Prokinetic drug utility in the treatment of gastroesophageal reflux esophagitis: a systematic review of randomized controlled trials

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ABSTRACT

Background: Esophagitis caused by gastroesophageal reflux disease (GERD) results in appreciable morbidity and economic burden. No systematic review has addressed the effectiveness of prokinetic drugs in the treatment of GERD esophagitis in adults.

Objective: To determine the utility of prokinetic drugs in improving symptoms and endoscopic lesions in patients with GERD esophagitis.

Methods: We included randomized controlled trials that compared prokinetic drugs with placebo. A systematic search included the Cochrane Controlled Trial Register, MEDLINE, CINAHL, LILACS, EMBASE, a manual search of books and article references, and contact with pharmaceutical companies. Reviewers assessed methodological quality and extracted data that were combined using a random effects model.

Results: Eighteen articles met the eligibility criteria; of these, 13 used prokinetic drugs alone, 4 tested prokinetic drugs as additional therapy in patients receiving histamine-2 receptor blockers, and 1 tested them in patients receiving proton pump inhibitors. Seven studies evaluated clinical improvement only, 5 addressed endoscopic improvement only, and 6 reported both outcomes. Four studies failed to provide adequate data for pooling; 3 of the 4 reported results that suggested symptomatic benefit with prokinetic agents. Nine studies (379 patients) that provided the required data suggested a higher incidence of clinical improvement with prokinetic drugs versus placebo (relative risk [RR] 1.70, 95% confidence interval [CI] 1.37–2.12, heterogeneity $p = 0.47$, $I^2 = 0\%$). Clinical improvement occurred in 53 out of 175 patients (30%) of the control group; applying the relative risk of 1.70 and associated confidence interval suggests that absolute increases in patients improved might vary from 18% to 41% (number needed to treat approximately 3 to 6). Improvement was similar in 4 studies in which the prokinetic agent was added to an antisecretory drug. The funnel plot, however, suggests the possibility of publication bias. Eleven studies (887 patients) suggested a higher likelihood of endoscopic improvement or healing esophagitis with prokinetic drugs (RR 1.26, 95% CI 1.03–1.53) but with significant heterogeneity (heterogeneity $p = .05$, $I^2 = 46.2\%$) that we couldn't explain with an a priori hypothesis. When we evaluated endoscopic healing as the main outcome we observed a trend toward better results in the treatment group, also with inexplicable heterogeneity (RR 1.36, CI 95% 0.97–1.89, $I^2 = 61\%$).

Conclusions: Randomized controlled trials provide moderate-quality evidence that prokinetic drugs improve symptoms in patients with reflux esophagitis and low-quality evidence that they have an impact on endoscopic healing.

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Esophagitis is a frequent complication of gastroesophageal reflux disease (GERD). The diversity of clinical manifestations and the lack of standardized diagnostic criteria across studies create difficulties in estimating its prevalence.[1,2] Pathophysiologic mechanisms include anatomic and functional changes of the gastroesophageal junction (hiatal hernia, decrease of the inferior esophageal sphincter tone and esophageal clearance).[3] Definitive diagnosis of esophagitis requires endoscopy and biopsy.[4]

Chronic esophagitis complications include bleeding, esophageal stenosis, Barrett metaplasia and adenocarcinoma. The goal of medical treatment is to decrease symptoms and complications by the suppression of gastric acid secretion and by ameliorating motor dysfunction. Therapeutic options include proton pump inhibitors (PPIs), histamine-2 receptor (H_2) antagonists and prokinetic drugs.

Prokinetic drugs have potential usefulness as adjunctive treatment of GERD by increasing lower esophageal sphincter pressure, enhancing gastric emptying, and improving peristalsis. A clinical practice guideline on GERD esophagitis[1] suggested the potential benefit of promotility agents, either as monotherapy or used in association with PPI. The authors emphasized the need for continued research into the role of these agents.

Any further research or recommendations regarding prokinetic agents should, however, be based on a systematic summary of evidence to date. Although systematic reviews have examined the short-term impact of prokinetic agents[5] on gastroesophageal reflux symptoms in patients without endoscopically proven esophagitis,[6] no systematic review has evaluated their effect on endoscopically proven esophagitis in adults. We therefore undertook a systematic review and meta-analysis to evaluate the real effectiveness of prokinetic drugs in patients with proven GERD esophagitis.

Methods

Eligibility criteria. We included all published and unpublished parallel-group randomized or quasi-randomized controlled trials published in Spanish, English, French, German, Italian or Portuguese that met the following criteria:

Patients: adults > 15 years with endoscopic diagnosis of reflux esophagitis (with or without histology).

Intervention: use of oral prokinetic agents (cisapride, mosapride, tegaserod, metoclopramide, domperidone, bethanechol, levosulpiride, cinitapride, clebopride) compared with placebo. Studies in which patients received antisecretory agents (PPI or H_2 antagonists) were included only if both the treatment and control groups received these agents according to the same protocol.

Outcomes: symptomatic improvement (heartburn, regurgitation, dysphagia, retrosternal pain) or endoscopic findings.

