

Prokinetic Drug Utility in the Treatment of Gastro-Esophageal Reflux Esophagitis: A Systematic Review of Randomized Controlled Trials

Short title: Prokinetic for the Treatment of Esophagitis

Abstract

Background knowledge. 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 comparing prokinetic drugs with placebo. A systematic search included Cochrane Controlled Trial Register, MEDLINE, CINAHL, LILACS, EMBASE and manual search of books and articles' references and contact with pharmaceutical companies. Reviewers assessed methodological quality, and extracted data that was combined using a random effects model.

Results. Seventeen articles fulfilled eligibility criteria; 13 used prokinetic drugs alone, 4 tested prokinetic drugs as additional therapy in patients receiving histamine-2 receptor blockers. Seven studies evaluated clinical improvement only, 5 addressed endoscopic improvement only, and 5 reported both outcomes. Four studies failed to provide adequate data for pooling; three of the four reported results suggesting symptomatic benefit with prokinetic agents. Eight studies (347 patients) that provided the required data suggested a higher incidence of clinical improvement with prokinetic drugs versus placebo (RR 1.68, 95% CI 1.31-2.17, heterogeneity $p = .39$, I^2 5.5%). Clinical improvement occurred in 47 out of 162 patients (29%) of the control group; applying the RR of 1.68 and associated confidence interval suggests that absolute increases in patients improved might vary from 16% to 38% (number needed to treat approximately 3 to 6). The funnel plot, however, suggests the possibility of publication bias.

Ten studies (859 patients) suggested a higher likelihood of endoscopic improvement or healing esophagitis with prokinetic drugs (RR 1.35, 95% CI, 1.05-1.72) but with significant heterogeneity (heterogeneity $p = .006$, I^2 60.7%) that we couldn't explain with *a priori* hypothesis.

Conclusions. Randomized Controlled Trials provide moderate quality evidence that prokinetic drugs improve symptoms in patients with reflux esophagitis and very low quality evidence that they impact on endoscopic healing.

Introduction

Esophagitis is a frequent complication of gastroesophageal reflux disease (GERD). The diversity of clinical manifestations and the lack of standardized diagnostic criteria across studies creates 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 biopsy⁴.

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 (PPI), histamine-2 receptor (H2) 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 esophagitis¹ 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. While systematic reviews have examined the short-term impact of prokinetic agents⁵ on gastroesophageal reflux symptoms in patients without endoscopically proven esophagitis, 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.

Materials and 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 older than 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, cinitrapide, clebopride) compared with placebo. If patients received antisecretory agents (PPI or H2 antagonists) studies were included only if patients in both treatment and control groups, received these agents according to the same protocol. *Outcomes*: any of symptomatic improvement (heartburn, regurgitation, dysphagia, retrosternal pain) or endoscopic findings.

We excluded studies with: *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 or less in the Jadad scale modified by Schulz criteria (score 0 to 8)⁶.

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

Search Strategy

We searched relevant articles in the following electronic databases: LILACS (1985-2003), MEDLINE (1966-2003), EMBASE (1980-2003), CINAHL (1982-2004), COCHRANE Controlled Trial Register (Cochrane Library 2003). The terms used were prokinetic agents, generic and brandnames, combined with reflux esophagitis and therapeutic articles. We also hand-searched abstracts reported in the European Congress of Gastroenterology, United European Gastroenterology Week and in the American Congress of the American

Gastroenterological Association. We reviewed the reference lists of included articles, other sources such as UpToDate (2003 version 11.2) and relevant Gastroenterology, Pharmacology and Internal Medicine textbooks. We also contacted a local expert and five 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 Jadad scale modified by Schulz criteria to evaluate and classify the articles' quality.⁶

Data abstraction

Two of the authors (MEM and FAS) independently abstracted the data in duplicate. Patients' characteristics, interventions (drugs used, dose, time of administration, co-interventions), outcome measures (symptomatic or endoscopic response, endoscopic healing and adverse events) were abstracted and disagreement was resolved through discussion. We made attempts to contact authors regarding confirmation or missing data; two authors answered our request.

Quantitative Data Synthesis and Statistical Analysis

We used weighted kappa 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 (CI) 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 Laird⁷. RevMan 4.2 was used to analyze all data.

