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

Rapat Pittayanon, MD^{1,2}, Yuhong Yuan, MD¹, Natasha P Bollegala, MD³, Reena Khanna, MD⁴, Brian E. Lacy, MD, FACG⁵, Christopher N. Andrews, MD⁶, Grigorios I. Leontiadis, MD, PhD, FACG¹ and Paul Moayyedi, MB, ChB, PhD, FACG¹

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.

SUPPLEMENTARY MATERIAL accompanies this paper at https://doi.org/10.1038/s41395-018-0258-6

Am J Gastroenterol https://doi.org/10.1038/s41395-018-0258-6

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

¹Department of Medicine, Division of Gastroenterology & Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, ON, Canada. ²Division of Gastroenterology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital The Thai Red Cross, Bangkok, Thailand. ³Department of Gastroenterology, Women's College Hospital, Toronto, ON, Canada. ⁴Department of Medicine, University of Western Ontario, London, ON, Canada. ⁵Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, FL, USA. ⁶Department of Medicine, University of Calgary, Calgary, AB, Canada. **Correspondence:** P.M. (email: moayyep@mcmaster.ca) **Received 31 May 2018; accepted 26 July 2018**

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 (≥ 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

© 2018 The American College of Gastroenterology

(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; l^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.

Study couple Test Total Weight M-H, Plandom, 95%, C1 M-H, Plandom, 95%, C1 AL-Querkin 1985 22 48 47 50 3.0% 0.69 (55, 1.08) De Groot 1987 26 61 35 60 2.5% 0.73 (0.51, 1.05) De Groot 1987 26 61 35 60 2.6% 0.73 (0.51, 1.05) De Groot 1987 26 61 35 60 2.6% 0.73 (0.51, 1.05) Frances 1987 81 17 14 17 17.2% 0.48 (0.24, 0.08) Frances 1987 61 55 62 61 4.5% 1.03 (0.53, 0.26) Model 1987 27 55 7.57 55 7.0% 0.67 (0.23, 0.36) Wong 1985 137 141 14 15 160 0.60 (0.33, 0.36) Wong 1985 137 52 157 2.00 0.36 (0.60, 1.16) Maturda 2010 167 2.31 (3.64 (1.76, 70, 0.27) 1.68 (0.88) (0.68) 1.68 (0.88, 0.28) <		Prokine	tic	Placeb	00		Risk ratio	Risk ratio		
1.2 + 1 Comparison planetics	Study or subgroup	Events	Total	Events	Total	Weight	M-H,Random,95% Cl	M-H,Random,95%Cl		
Ar Quantum 1985 22 44 47 50 3.0% 0.42 [0.3, 0.57] 0.44 [0.3, 0.57] 0.44 [0.3, 0.57] 0.55, 1.08] 0.55, 0.58] 0.57, 0.50, 0.58] 0.57, 0.50, 0.58] 0.57, 0.50, 0.58] 0.57, 0.50, 0.58] 0.57, 0.50, 0.58] 0.57, 0.50, 0.58] 0.57, 0.58, 0.58, 0.58, 0.58] 0.57, 0.58,	1.2.1 Cisapride vs placebo	0								
Champion 1997 48 83 86 40 30% 068 [0.59, 1.68] De Nute 1988 6 177 11 15 1.2% 0.48 [0.24, 0.88] Pancols 1987 8 171 14 17 1.7% 0.57 [0.33, 0.58] Hannen 1986 101 100 99 110 4.6% 1.03 [0.55, 1.21] Hannen 1986 117 14 17 17. 10.57 [0.33, 0.68] Hannen 1987 23 32 23 33 24 31 3.7% 1.07 [0.58, 1.31] Hannen 1988 1377 414 115 169 4.2% 0.38 [0.33, 1.68] Wang 1985 1377 414 115 169 4.2% 0.38 [0.33, 1.68] Wang 1985 1377 414 115 169 4.2% 0.38 [0.33, 1.68] Wang 1985 1377 414 115 169 4.2% 0.38 [0.33, 1.68] Wang 1985 1377 414 115 169 4.2% 0.38 [0.33, 1.68] Wang 1985 1377 414 115 169 4.2% 0.38 [0.30, 1.12] Subbal (65% C) 557 Heterogenetity, "2 2.2.8 ($P = 0.0001$)," $P = 95\%$ Heterogenetity," $P = 202, P = 233, 34 = 11 (P = 0.0001), P = 95\%$ Heterogenetity," $P = 202, P = 233, 34 = 11 (P = 0.0001), P = 95\%$ Heterogenetity," $P = 202, P = 233, 34 = 11 (P = 0.0001), P = 95\%$ Heterogenetity," $P = 202, P = 233, 34 = 11 (P = 0.0001), P = 95\%$ Heterogenetity," $P = 202, P = 233, 34 = 11 (P = 0.0001), P = 95\%$ Heterogenetity," $P = 202, P = 233, 34 = 11 (P = 0.0001), P = 95\%$ Heterogenetity," $P = 202, P = 233, 34 = 11 (P = 0.0001), P = 95\%$ Heterogenetity," $P = 0.02, P = 1157$ 740 $A = 25\%$ 0.28 [0.50, 1.15] Total overts 1157 740 $A = 25\%$ 0.28 [0.50, 1.05] Total overts 1157 740 $A = 25\%$ 0.28 [0.50, 0.68] Total overts 1157 740 $A = 25\%$ 0.28 [0.53, 0.28] Heterogenetity," $P = 0.02, P = 1222, 9 (P = 0.00)$ 1.2.3 Hopridov splaceb Heterogenetity," $P = 0.20, P = 1222, 9 (P = 0.00)$ 1.2.4 Hopsenot 1174 428 255 200 $A = 52\%$ 0.46 [0.53, 0.06] Total overts 66 726 Heterogenetity," $P = 0.20, P = 122, 9 (P = 0.00)$ 1.2.5 Hopsenot 9 mp dv 23 26 65% 4.6% 0.5% [0.76, 0.58] Total overts 665 726 Heterogenetity," $P = 0.20, P = 123, 0 = 176$ 4.5% 4.5% 4.6% [0.07, 0.08] 1.2.5 Hopsenot 9 mp dv 23 2.6\% 4.2% 4.5\% 0.07 [0.77, 0.28] 1.2.6 Hopsenot 9 mode 1.2 - 2.38 (P = 0.00) 1.2.6 Hopsenot 9 mp dv 23 0.2\% 0.28 [0.82, 0.96] Total overts 2.2 38 (P = 0.00) 1.2.6 Hopsenot 9 mode 1.2 - 2.38 (P = 0.00) 1.2.6 Hopsenot	AI-Quorian 1995	22	48	47	50	3.0%	0.49 [0.36, 0.67]			
De Groot 1997 26 61 85 00 2.6% 073 051.0.5] Prancel 1997 8 017 11 15 12.2% 0.48 (0.24.0.08] Prancel 1997 8 17 14 17 1.7% 0.57 (0.33.0.59] Prancel 1997 8 17 14 14 17 1.7% 0.57 (0.33.0.56) Prancel 1997 8 17 14 14 17 1.7% 0.57 (0.33.0.56) Prancel 1997 9 15 22 61 4.2% 1.01 (0.86, 1.71 Prancel 1997 2 75 4.5 17 3.0% 0.68 (0.44, 0.81) Prancel 1997 44 52 47 52 4.3% 0.58 (0.61, 1.44, 0.81) Prancel 1997 44 52 47 52 4.3% 0.88 (0.61, 1.44, 0.81) Prancel 1997 44 52 47 52 4.3% 0.98 (0.60, 1.15] Total events 22 557 Test for overall effect. $Z = 2.48 (P = 0.01)$ 1.2.2 Actimate v piecebo Naturated 2010 1 177 216 84 107 4.6% 0.98 (0.90, 1.07] Mateunda 2012 280 346 45 145 4.5% 0.98 (0.90, 1.07] Mateunda 2012 280 344 455 445 4.7% 0.98 (0.90, 1.07] Mateunda 2012 280 344 455 445 4.7% 0.98 (0.90, 1.07] Mateunda 2012 383 452 405 445 4.7% 0.98 (0.90, 1.07] Mateunda 2012 383 452 405 445 4.7% 0.98 (0.90, 1.07] Mateunda 2012 383 452 405 445 4.7% 0.98 (0.90, 1.07] Mateunda 2012 383 452 405 445 4.5% 0.98 (0.90, 1.07] Mateunda 2012 383 452 405 445 4.5% 0.98 (0.90, 1.07] Mateunda 2012 383 452 405 445 4.5% 0.98 (0.90, 1.07] Mateunda 2012 383 452 405 445 4.5% 0.98 (0.90, 1.07] Mateunda 2012 483 4.55 (P = 0.49); P = 0.0% Test for overall effect. Z = 2.10 (P = 0.000) 1.2.3 httpride v piecebo Holtman 2006 174 406 86 142 4.0% Matouda (69% C) 1 154 07 108 Table events 1927 128 344 Heterogenetity: $F = 0.07$; $F = 1.53$ of $F = 1(P = 0.27)$; $F = 0.5\%$ Test for overall effect. Z = 2.80 (P = 0.30) 1.2.4 Nagaenot 6 mg bid v piecebo Valia 2008.1 423 488 477 408 408 122 4.07 (0.57, 0.88] 1.2.4 AST-22 28 (P = 0.30) 1.2.4 Stragenetit for bid v piecebo Table events 192 28 Heterogenetity: $F = 0.07$; $F = 1.53$ of $F = (P = 0.000)$; $F = 97\%$ Test for overall effect. Z = 2.80 (P = 0.30) 1.2.4 Stragenetit for bid v piecebo Table events 192 3 47 Heterogenetity: $F = 0.07$; $F = 1.53$ of $F = (P = 0.0000)$; $F = 97\%$ Test for overall effect. Z = 0.87 (P = 0.300) 1.2.4 AST-22.90 piecebo Table events 192 4.07 (F = 0.17	Champion 1997	43	83	26	40	3.0%	0.80 [0.59, 1.08]			