We excluded studies with the following characteristics:

- *Patients:* those with esophageal involvement of a systemic illness (scleroderma, dermatomyositis), dysphagia of neurologic cause, previous gastrectomy or antireflux surgery.
- *Intervention:* use of prokinetics after satisfactory treatment with PPI or for symptomatic relapse.
- *Trial design*: trials with scores of ≤ 3 in the Jadad scale modified by Schulz criteria (score 0 to 8).[7]

Titles and abstracts were independently reviewed by 2 of the authors (MEM and FAS) to identify potentially eligible articles. We obtained full-text versions of potentially eligible articles, which the same 2 reviewers evaluated. In case of disagreement, 1 of 3 other reviewers (MFK, GG and HNC) made the eligibility decision.

Search strategy. We searched relevant articles in the following electronic databases: LILACS (1985–2007), MEDLINE (1966–2007), EMBASE (1980–2007), CINAHL (1982–2007), COCHRANE Controlled Trial Register (Cochrane Library 2007). The terms used were the names of prokinetic agents (both generic and proprietary), combined with reflux esophagitis and therapeutic categories. We also hand-searched abstracts reported at the 7th United European Gastroenterology Week (UEGW, November 1999), the 11th UEGW (November 2003) and at the Digestive Diesase Week and the 104th Annual Meeting of the American Gastroenterological Association (May 2003) We reviewed the reference lists of in-

cluded articles, other sources such as UptoDate (2007 version 15.1) and relevant gastroenterology, pharmacology and internal medicine textbooks. We also contacted a local expert and 5 pharmaceutical companies (Beta, Roux-Ocefa, Janssen-Cilag, Phoenix, and Cetus) to identify unpublished articles.

Quality. Two of the authors (MEM and FAS) independently evaluated concealment allocation, blinding and completeness of follow-up. The reviewers used the Jadad scale modified by Schulz criteria to evaluate and classify the quality of the studies.[7]

Data abstraction. Two of the authors (MEM and FAS) independently abstracted the data in duplicate. Patient characteristics, interventions (drugs used, dose, time of administration, co-interventions), outcome measures (symptomatic or endoscopic response, endoscopic healing and adverse events) were abstracted, and any disagreement was resolved through discussion. We made attempts to contact authors regarding confirmation or missing data; 2 authors answered our request. Abstracts provided no eligible studies.

Quantitative data synthesis and statistical analysis. We used weighted kappa scores to assess agreement between the reviewers on the selection of articles for inclusion. We calculated relative risk (RR) and absolute risk reduction (ARR) with 95% confidence intervals (CIs) for symptomatic and endoscopic response, and combined the RR from each study by means of a meta-analytic technique using a random effects model as described by DerSimonian and Laird.[8] RevMan 4.2 was used to analyze all data.

The authors of the trials used different scores to assess improvement (e.g., 0 to 100 symptom scale; categorical scale from absent to disabling symptoms). We used the authors' own criteria in each trial to classify patients as improved or unimproved. We considered outcomes of patients free of symptoms and patients with symptomatic improvement as equivalent, and pooled each outcome of interest based on the a priori expectation of a similar magnitude and direction of treatment effect. We classified "some improvement" with complete symptom resolution as a positive outcome and "no improvement" as a negative outcome.

Heterogeneity of the studies was evaluated both by the chi-square test with a threshold p value of < 0.05,

and by the I^2 statistic (considering important heterogeneity a proportion higher than 30%). For any outcome that crossed either threshold for heterogeneity, we explored sources of heterogeneity according to our a priori hypothesis, which included drugs used, the use of additional agents, dosing, duration of treatment and methodological quality. Specifically, we compared the results of studies grouped by the following factors:

- different drugs used (cisapride, metoclopramide, bethanechol, levosulpiride, domperidone, mosaprid)
- use of antisecretory agents (yes or no)
- dose of prokinetic drugs used per day (< 40 mg v. ≥ 40 mg of cisapride, < 40 mg v. ≥ 40 mg metoclopramide)
- treatment duration (≤ 8 weeks v. > 8 weeks)
- methodological qualtity (Jadad score 4 v. ≥ 5).

We used log-transformed RR and its standard error calculated from 95% CI and Z value to obtain p values for testing explanations of heterogeneity.

All data were analyzed on an intention-to-treat principle. Publication bias was evaluated using funnel plots.

Results

We identified 1,119 abstracts (Fig. 1). None of 15 studies provided by pharmaceutical companies fulfilled eligibility criteria. Eighteen[9-26] randomized controlled trials (RCTs) enrolling 1,155 patients (621 in the intervention and 504 in the placebo group; Table 1), all identified from electronic databases, proved eligible. Table 2 shows characteristics and methodological quality of the eligible trials. Eleven trials were rated 4 using the Jadad scale modified by Schulz criteria, and 7 were rated 5 or more; 11 trials were sponsored by pharmaceutical industry. Six RCTs failed to provide sponsorship information, and 1 had no sponsor.