The authors of trials used different scores to assess improvement (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 *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 less than .05, and by 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, use of additional agents, dosing, duration of treatment and methodological quality. Specifically, we compared the results of studies grouped by the following factors: 1- different drugs used (cisapride, metoclopramide, bethanechol, levosulpiride, domperidone); 2- use of antisecretory agents (yes or no); 3- dose of prokinetic drugs used per day (< 40mg vs \geq 40mg of cisapride, < 40mg vs \geq 40mg metoclopramide); 4- treatment duration (\leq 8 weeks vs >8 weeks); 5- methodological quality (Jadad score 4 vs \geq 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.

Funding Source

None

Results

We identified 1,011 abstracts (Figure 1). Studies provided by pharmaceutical companies were of low methodological quality and thus ineligible (13 non-randomized controlled trials), or (in the case of 2 RCTs) reported neither symptoms nor endoscopic improvement. Seventeen RCTs enrolling 1,123 patients (602 in the intervention and 491 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 rated 4 using the Jadad scale modified by Schulz criteria and six rated 5 or more; 11 trials were sponsored by pharmaceutical industry. Five RCTs failed to provide sponsorship information, and one had no sponsor.

Eleven trials evaluated the effect of cisapride. One trial evaluated 80mg/day dose, nine trials 40mg/day dose, two 30mg/day dose and only one 15mg/day dose. Metoclopramide was evaluated in 3 studies, one evaluated 30mg/day dose and two others 40mg/day dose. One study evaluated bethanechol. Two studies evaluated sulpiride and domperidone. Four trials compared the addition of a prokinetic drug versus placebo in patients already using an H-2 receptor blocker (3 cimetidine and 1 ranitidine). No trial evaluated the addition of a prokinetic agent to a PPI.

Table 3 and 4 show primary outcomes and adverse reactions.

Studies that did not provide data for pooling

Masci *et al*¹⁵ 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 significantly reducing regurgitation, heartburn and overall dyspeptic symptoms ($p < 0.05$ compared with control). Endoscopic features failed to reveal significant differences between groups.

Trabucchi *et al*²⁵ compared levosulpiride with placebo. They reported improvement in symptom score in most patients in 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 *et al*¹⁰ reported no significant difference on symptom score according to intensity, frequency and duration in the cisapride group compared to placebo.

Pehlivanov *et al*²⁰ found less heartburn episodes during daytime and less antacid tablets needed per patient in a week in the cisapride group versus placebo group, p value of .016 and .062, respectively.

Clinical Improvement

Eight studies (347 patients) evaluated clinical improvement. The pooled estimate showed a significant improvement with prokinetic drugs versus placebo (RR 1.68, 95% CI, 1.31-2.17). Results were consistent across studies ($p = .39$, I^2 5.5%). The absolute risk reduction was 27% (95% CI, 16-38) (Table 3).

Endoscopic Improvement

The pooled estimate of treatment effect on endoscopic healing or improvement from ten studies including 859 patients demonstrated a significant effect of prokinetic drug versus placebo (RR 1.35, 95% CI 1.05-1.72); the risk difference was 20% (CI 95% 6-34). The results were, however, extremely variable from study to study (test for heterogeneity $p = .006$, I^2 60.7%). 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.

Adverse events

Twelve trials reported adverse events. They showed a non significant increase on adverse reactions (RR 1.30, 95% CI, 0.93-1.83) with substantial variability between the studies (test for heterogeneity $p = .08$, I^2 39.4%), the risk difference was 9% (CI 95% 0-18%) (table 4).

Discussion

Our intent 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 68% with treatment (RR 1.68, 95% CI, 1.31-2.17), and 35% (RR 1.35, 95% CI 1.05-1.72) in the probability of endoscopic healing or improvement, but we didn't find a significant increase on adverse reactions with treatment (RR 1.30, 95% CI, 0.93-1.83). The last two outcomes showed substantial variability between the studies.

