Prokinetics for Functional Dyspepsia: A Systematic Review and Meta-analysis of Randomized Control Trials

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OBJECTIVE: **Prokinetics are recommended for the treatment of functional dyspepsia (FD) but systematic reviews give conflicting results on the efficacy of these agents. We have therefore conducted an updated systematic review to support the 2017 joint ACG/CAG dyspepsia guidelines.**

METHOD: **Electronic databases, including MEDLINE, EMBASE, and CENTRAL, were searched until September 2017 for randomized controlled trials (RCTs) comparing either prokinetics and placebo or two types of prokinetics to improve FD symptoms. The primary outcome was absence or improvement of dyspeptic symptoms at the end of treatment. Double-blind eligibility assessment and data extraction was performed. Pooled risk ratios of symptoms persisting or adverse events occurring, and standardized mean difference of quality-of-life (QoL) scores with 95% CI, using a random effects model, were calculated. Quality of evidence was assessed using GRADE.**

RESULTS: **The search identified 1388 citations; 38 studies in 35 papers were included. Of these, 29 trials comparing prokinetics with placebo were found. There was a statistically significant effect of prokinetic treatment in reducing global symptoms of FD (RR 0.81, 95% CI 0.74 to 0.89; I^2 91%; NNT 7), regardless of FD subtype or ethnicity. When comparing two types of prokinetic, the most commonly used comparator was domperidone. There was no difference in reducing global symptoms (RR 0.94, 95% CI 0.83 to 1.07). QoL was not improved with prokinetic treatment. The adverse events with individual prokinetics were not different from placebo, except for cisapride. The GRADE assessment rated the quality of the evidence in each outcome as very low.**

CONCLUSION: **From the current evidence, prokinetics may be effective for the treatment in all subtypes of FD, with very low quality of evidence. There was no difference between prokinetics for dyspeptic symptom improvement. High-quality RCTs with large sample sizes of FD patients are needed to verify the efficacy of prokinetics.**

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INTRODUCTION

Functional dyspepsia (FD) is a common gastrointestinal (GI) disorder recognized as a multi-factorial, difficult to treat condition that has a negative impact on quality of life (QoL) [1, 2]. GI dysmotility has been implicated in the pathophysiology of FD [2–4], and as many as 80% of patients with FD report symptoms after ingesting a meal [5]. Improving gastric emptying with a prokinetic may improve dyspeptic symptoms including those of postprandial fullness and epigastric pain [6]. However, the role of prokinetics in the treatment of FD is unclear [7]. Prokinetics have been recommended as first-line treatment in FD patients with the postprandial distress subtype (PDS) [3], whereas they were suggested as third-line treatment in the 2005 dyspepsia guideline from the American College of Gastroenterology (ACG) [8].

Since the publication of the ACG dyspepsia guideline [8], a variety of new prokinetic agents have been developed. Furthermore, cisapride, the most heavily studied prokinetic drug, is no longer available in most countries. We have therefore conducted a systematic review of prokinetics for the treatment of FD in order to

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inform an updated ACG dyspepsia guideline in collaboration with the Canadian Association of Gastroenterology (CAG) [9].

METHODS

Search strategy

We performed a systematic search of the Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic Reviews (CDSR) in the Cochrane Library (OvidSP); MEDLINE (OvidSP); Embase (OvidSP); and CINAH, from 1946 to 14 September 2017, to identify randomized controlled trials (RCTs) comparing a prokinetic agent either with placebo or with another prokinetic. For the treatment of FD, we searched the individual names of prokinetics including erythromycin, metoclopramide, domperidone, cisapride, mosapride, itopride, ABT-229, alosetron, tegaserod, mosapride, and acotiamide, as well as any other prokinetics identified through a literature review (e.g., prucalopride).

Study selection and patient population

The inclusion criteria were: (1) RCTs with parallel design (for studies using a cross-over design, only the first period of the study was included); (2) comparison of one prokinetic agent with either placebo or another prokinetic agent for the treatment of FD; (3) FD defined by either the Rome Criteria (I to IV [3, 10, 11]; or by criteria compatible with the Rome criteria; (4) adult patients aged 18 or over; (5) upper endoscopy reported as normal or with insignificant findings to explain symptoms; (6) no evidence of an organic, drug-induced or metabolic disorder to explain symptoms. Trials were excluded if: (1) the studies included only participants with primarily reflux or heartburn symptoms; (2) the objective was to evaluate herbal prokinetic agents or prokinetic with an anxiolytic effect (e.g., levosulpiride); (3) treatment duration was less than 7 days; (4) studies not involving either a placebo or comparator.

Choice of outcome

The primary outcome was an improvement in global symptoms of dyspepsia, reported as a binary outcome (yes or no). We used the most stringent definition of overall symptom improvement if more than one definition of symptom improvement was given. We recorded patient reported outcomes at the end of treatment but if that was not available we used overall symptom assessment by the caring physician / researcher. If global symptoms were not reported, we used epigastric pain/discomfort improvement as the outcome measure. Secondary outcomes were QoL and adverse events (AEs).

Validity assessment

Two authors (RP and YY) independently reviewed studies retrieved by the search strategy and excluded trials based on titles, abstracts, or both. Both study authors independently reviewed selected studies for complete analysis. One study author extracted data and entered it into RevMan. The other study author served to ensure the accuracy of this process. When the authors found different results, they re-checked the data and had a discussion to reach an agreement by consensus. If the authors were unable to reach a consensus, a senior author (PM) arbitrated. The data collected included the following: (1) participant characteristics—demographics, recruitment source, diagnostic criteria used by study authors, dyspepsia subtype; 2) details of interventions—name of medication, dose, schedule; 3) dyspeptic symptoms before and after the intervention—number of patients with dyspepsia symptoms, QoL, and AEs. Data were managed and analyzed according to an intention-to-treat analysis.