De Nute 1989 6 17 11 15 12." Princes 1987 10 103 99 110 4.0°. Hences 1986 101 103 99 110 4.0°. Hences 1986 101 103 99 110 4.0°. Hences 1986 102 17 44 145 17 12.°°. Hences 1986 112 27 144 145 17 12.°°. Subtrail 6(5% C) 960 078 37.0°. Hences 16(7) 2 2 57 45 57 3.0°. Hences 16(7) 2 2 57 145 17 12.°°. Hences 16(7) 2 2 57 145 17 12.°°. Hences 16(7) 2 2 57 145 17 12.°°. Hences 16(7) 2 2 57 145 17 14.°°. Hences 16(7) 2 2 58 445 20 10 2 57 14.°°. Hences 17 115 21 18 21 2.9%. Masueda 2010 1 17 2 11 9 4 107 4.0°. Hences 17 115 21 18 21 2.9%. Masueda 2010 1 17 2 19 3 53 66 3.5%. O 80 1080 0.081 0.071 15 21 7 10 4.4°. Subtrail 6(7) C) 900 7 4.0°. Hences 17 1157 740 48 0.028 10.60 1.151 14.°°. Subtrail (9°% C) 150 154 117 740 48 0.028 10.60 1.151 14.°°. Subtrail (9°% C) 150 154 116 4.0°. Subtrail (9°% C) 154 119 79 120 3.5%. O 81 [0.71 10 50.084] Hences 15 - 0 00.7 $f = 4.3.0(f = 5 (P = 0.002)$ 1.2.3 Honority 7 140 5 77 144 14 0.2% 0.08 [0.80 1.02] Tale versus 4.002 174 406 8 142 4.0%. O 80 [0.81 0.24] Hences 15 - 0 00.7 $f = 4.3.0(f = 5 (P = 0.002)$ 1.2.3 Honority 7 142 244 226 260 40.4.7% 0.08 [0.83 1.02] Tale versus 4.002 174 406 8 142 4.0%. O 80 [0.81 0.2.14] Hences 15 - 0 00.7 $f = 4.57.0 (P = 0.02)$ 1.2.4 Togatement 5 000 376 140 0.0001; $f^2 = 575.$ Teat for overall effect 2 = 10 (P = 0.07) 1.2.4 Togatement 67 79 707 707 10.5% 0.81 [0.70 [0.71 1.55] Hences 10 000 174 143 16 0 2.20 [0.80 1.02] Tale 2000 2 1 42 065 452 707 44.000 0.000 [0.71 145 0.09] Tale 2000 1 142 0.06 (P = 0.03) 1.2.4 Togatement 77 907 170 55 171 6.0% 0.31 [0.71, 0.58] 1.2.4 Togatement 77 907 172 55 171 6.0% 0.31 [0.71, 0.58] Hences 10 000 112 142 048 122 12.3.% 1.33 [1.05 1.70] Tale 2000 2 21 30 26 30 30 2.5% 0.03 [10.71, 0.58] 1.2.4 Abstrate 2000 2 14 3 16 4 12 (P = 0.00) [1.71 4.05% 0.03 [10.71,	De Groot 1997	26	61	35	60	2.6%	0.73 [0.51, 1.05]			
Functo 1987 8 17 14 17 1.7% 0.5% [0.83, 0.89] Holman 1980 01 09 9 10 10 42% 0.08 1.12] Holman 2002 51 8 8 28 51 4.2% 1.01 [0.86, 1.12] Resch 1987 2 7 7 24 41 57 3.3% 0.06 [0.46, 0.06] Wang 1965 137 444 145 169 42% 0.28 [0.83, 0.46] Wang 1957 46 52 47 52 4.3% 0.68 [0.86, 1.12] Wang 1957 46 52 47 52 4.3% 0.68 [0.86, 1.12] Subtal (9%) (7 0, 0.27) $= 33.3, 3, 3, d = 11$ ($P = 0.00001$); $l^2 = 95\%$ Test for ownall effect: $Z = 2.48$ ($P = 0.01$) 1.2.2 Acolamide valued Hetrogeneity: $r^2 = 0.07$, $r^2 = 33.3, d = 11$ ($P = 0.00001$); $l^2 = 95\%$ Test for ownall effect: $Z = 2.43$ ($P = 0.01$) 1.2.3 floptide valued Hetrogeneity: $r^2 = 0.07$, $r^2 = 33.3, d = 11$ ($P = 0.00001$); $l^2 = 95\%$ Test for ownall effect: $Z = 3.10$ ($P = 0.02$) 1.2.3 floptide valued Hetrogeneity: $r^2 = 0.07$, $r^2 = 33.3, d = 10$ Hetrogeneity: $r^2 = 0.07$, $r^2 = 4.33, d = 5$ ($P = 0.001$) 1.2.3 floptide valued Hetrogeneity: $r^2 = 0.07$, $r^2 = 4.33, d = 5$ ($P = 0.001$) 1.2.3 floptide valued Hetrogeneity: $r^2 = 0.07$, $r^2 = 4.33, d = 5$ ($P = 0.002$) 1.2.3 floptide valued Hetrogeneity: $r^2 = 0.07$, $r^2 = 4.33, d = 5$ ($P = 0.002$) 1.2.3 floptide valued Hetrogeneity: $r^2 = 0.07$, $r^2 = 4.33, d = 5$ ($P = 0.002$) 1.2.3 floptide valued Hetrogeneity: $r^2 = 0.07$, $r^2 = 4.33, d = 5$ ($P = 0.002$) 1.2.3 floptide valued Hetrogeneity: $r^2 = 0.07$, $r^2 = 1.32, d = 10$, $P = 0.002$) 1.2.4 floptide valued Hetrogeneity: $r^2 = 0.07$, $r^2 = 1.32, d = 10$ Hetrogeneity: $r^2 = 0.07$, $r^2 = 1.33, d = 1$ ($P = 0.022$), $r^2 = 35\%$ Test for ownall effect: $Z = 1.80$ ($P = 0.023$) 1.2.4 floptide valued Hetrogeneity: $r^2 = 0.07$, $r^2 = 1.33, d = 1$ ($P = 0.222$), $r^2 = 35\%$ Test for ownall effect: $Z = 1.80$ ($P = 0.03$) 1.2.4 floptide valued Hetrogeneity: $r^2 = 0.07$, $r^2 = 1.53, d = 1$ ($P = 0.222$), $r^2 = 35\%$ Test for ownall effect: $Z = 1.80$ ($P = 0.02$) 1.2.4 floptide valued Hetrogeneity: $r^2 = 0.07$, $r^2 = 1.53, d = 1$ ($P = 0.222$), $r^2 = 35\%$ Test for ownall effect: $Z = 0.87$ ($P =$	De Nutte 1989	6	17	11	15	1.2%	0.48 [0.24, 0.98]			
Hencen 1986 10 1 109 99 10 4.4% 1.02 [0.98, 1.12] Hencen 1987 27 57 41 57 30% 0.60 [0.98, 1.12] Hencen 1985 28 30 28 31 3.7% 1.07 [0.86, 1.34] Hencen 1985 28 30 28 31 3.7% 1.07 [0.86, 1.34] Hencen 1985 28 30 28 31 3.7% 1.07 [0.86, 1.34] Hencen 1995 137 414 115 169 422 43% 0.03 [0.80, 1.12] Subtal (95% C) 969 77 87, 077 [0.54, 0.39] 1.2.2 Acotsmic vs placebo Hencen 1997 2.2 57 Hencen 1997 2.2 58 Hencen 1997 2.2 57 Hencen 1997 2.2 58 Hencen 1997 2.2 57 Hencen 1997 2.2 58 Hencen 1997 2.2 54 Hencen 1997 2.2 5	Francois 1987	8	17	14	17	1.7%	0.57 [0.33, 0.99]			
$ \begin{array}{c} \mbox{rel} 1000 1000 \\ \mbox{rel} 1000 \\$	Hansen 1998	101	109	99	110	4.6%	1.03 [0.95, 1.12]	<u> </u>		
Particle 1987 2^{2} 5^{2} 4^{2} 5^{2} 4^{2} 5^{2} 4^{2} 5^{2} 3^{2} 5^{2}	Holtmann 2002	51	59	52	61	4.2%	1.01 [0.88, 1.17]	<u> </u>		
$\begin{aligned} \begin{array}{llllllllllllllllllllllllllllllllllll$	Reach 1097	20	50	20	51	3.7%				
$\begin{aligned} & \text{Vareng 1995} & 137 & 414 & 145 & 168 & 4.2\% & 0.38 [0.38, 0.46] \\ & \text{Solutional (Sovie, C)} & 689 & 678 & 37.0\% & 0.88 [0.86, 1.15] \\ & \text{Subtolal (Sovie, C)} & 526 & 557 \\ & \text{Heterogeneity}, t^2 = 0.20; t^2 = 2.31.33, d' = 11 (t^2 < 0.00001); t^2 = 95\% \\ & \text{Task for overall effect: 2 = 2.48 (t^2 = 0.01) \\ & 12.2 \text{ Acottemides variables} \\ & \text{Kasunch 2010} & 157 & 211 & 18 & 21 & 2.9\% & 0.83 [0.60, 1.15] \\ & \text{Matsuck 2010} & 157 & 211 & 18 & 21 & 2.9\% & 0.83 [0.60, 1.07] \\ & \text{Matsuck 2010} & 157 & 211 & 18 & 21 & 2.9\% & 0.83 [0.60, 1.07] \\ & \text{Matsuck 2010} & 187 & 138 & 53 & 66 & 3.5\% & 0.82 [0.64, 1.04] \\ & \text{Matsuck 2010} & 187 & 138 & 53 & 66 & 3.5\% & 0.82 [0.64, 1.04] \\ & \text{Matsuck 2010} & 157 & 740 \\ & \text{Heterogeneity}; t^2 = 0.00; t^2 = 4.43; dt^2 = 5 (t^2 = 0.48); t^2 = 0\% \\ & \text{Tack 2011} & 177 & 740 \\ & \text{Heterogeneity}; t^2 = 0.00; t^2 = 4.43; dt^2 = 5 (t^2 = 0.48); t^4 = 0\% \\ & \text{Hotman 2006} & 1153 & 71 & 0.68 [0.85, 1.06] \\ & \text{Matsuck 2010} & 1137 & 740 \\ & \text{Heterogeneity}; t^2 = 0.00; t^2 = 0.002) \\ & 1.23 \text{ lopide vs placebo} \\ & \text{Hotman 2006} & 174 & 406 & 68 & 142 & 4.0\% \\ & \text{Mog 2014} & 31 & 16 & 4 & 14 & 0.4\% \\ & \text{Mog 2014} & 14 & 40 & 22 & 40 & 1.8\% \\ & \text{Mog 2014} & 14 & 40 & 22 & 60 & 4.3\% \\ & \text{Mog 2014} & 14 & 40 & 22 & 60 & 4.3\% \\ & \text{Mog 2014} & 14 & 40 & 22 & 60 & 4.3\% \\ & \text{Mog 2014} & 31 & 16 & 4 & 14 & 0.4\% \\ & \text{Mog 2014} & 31 & 16 & 4 & 14 & 0.4\% \\ & \text{Mog 2014} & 31 & 16 & 4 & 14 & 0.4\% \\ & \text{Mog 2016} & 1, 423 & 685 & 456 & 75 & 4.6\% \\ & \text{Mog 2016} & 1, 423 & 685 & 452 & 675 & 4.6\% \\ & \text{Mog 2016} & 1, 423 & 685 & 452 & 675 & 4.6\% \\ & \text{Matsuck 2000} & 1, t^2 = 152.9, dt = 5(t^2 = 0.000) \\ & \text{Halerogeneity}, t^2 = 0.00; t^2 = 1.000 \\ & \text{Halerogeneity}, t^2 = 0.00; t^2 = 1.000 \\ & \text{Halerogeneity}, t^2 = 0.00; t^2 = 1.76 & 428 & 121 & 3.5\% \\ & \text{Halerogeneity}, t^2 = 0.00; t^2 = 1.76 & 4.2\% \\ & \text{Halerogeneity}, t^2 = 0.00; t^2 = 1.76 & 4.2\% \\ & \text{Halerogeneity}, t^2 = 0.00; t^2 = 1.76 & 4.2\% \\ & \text{Halerogeneity}, t^2 = 0.00; t^2 = 1.020 \\ & Halerogene$	Teixeria 2000	27	22	40	16	1.5%	0.60 [0.44, 0.81]			