Eleven trials evaluated the effect of cisapride. Of these, 1 trial evaluated 80 mg/d dose, 9 trials the 40 mg/d dose, 2 trials the 30 mg/d dose and only 1 trial the 15 mg/d dose. Metoclopramide was evaluated in 3 studies; 1 evaluated the 30 mg/d dose and the other 2 the 40 mg/d dose. One study evaluated bethanechol, 1 study evaluated mosapride and 2 studies evaluated each of sulpiride and domperidone. Four trials compared the addition of a prokinetic drug versus placebo in patients already using an H_2 receptor blocker (3

Potentially relevant RCTs identified and screened for retrieval = 1,119

1,052 excluded

Reasons for exclusion
Duplicate or updated publication (n = 52)
Not RCT (n = 528)
Patients, intervention, or outcome do not meet inclusion criteria (n = 451)
Language (n = 21)

Citations retrieved for more detailed evaluation = 67

49 excluded

Reasons for exclusion
Duplicate or updated publication (n = 13)
Not RCT (n = 5)
Patients, intervention, or outcome do not meet inclusion criteria (n = 28)
Language (n = 3)

RCTs included in this review = 18

Interobserver agreement kappa score 0.62

RCTs with data amenable to statistical analysis:
Symptom improvement (n = 9)
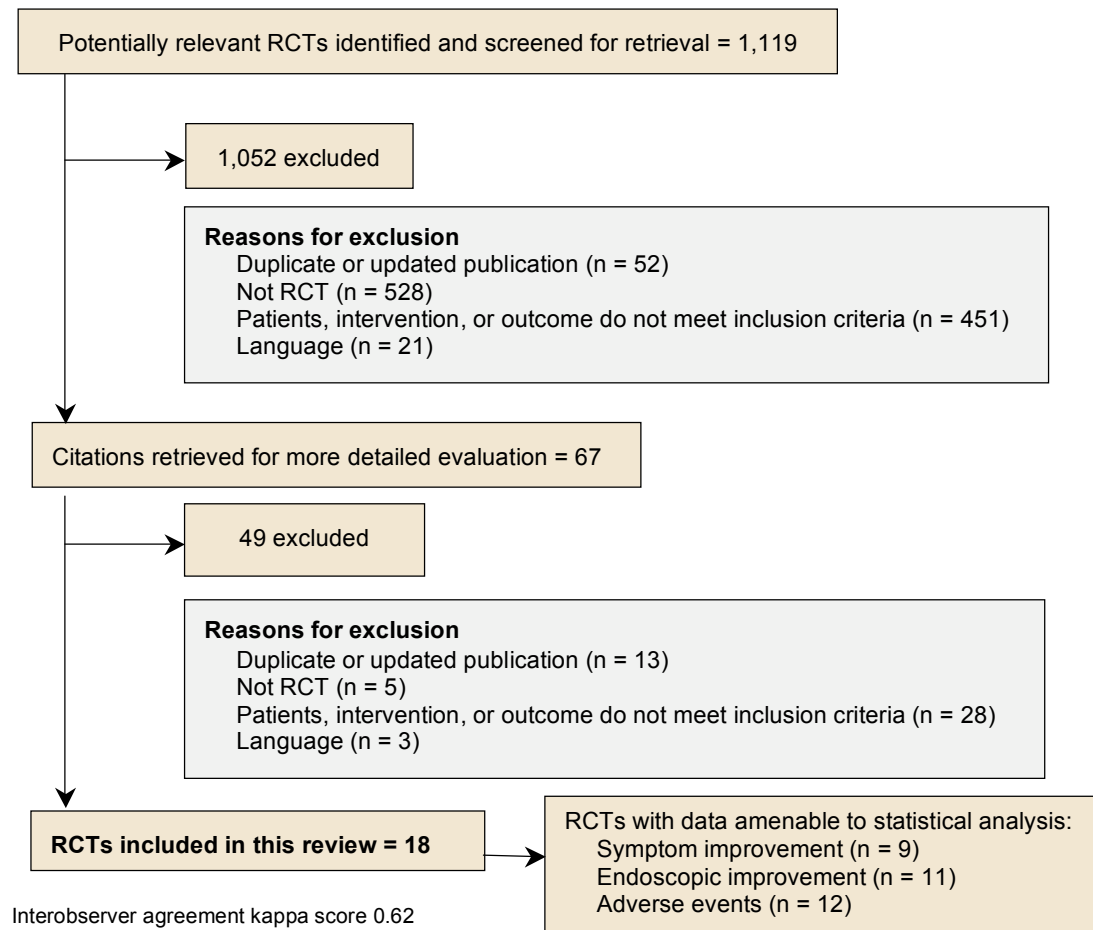Endoscopic improvement (n = 11)
Adverse events (n = 12)

Figure 1: Selection of studies for systematic review

cimetidine and 1 ranitidine). One trial evaluated the addition of a prokinetic agent to a PPI.

Tables 3 and 4 show primary outcomes and adverse reactions.

Studies that did not provide data for pooling.
Masci and colleagues[17] evaluated the presence and severity of reflux symptoms (dysphagia, regurgitation, heartburn, retrosternal pain, nausea), comparing levosulpiride, domperidone and placebo. They reported equal effectiveness of both drugs in significantly reducing regurgitation, heartburn and overall dyspeptic symptoms ($p < 0.05$ compared with control). Endoscopic features failed to reveal significant differences between groups.

Trabucchi and colleagues[26] compared levosulpiride with placebo. They reported improvement in symptom score in most patients in the treatment group. Endoscopic lesions disappeared in 20%, improved in

47% and failed to improve in 33%. The authors did not provide data for the placebo arm.