All trials were assessed using Cochrane's 'Risk of Bias' (RoB) tool, which evaluates the following domains: random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data addressed at short and long term (attrition bias); selective reporting (reporting bias); and other biases.

Statistical methods and sensitivity analyses

For the binary outcome, we presented the results as a risk ratio (RR) with 95% confidence intervals (CI). For the continuous outcomes, we presented the results as a standardized mean difference (SMD) with 95% CI. We assessed heterogeneity with the χ^2 test and I^2 statistic using a random effects model [12]. Possible sources for heterogeneity were evaluated by subgroup analyses according to the following criteria: subtypes of FD (PDS vs. epigastric pain syndrome (EPS) vs. mixed type); type of publication (full paper vs. conference abstract); study population (Western—any countries in North America, Europe, Australia, and New Zealand; Eastern—any countries in the Asian continent); use of validated dyspepsia questionnaires; length of follow-up ($\geq$4 weeks vs. $<$4 weeks); and studies assessed as high RoB vs. low vs. unclear RoB.

In order to assess the presence of small study effects and publication bias in the meta-analysis, a funnel plot and Egger's test were used. The levels of evidence in each outcome was based on the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach [13] with the consensus of two authors (RP and PM).

RESULTS

Study selection

Overall, 1388 citations were retrieved; 1316 were rejected based on title, abstract relevance, or duplication; 72 articles were fully reviewed. After further review an additional 37 full-text articles were excluded (Fig. 1). Final analysis included 38 studies from 35 papers (9 in Chinese and 1 in Portuguese). Of these, 29 trials from 26 articles [14–39] involving 10,044 participants (5949 patients in six prokinetic groups (cisapride [14–25], acotiamide [26–30], itopride [31–35], tegaserod [36], mosapride [37, 38], and ABT-229 [39]) and 4095 controls in placebo group) reported on complete resolution of symptoms or symptom improvement at the end of the study period. Another nine trials [40–48] with 2051 participants assessing five prokinetics (itopride, mosapride, cinitapride, domperidone, and DA-9701) contributed data for comparisons between prokinetics. The most commonly used comparator was

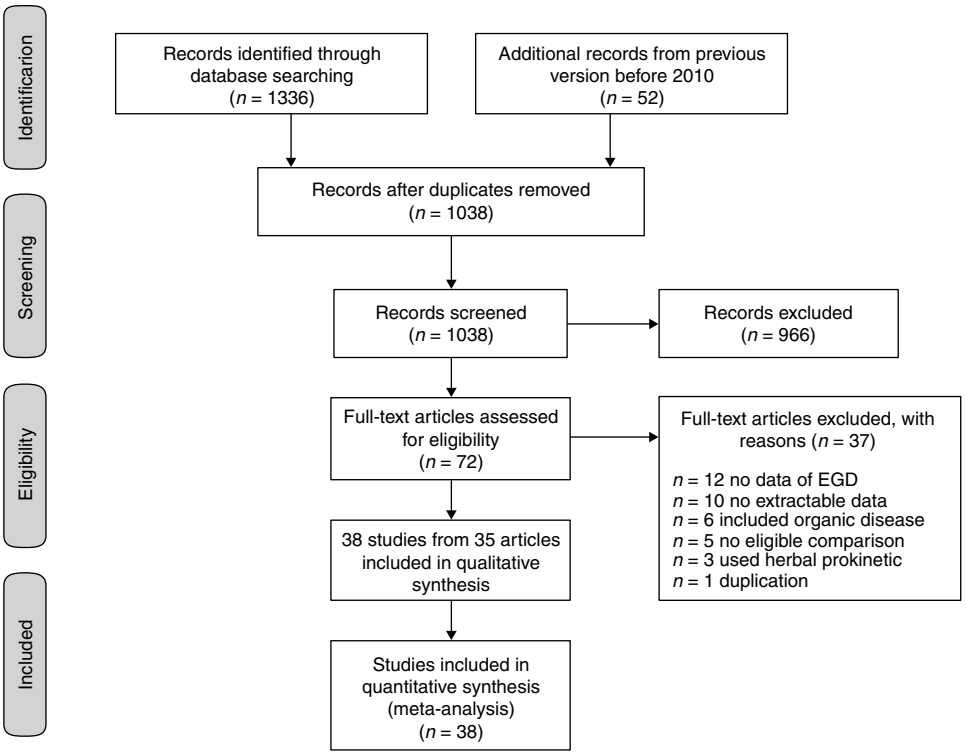

Fig. 1 Flow diagram of trial selection

domperidone 10 mg t.i.d. (7 of the 9 studies with 1527 participants) (see Supplementary Table **1**).

Most (29 studies) were rated as unclear RoB. Five and four trials had low and high RoB, respectively. The authors' judgements about each RoB domain in relevant trials were showed in Supplementary Figure **1**. Few studies [25, 26] assessed the efficacy of prokinetic therapy according to the results of gastric physiological test (e.g., gastric emptying time), so there is a lack of evidence to support such testing in directing prokinetic therapy.

Primary and secondary outcomes

The average percentage of symptom improvement was 40% in the prokinetic group, compared to 26.1% in the placebo group. There was a statistically significant effect of prokinetic treatment in reducing global symptoms of FD (RR of dyspeptic symptoms persisting 0.81, 95% CI 0.74 to 0.89; Number needed to treat (NNT) 7, 95% CI 5 to 12) with statistically significant heterogeneity; I^2 91% ($p < 0.00001$) (Fig. 2). The funnel plot was asymmetric (Egger's test, $p = 0.02$). When cisapride was removed from the analysis, the effect of prokinetic in global symptom improvement remained robust in 8397 participants (RR 0.87, 95% CI 0.80 to 0.94; $p = 0.0004$; NNT 12, 95% CI 8 to 27) but significant heterogeneity remained; I^2 86% ($p < 0.00001$).