$ \begin{array}{c} v_{0,0} = 1307 & 46 & 52 & 47 & 52 & 4.35 \\ \text{Stubbal (6%)} & 678 & 37.0\% & 0.38 [0.88, 1.12] \\ \text{Stubbal (6%)} & 0.201 (2.54, 0.39] \\ \text{Stubbal (6%)} & 0.21 (2.54, 0.39] \\ \text{Stubbal (6\%)} & 0.21 (2$	Wang 1995	137	414	145	169	4.2%	0.39 [0.33, 0.45]	<u> </u>		
Subtrain (c)(5%, C) $\frac{969}{12}$ $\frac{678}{2}$ $\frac{37.0\%}{2}$ $\frac{5.71}{2}$ $\frac{6.27}{2}$ $\frac{10}{2.4}$ $\frac{5.71}{2}$ $\frac{5.71}{2$	Yeoh 1997	46	52	47	52	4.3%	0.98 [0.86, 1.12]			
Total events 502 557 Heterogeneity: $r^2 = 0.02$; $r^2 = 2.33$, $d = 11$ ($P = 0.0001$); $l^2 = 95\%$ Test for overall effect: $Z = 2.48$ ($P = 0.01$) 1.2.2 Aoctamide vs placebo Matsuada 2010 1 1 187 216 94 107 4.0% 0.98 [0.90, 1.06] Matsuada 2010 2 200 346 99 116 4.6% 0.98 [0.90, 1.07] Matsuada 2012 393 4452 405 445 4.7% 0.93 [0.80, 0.98] Tatal events 1157 740 Heterogeneity: $r = 0.00$; $r^2 = 4.34$ ($r = 5.0 + 0.000$); $l^2 = 0\%$ Test for overall effect: $Z = 3.10$ ($P = 0.002$) 1.2.3 fupfield vs flacebo Heterogeneity: $r = 0.00$; $r^2 = 4.34$ ($r = 5.0 + 0.000$); $l^2 = 0.\%$ Test for overall effect: $Z = 3.10$ ($P = 0.002$) 1.2.3 fupfield vs flacebo Heterogeneity: $r = 0.00$; $r^2 = 4.34$ ($r = 5.0 + 0.000$); $l^2 = 97\%$ Test for overall effect: $Z = 1.80$ ($P = 0.002$) 1.2.3 fupfield vs flacebo Heterogeneity: $r = 0.00$; $r^2 = 1.34$ ($r = 1.0 + 0.000$); $l^2 = 97\%$ Test for overall effect: $Z = 1.80$ ($P = 0.007$) 1.2.4 fupgarend 6 mp bid vs placebo Vaki 2008 1 423 865 452 675 4.6% 0.92 [0.85, 1.00] Vaki 2008 1 423 865 452 675 4.6% 0.92 [0.85, 1.00] Vaki 2008 1 423 865 452 675 4.6\% 0.92 [0.85, 1.00] Vaki 2008 1 423 865 452 675 4.6\% 0.85 [0.70, 0.3] Vaki 2008 1 423 865 452 675 4.6\% 0.92 [0.85, 1.00] Vaki 2008 1 423 865 452 675 4.6\% 0.92 [0.85, 1.00] Vaki 2008 1 423 865 452 675 4.6\% 0.92 [0.85, 1.00] Vaki 2008 1 423 865 452 675 4.6\% 0.92 [0.85, 1.00] Vaki 2008 1 423 865 452 675 4.6\% 0.92 [0.85, 1.00] Vaki 2008 1 423 865 452 675 4.6\% 0.92 [0.85, 1.00] Vaki 2008 1 423 865 452 675 4.6\% 0.92 [0.85, 1.00] Vaki 2008 1 423 865 452 675 4.6\% 0.92 [0.85, 1.00] Vaki 2008 1 423 865 452 675 4.6\% 0.92 [0.85, 1.00] Vaki 2008 1 423 865 452 675 4.6\% 0.92 [0.85, 1.00] Vaki 2008 1 423 865 452 675 4.6\% 0.92 [0.85, 1.00] Vaki 2008 1 423 865 452 675 4.6\% 0.92 [0.73, 1.13] Total events 192 83 Heterogeneity: $r^2 = 0.07$; $r^2 = 1.30$ ($r^2 = 0.07$) Tal.4 forma 196 72 ($r^2 = 0.07$;	Subtotal (95% CI)		969		678	37.0%	0.71 [0.54, 0.93]	\bullet		
Heterogeneity: $t^2 = 0.20$, $t^2 = 231.33$, $df = 1/(P < 0.0001)$; $t^2 = 95%$. Test for overall effect: $Z = 2.48$ ($P = 0.01$) 1.2.2 Acotianido va placebo Kusunoki 2012 15 21 18 21 2.9% 0.83 (0.60, 1.15) Matsucka 2010.2 280 346 99 116 4.6% 0.98 (0.90, 1.07) Matsucka 2010.2 383 452 405 445 4.7% 0.98 (0.80, 0.90) Tack 2011 87 193 53 96 3.5% 0.92 (0.64, 1.04) Tack 2011 87 193 53 96 3.5% 0.92 (0.64, 1.07) Tack 2011 87 193 53 96 3.5% 0.92 (0.64, 1.07) Tack 2011 87 193 53 96 3.5% 0.92 (0.64, 1.07) Tack 2011 97 193 53 96 0.2% 0.92 (0.76, 1.07) Tack 2011 97 193 197 740 Heterogeneity: $t^2 = 0.00$; $t^2 = 4.43$, $df = 5 (P = 0.49)$; $t^2 = 0\%$. Test for overall effect: $Z = 3.10$ ($P = 0.002$) Tale vents 1157 740 Holman 2006 174 406 66 142 Holman 2016 53 119 79 10 3.5% 0.68 (0.53, 0.68) Taley 2001 12 44 264 226 200 4.5% 0.54 (0.67, 10.68) Taley 2001 12 44 264 22.69 4.5% 0.54 (0.67, 10.68) Taley 2001 12 2.86 815 300 330 4.0% 0.68 (0.53, 0.68) Taley 2002 2 268 515 300 330 4.0% 0.54 (0.67, 10.68) Taley 2002 2 268 515 300 330 4.0% 0.58 (0.71, 1.03) Taley 2001 45 316 726 0.00001); $t^2 = 97\%$ Test for overall effect: $Z = 1.80$ ($P = 0.07$) Taley 2002 17 42 56 57 4.6% 0.98 (0.71, 1.03) Taley 2001 45 336 656 452 675 4.6% 0.98 (0.72, 0.33) 1.2.5 Matspride va placebo Haterogeneity: $t^2 = 0.07$; $t^2 = 1.70$, $df = 1 (P = 0.00001)$; $t^2 = 97\%$ Test for overall effect: $Z = 1.80$ ($P = 0.03$) 1.2.6 Matspride va placebo Haterogeneity: $t^2 = 0.07$; $t^2 = 1.70$, $df = 1 (P = 0.022)$; $t^2 = 35\%$ Test for overall effect: $Z = 2.86$ ($P = 0.33$) 1.2.6 Matspride va placebo Haterogeneity: $t^2 = 0.07$; $t^2 = 1.50$, $df = 1 (P = 0.022)$; $t^2 = 35\%$ Test for overall effect: $Z = 2.86$ ($P = 0.03$) 1.2.6 Matspride va placebo Tale avents 192 33 48 20.5 heff Taley 2000 2 53 488 47 121 3.5% 1.33 (1.05, 1.70) Tale (95% C1) 488 171 4.5% 1.33 (1.05, 1.70) Tale (95% C1) 554 948 172 1.35\% 1.33 (1.05, 1.70) Tale avents 253 47 Heterogeneity: $t^2 = 0.01$; $t^2 = 1.57$, $df = 50$; $t^2 = 0.000$) Tal	Total events	502		557						
Test for overall effect: $Z = 2.48$ ($P = 0.01$) 1.2.2 Acotamide vs placebo Matsueda 2010_1 167 216 94 107 4.6% 0.963 (0.60, 1.15) Matsueda 2012_2 93 46 99 116 4.6% 0.968 (0.90, 1.08) Matsueda 2012_333 452 405 445 4.7% 0.958 (0.96, 0.98) Taley 2008_1 195 312_71 104 4.2% 0.92 (0.78, 1.07) Taley 2008_1 195 312_71 104 4.2% 0.92 (0.78, 1.07) Taley 2008_1 195 312_77 40 Heterogeneity: $i^2 = 0.00$, $j^2 = 4.43$, $dt = (P = 0.49)$; $l^2 = 0\%$. Taley 2008_1 127_4 406 86 142_4 0.0% 0.71 (0.59, 0.84] Hotmann 2006_1 174 406 86 142_4 0.0% 0.68 (0.53, 0.86] Shen 2014_1 14_4 40_22_4 40_1 1.8% 0.68 (0.53, 0.68] Shen 2014_1 14_4 40_22_4 40_0 1.8% 0.058 (0.53, 0.68] Shen 2014_1 14_4 40_22_4 40_0 1.8% 0.070 (0.47, 1.03] Taley 2008_1_1 242_4 226_2 26_2 0.4.3% 0.098 (0.83, 1.02] Vong 2014_3 16_4 4_1 4_0.4% 0.968 (0.53, 0.48] Matsueda 2010_2_1 236 685 726 Heterogeneity: $i^2 = 0.02$, $j^2 = 152.29$, $dt = 5 (P = 0.00001)$; $l^2 = 97\%$ Taley 2008_1_1 423_6 685 452_6 675 4.6% 0.92 (0.65, 1.00] Vaki 2008_2_3 56 662_4 420_654_654_656_0.988 (0.82, 0.96] Taley 2008_1_1 423_6 685 452_6 778 Heterogeneity: $i^2 = 0.02$, $j^2 = 1.70$, $dt = 1 (P = 0.19)$; $l^2 = 41\%$ Test for overall effect: $Z = 1.80$ ($P = 0.02$) Tale avents 770_872 Heterogeneity: $i^2 = 0.01$; $j^2 = 1.53$, $dt = 1 (P = 0.22)$; $l^2 = 35\%$ Tast for overall effect: $Z = 2.80$ ($P = 0.02$) Taley 2000_1 192 Subtata (0.9% C)) 2488_77_121_9.5% 1.33 [1.05, 1.70] Tale avents 253_488_77_121_9.5% 1.33 [1.05, 1.70] Taley 2000_2 1337_4 7330_95 Heterogeneity: $r^2 = 0.01$; $j^2 = 1.53$, $dt = 1 (P = 0.22)$; $l^2 = 35\%$ Tast for overall effect: $Z = 2.36$ ($P = 0.02$) Taley 2000_2 1488_77_1 = 20.9% ($P = 0.02$) Taley 2000_2 5468_77_1 = 20.9% ($P = 0.02$) Tale avents 253_47_7 = 20.9% ($P = 0.02$) Tale avents 253_47_7 = 20.9% ($P = 0.02$) Taley 2000_2 55_48_657_7 = 20.9% ($P = 0.02$) Taley	Heterogeneity: $\tau^2 = 0.20$;	$\chi^2 = 231.3$	33, d <i>f</i> = 1	1 (<i>P</i> < 0.	00001);	l ² = 95%				
