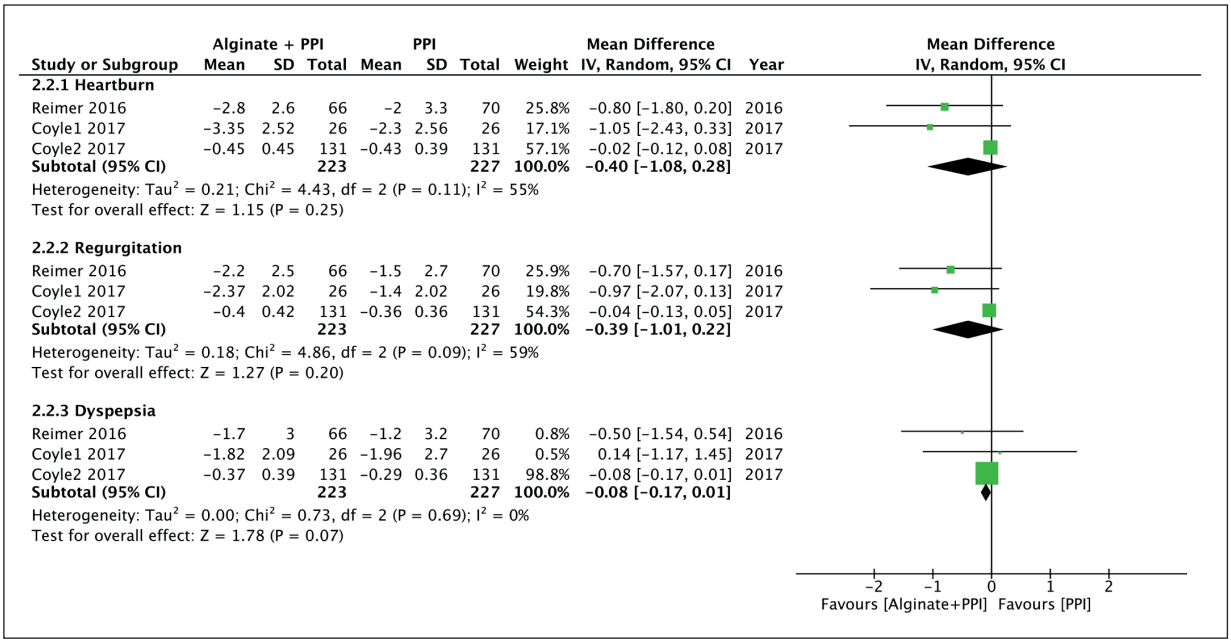

Figure 6. Meta-analysis of heartburn, regurgitation and dyspepsia scores for alginate + PPI *vs.* PPI.

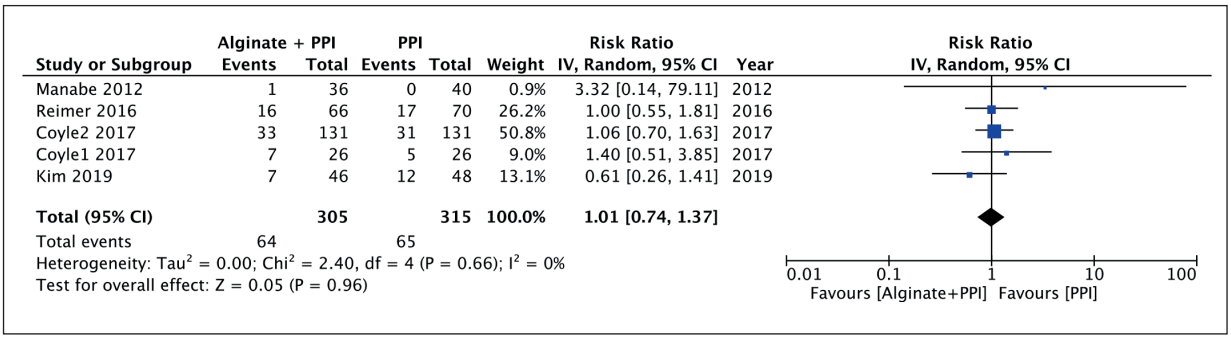

Figure 7. Meta-analysis of adverse events for alginate + PPI *vs.* PPI.

of the 95% CI very close to zero. The upper end of 95% CI for the pooled outcomes was also just above zero (heartburn: 0.04; regurgitation: 0.07; dyspepsia: 0.13) while the lower ends were >2 for all three symptoms. Thus, despite a non-significant result, there is evidence that alginates may lead to a better reduction of GERD symptoms as compared to placebo/antacids. The small effect size may be attributed to the short duration of two trials included in our meta-analysis[12,13]. It has been shown that placebo/antacid response in trials shorter than 2 weeks can be as high as 56%[14]. This can also explain the larger effect size seen in the trial of Lai et al[23] which measured outcomes at three weeks.