There were nine trials that compared two different prokinetics and the most commonly used comparator was domperidone 10 mg, which was reported in seven studies. When comparing other prokinetics vs. domperidone 10 mg t.i.d., there was no difference in reducing global symptoms (RR 0.94, 95% CI 0.83 to 1.07) (Fig. 3).

Pooled data from five trials ($n = 1774$) failed to show any differences in QoL scores when prokinetics were compared to placebo (SMD 0.11, 95% CI −0.10 to 0.33; I^2 32%, $p = 0.23$). No data was available comparing QoL between different types of prokinetics. Pooled data involving four different prokinetics (cisapride, acotiamide, itopride, and mosapride) in 17 separate studies ($n = 3811$), revealed that AEs were found in 29.3% of patients randomized to a prokinetic agent compared to 30.8% randomized to placebo. There was no association between a specific prokinetic and any AEs (RR 1.09, 95% CI 0.95 to 1.25; I^2 18%, $p = 0.25$), except for cisapride where there were overall greater adverse effects in the active treatment group (RR 1.31, 95% CI 1.03 to 1.65; $p = 0.03$; number needed to harm 23, 95%CI 10 to 238). The most common AEs were diarrhea, abdominal discomfort, and nausea. Pooled data from seven studies (5 itopride, 1 cinitapride, and 1 mosapride) demonstrated fewer AEs in these agents compared to domperidone (RR 0.69, 95% CI 0.50 to 0.97; $n = 1557$; I^2 0%, $p = 0.86$). In these studies, a significant difference was only seen between cinitapride 1 mg t.i.d. compared to domperidone 10 mg t.i.d. (RR 0.60, 95% CI 0.37 to 0.97).

Subgroup analysis

In term of individual prokinetics, cisapride (RR 0.71, 95% CI 0.54 to 0.93; NNT 4, 95% CI 3 to 17), acotiamide (RR 0.94, 95% CI 0.91 to 0.98; NNT 20, 95% CI 13 to 60), and tegaserod (RR 0.89, 95% CI 0.82 to 0.96; NNT 14, 95% CI 8 to 38) showed a statistically significant effect in reducing global symptoms of FD. (Fig. 2) There was no eligible study comparing the efficacy of domperidone vs. placebo for FD treatment. Furthermore, there was insignificant heterogeneity among seven studies comparing other prokinetics vs. domperidone (I^2 22%, $p = 0.27$); thus, subgroup analysis for domperidone studies are unlikely to derive a meaningful conclusion.

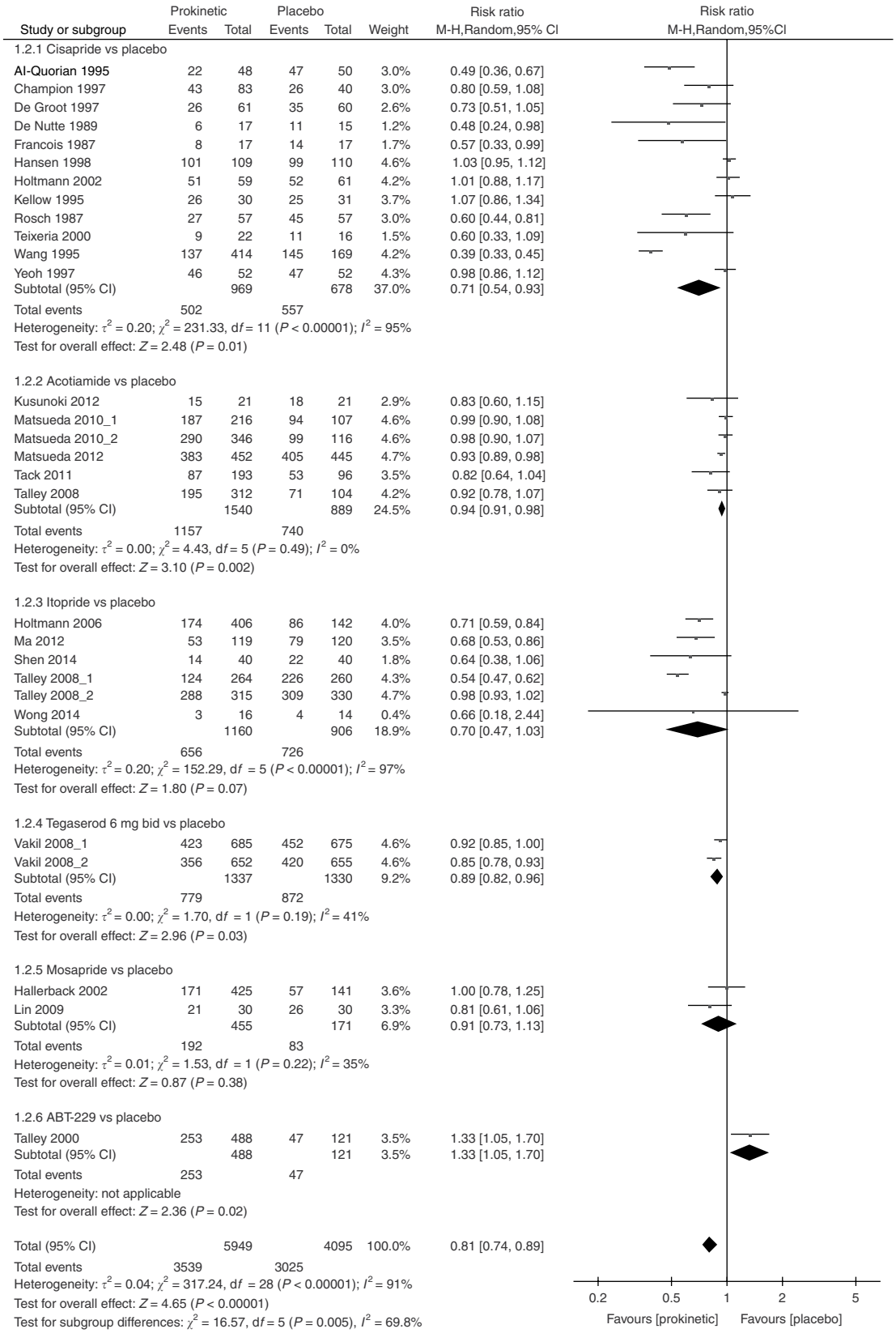

Fig. 2 Forrest plot comparing prokinetic and placebo in patients with functional dyspepsia in term of not symptom-free or no symptom improvement, subgrouped by individual prokinetic