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Test for overall effect: $Z =$	2.48 (<i>P</i> =	0.01)							
$1.22 \text{ Accounted by placebo} \\ \text{Matsueda 2010_1} & 167 & 216 & 94 & 107 & 4.6\% & 0.98 [0.90, 1.15] \\ \text{Matsueda 2012_2} & 383 & 452 & 405 & 445 & 4.7\% & 0.98 [0.90, 1.08] \\ \text{Matsueda 2012_383 & 452 & 405 & 445 & 4.7\% & 0.98 [0.90, 1.07] \\ \text{Taley 2006_1} & 193 & 53 & 96 & 3.5\% & 0.82 [0.64, 1.04] \\ \text{Taley 2006_1} & 195 & 122 & 71 & 104 & 4.2\% & 0.92 [0.78, 1.07] \\ \text{Subtral (95K; C1)} & 1540 & 889 & 24.5\% & 0.92 [0.78, 1.07] \\ \text{Total events} & 1157 & 740 \\ \text{Heterogeneity: } -0007_2^2 = 4.43 & 4.65 & (P = 0.49); i^2 = 0\% \\ \text{Test for overall effect: Z = 3.10 (P = 0.002) \\ \text{Haterogeneity: } -0007_2^2 = 4.43 & (P = 0.49); i^2 = 0\% \\ \text{Test for overall effect: Z = 3.10 (P = 0.002) \\ \text{Haterogeneity: } -0007_2 = 4.43 & (P = 0.49); i^2 = 0\% \\ \text{Taley 2006_1} & 124 & 264 & 226 & 200 & 4.3\% & 0.66 [0.53, 0.86] \\ \text{Shen 2014_1} & 14 & 40 & 22 & 40 & 1.5\% & 0.66 [0.162, 4.06] \\ \text{Matsueda 2012_2} & 53 & 119 & 79 & 120 & 3.5\% & 0.68 [0.53, 0.86] \\ \text{Shen 2014_1} & 164 & 244 & 226 & 200 & 4.3\% & 0.96 [0.162, 4.06] \\ \text{Matsueda 2012_2} & 53 & 119 & 79 & 120 & 3.5\% & 0.68 [0.53, 0.86] \\ \text{Shen 2014_1} & 164 & 244 & 266 & 206 & 4.3\% & 0.96 [0.162, 4.06] \\ \text{Matsueda 2012_2} & 53 & 158 & 509 & 330 & 4.7\% & 0.98 [0.93, 1.02] \\ \text{Vong 2014_3} & 16 & 4 & 14 & 0.4\% & 0.96 [0.162, 4.06] \\ \text{Taley 2006_1} & 423 & 665 & 452 & 675 & 4.6\% & 0.85 [0.76, 0.93] \\ \text{Subtoal (95K; C1)} & 1337 & 1330 & 9.2\% & 0.89 [0.82, 0.96] \\ \text{Tale avents} & 70 & 872 \\ \text{Heterogeneity: } i^2 = 0.01; i^2 = 153, d^2 = 1 (P = 0.22); i^2 = 35\% \\ \text{Test for overall effect: Z = 1.80 (P = 0.03) \\ 1.2.6 \text{ Matsueda 2012_2} & 130 & 26 & 30 & 35\% \\ \text{Tale avents} & 253 & 47 \\ \text{Taley 2006_2} & 130 & 46 & 71 & 12 & 3.5\% & 1.33 [1.05, 1.70] \\ \text{Total events} & 253 & 47 \\ \text{Taley 2006_2} & 254 & 486 & 47 & 121 & 3.5\% & 1.33 [1.05, 1.70] \\ \text{Total events} & 253 & 47 \\ \text{Heterogeneity: } i^2 = 0.01; i^2 = 153, d^2 = 1(P = 0.02); i^2 = 31\% \\ \text{Taley 2006_2} & 206 i^2 = 172, d, d = 20(P = 0.000) \\ \text{Total events} & 253 & 47 \\ \text{Heterogeneity: } i^2 = 0.01; i^$										
Kusunda 2010_1 15 21 18 21 2.9% 0.83 (0.60, 1.5) Matsueda 2010_1 167 216 94 107 4.6% 0.93 (0.90, 1.6) Matsueda 2010_2 290 346 99 116 4.6% 0.93 (0.90, 1.6) Tack 2011 87 193 53 96 3.5% 0.82 (0.64, 1.04) Tack 2011 87 193 53 96 3.5% 0.82 (0.64, 1.04) Tack 2011 187 174 406 86 142 4.0% 0.92 (0.78, 1.07) Tack 2011 157 740 Heterogeneity, $r^2 = 0.02$; $r^2 = 152, 29, dr = 5 (P = 0.49); l^2 = 0%$ Test for overall effect. Z = 3.10 (P = 0.002) 1.2.3 (top/td vs placebo Hotoman 2006 174 406 86 142 4.0% 0.71 (0.59, 0.84) Ma 2012 53 119 79 120 3.5% 0.68 (0.53, 0.86) Shen 2014 14 40 22 40 1.8% 0.64 (0.38, 1.06) Talley 2006_1 124 226 226 260 4.3% 0.54 (0.47, 0.62) Talley 2005_1 124 226 426 260 4.3% 0.54 (0.47, 0.62) Talley 2002_2 288 315 309 304 4.7% 0.98 (0.93, 1.02) Wong 2014 3 16 4 14 0.4% 0.56 (0.18, 2.44) Subbal (9% Cl) 1160 900 18.9% 0.70 (0.47, 1.03) Total events e^{56} 726 Heterogeneity, $r^2 = 0.20; r^2 = 152, 29, dr = 5 (P = 0.000)1; l^2 = 97%$ Test for overall effect. Z = 1.80 (P = 0.07) 1.2.4 Togaserod 6 mg bid vs placebo Vaki 2008_1 43 365 452 675 4.6% 0.92 (0.85, 1.00) Vaki 2008_1 43 365 452 675 4.6% 0.92 (0.85, 1.00) Vaki 2008_1 43 0.65 5 171 6.9% 0.89 (0.82, 0.96) Total events 79 872 Total events 79 872 Total events 79 872 Test for overall effect. Z = -1.80 (P = 0.03) 1.2.5 Mosapride vs placebo Halerodack 2002 171 425 57 141 3.6% 1.00 (0.78, 1.25) La 2.009 21 30 2.6 0.38 3.10 (0.73, 1.13) 1.2.5 Mosapride vs placebo Halerodack 2002 171 425 57 141 3.6% 1.03 (0.07, 1.25) Total events 22 - 9.6 (P = 0.03) 1.2.5 Mosapride vs placebo Talley 2000 253 488 47 121 3.5% 1.33 (1.05, 1.70) Total events 23 47 Heterogeneity, $r^2 = 0.01; r^2 = 1.73, dr = 1 (P = 0.22); r^2 = 35\%$ Test for overall effect. 2 = -0.57 (P = 0.02) Total events 23 47 Heterogeneity, $r^2 = 0.01; r^2 = 1.73, dr = 1 (P = 0.02); r^2 = 91\%$ Total events 23 47 Heterogeneity, $r^2 = 0.01; r^2 = 1.53, dr = 1 (P = 0.02); r^2 = 91\%$ Total events 23 47 Heterogeneity, $r^2 = 0.01; r^2 = 1.70, dr = 0.19; r^2 = 91\%$ F	1.2.2 Acotiamide vs place	bo								
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Kusunoki 2012	15	21	18	21	2.9%	0.83 [0.60, 1.15]			
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Matsueda 2010_1	187	216	94	107	4.6%	0.99 [0.90, 1.08]	I		
$ \begin{array}{c} \text{matsubal 2012} & 333 & 403 & 403 & 404 & 4.7.8 \\ \text{Table 20208} & 155 & 312 & 71 & 104 & 4.2\% & 0.92 [0.78, 1.07] \\ \text{Table 20208} & 155 & 312 & 71 & 104 & 4.2\% & 0.92 [0.78, 1.07] \\ \text{Table 20208} & 155 & 312 & 71 & 104 & 4.2\% & 0.92 [0.78, 1.07] \\ \text{Total events} & 1157 & 740 \\ \text{Heterogeneity}; r^2 = 0.00; r^2 = 4.43, d^2 = 5 (P = 0.49); r^2 = 0\% \\ \text{Test for overall effect: } Z = 3.10 (P = 0.002) \\ \text{Table 2008} & 174 & 406 & 86 & 142 & 40\% & 0.71 [0.59, 0.84] \\ \text{Mat2012} & 53 & 119 & 79 & 120 & 3.5\% & 0.68 [0.53, 0.86] \\ \text{Shen 2014} & 14 & 400 & 22 & 40 & 1.8\% & 0.64 [0.38, 1.06] \\ \text{Table 2008} & 1 & 124 & 264 & 226 & 260 & 4.3\% & 0.56 [0.47, 0.62] \\ \text{Table 2008} & 1 & 124 & 264 & 226 & 260 & 4.3\% & 0.56 [0.47, 0.62] \\ \text{Table 2008} & 1 & 124 & 264 & 226 & 260 & 4.3\% & 0.58 [0.47, 0.62] \\ \text{Table 2008} & 1 & 124 & 264 & 226 & 260 & 4.3\% & 0.58 [0.47, 0.62] \\ \text{Table 2008} & 2 & 288 & 315 & 309 & 303 & 4.7\% & 0.98 [0.93, 1.02] \\ \text{Vong 2014} & 3 & 16 & 4 & 14 & 4.0\% & 0.66 [0.18, 2.44] \\ \text{Subtal (95\% CI)} & 1160 & 906 & 18.9\% & 0.70 [0.47, 1.03] \\ \text{Total events} & 656 & 726 \\ \text{Heterogeneity}; r^2 = 0.00; r^2 = 152, 29, d' = 5 (P < 0.00001); r^2 = 97\% \\ \text{Test for overall effect: } Z = 1.80 (P = 0.07) \\ 1.2.5 (\text{Msaperide vs placebo} \\ \text{Halerback 2002} & 171 & 425 & 57 & 141 & 3.6\% & 0.09 [0.78, 1.25] \\ \text{In 2009} & 21 & 30 & 26 & 30 & 3.3\% & 0.81 [0.61, 1.06] \\ \text{Subtal (95\% CI)} & 438 & 47 & 121 & 3.5\% & 1.33 [1.05, 1.70] \\ \text{Table events} & 253 & 4.07 \\ \text{Heterogeneity}; r^2 = 0.01; r^2 = 152, d' = 1 (P = 0.22); r^2 = 35\% \\ \text{Test for overall effect: } Z = -2.87 (P = 0.03) \\ 1.2.6 \text{ ABT}:229 \text{ vs placebo} \\ \text{Table events} & 253 & 4.7 \\ \text{Heterogeneity}; r^2 = 0.01; r^2 = 172.4, d' = 28 (P < 0.0001); r^2 = 91\% \\ \text{Test for overall effect: } Z = -2.45 (P = 0.002) \\ \text{Total events} & 253 & 4.07 \\ \text{Heterogeneity}; r^2 = 0.01; r^2 = 157, d' r = 26 (P < 0.0001); r^2 = 91\% \\ \text{Test for overall effect: } Z = -2.45 (P < 0.0001) \\ Test resurg differences; r^2 = 1657, d' r = 26 (P < 0.0001); $	Matsueda 2010_2	290	346	99 405	116	4.6%	0.98 [0.90, 1.07]			