Our meta-analysis failed to demonstrate any significant benefit of alginate addition to PPI . There was no statistically significant difference in total HRDQ/RDQ scores, as well as in the severity of heartburn, regurgitation, and dyspepsia scores between the two groups. Similarly, MD of individual studies comparing alginate treatment with placebo/antacids were non-significant, and the lower end of the total effect size was close to -1. Tree trials, directly comparing alginates with PPIs[10,20,21] did not show any benefit of alginate treatment. Our results are in agreement with previous meta-analysis of Leiman et al[14] that reported significantly higher treatment response with alginates compared to placebo/antacids (OR: 4.42; 95% CI 2.45–7.97) but demonstrated no statistically significant difference between alginates vs PPIs and Histamine-2 receptor antagonists (OR:0.58; 95% CI 0.27–1.22). Despite similar results, our review significantly differs from that of Leiman et al[14]. The European Medicines Agency guidance[29] recommends that the primary outcome of trials on GERD patients be a responder analysis which should be based on the number of patients experiencing a clinically relevant reduction of GERD symptoms. However, in order to pool outcomes of different studies, the definition of "treatment response" needs to be similar across trials. Due to significant difference in definitions between the included studies, and under-reporting of data by some of the trials, such "response analysis" for pooling ORs was not attempted in our review, and only a descriptive analysis was carried out. Our analysis, therefore, provides explicit evidence on the efficacy of alginates by pooling change of symptoms score measured on a linear scale. A second important difference is that our review summarized recent studies with the addition of four new RCTs[10-12,19,] thus presenting the latest updated evidence.

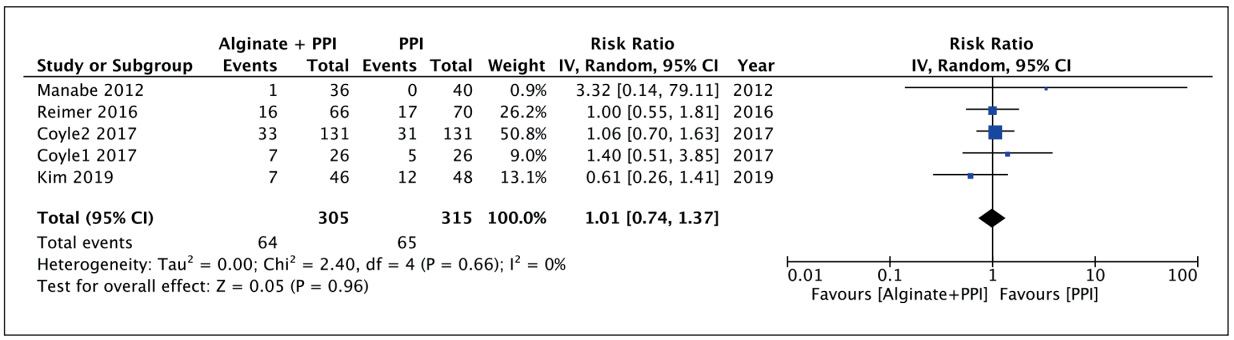

Figure 8. Meta-analysis of treatment withdrawal for alginate + PPI *vs.* PPI.

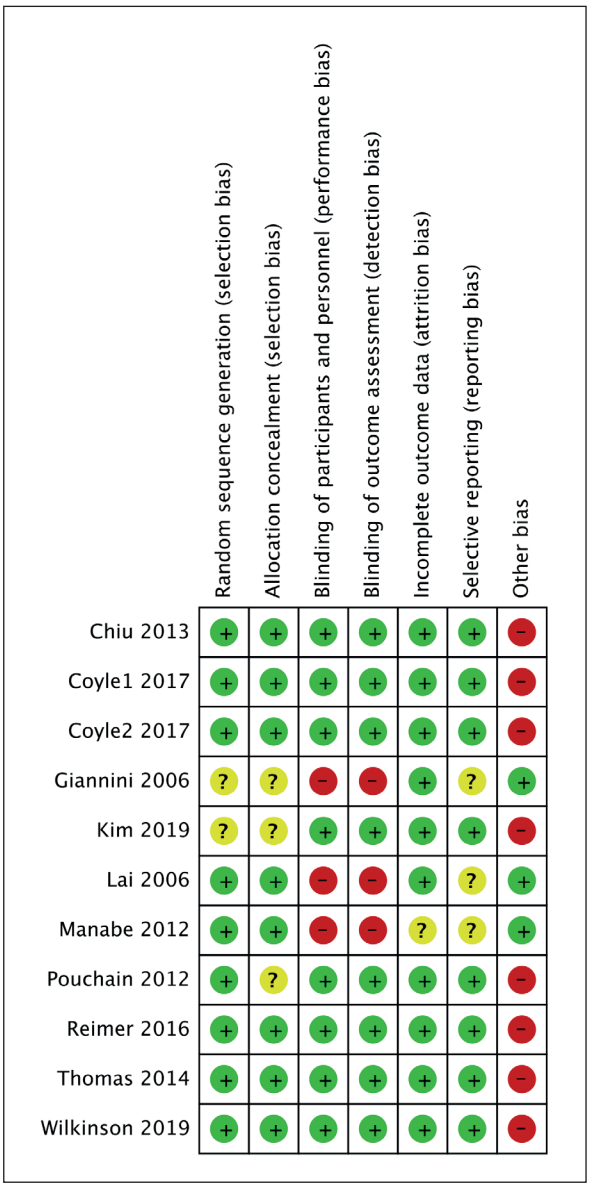

Figure 9. Risk of bias summary.

In addition to treatment efficacy, our study analyzed safety profile of alginates compared to standard/placebo treatment. Data on drug safety was reported by the majority of trials and pooled analysis indicated no increased risk of adverse events with alginate formulations. The number of treatment withdrawals was also not significantly increased with alginates.