Finizia and colleagues[11] reported no significant difference on symptom score according to intensity, frequency and duration in the cisapride group compared to placebo.

Pehlivanov and colleagues[21] found fewer heartburn episodes during daytime and fewer antacid tablets needed per patient in a week in the cisapride group versus the placebo group, with a p value of 0.016 and 0.062, respectively.

Clinical improvement. Nine studies (379 patients) evaluated clinical improvement. The pooled estimate showed a significant improvement with prokinetic drugs versus placebo (RR 1.70, 95% CI 1.37–2.12). Results were consistent across studies ($p = 0.47$, $I^2 = 0\%$). The ARR was 30% (95% CI 18%–41%) (Table 3).

Table 1: General characteristics of randomized controlled trials included in analysis

Study (country and year)	n	Drug, dose, posology	Concomitant treatment in experimental and control groups	Treatment duration
Baldi et al[9] (Italy 1988)	63	Cisapride 10 mg × 4	None	12 w
Collins et al[10] (UK 1987)	18	Cisapride 10 mg × 3	None	4 w
Finizia et al[11] (Sweden 2002)	30	Cisapride 20 mg × 2	None	2 w
Galmiche et al[12] (France 1988)	47	Cisapride 10 mg × 4 + cimetidine	Cimetidine	12 w
Hatlebakk et al[13] (Norway 1999)	107	Cisapride 20 mg × 2	None	8 w
Lepoutre et al[14] (Belgium 1990)	20	Cisapride 10 mg × 4	None	16 w
Lieberman et al[15] (US 1986)	25	Metoclopramide 10 mg × 4 + cimetidine	Cimetidine	8 w
Madan et al[16] (India 2004)	32	Lansoprazole 40 mg × 2 + mosapride 5 mg x 3	Lansoprazole	8 w
Masci E et al[17] (Italy 1992)	30*	Levosulpiride 25 mg × 3 / domperidone 10 mg x 3	None	12 w
McCallum et al[18] (US 1984)	19	Metoclopramide 10 mg × 4	None	4 w
McKenna et al[19] (UK 1995)	344	Cisapride 20 mg × 2 + ranitidine	Ranitidine	12 w
Nicolaidis et al[20] (1987 Greece)	40	Cisapride 10 mg × 3	None	4 w
Nicolaidis et al[20] (1987 Greece)	40	Cisapride 5 mg × 3	None	4 w
Pehlivanov et al[21] (2002 US)	10	Cisapride 10 mg × 4	None	5 d
Richter et al[22] (1995 US)	177	Cisapride 10 mg × 4	None	12 w
Richter et al[22] (1995 US)	177	Cisapride 20 mg × 4	None	12 w
Robertson[23] (1993 UK)	46	Cisapride 10 mg × 4	None	12 w
Temple[24] (1983 UK)	73	Metoclopramide 10 mg × 3 + cimetidine	Cimetidine	12 w
Thanik et al[25] (1980 US)	44	Bethanechol 25 mg × 4	None	4 w
Trabucchi et al[26] (1991 Italy)	30	L-sulpiride 25 mg × 3	None	4 w

*Number of patients enrolled in each arm was not reported.
UK = United Kingdom; US = United States; w = weeks; d = days

Endoscopic improvement. Five of 11 studies used a validated scale (Savary-Miller [3], Los Angeles [1], Hetzel [1]); the other 6 scales used were similar to one another. The pooled estimate of treatment effect on endoscopic healing or improvement from 11 studies including 887 patients demonstrated a significant effect of prokinetic drug versus placebo (RR 1.26, 95% CI 1.03–1.53); the risk difference was 16% (CI 95% 3%–29%). The results were, however, variable from study to study (test for heterogeneity p = 0.05, I^2 = 46.2%). We therefore explored the possible sources of heterogeneity according to our a priori hypothesis. The a priori hypotheses failed to explain the variability in study results.

Endoscopic healing. The pooled estimate of treatment effect on endoscopic healing from eight studies including 796 patients demonstrated a trend toward better results with prokinetic treatment (RR 1.36, 95% CI 0.97–1.89) with significant heterogeneity between groups (test for heterogeneity p = 0.001, I^2 = 61.4%).

Once again, our a priori hypotheses failed to explain the variability observed.

Adverse events. Twelve trials reported adverse events. They showed a non-significant increase in adverse reactions (RR 1.30, 95% CI 0.93–1.83), with substantial variability between the studies (test for heterogeneity p = 0.08, I^2 = 39.4%); the risk difference was 9% (CI 95% 0%–18%) (Table 4).