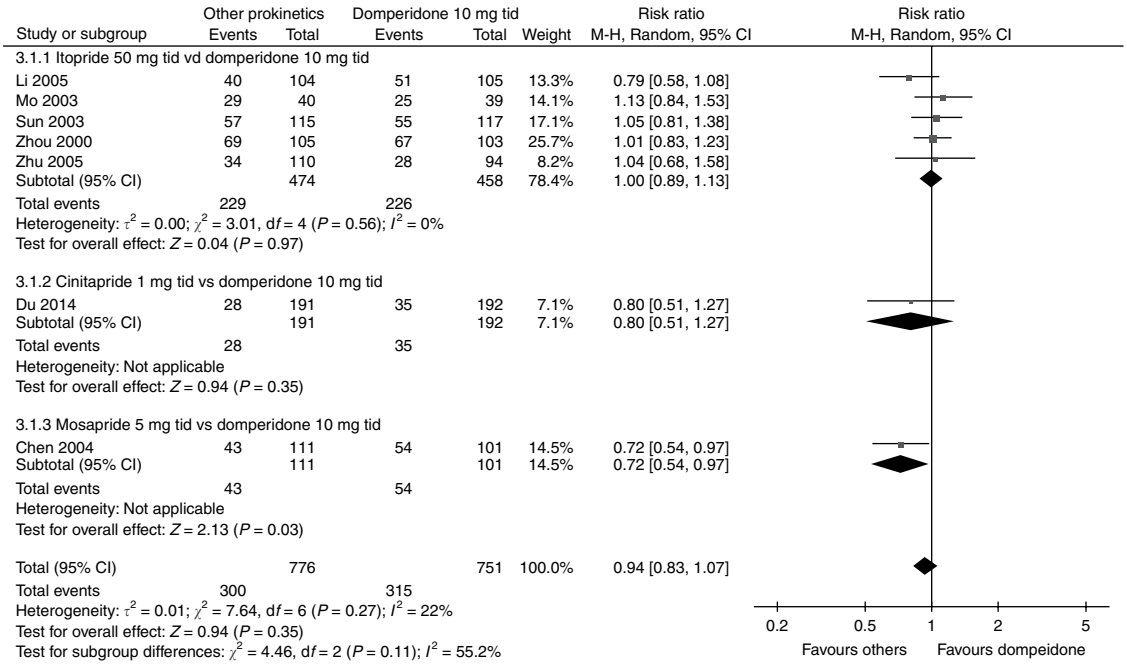

Fig. 3 Forrest plot comparing other prokinetic and domperidone 10 mg t.i.d. in patients with functional dyspepsia in term of not symptom-free or no symptom improvement

Evaluation of outcomes based on FD subtype was performed in 30 studies. Analysis of 11 studies involving 5822 participants with the PDS subtype (3390 prokinetics users and 2432 controls) showed significant improvement in the prokinetic group (RR 0.82, 95% CI 0.70 to 0.95) with considerable heterogeneity (I^2 93%; $p < 0.00001$). Two studies evaluated patients with EPS subtype ($n = 124$) and found a greater likelihood of efficacy with prokinetic use in global symptom improvement compared to placebo (RR 0.67, 95% CI 0.48 to 0.93) with no significant heterogeneity (I^2 6%; $p = 0.3$). There were 14 trials with 3837 participants that evaluated symptom improvement in mixed PDS/EPS subgroups and these demonstrated the efficacy of prokinetic therapy in reducing global dyspeptic symptoms (RR 0.86, 95% CI 0.76 to 0.97) with considerable heterogeneity (I^2 91%: $p < 0.00001$). Another three trials with 259 participants did not differentiate FD subtypes. Analysis revealed a benefit of prokinetic (RR 0.62, 95% CI 0.44 to 0.87) with substantial heterogeneity (I^2 58%: $p = 0.09$). No statistically significant difference was seen in testing for subgroup differences (I^2 34.3%, $p = 0.21$) (Fig. 4).

According to the type of publication, most studies (26/29) were published as full articles and these demonstrated the efficacy of prokinetics with regard to improving global dyspepsia symptoms compared to placebo, although considerable heterogeneity was noted (RR 0.81, 95% CI 0.74 to 0.89; participants = 9309; I^2 92%, $p < 0.0001$). Three trials, published only in abstract form, demonstrated no significant difference between prokinetics and placebo for relief of global dyspepsia symptoms (RR 0.88, 95% CI 0.77 to 1.00; participants = 735; I^2 0%) (Supplementary Figure **2**).

Eighteen trials with 7126 participants were conducted in Western countries (United States, Canada, Europe, and Australia) whereas 11 studies involving 2918 patients were conducted in Asia (Japan, China, India, Korea, Singapore, Malaysia, and Saudi Arabia). Studies from both regions showed evidence of prokinetics reducing global dyspeptic symptoms with considerable heterogeneity (RR 0.85, 95% CI 0.77 to 0.94; I^2 87% and RR 0.75, 95% CI 0.62 to 0.91; I^2 95%, respectively) (Fig. 5). However, the NNT was two times higher in the Western population (10, 95% CI 6 to 24) than in patients from Eastern countries (5, 95% CI 3 to 13).