Our review has a number of limitations. While 11 trials were included in the review, the number of studies in the meta-analysis of treatment outcomes was limited There was large heterogeneity in our analysis which can be attributed to the differences in the study populations (e.g., disease severity) and study duration, as well as variations in the composition of alginate formulations, with some studies using combination of alginates with antacids (Gaviscon DA) and some using pure alginate (Lamina G®). Recent studies do not provide evidence that antacids significantly improve GERD symptoms[30]. Additionally, several trials included in our review were sponsored, raising a possibility of conflict of interests. Lastly, inconsistent definitions and reporting in the included studies did not allow a meta-analysis of several outcomes, such as complete response to therapy, symptom-free days, and nights without symptoms.

Despite these limitations, our meta-analysis provides a significant update on the efficacy and safety of alginates for GERD. We analysed recent studies only (post-2000) to present current evidence on alginates. In contrast to the previous review[14], we carried out pooled analysis of RDQ/HRDQ scores and symptom-wise scores to present comprehensive evidence. A detailed qualitative and quantitative (where possible) analysis was carried out from high-quality studies. Lastly, we grouped studies comparing alginates with antacids/placebo and PPI separately to clearly identify the role of these drugs in the management of GERD.

Conclusions

Our study indicates that alginates may have greater efficacy than placebo/antacids in improving outcomes of GERD. Current evidence on the efficacy of alginate-based formulations vs PPI or the role of added alginates with PPI is, however, questionable and suggests no difference between the two drugs. The risk of adverse events with alginates is no greater than that of placebo or PPIs. There is a need for further independent trials comparing similar alginate formulations with placebo and PPIs, reporting similar outcome measures for both long and short term treatment duration.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

CZ conceived and designed the study. JW and MG collected the data and performed the literature search. CZ was involved in the writing of the manuscript. All authors have read and approved the final manuscript.

Ethical approval

Not applicable

Conflict of Interests

The authors declared there is no conflict of interest.

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DISEASES OF THE ESOPHAGUS

ISDE The International Society for Diseases of the Esophagus

Original Article

Alginate therapy is effective treatment for GERD symptoms: a systematic review and meta-analysis

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SUMMARY. **In patients with gastroesophageal reflux disease (GERD) and erosive esophagitis, treatment with proton pump inhibitors (PPIs) is highly effective. However, in some patients, especially those with nonerosive reflux disease or atypical GERD symptoms, acid-suppressive therapy with PPIs is not as successful. Alginates are medications that work through an alternative mechanism by displacing the postprandial gastric acid pocket. This study performed a systematic review and meta-analysis to examine the benefit of alginate-containing compounds in the treatment of patients with symptoms of GERD. PubMed/MEDLINE, Embase, and the Cochrane library electronic databases were searched through October 2015 for randomized controlled trials comparing alginate-containing compounds to placebo, antacids, histamine-2 receptor antagonists (H2RAs), or PPIs for the treatment of GERD symptoms. Additional studies were identified through a bibliography review. Non-English studies and those with pediatric patients were excluded. Meta-analyses were performed using random-effect models to calculate odds ratios (OR). Heterogeneity between studies was estimated using the I^2 statistic. Analyses were stratified by type of comparator. The search strategy yielded 665 studies and 15 (2.3%) met inclusion criteria. Fourteen were included in the meta-analysis ($N = 2095$ subjects). Alginate-based therapies increased the odds of resolution of GERD symptoms when compared to placebo or antacids (OR: 4.42; 95% CI 2.45–7.97) with a moderate degree of heterogeneity between studies ($I^2 = 71\%$, $P = .001$). Compared to PPIs or H2RAs, alginates appear less effective but the pooled estimate was not statistically significant (OR: 0.58; 95% CI 0.27–1.22). Alginates are more effective than placebo or antacids for treating GERD symptoms.**

KEY WORDS: **alginate, gastroesophageal reflux disease, meta-analysis.**

INTRODUCTION

Approximately 25% of the Western population has symptoms of gastroesophageal reflux disease (GERD) at least weekly.[1] GERD also is among the most frequent reasons for outpatient gastroenterology consultation.[2] Current professional guidelines recommend medical management of GERD primarily with proton pump inhibitors (PPIs),[3,4] the most effective therapy for erosive esophagitis.[5] In some patients with GERD symptoms, especially those with nonerosive reflux disease (NERD), suppression of gastric acid with PPIs is not as effective.[3]

An alternative approach to manage symptomatic GERD is to impede the flow of acidic refluxate. Alginic acid derivatives, or alginates, treat GERD via a unique mechanism by creating a mechanical barrier that displaces the postprandial acid pocket.[6] In the presence of gastric acid, they precipitate into a gel and form a raft that localizes to the acid pocket in the proximal stomach.[7] Although available in many countries over-the-counter for several decades, often in combination with antacids, this class of medications recently

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has been the focus of renewed research interest.[8] By providing an impediment to distal esophageal acid exposure, alginates may be superior to other measures or particularly useful as an additional option for patients with GERD not responding to antisecretory therapy. In this study, we aimed to determine if alginate-containing compounds are an effective treatment for patients with symptomatic GERD.