$\begin{aligned} \begin{array}{c} \mbox LOT & D & 133 & 0.5 & 302 & 0.7 & 104 & 4.2\% & 0.92 & [0.57, 10.7] \\ \mbox Liley 2008 & 135 & 312 & 71 & 104 & 4.2\% & 0.92 & [0.81, 0.7] \\ \mbox Liley 2008 & 1157 & 740 \\ \mbox Heterogeneity: t^2 = 0.01, t^2 = 4.43, df = 5 (P = 0.49); f^2 = 0\% \\ \mbox Test for overall effect: Z = 3.10 & (P = 0.002) \\ \mbox Liley 2008 & 174 & 406 & 86 & 142 & 4.0\% & 0.71 & [0.59, 0.84] \\ \mbox Laley 2008 & 174 & 406 & 86 & 142 & 4.0\% & 0.64 & [0.38, 1.06] \\ \mbox Laley 2008 & 1 & 124 & 264 & 226 & 260 & 4.3\% & 0.54 & [0.47, 0.62] \\ \mbox Laley 2008 & 1 & 124 & 264 & 226 & 260 & 4.3\% & 0.54 & [0.47, 0.62] \\ \mbox Laley 2008 & 1 & 124 & 264 & 226 & 260 & 4.3\% & 0.54 & [0.47, 0.62] \\ \mbox Laley 2008 & 2 & 288 & 315 & 309 & 300 & 4.7\% & 0.88 & [0.38, 1.02] \\ \mbox Laley 2008 & 2 & 288 & 315 & 309 & 300 & 4.7\% & 0.88 & [0.38, 1.02] \\ \mbox Laley 2008 & 2 & 286 & 316 & 9.0\% & 0.56 & [0.47, 0.63] \\ \mbox Laley 2008 & 2 & 0.20; t^2 = 152, 20; df = 5 (P < 0.00001); t^2 = 97\% \\ \mbox Test for overall effect: Z = 1.30 & (P = 0.07) \\ \mbox Laley 2008 & 2 & 366 & 652 & 420 & 655 & 4.6\% & 0.85 & [0.58, 1.00] \\ \mbox Lale vents & 77 & 872 \\ \mbox Heterogeneity: t^2 = 0.00; t^2 = 1.70, df = 1 & (P = 0.19); t^2 = 41\% \\ \mbox Lalevents & 77 & 872 \\ \mbox Heterogeneity: t^2 = 0.00; t^2 = 1.50, df = 1 & (P = 0.02); t^2 = 35\% \\ \mbox Lalevents & 192 & 83 \\ \mbox Heterogeneity: t^2 = 0.01; t^2 = 153, df = 1 & (P = 0.22); t^2 = 35\% \\ \mbox Test for overall effect: Z = 2.36 & (P = 0.02) \\ \mbox Lalevents & 253 & 47 \\ \mbox Heterogeneity: t^2 = 0.04; t^2 = 31724, df = 28 & (P < 0.0001); t^2 = 91\% \\ \mbox Lale Vents & 253 & 428 & 47 & 121 & 3.5\% & 1.33 & [1.05, 1.70] \\ \mbox Lalevents & 253 & 428 & 47 & 121 & 3.5\% & 1.33 & [1.05, 1.70] \\ \mbox Lalevents & 253 & 47 & 124 & 3.5\% & 1.33 & [1.05, 1.70] \\ \mbox Lalevents & 253 & 47 & 124 & 3.5\% & 1.33 & [1.05, 1.70] \\ \mbox Lalevents & 253 & 47 & 124 & 3.5\% & 1.33 & [1.05, 1.70] \\ \mbox Lalevents & 253 & 47 & 124 & 3.5\% & 1.33 & [1.05, 1.70] \\ \mbox Lalevents & 253 & 47 & 124 & 3.5\% & 1.33 & $	Tack 2011	203	102	405	445	4.7%	0.93 [0.69, 0.96]			
Subtatives (65% CI) 100 1540 1689 24.5% 0.94 [0.91, 0.98] Total events 1157 740 Heterogeneity: $r^2 = 0.00; r^2 = 4.43; df = 5 (P = 0.49); r^2 = 0\%$ Test for overall effect: $Z = 3.10 (P = 0.002)$ 1.2.3 (Doride vs placebo Holtmann 2006 174 406 86 142 40% 0.71 [0.59, 0.84] Ma 2012 53 119 79 120 3.5% 0.68 [0.53, 0.68] Shen 2014 14 40 22 40 1.8% 0.64 [0.38, 1.06] Talley 2008, 2 288 315 309 330 4.7% 0.98 [0.93, 1.02] Talley 2008, 2 288 315 309 330 4.7% 0.98 [0.93, 1.02] Total events 656 728 Heterogeneity: $r^2 = 0.20; r^2 = 152.29, df = 5 (P < 0.00001); r^2 = 97% Test for overall effect: Z = 1.80 (P = 0.07)1.2.4 Togaserod 6 mg bid vs placeboVaki 2008.1 423 468 452 675 4.6% 0.92 [0.85, 1.00]Vaki 2008.2 356 652 420 655 4.6% 0.92 [0.85, 0.96]Subtati (95% CI) 1160 906Vaki 2008.2 356 652 420 655 4.6% 0.92 [0.85, 0.96]Total events 779 672Heterogeneity: r^2 = 0.00; r^2 = 1.70, df = 1 (P = 0.19); r^2 = 41% Test for overall effect: Z = 2.96 (P = 0.03)1.2.5 Mosapride vs placeboHalterback 2002 171 425 57 141 3.6% 1.00 [0.78, 1.25]Ln 2009 21 30 26 30 3.3%Total events 192Heterogeneity: r^2 = 0.01; r^2 = 1.53, df = 1 (P = 0.22); r^2 = 35\% Test for overall effect: Z = 0.87 (P = 0.38)1.2.6 ABT229 vs placeboTalley 2000 253 488 47 121 3.5% 1.33 [1.05, 1.70]Total events 253 47Heterogeneity: r^2 = 0.01; r^2 = 1.53, df = 1 (P = 0.22); r^2 = 35\% Test for overall effect: Z = 2.36 (P = 0.02)Total events 253 47Heterogeneity: r^2 = 0.01; r^2 = 1.53, df = 1 (P = 0.22); r^2 = 35\%Test for overall effect: Z = 2.36 (P = 0.02)Total events 253 47Heterogeneity: r^2 = 0.01; r^2 = 1.57, df = 1 (P < 0.0001); r^2 = 91\%Test for overall effect: Z = 2.36 (P = 0.02)Total events 3539 3025Heterogeneity: r^2 = 0.04; r^2 = 172.4, df = 28 (P < 0.0001); r^2 = 91\%Test for overall effect: Z = 2.465 (P < 0.0001)Test for subproduct filterower 2; r = 1657, df = 5 (P < 0.005), r^2 = 91\%Test for overall effect: Z = 2.45 (P < 0.005)Test for overall effect: Z = 2.45 (P < 0.$	Talley 2008	195	312	71	104	4.2%	0.02 [0.04, 1.04]			
Total events 1157 740 Heterogeneity: $t^2 = 0.01; t^2 = 4.43, df = 5 (P = 0.49); t^2 = 0%$ Test for overall effect: $Z = 3.10 (P = 0.002)$ 1.2.3 Itopride vs placebo Holmann 2006 174 406 86 142 40% O, 71 [0.59, 0.84] Ma 2012 53 119 77 120 3.5% 0.68 [0.53, 0.86] Shen 2014 14 40 22 40 1.8% 0.64 [0.38, 1.06] Talley 2008_1 124 224 226 240 4.3% 0.54 [0.47, 0.82] Talley 2008_2 288 315 309 330 4.7% 0.98 [0.83, 0.18] Wong 2014 3 16 4 14 0.4% 0.66 [0.18, 2.44] Wong 2014 3 16 4 14 0.4% 0.66 [0.18, 2.44] Wong 2014 3 16 4 14 0.4% 0.66 [0.18, 2.44] Wong 2014 3 16 4 14 0.4% 0.66 [0.18, 2.44] Wong 2014 3 16 4 14 0.4% 0.98 [0.83, 0.02] Wong 2014 3 16 5 452 675 4.6% 0.92 [0.85, 1.00] Vaki 2008_2 36 652 420 655 4.6% 0.85 [0.78, 0.93] Subtola (95% Cl) 1337 1330 9.2% 0.89 [0.82, 0.96] Total events 779 872 Heterogeneity: $t^2 = 0.02; t^2 = 152.94, df = 5 (P < 0.0001); t^2 = 97\%$ Test for overall effect: $Z = 2.96 (P = 0.03)$ 1.2.5 Mosapride vs placebo Halerogacely: $t^2 = 0.03; t^2 = 1.70, df = 1 (P = 0.19); t^2 = 41\%$ Test for overall effect: $Z = 2.96 (P = 0.03)$ 1.2.5 Mosapride vs placebo Talley 2000 21 30 28 30 3.3% 0.81 [0.61, 1.06] Subtola (95% Cl) 438 47 121 3.5% 1.33 [1.05, 1.70] Total events 192 83 Heterogeneity: $t^2 = 0.03; t^2 = 1.53, df = 16, P = 0.22); t^2 = 35\%$ Test for overall effect: $Z = 2.36 (P = 0.02)$ Total events 253 47 Heterogeneity: $t^2 = 0.04; x^2 = 31724, df = 28 (P < 0.0001); t^2 = 91\%$ Total events 253 47 Heterogeneity: $t^2 = 0.04; x^2 = 31724, df = 28 (P < 0.0001); t^2 = 91\%$ Total events 253 47 Heterogeneity: $t^2 = 0.04; x^2 = 172, df = 26 (P < 0.0001); t^2 = 91\%$ Total events 253 47 Heterogeneity: $t^2 = 0.04; x^2 = 31724, df = 28 (P < 0.0001); t^2 = 91\%$ Total events 253 405 47 Heterogeneity: $t^2 = 0.04; x^2 = 155, df = 165, f df = 5 (P < 0.0001); t^2 = 91\%$ Total events 253 405 10.00% 0.81 [0.74, 0.89] $total events 253 + 105, f df = 26 (P < 0.0001); t^2 = 91\%$ Total events 253 + 105, f df = 26 (P < 0.0001); t^2 = 91\% Total events 253 + 105, f df = 26	Subtotal (95% CI)	155	1540	/ 1	889	24.5%	0.94 [0.91, 0.98]	•		