Only three trials from two papers ($n = 1199$) used a validated dyspepsia assessment tool (Leeds Dyspepsia questionnaire) [31, 35] and reported no statistically significant difference between a prokinetic agent and placebo (RR 0.71, 95% CI 0.35 to 1.46). All other trials used non-valid assessment tools and showed the efficacy of prokinetics at relieving global symptoms ($n = 8845$; RR 0.82, 95% CI 0.75 to 0.90; I^2 89%, $p < 0.00001$) (Supplementary Figure **3**).

Six trials used <1 month of treatment and follow-up in 473 individuals. Analysis revealed no significant difference between prokinetic and placebo at relieving symptoms of dyspepsia (RR 0.77, 95% CI 0.59 to 1.01; $p = 0.06$). There was significant heterogeneity among these trials (I^2 77%, $p = 0.0007$). In those treated with a prokinetic agent compared to placebo for at least 1 month there was a significant reduction in dyspepsia symptoms ($n = 9571$) (RR 0.81, 95% CI 0.74 to 0.90; I^2 92%, $p < 0.00001$) (Supplementary Figure **4**).

Four studies with 1049 individuals had a high RoB and showed no statistically significant differences between prokinetic agents and placebo (RR 0.67, 95% CI 0.39 to 1.15) with significant heterogeneity between the studies ($I^2 = 97\%$, $p < 0.00001$). Conversely, 21 trials with unclear RoB ($n = 4883$) and four trials with low RoB ($n = 4112$) showed significant efficacy of prokinetic agents at improving global dyspeptic symptoms (RR 0.84, 95% CI 0.76

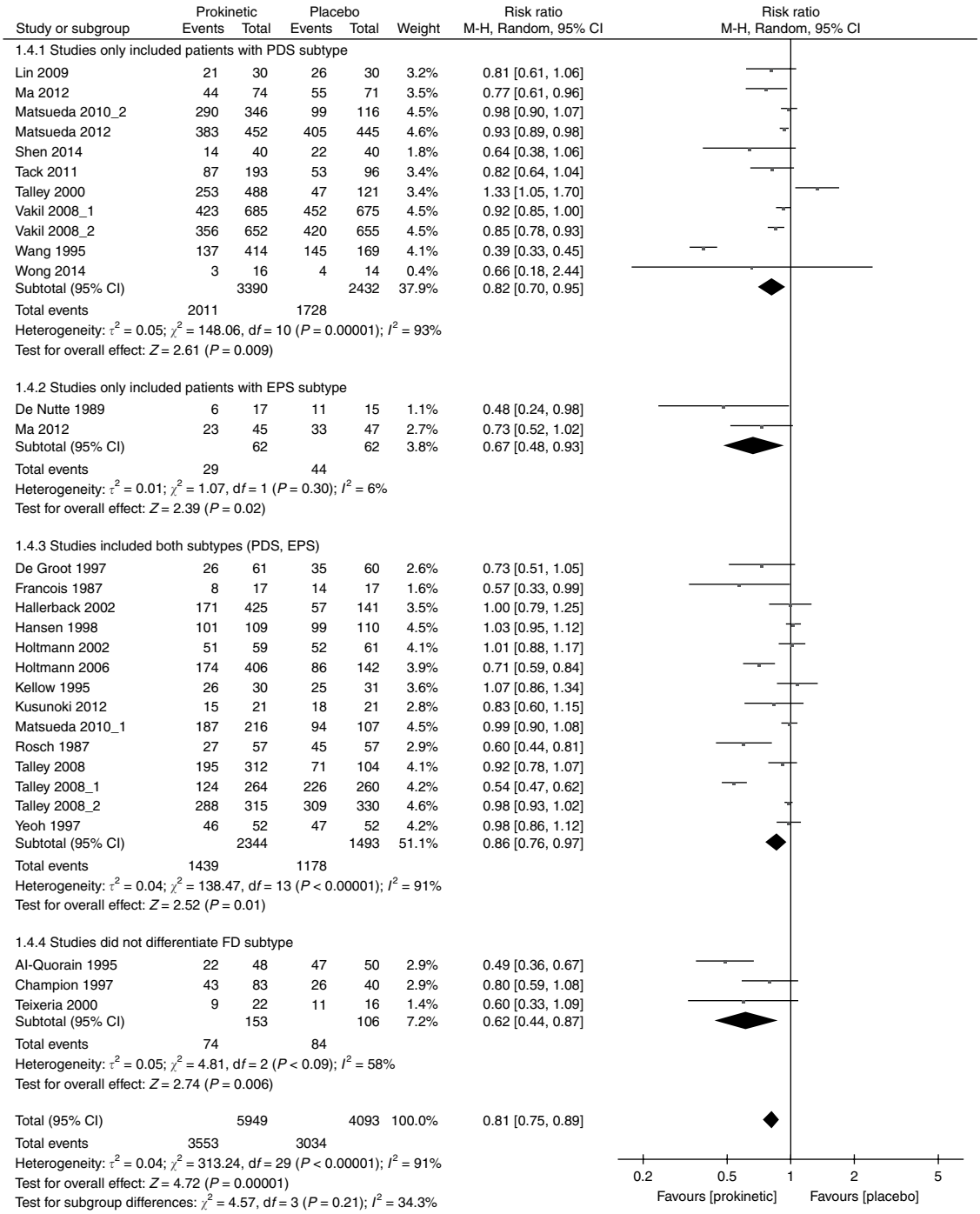

Fig. 4 Forrest plot comparing prokinetic and placebo in patients with functional dyspepsia in term of not symptom-free or no symptom improvement, subgrouped by functional dyspepsia subtype

to 0.93; I^2 87%, $p < 0.0001$; NNT 8, 95% CI 5 to 19 and RR 0.87, 95% CI 0.80 to 0.95; I^2 76%, $p < 0.0001$; NNT 11, 95% CI 7 to 28, respectively) (Fig. 6).