MATERIALS AND METHODS

Literature search

Articles were identified by searches of PubMed/MEDLINE, Embase, and the Cochrane databases through October 2015. Searches were based on controlled vocabulary including medical subject heading (MeSH) terms when possible ('alginates' and 'gastroesophageal reflux'). In addition, relevant keywords and variations of root words were also included in the search ('alginate,' 'alginic,' 'alginic acid,' 'alginic acid-polyethyl methacrylate,' 'algicon,' 'gaviscon,' 'pyrogastrone,' 'antacid,' 'antacid agent,' 'aluminum hydroxide,' 'magnesium trisilicate,' 'sodium bicarbonate drug combination,' 'gastro-oesophageal reflux,' 'gastrooesophageal reflux,' 'oesophageal reflux,' 'non-erosive reflux disease,' 'GERD,' 'GORD,' 'NERD,' 'NORD,' 'endoscopy negative reflux disease,' 'ENRD'). The search was conducted by combining terms representing disease therapies with terms representing the disease itself (for example, 'alginates AND gastroesophageal reflux disease'). Next, the bibliographies of articles included in the final analysis as well as relevant reviews were screened for additional articles. Third, the website ClinicalTrials.gov was searched for additional studies not indexed in the above databases. Authors of relevant studies and manufacturers of alginate therapies (Reckitt-Benckiser, GlaxoSmithKline, and Prestige Brands) were contacted to inquire about completed studies not yet published. Two independent reviewers (DAL and BPR) evaluated articles at the title, abstract, and full-text review stages. Disagreements were resolved by consensus.

Data extraction and risk of bias assessment

All randomized controlled trials of alginates in adult patients (greater than 18 years of age) with GERD and written in English were included in the review. Exclusion criteria included studies that examined patients with erosive esophagitis, patients less than 18 years of age, studies that compared alginate formulations to each other and studies published as abstracts only. Using a standardized form, the two reviewers (DAL and BPR) independently extracted data for inclusion in the analysis and assessed trial risk of bias using the Cochrane Risk of Bias Tool.[9] Any disagreements were resolved by consensus.

Statistical analysis

Pooled estimates for the effect of alginate-containing formulations compared with alternative therapies were computed for the outcome of GERD symptom relief, which was based on the definition provided in each study. The primary analyses were stratified by therapy type. Neither placebo and antacids nor alginates have long-term effects on GERD;[10] therefore, the former were combined as a single comparator group (temporary acid neutralizing therapy) with alginates. Acid-suppressive therapies (PPIs and H2RAs) were the other comparison group. In one study with multiple experimental and control arms, groups with similar active components (alginate and alginate plus antacid) were combined to create a single pair-wise comparison (placebo);[11] in another multiarmed study, similar control arms were combined (placebo and antacid) to create a pair-wise comparison with the active comparator (alginate plus antacid).[12] Heterogeneity was analyzed by calculating the I^2 measure of inconsistency and was considered statistically significant if $I^2 > 50\%$ and $P < 0.1$ by the Chi-square test.

Pooled estimates were reported as odds ratios (ORs) derived from a random-effect model, given the potential for heterogeneity between studies. To examine potential contributors to heterogeneity, prespecified subgroup analyses were performed. Studies were grouped by geographic location, year of publication (prior to 1990 and after 1990), number of centers involved (single versus multicenter) and study duration (less than or equal to 2 weeks versus 1 month or greater). Contribution to heterogeneity was assessed by the I^2 statistic to determine which factors eliminated or reduced heterogeneity to a minimal level ($I^2 < 50\%$). Given the overall small number of studies, there was insufficient power to assess for reporting bias using a Begg's test and it was therefore not performed.

All statistical analyses were performed using the STATA software (version 13.0; StataCorp, College Station, TX). All components of this study were exempted from approval by the institutional review board at the University of Pennsylvania. The study was indexed within the PROSPERO register (2015:CRD42015017908).

RESULTS

Article search and identification

The initial database search identified 660 studies; five additional articles were found through a supplemental review (Fig. 1). After evaluating titles and