The GRADE system of rating quality of evidence provides a structure for assessing the quality of the evidence²⁶. In the GRADE system, randomized trials constitute high quality evidence unless there are important limitations. The 12 trials addressing symptomatic improvement were of moderate to high quality, results were consistent, confidence intervals reasonably narrow, and the results apply directly to the relevant population (table 5). The trials, however, were small, a number were industry funded, and the funnel plot, suggested 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 prokinetic agents. The results, however, were not consistent across studies (test for heterogeneity $p = .006$, I^2 60.7%) (and our a priori hypotheses failed to explain differences in the magnitude of effect across studies), the confidence intervals around the effect wide (RR 1.35, 95% CI 1.05-1.72), and the studies concerns about publication bias arise. We therefore conclude that the results provide only very 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 $p = .08$, I^2 39.4%) and the confidence intervals wide (RR 1.30, 95% CI, 0.93-1.83). 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.^{27, 28, 29}

Strengths of our systematic review includes explicit, detailed eligibility criteria; a comprehensive search; restriction to RCTs of moderate or high methodological quality; high levels of agreement on issues requiring judgement; and our use of the systematic GRADE approach to rate the quality of the evidence. Limitations are in the number of patients studied, and the methodological limitations (in particular the possibility of publication bias) that we have highlighted.

In summary, while patients with GERD are likely to benefit symptomatically from 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 in making their therapeutic decisions.

Acknowledgement

We would like to thank Karin Kirmayr, Lisandro Pereyra, Martin Diaz, Clara Perret and Jose Mella, who provided aid for the translation and final details in the drafting of the manuscript.

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Figure 1 outlines the flow of articles considered for the review.