Discussion

Our intention was to determine the quality of evidence and apparent magnitude of impact of prokinetic agents on symptoms, endoscopic healing, and adverse effects in patients with gastroesophageal reflux. We found an increase in the probability of symptom improvement of 70% with treatment (RR 1.70, 95% CI 1.37–2.12), and an increase of 26% (RR 1.35, 95% CI 1.03–1.53) in the probability of endoscopic healing or improvement, but we did not find a significant increase in adverse reactions with treatment (RR 1.30,

Table 2: Quality of randomized controlled trials included in analysis

Study	Blinding	Method of blindng	Follow-up	Jadad scale modified by Schulz criteria (score 0–8)	Industry sponsored
Baldi et al[9]	No	Patients and investigators*	59%	4	NA
Collins et al[10]	No	Patients, health care providers and investigators*	100%	5	Yes
Finizia et al[11]	No	Patients and investigators*	100%	4	Yes
Galmiche et al[12]	No	Patients and investigators*	100%	4	NA
Hatlebakk et al[13]	Yes	Patients, health care providers and data collectors	100%	7	Yes
Lepoutre et al[14]	No	Patients and investigators*	100%	4	NA
Lieberman et al[15]	No	Patients and investigators*	96%	4	Yes
Madan et al[16]	Yes	Patients, health care providers, follow-up endoscopists and investigators	100%	8	NA
Masci et al[17]	No	Double blind*	NA	4	Yes
McCallum et al[18]	No	Patients and investigators*	95%	5	No
McKenna et al[19]	Probably	Patients, follow-up endoscopists and investigators*	92%	4	Yes
Nicolaidis et al[20]	No	Patients and investigators*	100%	5	NA
Pehlivanov et al[21]	No	Patients and investigators*	100%	4	Yes
Richter et al[22]	No	Patients and investigators*	89%	5	Yes
Robertson et al[23]	No	Double blind*	96%	4	Yes
Temple et al[24]	No	Patients and investigators* (double dummy technique)	96%	4	Yes
Thanik et al[25]	No	Patients and investigators*	100%	5	Yes
Trabucchi et al[26]	No	Double blind*	NA	4	NA

*Not defined further. NA = not available.

95% CI 0.93–1.83). The last 2 outcomes showed substantial variability between the studies.

The GRADE system of rating quality of evidence provides a structure for assessing the quality of the evidence.[27] In the GRADE system, randomized trials constitute high-quality evidence unless there are important limitations. The 12 trials that addressed symptomatic improvement were of moderate to high quality; their results were consistent, the confidence intervals reasonably narrow, and the results applied directly to the relevant population (Table 5). However, the trials were small, a number were funded by industry, and the funnel plot (see Appendices) suggests the possibility of publication bias — a substantial risk when evidence comes from a number of small trials. In our judgment, therefore, we have moderate evidence of symptomatic benefit with prokinetic agents.

With respect to endoscopic improvement, the 10 relevant randomized trials were of moderate to high quality and provide direct evidence regarding the impact of prokentic agents. The results, however, were not consistent across studies (test for heterogeneity $p = 0.05$, $I^2 = 46.2\%$) and our a priori hypotheses failed to explain differences in the magnitude of effect across studies. Moreover, the confidence intervals around the effect were wide (RR 1.26, 95% CI 1.03–1.53), and the pattern of results suggest the possibility of publication bias. We therefore conclude that the results provide only weak evidence supporting the benefits of prokinetic agents on endoscopic healing.

With respect to adverse effects, these randomized trials were of moderate to high quality and the results are directly applicable to the patient population. The results are, however, inconsistent (test for heterogeneity $p = 0.08$, $I^2 = 39.4\%$) and the confidence intervals wide (RR 1.30, 95% CI 0.93–1.83). The results therefore provide weak evidence of toxicity of prokinetic agents. Furthermore, the studies are extremely underpowered to detect rare but serious side effects. Case reports of cardiovascular adverse effects remain, therefore, an important concern.[28–30]

Table 3: Prokinetic drug utility

Agent and outcome	No. of studies (patients)	Patients improved, n (total)		RR of random effect (95% CI)	Risk difference for random effect (95% CI)
		Treatment group	Control group		
Cisapride < 40 mg/d					
Clinical improvement	2 (58)	29 (37)	9 (21)	1.77 (1.03–3.04)	34% (9–60)
Cisapride ≥ 40 mg/d					
Endoscopic improvement or healing	3 (244)	98 (151)	46 (93)	1.57 (1.01–2.42)	36% (1–72)
Clinical improvement	4 (220)	52 (113)	33 (107)	1.49 (1.13–1.96)	16% (6–27)
Cisapride (any dose)					
Endoscopic improvement or healing	6 (757)	254 (378)	200 (379)	1.43 (1.1–1.85)	26% (10–41)
Clinical improvement	6 (278)	81 (150)	42 (128)	1.54 (1.21–2.11)	19% (9–29)
Metoclopramide 30 mg/d					
Endoscopic improvement or healing	1 (73)	8 (33)	18 (40)	0.54 (0.27–1.08)	–21% (–42 to 0)
Metoclopramide 40 mg/d					
Endoscopic improvement or healing	2 (45)	15 (24)	10 (21)	1.26 (0.5–3.19)	13% (–34 to 60)
Clinical improvement	1 (22)	9 (13)	2 (9)	3.12 (0.87–11.15)	47% (10–84)
Metoclopramide (any dose)					
Endoscopic improvement or healing	3 (118)	23 (57)	28 (61)	0.93 (0.45–1.94)	–1% (–36 to 35)
Clinical improvement	1 (22)	9 (13)	2 (9)	3.12 (0.87–11.15)	47% (10–84)
Bethanechol 100 mg/d					
Endoscopic improvement or healing	1 (44)	14 (22)	8 (22)	1.75 (0.93–3.31)	27% (–1 to 56)
Clinical improvement	1 (44)	10 (22)	3 (22)	3.67 (1.18–11.37)	36% (11–62)
Mosapride 15 mg/d					
Endoscopic improvement or healing	1 (32)	12 (17)	6 (11)	1.29 (0.7–2.41)	16% (–20 to 53)
Clinical improvement	1 (32)	18 (19)	7 (13)	2.05 (1.13–3.73)	49% (20–77)
All prokinetics					
Endoscopic improvement or healing	11 (947)	303 (474)	252 (473)	1.26 (1.03–1.53)	16% (3–294)
Clinical improvement	9 (379)	119 (204)	53 (175)	1.70 (1.37–2.12)	30% (18–41)