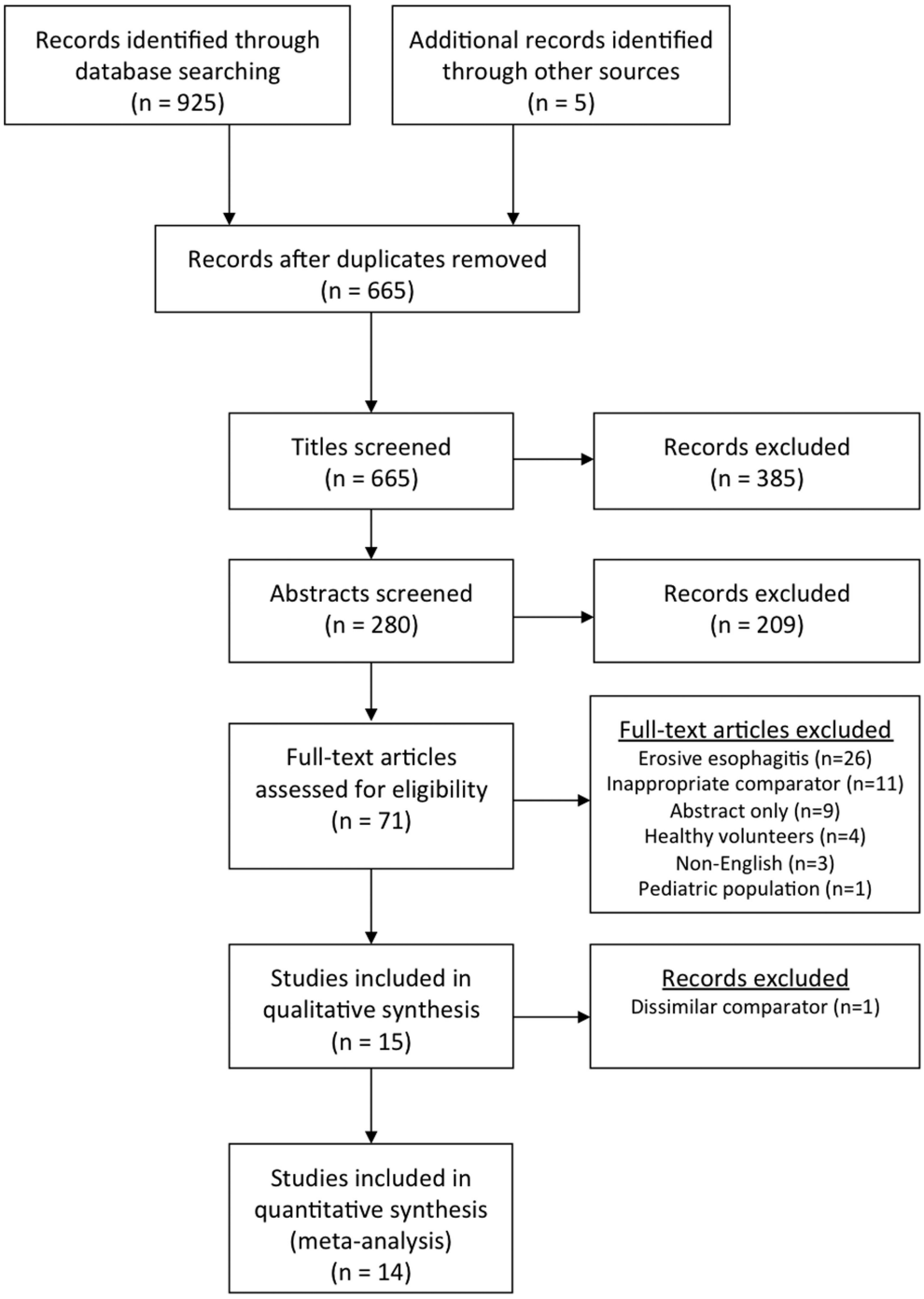

Fig. 1 PRISMA flow diagram of article search and identification.

abstracts, 594 studies were excluded. Of the remaining 71 studies, 15 met inclusion criteria after a fulltext review (Table 1). All studies were randomized controlled trials (RCTs). Ultimately, 14 studies ($N = 2095$) were included in the meta-analysis and two separate comparisons were performed. Alginate-based therapies were compared to either placebo or antacid therapy in nine studies ($N = 900$) and to PPIs and H2RAs in five studies ($N = 1195$). The single study that was not included in a meta-analysis evaluated cisapride as a comparator, a drug no longer commercially available in many countries, and one that does not act via an acid-neutralizing or acid-suppressive mechanism.[13]

All studies evaluated symptomatic GERD response with improvement defined as either complete resolution or significant improvement in typical symptoms.

Despite all studies being RCTs, the risk of bias appeared most prominent with respect to detection (blinding of outcome assessment), performance (blinding of participants and personnel), and attrition (incomplete outcome data) across all studies (Table 2).