Haterogeneity: $t^2 = 0.00$; $t^2 = 4.43$, $dt = 5$ ($P = 0.49$); $t^2 = 0\%$ Test for overall effect: $Z = 3.10$ ($P = 0.002$) 1.2.3 Itopride vs placebo Holtmann 2006 174 406 86 142 4.0% 0.71 [0.59, 0.84] Ma 2012 53 119 79 120 3.5% 0.68 [0.53, 0.66] Talley 2008_1 124 264 226 260 4.3% 0.54 [0.47, 0.62] Talley 2008_1 124 264 226 260 4.3% 0.95 [0.18, 2.44] Subtol (95% C)) 1160 9906 18.9% 0.70 [0.47, 1.03] Total events 656 726 Heterogeneity: $t^2 = 0.02$; $t^2 = 152.29$, $dt = 5$ ($P < 0.00001$); $t^2 = 97\%$ Test for overall effect: $Z = 1.80$ ($P = 0.07$) 1.2.4 Tegaserod 6 mg bid vs placebo Vaki 2008_1 43 665 452 675 4.6% 0.92 [0.85, 1.00] Vaki 2008_2 436 652 452 675 4.6% 0.85 [0.78, 0.93] Subtola (95% C)) 1337 1330 9.2% 0.89 [0.82, 0.96] Total events 779 872 Heterogeneity: $t^2 = 0.02$; $t^2 = 1.70$, $dt = 1$ ($P = 0.19$); $t^2 = 41\%$ Test for overall effect: $Z = 2.96$ ($P = 0.02$) 1.2.5 Mosapride vs placebo Hallerback 2002 171 425 57 141 3.6% 1.00 [0.78, 1.25] Subtola (95% C)) 1455 171 6.9% 0.91 [0.73, 1.13] Total events 192 83 Heterogeneity: $t^2 = 0.01$; $t^2 = 1.53$, $dt = 1$ ($P = 0.22$); $t^2 = 35\%$ Test for overall effect: $Z = 2.96$ ($P = 0.22$) 1.2.6 MF229 vs placebo Talley 2000 253 488 47 121 3.5% 1.33 [1.05, 1.70] Subtola (95% C)) 488 171 1.3.5% 1.33 [1.05, 1.70] Subtola (95% C)) 488 121 3.5% 1.33 [1.05, 1.70] Total events 253 47 Heterogeneity: $t^2 = 0.04$; $t^2 = 372.24$, $dt = 20$ ($P < 0.00001$); $t^2 = 91\%$ Test for overall effect: $Z = 2.86$ ($P = 0.02$) Total (95% C)) 5949 4095 100.0% 0.81 [0.74, 0.89] Total events 3539 3025 Total (95% C)) 5949 4095 100.0% 0.81 [0.74, 0.89] Total events 253 47 Heterogeneity: $t^2 = 0.04$; $t^2 = 377.24$, $dt = 20$ ($P < 0.00001$); $t^2 = 91\%$ Test for overall effect: $Z = 2.86$ ($P = 0.0001$) Total events 3539 3025 Total events 3539 3025 Total events 253 47 Heterogeneity: $t^2 = -0.04$; $t^2 = 377.24$, $dt = 20$ ($P < 0.00001$); $t^2 = 91\%$ Test for overall effect: $Z = 2.65$, $t^2 = (5.57, d = 5 (P = 0.0000)$, $t^2 = 9$	Total events	1157		740						
Test for overall effect: $Z = 3.10$ ($P = 0.002$) 1.2.3 ltopride vs placebo Holtman 2006 174 406 86 142 4.0% 0.68 [0.53, 0.66] Shen 2014 14 40 22 40 1.8% 0.64 [0.38, 1.06] Talley 2008_1 124 264 226 260 4.3% 0.54 [0.47, 0.62] Talley 2008_2 288 315 309 330 4.7% 0.86 [0.53, 1.02] Wong 2014 3 16 4 14 0.4% 0.66 [0.18, 2.44] Subtoal (95% C()) 1160 906 18.9% 0.70 [0.47, 1.03] Total events 656 726 Heterogeneity: $c^2 = 0.20$; $z^2 = 152.9$, $df = 5$ ($P < 0.00001$); $l^2 = 97\%$ Test for overall effect: $Z = 1.80$ ($P = 0.07$) 1.2.4 Tegaserod 6 mg bid vs placebo Vaki 2008_1 423 665 452 675 4.6% 0.82 [0.85, 1.00] Vaki 2008_2 356 652 420 655 4.6% 0.89 [0.82, 0.96] Total events 779 872 Heterogeneity: $c^2 = 0.00$; $z^2 = 1.70$, $df = 1$ ($P = 0.19$); $l^2 = 41\%$ Test for overall effect: $Z = 2.96$ ($P = 0.03$) 1.2.5 Mosapride vs placebo Halerodax 2002 171 425 57 141 3.6% 1.00 [0.78, 1.25] Lin 2009 2 171 425 57 141 3.6% 1.00 [0.78, 1.25] Lin 2009 2 171 425 57 141 3.6% 1.00 [0.78, 1.25] Lin 2009 2 171 425 57 141 3.6% 1.00 [0.78, 1.25] Total events 192 83 Heterogeneity: $c^2 = 0.01$; $z^2 = 153$, $df = 1$ ($P = 0.22$); $l^2 = 35\%$ Test for overall effect: $Z = 2.96$ ($P = 0.03$) 1.2.5 MSET229 vs placebo Tataley 200 253 488 47 121 3.5% 1.33 [1.05, 1.70] Subtoal (95% Cl) 294 94 4095 100.0% 0.81 [0.74, 0.89] Total events 253 47 Heterogeneity: $c^2 = 0.01$; $z^2 = 152$, $df = 10.22$; $l^2 = 91\%$ Total events 253 47 Heterogeneity: $c^2 = 0.01$; $z^2 = 37.24$, $df = 28$ ($P < 0.0001$); $l^2 = 91\%$ Total events 353 47 Heterogeneity: $c^2 = 0.01$; $z^2 = 15.7$, $df = 10 (P - 0.29)$; $l^2 = 91\%$ Total events 253 47 Heterogeneity: $c^2 = 0.01$; $z^2 = 15.7$, $df = 28 (P < 0.0001$); $l^2 = 91\%$ Total events 353 9 3025 Heterogeneity: $c^2 = 0.01$; $z^2 = 15.7$, $df = 5 (P < 0.0001$); $l^2 = 91\%$ Total events 353 405 Total events 353 405 Test for overall effect: $Z = 4.68 (P < 0.00001$); $l^2 = 91\%$ Test for subroup differences; $z^2 = 16.57$, $df = 5 (P < 0.00001$); $l^2 = 91\%$ Favours [proki	Heterogeneity: $\tau^2 = 0.00$;	$\chi^2 = 4.43$	df = 5(H)	P = 0.49);	$l^2 = 0\%$					
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Test for overall effect: Z =	3.10 (<i>P</i> =	0.002)							
1.2.3 (Expride ve placebo + bit is provide version in the image of t										
Holtman 2006 174 406 86 142 40% 0.71 [0.59, 0.84] Ma 2012 53 119 79 120 3.5% 0.68 [0.53, 0.68] Talley 2008_1 124 246 226 260 4.3% 0.54 [0.47, 0.62] Talley 2008_2 2 88 315 309 330 4.7% 0.98 [0.93, 1.02] Wong 2014 3 16 4 14 0.4% 0.66 [0.18, 2.44] Subtoal (95% CI) 1160 906 18.9% 0.70 [0.47, 1.03] Total events 656 726 Heterogeneity: $t^2 = 0.20$; $t^2 = 152.29$, $df = 5$ ($P < 0.00001$); $l^2 = 97\%$ Test for overall effect: $Z = 1.80$ ($P = 0.07$) 1.2.4 Tegaserod 6 mg bid vs placebo Vaki 2008_2 356 652 420 655 4.6% 0.85 [0.78, 0.33] Subtoal (95% CI) 1337 1330 9.2% 0.89 [0.82, 0.96] Total events 779 872 Heterogeneity: $t^2 = 0.00$; $t^2 = 1.70$, $df = 1$ ($P = 0.19$); $l^2 = 41\%$ Test for overall effect: $Z = 2.96$ ($P = 0.03$) 1.2.5 Mosapride vs placebo Vaki 2009 2 12 30 26 30 3.3% 0.81 [0.61, 1.06] Subtoal (95% CI) 455 171 6.9% 0.91 [0.73, 1.13] Total events 192 Heterogeneity: $t^2 = 0.01$; $t^2 = 1.53$, $df = 1$ ($P = 0.22$); $l^2 = 35\%$ Tast for overall effect: $Z = 2.86$ ($P = 0.02$) 1.2.6 ABT-229 vs placebo Talley 200 253 488 47 121 3.5% 1.33 [1.05, 1.70] Subtoal (95% CI) 458 472 HO = 0.38 1.2.6 ABT-229 ks placebo Total events 253 47 Heterogeneity: $t^2 = 0.01$; $t^2 = 1.52$, $df = 1$ ($P = 0.22$); $l^2 = 35\%$ Total events 253 47 Heterogeneity: $t^2 = 0.04$; $t^2 = 317.24$, $df = 28$ ($P < 0.0001$); $l^2 = 91\%$ Total events 253 47 Heterogeneity: $t^2 = 0.04$; $t^2 = 317.24$, $df = 28$ ($P < 0.00001$); $l^2 = 91\%$ Total events 253 402 Total events 253 502 Total events 253 402 Total events 253 502 Total events 253 502 Total events 253 502 Total events 253 502 Total events 253 502 Tota	1.2.3 Itopride vs placebo									