Quality of the evidence

In comparing the efficacy of prokinetic agents compared to placebo, the GRADE assessment of the quality of the evidence is very low in all outcomes. This is due to concerns around RoB in trial design (e.g., unexplained random sequence generation, allocation concealment, blinding method for participants and medical personnel, outcome assessors), unexplained heterogeneity, and possible publication bias in primary outcome; unexplained heterogeneity and imprecision in QoL; possible publication bias, and imprecision in AEs (Table 1).

For comparing other prokinetics vs. domperidone, the quality of evidence is very low in both primary outcome and AEs due to the concerns around RoB in trial design and imprecision (Table 2).

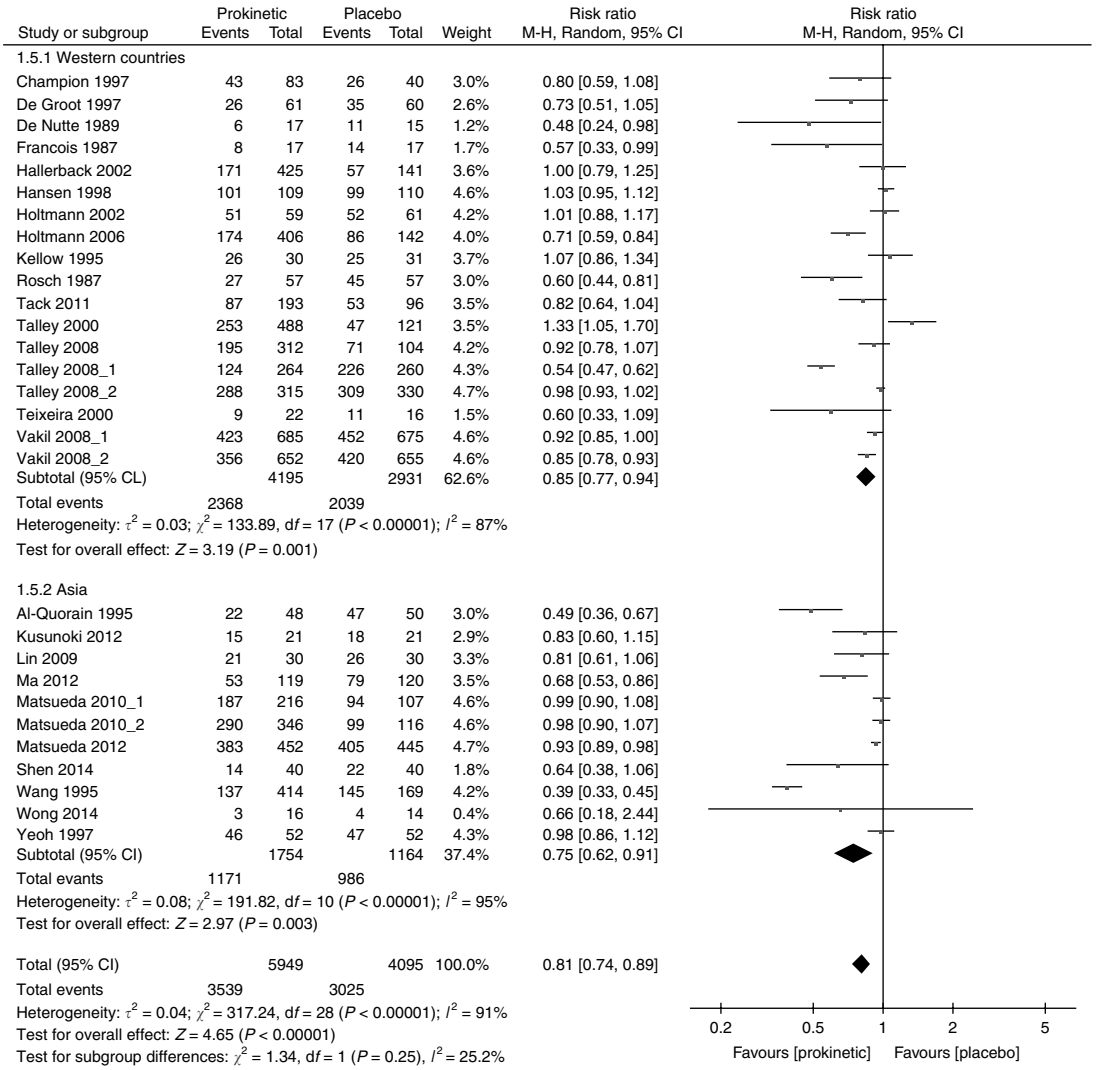

Fig. 5 Forrest plot comparing prokinetic and placebo in patients with functional dyspepsia in term of not symptom-free or no symptom improvement, subgrouped by region of study

DISCUSSION

Treating FD can be difficult as multiple treatment options exist, although none are specifically approved by either the European Medicine Agency or the Food and Drug Association. Although, there are limited prokinetics available in North America, these medications are used in FD treatment internationally, particularly in Asia. For that reason, we undertook this systematic review and meta-analysis of prokinetic agents for the treatment of FD to inform clinicians of the efficacy of this approach.

We believe that the results of this comprehensive review are accurate and valid as the search methodology included all RCTs regardless of publication type and language of publication. We also believe that the results reflect the best available current evidence demonstrating the efficacy of prokinetic agents for treating FD.

The results showed that prokinetics can improve dyspeptic symptoms from pooled data with a moderate NNT of 7. However, when cisapride was removed from the analysis, the NNT increases to 12; higher than the NNT for a proton pump inhibitor and a tricyclic anti-depressant treatment in the treatment of FD (NNT = 10 and 6, respectively) [9]. Moreover, the funnel plot was asymmetric (Egger's test, $p = 0.02$) implying reporting bias or other small study effects may in part be driving the benefit of prokinetic agents compared to placebo in this meta-analysis. Additionally, there was significant heterogeneity between trials and the quality of evidence is very low. Consequently, this finding should be interpreted with caution.