Table 1 Characteristics of studies included in this systematic review

Study	Study design	GERD diagnosis and/or severity	Comparators (*N*)	Duration (formulation)	Outcome	Results
Placebo or antacid as comparators						
Beeley and Warner[11]	Randomized, double-blind, three-arm cross-over Single Center	Typical symptoms and presence of hiatal hernia on barium	Alginate (28) vs. alginate + antacid (28) vs. placebo (28)	2 weeks (Tablet)	Improvement in regurgitation	Alginate (19/28) vs. alginate + antacid (25/28) vs. placebo (12/28)
Stanciu and Bennett[12]	Randomized, single-blind, three-arm parallel group multicenter	Typical symptoms	Alginate + antacid (20) vs. antacid (20) vs. placebo (20)	2 weeks (Tablet)	Global improvement of symptoms	Alginate + antacid (11/20) vs. antacid (5/20) vs. placebo (7/20)
Barnardo *et al.*[14]	Randomized, double-blind cross-over single center	Typical symptoms and reflux on barium	Alginate + antacid (26) vs. antacid (26)	6 weeks (Tablet)	Global acceptability of treatment	Alginate + antacid (21/26) vs. antacid (5/26)
Chevrel[15]	Randomized, open-label, cross-over single center	Typical symptoms and reflux on barium	Alginate (44) vs. antacid (44)	2 weeks (liquid)	Global improvement of symptoms	Alginate (37/44) vs. antacid (10/44)
Lang and Dougall[16]	Randomized, parallel group multicenter	Reflux dyspepsia of pregnancy	Alginate + antacid (50) vs. antacid (47)	2 weeks (liquid)	Improvement in nighttime reflux symptoms	Alginate (41/50) vs. antacid (36/47)
Chatfield[17]	Randomized, double-blind, parallel group multicenter	Typical symptoms ≥ 2 days/week	Alginate + antacid (46) vs. placebo (48)	4 weeks (liquid)	Global improvement of symptoms	Alginate + antacid (39/46) vs. placebo (17/48)
Giannini *et al.*[18]	Randomized, open-label, parallel group multicenter	Typical symptoms ≥ 3 days/week	Alginate + antacid (87) vs. antacid (92)	2 weeks (liquid)	Complete absence of symptoms	Alginate + antacid (71/87) vs. antacid (68/92)
Lai *et al.*[19]	Randomized, open-label, parallel group single center	Typical symptoms and EGD without erosions	Alginate (69) vs. antacid (65)	6 weeks (tablet)	Global improvement of symptoms assessed by physician	Alginate (42/65) vs. antacid (18/56)
Thomas[20]	Randomized, double-blind, parallel group single center	Typical symptoms ≥ 5 days/week	Alginate + antacid (56) vs. placebo (54)	1 week (tablet)	Overall treatment response	Alginate + antacid (47/56) vs. placebo (34/54)
Proton pump inhibitor or histamine-2 receptor antagonist as comparators						
Bennett *et al.*[21]	Randomized, parallel group single Center	Typical symptoms and positive pH test	Alginate + antacid (19) vs. alginate + antacid + H2RA (17)	6 weeks (tablet)	Global improvement of symptoms	Alginate + antacid (12/19) vs. alginate + antacid + H2RA (15/17)
Goves *et al.*[22]	Randomized, single-blind, parallel group multicenter	Typical symptoms ≥ 2 days/week	Alginate (337) vs. PPI (333)	2 weeks (liquid)	Complete resolution of symptoms	Alginate (27/337) vs. PPI (90/333)
Poynard *et al.*[13]	Randomized, open-label, parallel group multicenter	Typical symptoms ≥ 2 days/week	Alginate (180) vs. 5HTR agonist (173)	4 weeks (liquid)	Global improvement of symptoms	Alginate (158/180) vs. 5HTR agonist (120/173)
Manabe *et al.*[23]	Randomized, open-label, parallel group multicenter	Typical symptoms ≥ 2 days/week *and* EGD without erosions	Alginate + PPI (26) vs. PPI (31)	4 weeks (liquid)	Complete resolution of regurgitation	Alginate + PPI (18/26) vs. PPI (20/31)
Pouchain *et al.*[24]	Randomized, double-blind, parallel group multicenter	Typical symptoms ≥ 2 days/week	Alginate (120) vs. PPI (121)	1 week (liquid)	Self-assessed heartburn/pain relief	Alginate (62/120) vs. PPI (74/121)
Chiu *et al.*[25]	Randomized, double-blind, parallel group Multicenter	Typical symptoms ≥ 2 days/week and EGD without erosions	Alginate (92) vs. PPI (91)	4 weeks (liquid)	Relief of heartburn or regurgitation	Alginate (49/92) vs. PPI (46/91)

Typical symptoms include heartburn, volume regurgitation, dyspepsia, and/or retrosternal chest pain.
EGD, upper endoscopy; GERD, gastroesophageal reflux disease; H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor; UK, United Kingdom; 20 mg omeprazole daily; 5HTR, serotonin receptor, 20 mg cisapride daily; 400 mg cimetidine four times daily.

Table 2 Risk of bias assessment for studies included in this systematic review

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting
Antacid and placebo as comparators						
Beeley and Warner[11]	yellow	yellow	green	green	green	green
Stanciu and Bennet[12]	yellow	yellow	yellow	green	green	green
Barnardo et al.[14]	yellow	yellow	green	green	red	green
Chevrel 1980[15]	green	yellow	yellow	red	green	green
Lang and Dougall[16]	yellow	yellow	yellow	yellow	red	green
Chatfield[17]	yellow	yellow	green	green	red	green
Giannini et al.[18]	yellow	yellow	red	red	green	green
Lai et al.[19]	green	green	red	red	yellow	green
Thomas et al.[20]	green	green	green	green	green	green
Proton pump inhibitors and histamine-2 receptor antagonists as comparators						
Bennett et al.[21]	yellow	yellow	green	red	green	green
Goves et al.[22]	yellow	yellow	red	red	green	green
Poynard et al.[13]	green	yellow	yellow	red	green	green
Manabe et al.[23]	green	yellow	red	red	green	green
Pouchain et et al.[24]	green	yellow	green	green	green	green
Chiu et al.[25]	green	green	green	green	yellow	green

Red – high risk of bias; yellow – uncertain risk of bias; green – low risk of bias

Placebo and antacid therapy as comparators

Alginate therapy was uniformly favored over placebo or antacids in all studies (Fig. 2). Overall, there was a statistically significant treatment benefit for alginate-based therapies with an odds ratio of 4.42 (95% CI 2.45–7.97). When excluding those studies with the largest treatment effects,[14,15] the overall estimate did not change significantly. The heterogeneity between these studies was moderate ($I^2 = 71\%$, $P = .001$).