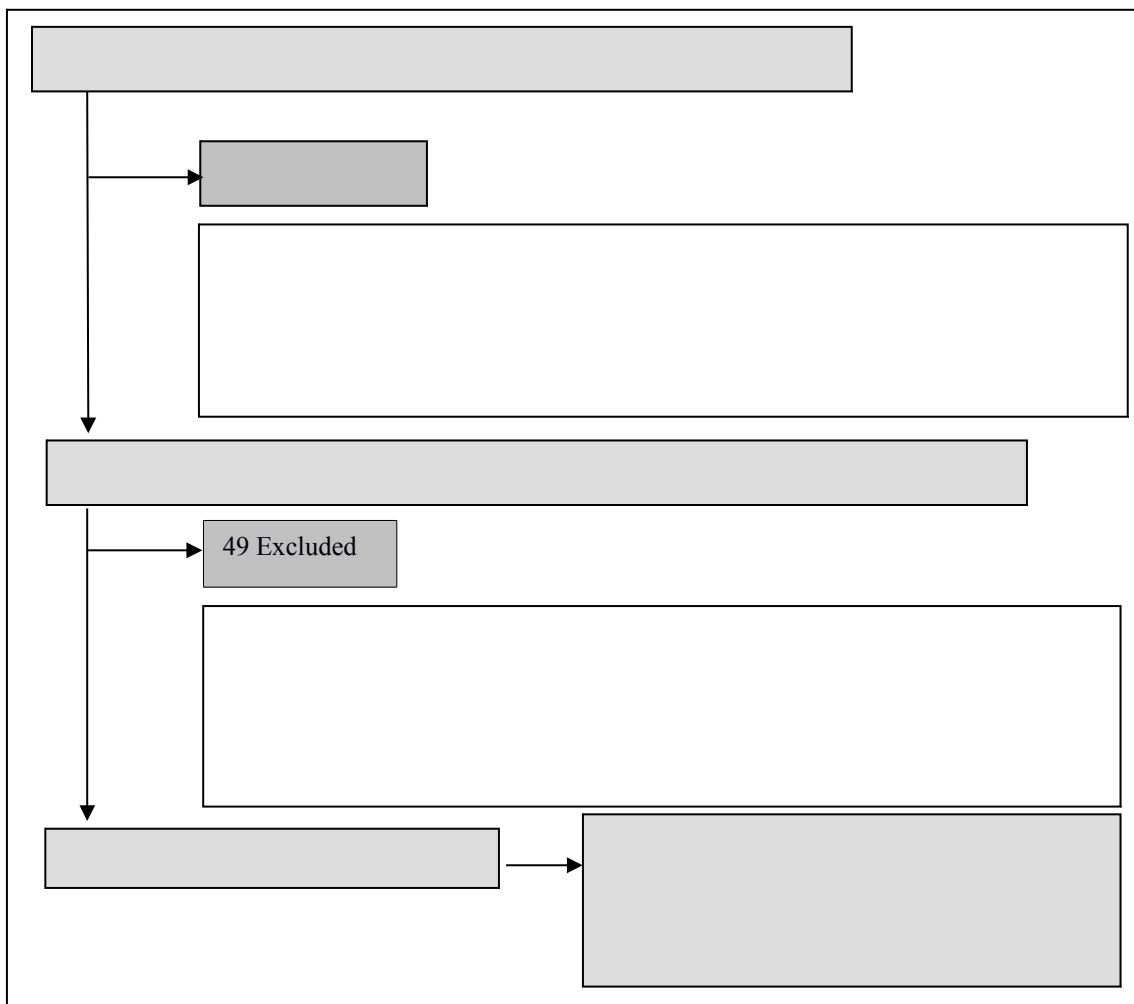


Table 1. General Characteristics of 17 Included RCTs

Reference (country) year	N° of patients	Drug, Dose, Posology	Concomitant treatment in experimental and control groups	Treatment duration
Baldi F et al. (Italy) 1988 (5)	63	Cisapride 10mg x 4	None	12 weeks
Collins BJ et al. (United Kingdom) 1987 (6)	18	Cisapride 10mg x 3	None	4 weeks
Finizia C et al. (Sweden) 2002 (7)	30	Cisapride 20mg x 2	None	2 weeks
Galmiche JP et al. (Francia) 1988 (8)	47	Cisapride 10mg x 4 + Cimetidine	Cimetidine	12 weeks
Hatlebakk JG et al. (Norway) 1999 (9)	107	Cisapride 20mg x 2	None	8 weeks
Lepoutre L et al. (Belgium) 1990 (10)	20	Cisapride 10mg x 4	None	16 weeks
Lieberman DA et al. (USA) 1986 (11)	25	Metoclopramide 10mg x 4 + Cimetidine	Cimetidine	8 weeks
McCallum et al. (USA) 1984 (13)	19	Metoclopramide 10mg x 4	None	4 weeks
Mc Kenna CJ et al. (United Kingdom) 1995 (14)	344	Cisapride 20mg x2 + Ranitidine	Ranitidine	12 weeks
Masci E et al. (Italy) 1992 (12)	30 *	Levosulpiride 25mg x3/ Domperidone 10mg x 3	None	12 weeks
Nicolaidis CL et al. (Greece) 1987 (15)	40	Cisapride 10mg x 3	None	4 weeks
Nicolaidis CL et al. (Greece) 1987 (15)	40	Cisapride 5mg x 3	None	4 weeks
Pehlivanov N et al. (USA) 2002 (16)	10	Cisapride 10mg x 4	None	5 days
Richter JE et al. (USA) 1995 (17)	177	Cisapride 10mg x 4	None	12 weeks
Richter JE et al. (USA) 1995 (17)	177	Cisapride 20mg x 4	None	12 weeks
Robertson CS et al. (United Kingdom) 1993 (18)	46	Cisapride 10mg x 4	None	12 weeks
Temple JG et al.(United Kingdom) 1983 (19)	73	Metoclopramide 10mg x 3 + Cimetidine	Cimetidine	12 weeks
Thanik KD et al. (USA) 1980 (20)	44	Bethanechol 25mg x 4	None	4 weeks
Trabucchi E et al. (Italy) (21)	30	L-sulpiride 25 mg x 3	None	4 weeks