Ma 2012 53 119 79 120 3.5% 0.68 [0.53, 0.68] Talley 2008, 1 124 264 226 260 4.3% 0.54 [0.47, 0.62] Talley 2008, 2 288 315 309 330 4.7% 0.98 [0.93, 1.02] Wong 2014 3 16 4 14 0.4% 0.56 [0.18, 2.44] Subtoal (95% CI) 1160 906 18.9% 0.70 [0.47, 1.03] Total events 656 726 Heterogeneity: $r^2 = 0.20$; $r^2 = 152.29$, $df = 5$ ($P = 0.0001$); $l^2 = 97\%$ Test for overall effect: $Z = 1.80$ ($P = 0.07$) 1.2.4 Tegaserod 6 mg bid vs placebo Vakil 2008, 2 365 652 420 655 4.6% 0.92 [0.85, 1.00] Vakil 2008, 2 365 652 420 655 4.6% 0.85 [0.78, 0.93] Subtoal (95% CI) 1337 1330 9.2% 0.89 [0.82, 0.96] 1.2.5 Mosapride vs placebo Hallerback 2002 171 425 57 141 3.6% 1.00 [0.78, 1.25] Lin 2009 21 130 26 30 3.3% 0.81 [0.61, 1.06] Subtoal (95% CI) 4455 171 6.9% 0.91 [0.73, 1.13] 1.2.6 ABT-229 vs placebo Talley 2000 253 488 47 121 3.5% 1.33 [1.05, 1.70] Subtoal (95% CI) 488 121 3.5% 1.33 [1.05, 1.70] Total events 253 47 Heterogeneity: $r^2 = 0.01$; $r^2 = 1.53$, $df = 1$ ($P = 0.22$); $l^2 = 35\%$ Test for overall effect: $Z = 2.36$ ($P = 0.02$) Total events 253 47 Heterogeneity: $r^2 = 0.01$; $r^2 = 1.53$, $df = 1$ ($P = 0.22$); $l^2 = 35\%$ Test for overall effect: $Z = 2.36$ ($P = 0.02$) Total events 253 47 Heterogeneity: $r^2 = 0.01$; $r^2 = 1.53$, $df = 1$ ($P = 0.22$); $l^2 = 35\%$ Test for overall effect: $Z = 2.36$ ($P = 0.02$) Total events 253 47 Heterogeneity: $r^2 = 0.01$; $r^2 = 1.53$, $df = 1$ ($P = 0.22$); $l^2 = 35\%$ Test for overall effect: $Z = 2.36$ ($P = 0.02$) Total events 253 47 Heterogeneity: $r^2 = 0.01$; $r^2 = 4172$, $df = 2.8$ ($P < 0.0001$); $l^2 = 91\%$ Total events 253 47 Heterogeneity: $r^2 = 0.01$; $r^2 = 317.24$, $df = 2.8$ ($P < 0.0001$); $l^2 = 91\%$ Test for overall effect: $Z = 4.56$ ($P < 0.00001$); $r^2 = 91\%$ Test for overall effect: $Z = 4.56$ ($P < 0.00001$); $r^2 = 91\%$ Test for overall effect: $Z = 4.56$ ($P < 0.00001$); $r^2 = 91\%$ Test for overall effect: $Z = 4.56$ ($P < 0.00001$); $r^2 = 91\%$ Test for overall effect: $Z = 4.56$ ($P < 0.00001$); $r^2 = 9.6\%$	Holtmann 2006	174	406	86	142	4.0%	0.71 [0.59, 0.84]			
Shen 2014 14 40 22 40 1.8% 0.64 [0.38, 1.06] Talley 2008, 2 288 315 309 330 4.7% 0.98 [0.93, 1.02] Wong 2014 3 16 4 14 0.4% 0.66 [0.18, 2.44] Subtotal (95% CI) 1160 906 18.9% 0.70 [0.47, 1.03] Total events 656 726 Heterogeneity: $z^2 = 0.20; z^2 = 152.29$, $dt = 5 (P < 0.0001); t^2 = 97\%$ Tast for overall effect: $Z = 1.80 (P = 0.7)$ 1.2.4 Tegaserod 6 mg bid vs placebo Vaki 2008_1 423 685 452 675 4.6% 0.92 [0.85, 1.00] Vaki 2008_2 356 652 420 655 4.6% 0.85 [0.78, 0.93] Subtotal (95% CI) 1337 1330 9.2% 0.89 [0.82, 0.96] Total events 779 872 Heterogeneity: $z^2 = 0.00; z^2 = 1.70$, $dt = 1 (P = 0.19); t^2 = 41\%$ Tast for overall effect: $Z = 1.80 (P = 0.07)$ 1.2.5 Mosapride vs placebo Hallerback 2002 171 425 57 141 3.6% 1.00 [0.78, 1.25] Lin 2009 21 30 26 30 3.3% 0.81 [0.61, 1.06] Subtotal (95% CI) 485 171 6.9% 0.91 [0.73, 1.13] Total events 192 83 Heterogeneity: $z^2 = 0.01; z^2 = 1.53, dt = 1 (P = 0.22); t^2 = 35\%$ Tast for overall effect: $Z = 2.36 (P = 0.02)$ 1.2.6 ABT-229 vs placebo Talley 2000 253 488 47 121 3.5% 1.33 [1.05, 1.70] Subtotal (95% CI) 488 121 3.5% 1.33 [1.05, 1.70] Total events 253 47 Heterogeneity: $z^2 = 0.04; z^2 = 317.24, dt = 28 (P < 0.00001); t^2 = 91\%$ Total events 3339 3025 Heterogeneity: $z^2 = 0.04; z^2 = 317.24, dt = 28 (P < 0.00001); t^2 = 91\%$ Tast for overall effect: $Z = 2.96 (P = 0.02)$ Total events 253 47 Heterogeneity: $z^2 = 0.04; z^2 = 317.24, dt = 28 (P < 0.00001); t^2 = 91\%$ Tast for overall effect: $Z = 4.56 (P < 0.00001)$ Total events 3339 3025 Heterogeneity: $z^2 = 0.04; z^2 = 317.24, dt = 28 (P < 0.00001); t^2 = 91\%$ Tast for overall effect: $Z = 4.56 (P < 0.00001)$ Total events 253 47 Heterogeneity: $z^2 = 0.04; z^2 = 317.24, dt = 28 (P < 0.00001); t^2 = 91\%$ Total events 3339 3025 Heterogeneity: $z^2 = 0.05; dt = 5 (P = 0.005), t^2 = 69.8\%$ Favours [placebo]	Ma 2012	53	119	79	120	3.5%	0.68 [0.53, 0.86]			
Talley 2008_1 1 124 264 226 260 4.3% 0.54 [0.47, 0.62] Talley 2008_2 288 315 309 330 4.7% 0.68 [0.38, 1.02] Wong 2014 3 16 4 14 0.4% 0.66 [0.18, 2.44] Subtal (95% CI) 1160 906 18.9% 0.70 [0.47, 1.03] Total events 656 726 Heterogeneity: $r^2 = 0.20; \chi^2 = 152.29, df = 5 (P < 0.00001); l^2 = 97\%$ Test for overall effect: $Z = 1.80 (P = 0.07)$ 1.2.4 Tegaserod 6 mg bid vs placebo Vakil 2008_2 356 652 420 655 4.6% 0.82 [0.85, 1.00] Vakil 2008_2 356 652 420 655 4.6% 0.85 [0.78, 0.93] Subtolal (95% CI) 1337 1330 9.2% 0.89 [0.82, 0.96] Total events 779 872 Heterogeneity: $r^2 = 0.00; \chi^2 = 1.70, df = 1 (P = 0.19); l^2 = 41\%$ Test for overall effect: $Z = 2.96 (P = 0.03)$ 1.2.5 Mosapride vs placebo Hallertack 2002 171 425 57 141 3.6% 1.00 [0.78, 1.25] Lin 2009 21 30 26 30 3.3% 0.81 [0.61, 1.06] Subtotal (95% CI) 4455 171 6.9% 0.91 [0.73, 1.13] Total events 192 83 Heterogeneity: $r^2 = 0.01; r^2 = 1.53, df = 1 (P = 0.22); l^2 = 35\%$ Test for overall effect: $Z = 0.87 (P = 0.38)$ 1.2.6 ABT-229 vs placebo Talley 2000 253 488 47 121 3.5% 1.33 [1.05, 1.70] Subtotal (95% CI) 488 121 3.5% 1.33 [1.05, 1.70] Total events 253 47 Heterogeneity: rot applicable Test for overall effect: $Z = 2.36 (P = 0.02)$ Total (95% CI) 5949 4095 100.0% 0.81 [0.74, 0.89] Total events 3539 3025 Heterogeneity: $r^2 = 0.04; r^2 = 317.24, df = 28 (P < 0.00001); l^2 = 91% Test for overall effect: Z = 4.65 (P < 0.0001); l^2 = 91% Test for overall effect: Z = 4.65 (P < 0.0001); l^2 = 91%Test for overall effect: Z = 4.65 (P < 0.0001); l^2 = 91% Test for subgroup differences; l^2 = 1.57, df = 5 (P = 0.005), l^2 = 69.8%$	Shen 2014	14	40	22	40	1.8%	0.64 [0.38, 1.06]			
Talley 2008_2 2 288 315 309 330 4.7% 0.98 [0.93, 1.02] Vong 2014 3 16 4 14 0.4% 0.66 [0.18, 2.44] Subtotal (95% CI) 1160 906 18.9% 0.70 [0.47, 1.03] Total events 656 726 Heterogeneity: $r^2 = 0.20; r^2 = 152.9, df = 522.9, df = 5122.9, df = 512.9, df = 5122.9, df = 512.9, df = 51$	Talley 2008_1	124	264	226	260	4.3%	0.54 [0.47, 0.62]			