We subsequently explored this heterogeneity through subgroup analyses. Geographic region (Europe versus Asia) and year of publication assessed by before or after 1990 did not account for the heterogeneity as results were stable by geographic region and over time. Study setting defined by single center or multicenter did not account for the heterogeneity. Study duration may have accounted for some of the heterogeneity as there was less heterogeneity when

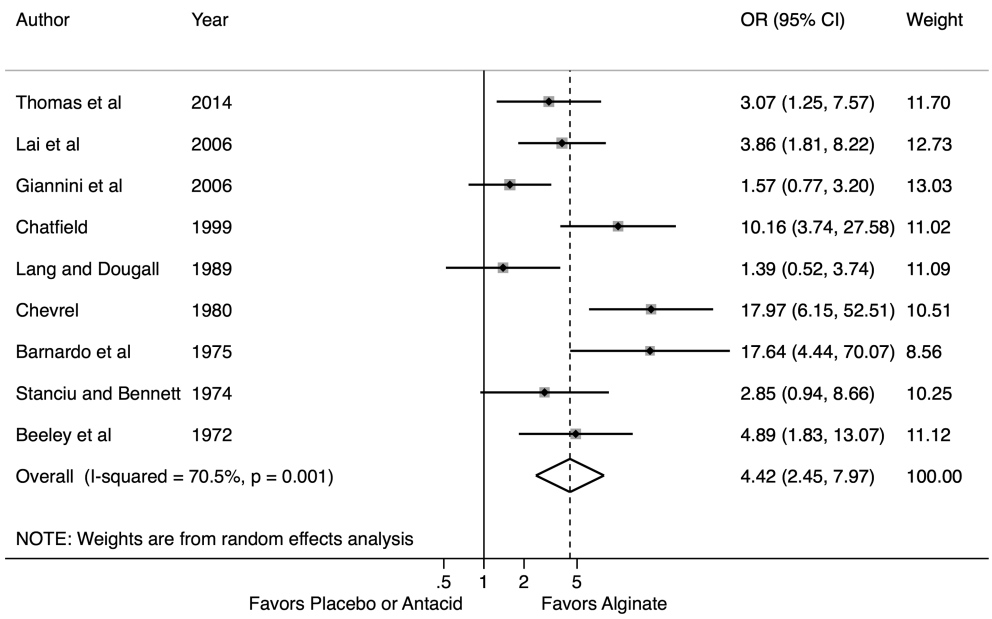

Fig. 2 Forest plot of meta-analysis for alginate therapy versus placebo or antacid.

combining only those studies ($N = 3$) lasting longer than 2 weeks ($I^2 = 57\%$, $P = 0.10$).

Proton pump inhibitor and histamine-2 receptor antagonist as comparators

Five studies evaluated alginate benefit versus acid-suppressive therapy with PPIs or H2RAs (Fig. 3). In four, alginate was compared against PPIs, while in the fifth a H2RA was the comparator. Measured against these comparators, alginates are not favored (OR: 0.58; 95% CI 0.27–1.22) but there was a high degree of heterogeneity ($I^2 = 82\%$, $P < .001$). There were too few studies to assess if specific subgroups accounted for the heterogeneity. When excluding the only study to examine H2RAs against alginates, the meta-estimate did not change significantly. Those studies published within the last 5 years ($N = 3$ studies) demonstrated less difference between therapies (OR: 0.88, 95% CI 0.61–1.26) with no heterogeneity ($I^2 = 0\%$, $P = .37$).[23–25]

DISCUSSION

This systematic review and meta-analysis provide a comprehensive estimate of the utility of alginate-based therapy in the management of adults with GERD symptoms. The pooled data from the clinical trials demonstrated that alginates are superior to placebo and antacids for controlling GERD symptoms in adults. In addition, we found that when compared to acid-suppressive therapy with PPIs or H2RAs, alginates alone appeared less effective but the pooled estimate was not statistically significant. While current treatment guidelines recommend the use of acid suppression as first-line therapy for patients with chronic GERD symptoms, many patients have only intermittent or mild symptoms. Our study suggests that alginates alone provide superior benefit over antacids and therefore they could be considered as an initial treatment for patients with mild GERD symptoms for whom chronic acid suppression was either undesirable or deemed unnecessary.

Alginate-based compounds have been available for several decades. In the United States, they are typically sold under the brand name Gaviscon in both tablet and liquid formulations, which are available without a prescription. These products cite their active ingredients as aluminum hydroxide and magnesium trisilicate or magnesium carbonate, respectively. Alginic acid is listed as an inactive ingredient. The brand name Gaviscon, however, is used to market alginate-based therapies in a number of other countries including Canada and throughout Europe. Formulations like 'Gaviscon Acid Breakthrough' in Canada lists alginic acid as an active ingredient, similar to 'Gaviscon Advance' in the United Kingdom. Recently, there has been a resurgence of interest in alginates as a therapy for GERD, including for patients with continued symptoms despite acid suppression therapy.[8]

A previous narrative review published in 2000 summarized the literature on alginate therapy.[26] The review suggested superiority of alginates compared to placebo with at least equal efficacy compared to conventional antacids, although it was not limited to clinical trials. A 2006 meta-analysis favored alginate therapy over placebo.[27] However, Tran *et al.* included only three studies, all of which compared placebo to an alginate–antacid combination and thus