RR = relative risk; CI = confidence interval; d = day

Table 4: Adverse effects

Adverse effects	Intervention	RR of random effect (95% CI)	Risk difference of random effect (95% CI)		No. of studies
General	Any prokinetic and dose	1.30 (0.93–1.83)	9%	(0–18)	12
Gastrointestinal (any)	Any prokinetic and dose	1.09 (0.66–1.79)	0%	(–5 to 5)	8
Neurological (any)	Any prokinetic and dose	1.03 (0.58–1.84)	0.04%	(–0.04 to 0.12)	9
Gastrointestinal (any)	Cisapride (any dose)	1.05 (0.64–1.74)	0%	(–0.07 to 0.06)	7
Neurological (any)	Cisapride (any dose)	0.61 (0.32–1.15)	–0.02%	(–0.09 to 0.05)	6
Headache	Cisapride > 40 mg/d	0.65 (0.33–1.28)	0%	(–0.08 to 0.08)	4
Diarrhea	Cisapride > 40 mg/d	0.99 (0.47–2.09)	–0.01%	(–0.09 to 0.07)	3
Neurological (any)	Metoclopramide (any dose)	2.41 (1.25–4.64)	34%	(–16 to 83)	2

RR = relative risk; CI = confidence interval; d = day

Table 5: Overall quality of evidence

	Study quality	Precision of estimates	Consistent results	Direct results	Reporting bias	Quality of evidence	RR (95% CI)
Symptom improvement	No serious limitations	Adequate	Yes	Yes	Suggested	Moderate	1.68 (1.31–2.17)
Endoscopic healing	No serious limitations	Wide CI	No	Yes	Suggested	Very low	1.35 (1.05–1.72)
Adverse effects	No serious limitations	Wide CI	No	Yes	No	Low	1.30 (0.93–1.83)

RR = relative risk; CI = confidence interval

Strengths of our systematic review include explicit, detailed eligibility criteria; a comprehensive search; restriction to RCTs of moderate or high methodological quality; high levels of agreement on issues requiring judgment; and our use of the systematic GRADE approach to rate the quality of the evidence. Limitations pertain to the number of patients studied and the methodological concerns that we have highlighted (in particular, the possibility of publication bias). With respect to relevance, although cisapride is no longer available in most markets, an alternative agent, mosapride, may take its place. The one trial of mosapride in this review is notable both for its high methodological quality and the fact that it detected a benefit of mosapride in patients already receiving a PPI.

Although the enthusiasm for PPIs in the treatment of reflux esophagitis is appropriate, we do not believe it warrants the neglect of other agents. The previous lack of systematic review and meta-analysis, as presented here reflects, in our view, a certain neglect.

In summary, although patients with reflux esophagitis are likely to benefit symptomatically from the use of prokinetic agents, some uncertainty remains. The magnitude of side effects and toxicity is uncertain. Clinicians must also consider the higher-quality evidence available for other agents (particularly PPIs, which are superior to prokinetic agents) in making their therapeutic decisions.

REFERENCES

1. DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *Am J Gastroenterol* 2005;100(1):190-200.

2. Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2005;54(5):710-717.

3. Bunnett NW, Lingappa VR. Reflux esophagitis. In: *Pathophysiology of disease: an introduction to clinical medicine,* 5th ed. New York: McGraw-Hill; 2006.

4. Peters JH, DeMeester TR. Esophagus and diaphragmatic hernia. Part II: specific considerations. In: *Schwartz's Principles of Surgery*, 8th ed. New York: McGraw-Hill, 2005.

5. van Pinxteren B, Numans ME, Bonis PA, Lau J. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. In: The Cochrane Library, Issue 2, 2005. Oxford: Update Software.

6. Augood C, MacLennan S, Gilbert R, Logan S. Cisapride treatment for gastro-oesophageal reflux in children. In: The Cochrane Library, Issue 2, 2005. Oxford: Update Software.

7. Moher D, Cook DJ, Jadad AR, Tugwell P, Moher M, Jones A, et al. Assessing the quality of reports of randomized trials: implications for the conduct of meta-analyses. *Health Technology Assessment* 1999; 3(12).

8. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-188.

9. Baldi F. Cisapride versus placebo in reflux esophagitis: a multi-center double-blind trial. *J Clin Gastroenterol* 1988;10(6):614.

10. Collins BJ, Spence RA, Ferguson R, Laird J, Love AH. Cisapride: influence on oesophageal and gastric emptying and gastro-oesophageal reflux in patients with reflux oesophagitis. *Hepatogastroenterology* 1987;34(3):113-116.

11. Finizia C, Lundell L, Cange L, Ruth M. The effect of cisapride on oesophageal motility and lower sphincter function in patients with gastro-oesophageal reflux disease. *Eur J Gastroenterol Hepatol* 2002;14(1):9-14.