Cisapride, acotiamide and tegaserod were identified as the effective individual prokinetic agents compared to placebo. However, cisapride was not recommended as it was associated with life-threatening arrhythmias due to prolonged QT intervals and has been withdrawn from the market in most countries. In addition, the trials of cisapride were rated as unclear or high RoB. Only 4 trials in this review were considered as low RoB – 2 involving tegaserod, and 1 each involving acotiamide and itopride. Therefore, there is good evidence to support the efficacy of tegaserod and acotiamide over placebo as well as a trend to benefit of

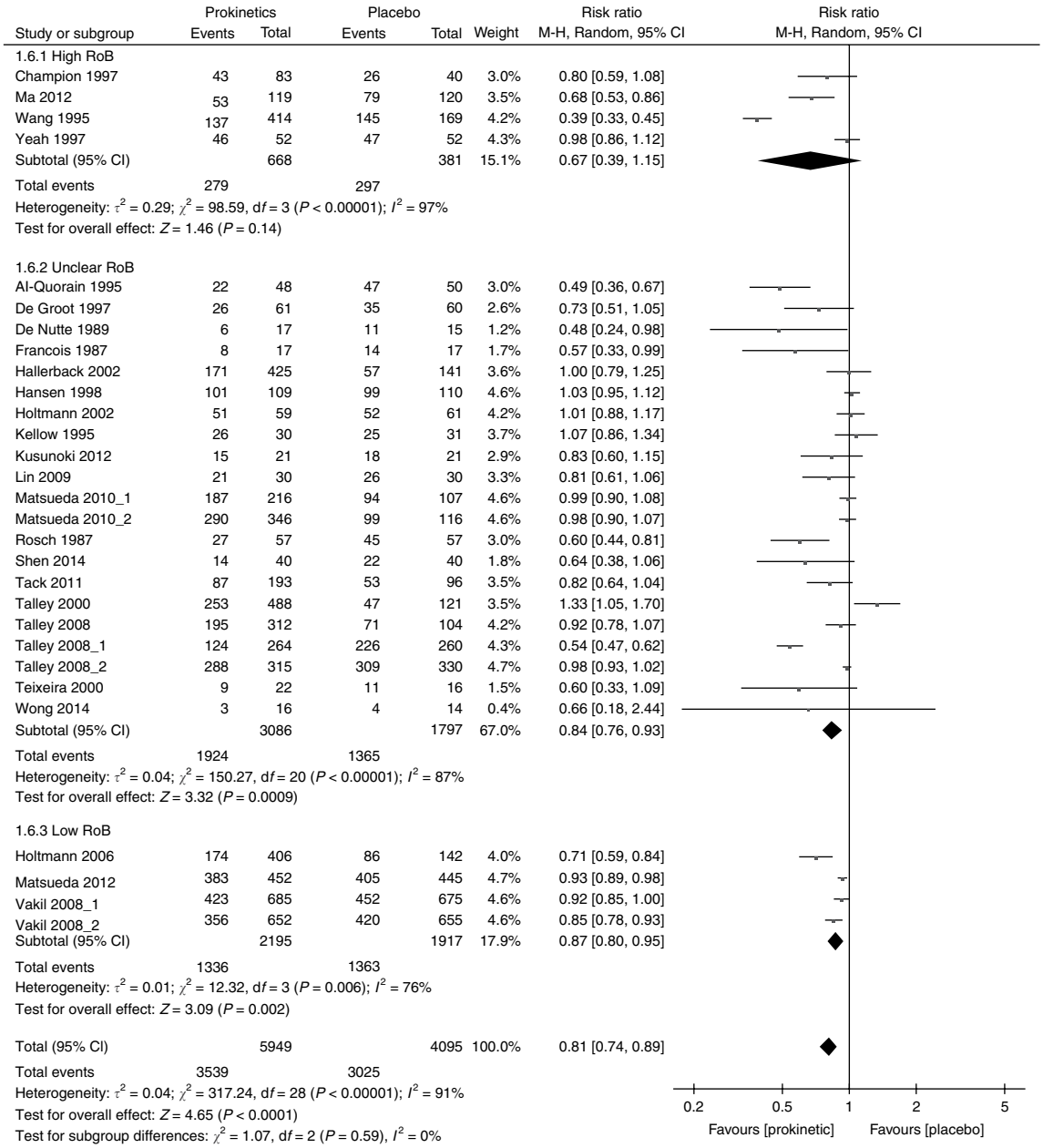

Fig. 6 Forrest plot comparing prokinetic and placebo in patients with functional dyspepsia in term of not symptom-free or no symptom improvement, subgrouped by risk of bias

itopride for FD symptoms. This may due to the combination of improved gastric accommodation and gastroprokinetic properties of tegaserod and acotiamide [26, 49]. Nevertheless, there was insufficient evidence to conclude whether any prokinetic was the most effective.

Both Western and Eastern trials demonstrated the efficacy of prokinetics in reducing dyspeptic symptoms. Furthermore, patients in Eastern countries (NNT 5; 95% CI 3 to 13) seem to have a greater response to prokinetics, compared to patients in Western countries (NNT 10; 95% CI 6 to 24). This may relate to differences in the quality of the studies. It may also be due to patient factors (e.g., genetics, diet, culture, physiology). This finding supported the 2015 FD guideline in Japan which recommends prokinetic as a first-line treatment in patients with FD [50]. Conversely, prokinetic agents are suggested as third-line treatments in recent ACG/CAG guideline for FD treatment because no prokinetics from eligible studies are commercially available in North America, and due to the very low quality of evidence of included trials [9]. Despite a wide range (95% CI) of NNT (6 to 24) in Western populations, our data shows the benefits of prokinetic agents in reducing dyspeptic symptoms which can be used to improve patient outcomes.