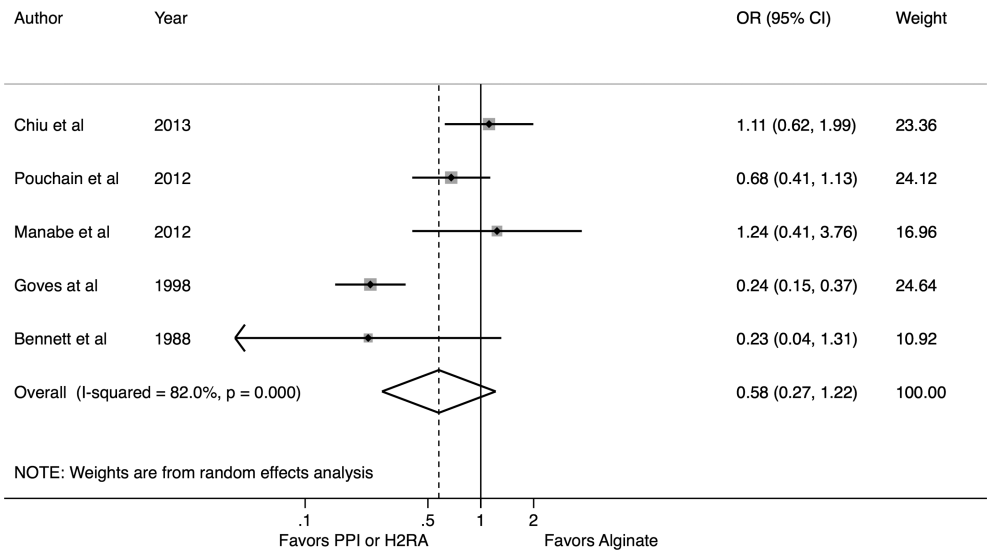

Fig. 3 Forest plot of meta-analysis for alginate therapy versus proton pump inhibitors or histamine-2 receptor antagonists.

may have overestimated the treatment effect of alginates. Several individual studies have been published since that time further evaluating the role of alginates compared to placebo and antacids as well as investigating alginates versus acid-suppressive therapy with PPIs.[18–20,23–25] Therefore, we performed an updated systematic review and meta-analysis.

We evaluated the benefit of alginates compared to other forms of medical therapy for symptomatic GERD. We excluded studies of erosive esophagitis, for which PPIs are clearly indicated as first-line therapy.[28,29] All studies included in our analysis required patients to have typical symptoms of GERD, but entrance criteria for many did not require endoscopy or ambulatory pHmetry. Therefore, it is likely that some of the patients in these studies had erosive esophagitis. It is expected that alginate therapy would be less effective for erosive esophagitis and as such we may have under estimated the therapeutic benefit relative to placebo or antacids.

An earlier meta-analysis found PPIs modestly beneficial compared to H2RAs and prokinetics for endoscopy-negative reflux disease;[30] our analysis slightly favors PPIs compared to alginates, though the results were not statistically significant. In contrast, in both of the studies that compared alginates to PPIs among patients with endoscopy-negative reflux disease alginates were slightly favored but this did not meet statistical significance.[23,25] While increasing evidence points to alginates displacing the postprandial acid pocket and inhibiting acid exposure in the esophagus, the precise mechanism of action of alginates remains uncertain.[6,31] Patients with nonerosive reflux and GERD symptoms may be deriving additional benefit through mechanical or other mechanisms independent of displacing or neutralizing the acid pocket.

Among the strengths of the current study is the more robust pooled estimate versus the previous work. The majority of clinical studies on alginates are European so we performed an Embase search, which includes in-depth indexing of pharmaceuticals as well as a richer source of European journals than MEDLINE/PubMed alone.[32] Also, we compared alginates and combination alginates plus antacids to placebo and antacids alone, respectively, to assess for the effect of the alginate. While some formulations of alginate-containing therapies include an antacid, there is no evidence that antacids significantly improve GERD beyond immediate and temporary symptom relief and alginates themselves have only minimal acid neutralizing effects.[10,33] Adding an active ingredient as a comparator might be expected to diminish the difference in measured efficacy of the two treatments. However, the benefit of alginates was substantial and independent of whether antacids were part of the alginate formulation.

We observed heterogeneity in the results of the clinical trials. Some differences between studies were evident such as criteria used for diagnosing GERD. This is not entirely unexpected given that included studies were performed over the course of more than 40 years. However, severity of GERD symptoms was moderate to severe and mostly similar between studies, even when comparing those performed prior to and following publication of the Montreal Consensus requiring typical symptoms of heartburn and regurgitation to occur at least 2 days per week.[34] Study duration may have accounted for some of the observed heterogeneity in studies comparing alginates to placebo or antacids. This may relate to the transient efficacy of placebo and antacids in clinical trials. The response rate of placebo- or antacid-treated patients in trials with durations greater than 2 weeks was approximately 31% as compared to 56% among trials that

were two weeks of duration or less. In contrast, the overall response rate in the active treatment arms was relatively similar regardless of treatment duration.

Across studies, there were small differences in endpoints with most evaluating for either subjective improvement or complete elimination in global GERD symptoms, though some evaluated for more specific findings such as regurgitation or pregnancy-related reflux. As a result, it is not possible to determine which population is definitively most likely to benefit from alginate therapy. Instead, our data provide more general support for the value of alginates, particularly with renewed interest in minimizing PPI usage.[35] Further trials are needed to focus on whether there is an adjunctive benefit to adding alginate for those already on acid suppression or if there is a specific patient group for whom alginates are most effective.

In summary, data from the available clinical trials support the efficacy of alginates for the treatment of symptomatic GERD. They were superior to placebo and antacids. These data also support the need for larger randomized controlled trials of alginates plus PPIs to test their efficacy as an adjunctive agent in patients on acid suppression with incomplete symptom control.

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