12. Galmiche JP, Brandstatter G, Evreux M, Hentschel E, Kerstan E, Kratochvil P, et al. Combined therapy with cisapride and cimetidine in severe reflux oesophagitis: a double blind controlled trial. *Gut* 1988;29(5):675-681.

13. Hatlebakk JG, Hyggen A, Madsen PH, Walle PO, Schulz T, Mowinckel P, et al. Heartburn treatment in primary care: randomised, double blind study for 8 weeks. *BMJ* 1999;319(7209):550-553.

14. Lepoutre L, Van der Spek P, Vanderlinden I, Bollen J, Laukens P. Healing of grade-II and III oesophagitis through motility stimulation with cisapride. *Digestion* 1990;45(2):109-114.

15. Lieberman DA, Keeffe EB. Treatment of severe reflux esophagitis with cimetidine and metoclopramide. *Ann Intern Med* 1986;104(1):21-26.

16. Madan K, Ahuja V, et al. Comparison of efficacy of pantoprazole alone versus pantoprazole plus mosapride in therapy of gastro-oesophageal reflux disease: A randomized trial. *Dis Esophagus* 2004;17(4):274-278.

17. Masci E, Sorghi M, Tosi T, Testoni PA, Tottobello A. Levosulpiride and domperidone in the treatment of reflux esophagitis: results of a double-blind study versus placebo. *Curr Ther Res Clin Exp* 1992;51(6):814-818.

18. McCallum RW, Fink SM, Winnan GR, Avella J, Callachan C. Metoclopramide in gastroesophageal reflux disease: rationale for its use and results of a double-blind trial. *Am J Gastroenterol* 1984;79(3):165-172.

19. McKenna CJ, Mills JG, Goodwin C, Wood JR. Combination of ranitidine and cisapride in the treatment of reflux oesophagitis. *Eur J Gastroenterol Hepatol* 1995;7(9):817-822.

20. Nicolaidis CL, Kehagiolou K, Mantzanaris G, Papadatou-Marinou A, Saklaridis J, Georgiotis D, et al. Therapeutic effect of two dosages of cisapride in controlling chronic reflux symptoms in esophagitis patients. *Curr Ther Res Clin Exp* 1987;42(6):1059-1065.

21. Pehlivanov N, Sarosiek I, Whitman R, Olyaee M, McCallum R. Effect of cisapride on nocturnal transient lower oesophageal sphincter relaxations and nocturnal gastro-oesophageal reflux in patients with oesophagitis: a double-blind, placebo-controlled study. *Aliment Pharmacol The*r 2002;16(4):743-747.

22. Richter JE, Long JF. Cisapride for gastroesophageal reflux disease: a placebo-controlled, double-blind study. *Am J Gastroenterol* 1995r;90(3):423-430.

23. Robertson CS, Evans DF, Ledingham SJ, Atkinson M. Cisapride in the treatment of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 1993;7(2):181-90.

24. Temple JG, Bradby GV, O'Connor FO, Panesar KS, Mulligan TO, Robinson TJ, et al. Cimetidine and metoclopramide in oesophageal reflux disease. *Br Med J (Clin Res Ed)* 1983;286(6381):1863-1864.

25. Thanik KD, Chey WY, Shah AN, Gutierrez JG. Reflux esophagitis: effect of oral bethanechol on symptoms and endoscopic findings. *Ann Intern Med* 1980;93(6):805-808.

26. Trabucchi E, Radaelli E, Castoldi L, Abelli P, Brambilla A, Fichera G, Diamantini S, Pace M, Foschi D. The effects of L-sulpiride on reflux oesophagitis. *Drugs Exp Clin Res* 1991;17(6):317-321.

27. Guyatt G, Gutterman D, Baumann MH, Addrizzo-Harris D, Hylek EM, Phillips B. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians task force. *Chest* 2006; 129(1):174-181.

28. Wysowski DK, Bacsanyi J. Cisapride and fatal arrhythmia. *N Engl J Med* 1996;335:290-291.

29. Piquette RK. Torsade de pointes induced by cisapride/clarithromycin interaction. *Ann Pharmacother* 1999;33:22-6.

30. Vitola J, Vukamovic J, Roden DM. Cisapride-induced torsades de pointes. *J Cardiovasc Electrophysiol* 1998;9:1109-1113.