Abbreviations: PD/CT, prokinetic drug/comparison treatment; NA, not available

* **Number of patients enrolled in each arm weren't reported.**

Table 2. Quality of RCTs

Reference (country) year	Concealment allocation	Blinding	Follow-up	Jadad scale modified by Schulz criteria (Score 0-8)	Pharmaceutical Industry sponsored
Baldi F et al. (Italy) 1988 (5)	Definitely not	Patients and investigators #	59%	4	NA
Collins BJ et al. (United Kingdom) 1987 (6)	Definitely not	Patients, health care providers and investigators #	100%	5	YES
Finizia C et al. (Sweden) 2002 (7)	Definitely not	Patients and investigators #	100%	4	YES
Galmiche JP et al. (Francia) 1988 (8)	Definitely not	Patients and investigators #	100%	4	NA
Hatlebakk JG et al. (Norway) 1999 (9)	Certain	Patients, health care providers and data collectors	100%	7	YES
Lepoutre L et al. (Belgium) 1990 (10)	Definitely not	Patients and investigators #	100%	4	NA
Lieberman DA et al. (USA) 1986 (11)	Definitely not	Patients and investigators #	96%	4	YES
McCallum et al. (USA) 1984 (13)	Definitely not	Patients and investigators #	95%	5	NO
Mc Kenna CJ et al. (United Kingdom) 1995 (14)	Probably	Patients, follow-up endoscopists and investigators #	92%	4	YES
Masci E et al. (Italy) 1992 (12)	Definitely not	double blind #	NA	4	YES
Nicolaidis CL et al. (Greece) 1987 (15)	Definitely not	Patients and investigators #	100%	5	NA
Pehlivanov N et al. (USA) 2002 (16)	Definitely not	Patients and investigators #	100%	4	YES
Richter JE et al. (USA) 1995 (17)	Definitely not	Patients and investigators #	89%	5	YES
Robertson CS et al. (United Kingdom) 1993 (18)	Definitely not	double blind #	96%	4	YES
Temple JG et al.(United Kingdom) 1983 (19)	Definitely not	Patients and investigators # (Double dummy technique)	96%	4	YES
Thanik KD et al. (USA) 1980 (20)	Definitely not	Patients and investigators #	100%	5	YES
Trabucchi E et al. (Italy) (21)	Definitely not	double blind #	NA	4	NA

Not defined further.

NA **Not available.**

Table 3. Prokinetic Drug Utility

Outcome	No. of Studies/ patients	Treatment Group n improved/ n total	Control Group n improved/ n total	RR (CI 95%) random effect	Risk Difference (CI 95%) random effect
1) Cisapride <40mg/d					
Clinical improvement	2/58	29/37	9/21	1.77 (1.03-3.04)	34% (9-60)
2) Cisapride ≥40mg/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)
3) Cisapride (any doses)					
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)
4) Metoclopramide 30mg/d					
Endoscopic improvement or healing	1/73	8/33	18/40	0.54 (0.27-1.08)	-21% (-42-0)
5) Metoclopramide 40mg/d					
Endoscopic improvement or healing	2/45	15/24	10/21	1.26 (0.5-3.19)	13% (-34-60)
Clinical improvement	1/22	9/13	2/9	3.12 (0.87-11.15)	47% (10-84)
6) Metoclopramide (any doses)					
Endoscopic improvement or healing	3/118	23/57	28/61	0.93 (0.45-1.94)	-1% (-36-35)
Clinical improvement	1/22	9/13	2/9	3.12 (0.87-11.15)	47% (10-84)
7) Bethanechol 100mg/d					
Endoscopic improvement or healing	1/44	14/22	8/22	1.75 (0.93-3.31)	27% (-1-56)
Clinical improvement	1/44	10/22	3/22	3.67 (1.18-11.37)	36% (11-62)
8) All prokinetics					
Endoscopic improvement or healing	10/859	291/457	207/402	1.35 (1.05-1.72)	20% (6-34)
Clinical improvement	8/347	101/185	47/162	1.68 (1.31-2.17)	27% (16-38)

Table 4. Adverse effects

Adverse effects	Intervention	RR (CI 95%) random effect	Risk Difference (CI 95%) random effect	No. of studies
General AE	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% (-5-5)	8
Neurological (any)	Any prokinetic and dose	1,03 (0,58-1,84)	0.04% (-0.04-0.12)	9
Gastrointestinal (any)	Cisapride (any dose)	1,05 (0,64-1,74)	0% (-0.07-0.06)	7
Neurological (any)	Cisapride (any dose)	0,61 (0,32-1,15)	-0.02% (-0.09-0.05)	6
Headache	Cisapride > 40mg/d	0,65 (0,33-1,28)	0% (-0.08-0.08)	4
Diarrhea	Cisapride > 40mg/d	0,99 (0,47-2,09)	-0.01% (-0.09-0.07)	3
Neurological (any)	Metoclopramide (any dose)	2.41 (1.25-4.64)	34% (-16-83)	2