It should be noted that there were no eligible studies assessing the effectiveness of metoclopramide or domperidone in FD. These are the only upper gut prokinetics available in North America. Domperidone and metoclopramide are both dopamine

Table 1 GRADE assessment for prokinetic vs. placebo studies

Prokinetic compared to placebo for functional dyspepsia

Patient or population: Functional dyspepsia

Setting: Out-patients

Intervention: Prokinetic

Comparison: Placebo

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Prokinetic				
Not symptom-free or no symptom improvement	74 per 100	60 per 100 (55 to 66)	RR 0.81 (0.74 to 0.89)	10044 (29 RCTs)	Very low [b,c,d,e]	
Change of QoL scores	—	—	—	1774 (5 RCTs)	Very low [f,g,h]	Higher scores mean better quality of life.
Adverse events	31 per 100	34 per 100 (29 to 39)	RR 1.09 (0.95 to 1.25)	3811 (17 RCTs)	Very low [b,c,e,f,i]	

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
CI confidence interval, *RR* risk ratio, *SMD* standardized mean difference
[a]The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)
[b]Downgraded one level due to study limitations: most information (>60%) were obtained from studies with unclear risk of bias for random sequence generation and/or allocation, one or more study were considered to be high risk of bias
[c]One study was open-labeled design
[d]Downgraded one level due to serious inconsistency: significant heterogeneity without plausible explanations
[e]Downgraded one level due to other considerable in publication bias: the funnel plot was asymmetrical, probably from small study effect
[f]One study was considered to be high risk of bias
[g]Downgraded one level due to serious inconsistency: significant heterogeneity with some possible explanations
[h]Downgraded two levels due to imprecision (95% CI of pooled data included no effect and small number of included trials)
[i]Downgraded one level due to imprecision (95% CI of pooled data included no effect)

(D2) antagonists, which share a similar mechanism of action to some other prokinetics included in this review (such as itopride, which has both D2 antagonism and acetylcholinesterase activity). However, there is no eligible randomized trial evaluating the effectiveness of metoclopramide or domperidone in this systematic review.

Regarding FD subtypes, the majority of low RoB trials (3 from 4 studies with 2439 participants) evaluated FD patients with PDS subtype and showed benefit of prokinetic in reducing global symptoms. This supports the Rome IV for using prokinetics in patients with PDS subtype [3]. However, there is no statistically significant difference in response to prokinetics between dyspepsia subtypes in subgroup analyses with responses being similar in each group. This supports the ACG/CAG recommendation that prokinetic therapy be used third-line regardless of dyspepsia subgroup.

Although this is the most comprehensive review of prokinetics and FD, limitations of the available evidence need to be considered. One, most of included studies (72%) were rated as unclear RoB. Therefore, we are unable to define any strong recommendation for prokinetic treatment in FD patients at this moment. Two, four trials were considered to be at high RoB and three of these were conducted in Eastern countries. This may, in part, be responsible for the reported benefits of prokinetic agents in Eastern populations. Nevertheless, the numbers of patients in high RoB studies accounted for only 10% of the overall population, which would not invalidate our results.

In conclusion, the evidence suggests the benefit of prokinetics for all subtypes of FD treatment in either Western or Eastern populations, albeit with a very low quality of evidence. There was insufficient evidence to conclude which prokinetic was the most effective. Based on our data prokinetics do not appear to significantly improve QoL, although a bigger sample size may be required to demonstrate small changes in QoL. Apart from cisapride, prokinetics appear to be well-tolerated for short-term treatment. Thus, prokinetic agents appear to be a reasonable treatment option for FD patients who have not responded to other therapies.

CONFLICTS OF INTEREST

Guarantor of the article: Paul Moayyedi.

Specific author contributions: Conception and design of the study, Paul Moayyedi, Natasha P Bollegala, Reena Khanna, Grigorios I. Leontiadis and Rapat Pittayanon; collecting data, Yuhong Yuan, Natasha P Bollegala, Reena Khanna, and Rapat Pittayanon; interpreting data, Rapat Pittayanon, Yuhong Yuan and Paul

Table 2 GRADE assessment for prokinetic vs. domperidone studies

Other prokinetics compared to domperidone 10 mg tid for functional dyspepsia

Patient or population: Functional dyspepsia

Setting: Out-patients

Intervention: Other prokinetics

Comparison: Domperidone 10 mg tid

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with domperidone 10 mg tid	Risk with Other prokinetics				
Not symptom free or no symptoms improvement (itopride 50 tid, cinitapride 1 mg tid, mosapride 5 mg tid vs. domperidone 10 mg tid)	42 per 100	39 per 100 (35 to 45)	RR 0.94 (0.83 to 1.07)	1527 (7 RCTs)	Very low [b,c]	
Adverse events	10 per 100	7 per 100 (5 to 9)	RR 0.69 (0.50 to 0.97)	1557 (7 RCTs)	Very low [b,d,e]	

*GRADE Working Group grades of evidence*G
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
CI confidence interval, *RR* risk ratio, *SMD* standardized mean difference
[a]The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[b]Downgraded one level due to study limitation (most information (>60%) were obtained from studies with unclear risk of bias for random sequence generation and/or allocation)
[c]Downgraded two levels due to imprecision (95% CI of pooled data included no effect and small number of included trials)
[d]Downgraded one level due to imprecision (there were lesser events than 300 and wide 95% CI)
[e]Downgraded one level due to imprecision (95% CI of pooled data was very close to no effect)

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Gastrointestinal (GI) dysmotility is one cause of functional dyspepsia (FD).
- ✓ The role of prokinetic medications for accelerating GI motility in FD treatment is inconclusive.

WHAT IS NEW HERE

- ✓ With very low quality of evidence, prokinetics are well-tolerated (except for cisapride) and effective in reducing dyspeptic symptom in all subtypes of FD (NNT = 7; 95% CI 5 to 12), but do not improve quality of life.
- ✓ Both Western and Asian patients with FD benefit from prokinetic treatment, although Asian populations may respond better (NNT in Eastern = 5; 95% CI 3 to 13 vs. NNT in Western = 10; 95% CI 6 to 24).
- ✓ There is insufficient evidence to conclude if one prokinetic is superior to another for FD treatment.

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