APPENDICES

Review: Prokinetic Drug Utility in the Treatment of Gastro-Esophageal Reflux Esophagitis: A Systematic Review
Comparison: 12 All prokinetics
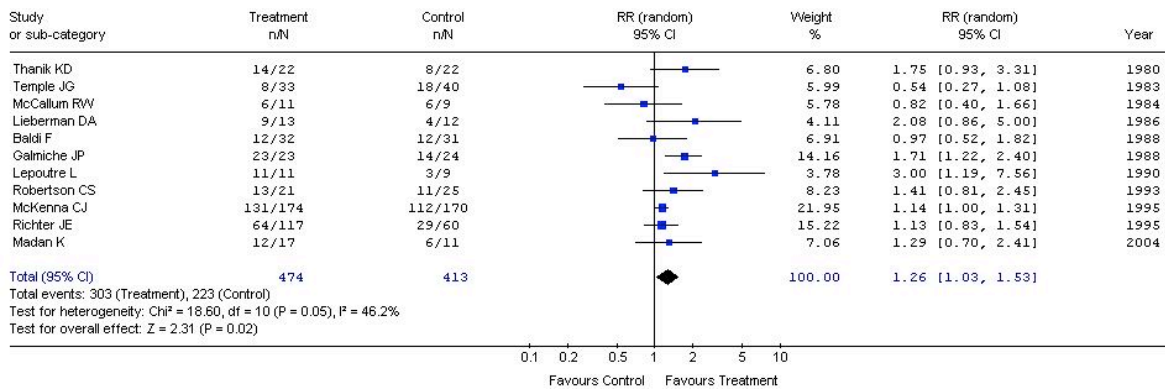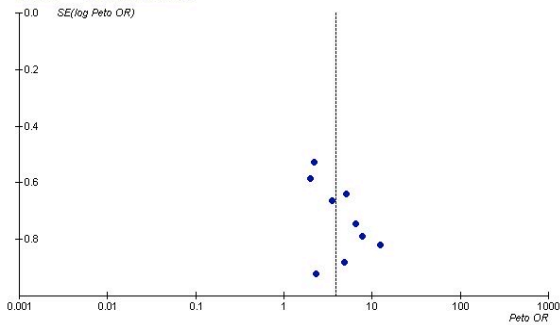Outcome: 03 Clinical improvement

Study or sub-category	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI	Year
Thanik KD	11/22	3/22		3.76	3.67 [1.18, 11.37]	1980
Lieberman DA	9/13	2/12		2.78	4.15 [1.11, 15.49]	1986
Collins BJ	6/9	4/9		6.45	1.50 [0.63, 3.56]	1987
Nicolaidis CL	23/28	5/12		10.08	1.97 [0.99, 3.94]	1987
Galmiche JP	20/23	15/24		39.80	1.39 [0.98, 1.97]	1988
Lepoutre L	7/11	2/9		2.85	2.86 [0.78, 10.52]	1990
Robertson CS	13/21	11/25		15.64	1.41 [0.81, 2.45]	1993
Hatlebakk JG	12/58	5/49		5.11	2.03 [0.77, 5.36]	1999
Madan K	18/19	6/13		13.54	2.05 [1.13, 3.73]	2004
Total (95% CI)	204	175		100.00	1.70 [1.37, 2.12]	

Total events: 119 (Treatment), 53 (Control)
Test for heterogeneity: Chi² = 7.68, df = 8 (P = 0.47), I² = 0%
Test for overall effect: Z = 4.74 (P < 0.00001)

0.1   0.2   0.5   1   2   5   10
Favours control   Favours treatment

Appendix 1: Forest plot — all prokinetic agents, clinical improvement

Review: Prokinetic Drug Utility in the Treatment of Gastro-Esophageal Reflux Esophagitis: A Systematic Review
Comparison: 12 All prokinetics
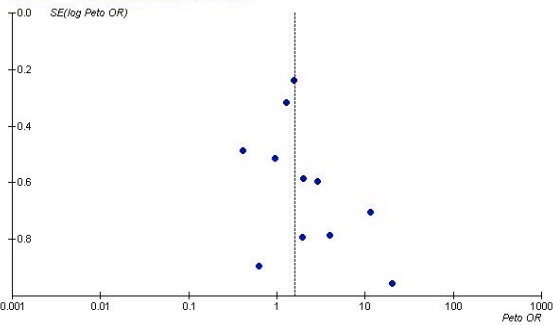Outcome: 02 Endoscopic healing or improvement

Study or sub-category	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI	Year
Thanik KD	14/22	8/22		6.80	1.75 [0.93, 3.31]	1980
Temple JG	8/33	18/40		5.99	0.54 [0.27, 1.08]	1983
McCallum RW	6/11	6/9		5.78	0.82 [0.40, 1.66]	1984
Lieberman DA	9/13	4/12		4.11	2.08 [0.86, 5.00]	1986
Baldi F	12/32	12/31		6.91	0.97 [0.52, 1.82]	1988
Galmiche JP	23/23	14/24		14.16	1.71 [1.22, 2.40]	1988
Lepoutre L	11/11	3/9		3.78	3.00 [1.19, 7.56]	1990
Robertson CS	13/21	11/25		8.23	1.41 [0.81, 2.45]	1993
McKenna CJ	131/174	112/170		21.95	1.14 [1.00, 1.31]	1995
Richter JE	64/117	29/60		15.22	1.13 [0.83, 1.54]	1995
Madan K	12/17	6/11		7.06	1.29 [0.70, 2.41]	2004
Total (95% CI)	474	413		100.00	1.26 [1.03, 1.53]	

Total events: 303 (Treatment), 223 (Control)
Test for heterogeneity: Chi² = 18.60, df = 10 (P = 0.05), I² = 46.2%
Test for overall effect: Z = 2.31 (P = 0.02)

0.1   0.2   0.5   1   2   5   10
Favours Control   Favours Treatment

Appendix 2: Forest plot — all prokinetic agents, endoscopic healing or improvement

Appendix 3: Funnel plots — all prokinetic agents, clinical improvement (left), endoscopic healing or improvement (right)