Figure 2. Meta analysis

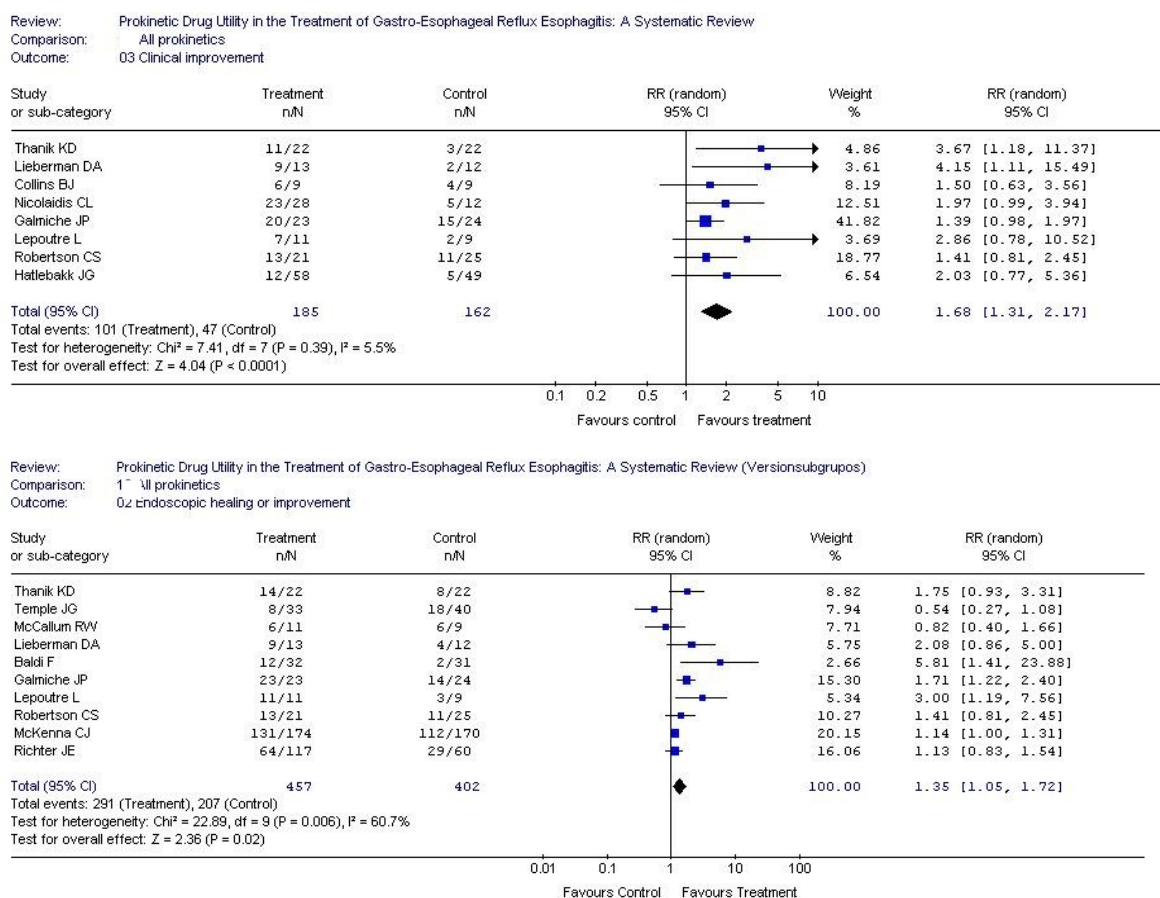


Table 5. Overall Quality of evidence

	Study quality	Precision of estimates	Consistency of results	Directness of results	Likelihood of reporting bias	Overall quality of evidence	Relative risk and 95% CI
Symptom improvement	No serious limitations	Adequate precision	YES	YES	Suggested	Moderate	1.68 (1.31-2.17)
Endoscopic healing	No serious limitations	Wide confidence interval	NO	YES	Suggested	Very low	1.35 (1.05-1.72)
Adverse effects	No serious limitations	Wide confidence interval	NO	YES	No	Low	1.30 (0.93-1.83)