Wong 2014 3 16 4 14 0.% 0.66 $[0.18, 2.44]$ Subtal (95% CI) 1160 906 18.9% 0.70 $[0.47, 1.03]$ Total events 656 726 Heterogeneity: $r^2 = 0.20; r^2 = 152.29, df = 5 (P < 0.00001); l^2 = 97\%$ Test for overall effect: $Z = 1.80 (P = 0.07)$ 1.2.4 Tegaserod 6 mg bid vs placebo Vakil 2008_1 423 665 452 675 4.6% 0.92 $[0.85, 1.00]$ Vakil 2008_2 356 652 420 655 4.6% 0.85 $[0.78, 0.93]$ Subtal (95% CI) 1337 1330 9.2% 0.89 $[0.82, 0.96]$ Total events 779 872 Heterogeneity: $r^2 = 0.00; r^2 = 1.70, df = 1 (P = 0.19); l^2 = 41\%$ Test for overall effect: $Z = 2.96 (P = 0.03)$ 1.2.5 Mosapride vs placebo Hallerback 2002 171 425 57 141 3.6% 1.00 $[0.78, 1.25]$ Lin 2009 21 30 26 30 3.3% 0.81 $[0.61, 1.06]$ Subtal (95% CI) 455 171 6.9% 0.91 $[0.73, 1.13]$ Total events 192 83 Heterogeneity: $r^2 = 0.01; r^2 = 1.53, df = 1 (P = 0.22); l^2 = 35\%$ Test for overall effect: $Z = 0.87 (P = 0.38)$ 1.2.6 ABT-229 vs placebo Talley 2000 253 488 47 121 3.5% 1.33 $[1.05, 1.70]$ Subtal (95% CI) 488 121 3.5% 1.33 $[1.05, 1.70]$ Total events 253 47 Heterogeneity: rot applicable Test for overall effect: $Z = 2.36 (P = 0.02)$ Total effect: $Z = 0.37 (P = 0.38)$ 1.2.6 ABT-229 vs placebo Talley 2000 253 488 47 121 3.5% 1.33 $[1.05, 1.70]$ Total events 253 47 Heterogeneity: rot applicable Test for overall effect: $Z = 2.36 (P = 0.02)$ Total effect: $Z = 2.36 (P = 0.02)$ Total effect: $Z = 4.65 (P < 0.00001); l^2 = 91\%$ Test for overall effect: $Z = 4.65 (P < 0.00001); l^2 = 91\%$ Test for overall effect: $Z = 4.65 (P < 0.00001); l^2 = 91\%$ Test for overall effect: $Z = 4.65 (P < 0.00001); l^2 = 91\%$ Test for overall effect: $Z = 4.65 (P < 0.00001); l^2 = 91\%$ Test for overall effect: $Z = 4.65 (P < 0.00001); l^2 = 91\%$ Test for overall effect: $Z = 4.65 (P < 0.00001); l^2 = 91\%$ Favours [prokinetic] Favours [prokinetic] Favours [prokinetic]	Talley 2008_2	288	315	309	330	4.7%	0.98 [0.93, 1.02]			
Subtotal (95% CI) 1100 500 10.5% 0.10 [0.47, 1.03] Total events 656 726 Heterogeneity: $t^2 = 0.20; t^2 = 152.29, df = 5 (P < 0.00001); t^2 = 97%$ Test for overall effect: $Z = 1.80 (P = 0.07)$ 1.2.4 Tegaserod 6 mg bid vs placebo Vaki 2008_1 423 685 452 675 4.6% 0.92 [0.85, 1.00] Vaki 2008_2 356 652 420 655 4.6% 0.85 [0.76, 0.93] Subtotal (95% CI) 1337 1330 9.2% 0.89 [0.82, 0.96] Total events 779 872 Heterogeneity: $t^2 = 0.00; t^2 = 1.70, df = 1 (P = 0.19); t^2 = 41\%$ Test for overall effect: $Z = 2.96 (P = 0.03)$ 1.2.5 Mosapride vs placebo Hallerback 2002 171 425 57 141 3.6% 1.00 [0.78, 1.25] Lin 2009 21 30 26 30 3.3% 0.81 [0.61, 1.06] Subtotal (95% CI) 455 1771 6.9% 0.91 [0.73, 1.13] Total events 192 83 Heterogeneity: $t^2 = 0.01; t^2 = 1.53, df = 1 (P = 0.22); t^2 = 35\%$ Test for overall effect: $Z = 0.36 (P = 0.38)$ 1.2.6 ABT-229 vs placebo Talley 2000 253 488 47 121 3.5% 1.33 [1.05, 1.70] Subtotal (95% CI) 488 121 3.5% 1.33 [1.05, 1.70] Total events 253 47 Heterogeneity: $t^2 = 0.04; t^2 = 317.24, df = 28 (P < 0.00001); t^2 = 91\%$ Test for overall effect: $Z = 2.36 (P = 0.02)$ Total events 253 47 Heterogeneity: $t^2 = 0.04; t^2 = 317.24, df = 28 (P < 0.00001); t^2 = 91\%$ Test for overall effect: $Z = 4.56 (P < 0.00001)$ Total events 253 47 Heterogeneity: $t^2 = 0.04; t^2 = 317.24, df = 28 (P < 0.00001); t^2 = 91\%$ Test for overall effect: $Z = 4.56 (P < 0.00001)$ Total events 253 47 Heterogeneity: $t^2 = 0.04; t^2 = 317.24, df = 28 (P < 0.00001); t^2 = 91\%$ Test for overall effect: $Z = 4.56 (P < 0.00001)$ Test for overall effect: $Z = 4.56 (P < 0.00001)$ Favours [prokinetic] Favours [placebo]	Wong 2014 Subtotal (95% CI)	3	16	4	14	0.4%	0.66 [0.18, 2.44]			
$\begin{array}{c} \text{Ideal repeating: } t^2 = 0.26; t^2 = 152.29, \text{ df } 15 (P < 0.00001); l^2 = 97\%\\ \text{Test for overall effect: $Z = 1.80$ (P = 0.07$)\\ 1.2.4 Tegaserod 6 mg bid vs placebo\\ \text{Vakil 2008_1} & 423 & 685 & 452 & 675 & 4.6\% & 0.92 [0.85, 1.00]\\ \text{Vakil 2008_2} & 356 & 652 & 420 & 655 & 4.6\% & 0.89 [0.82, 0.96]\\ \text{Total events} & 779 & 872\\ \text{Heterogeneity: } t^2 = 0.00; t^2 = 1.70, \text{ df } = 1 (P = 0.19); l^2 = 41\%\\ \text{Test for overall effect: $Z = 2.96$ (P = 0.03)\\ 1.2.5 \text{ Mosapride vs placebo}\\ \text{Hallerback 2002} & 171 & 425 & 57 & 141 & 3.6\% & 1.00 [0.78, 1.25]\\ \text{Lin 2009} & 21 & 30 & 26 & 30 & 3.3\% & 0.81 [0.61, 1.06]\\ \text{Subtotal (95\% CI)} & 455 & 171 & 6.9\% & 0.91 [0.73, 1.13]\\ \text{Total events} & 192 & 83\\ \text{Heterogeneity: } t^2 = 0.01; t^2 = 1.53, \text{ df } = 1 (P = 0.22); t^2 = 35\%\\ \text{Test for overall effect: $Z = 0.87$ (P = 0.38)\\ 1.2.6 \text{ ABT:} 229 \text{ vs placebo}\\ \text{Talley 2000} & 253 & 488 & 47 & 121 & 3.5\% & 1.33 [1.05, 1.70]\\ \text{Total events} & 253 & 47\\ \text{Heterogeneity: not applicable}\\ \text{Test for overall effect: $Z = 2.36$ (P = 0.02)\\ \text{Total events} & 253 & 47\\ \text{Heterogeneity: not applicable}\\ \text{Test for overall effect: $Z = 0.67$ (P = 0.000); t^2 = 91\%\\ \text{Total events} & 539 & 3025\\ \text{Heterogeneity: t^2 = 0.04; t^2 = 317.24, \text{ df } = 28$ (P < 0.00001); t^2 = 91\%\\ \text{Test for overall effect: $Z = 4.56$ (P < 0.00001)}\\ \text{Test for overall effect: $Z = 4.56$ (P < 0.00001); t^2 = 91\%\\ \text{Test for overall effect: $Z = 4.56$ (P < 0.00001)}\\ \text{Favours [prokinetic]} Favours [placebo]\\ \end{array}$	Subiolal (95% CI)	050	1100	700	900	10.9%	0.70 [0.47, 1.03]			
Test for overall effect: $Z = 1.80$ ($P = 0.07$) 1.2.4 Tegaserod 6 mg bid vs placebo Vakil 2008_1 423 685 452 675 4.6% 0.92 [0.85, 1.00] Vakil 2008_2 356 652 420 655 4.6% 0.85 [0.78, 0.93] Subtotal (95% Cl) 1337 1330 9.2% 0.89 [0.82, 0.96] Total events 779 872 Heterogeneity: $t^2 = 0.00; t^2 = 1.70, df = 1$ ($P = 0.19$); $l^2 = 41\%$ Test for overall effect: $Z = 2.96$ ($P = 0.03$) 1.2.5 Mosapride vs placebo Hallerback 2002 171 425 57 141 3.6% 1.00 [0.78, 1.25] Lin 2009 21 30 26 30 3.3% 0.81 [0.61, 1.06] Subtotal (95% Cl) 455 171 6.9% 0.91 [0.73, 1.13] Total events 192 83 Heterogeneity: $t^2 = 0.01; t^2 = 1.53, df = 1$ ($P = 0.22$); $l^2 = 35\%$ Test for overall effect: $Z = 0.87$ ($P = 0.38$) 1.2.6 ABT-229 vs placebo Talley 2000 253 488 47 121 3.5% 1.33 [1.05, 1.70] Subtotal (95% Cl) 488 121 3.5% 1.33 [1.05, 1.70] Total events 253 47 Heterogeneity: $t^2 = 0.04; t^2 = 317.24, df = 28$ ($P = 0.005$) Total events 0.5339 3025 Heterogeneity: $t^2 = 0.04; t^2 = 317.24, df = 28$ ($P = 0.005$) Total events 253 47 Heterogeneity: $t^2 = 0.04; t^2 = 317.24, df = 28$ ($P = 0.005$), $t^2 = 91\%$ Test for overall effect: $Z = 4.65$ ($P < 0.00001$); $t^2 = 91\%$ Test for overall effect: $Z = 4.65$ ($P < 0.00001$); $t^2 = 91\%$ Test for overall effect: $Z = 4.65$ ($P < 0.0001$) Test for subgroup differences: $t^2 = 16.5$ ($d = 28$ ($P = 0.005$), $t^2 = 69.8\%$	Heterogeneity: $\tau^2 = 0.20$:	000 2 - 152 2	Q df =	720 5 (P < 0.0	0001).	² - 97%				
$\begin{array}{c} 1.2.4 \text{ Tegaserod 6 mg bid vs placebo} \\ Vakil 2008_1 & 423 & 685 & 452 & 675 & 4.6\% & 0.92 [0.85, 1.00] \\ Vakil 2008_2 & 356 & 652 & 420 & 655 & 4.6\% & 0.85 [0.78, 0.93] \\ Subtotal (95\% CI) & 1337 & 1330 & 9.2\% & 0.89 [0.82, 0.96] \\ Total events & 779 & 872 \\ Heterogeneity: t^2 = 0.00; \chi^2 = 1.70, df = 1 \ (P = 0.19); f^2 = 41\% \\ \text{Test for overall effect: } Z = 2.96 \ (P = 0.03) \\ 1.2.5 \text{ Mosapride vs placebo} \\ Hallerback 2002 & 171 & 425 & 57 & 141 & 3.6\% & 1.00 [0.78, 1.25] \\ Lin 2009 & 21 & 30 & 26 & 30 & 3.3\% & 0.81 [0.61, 1.06] \\ \text{Subtotal (95\% CI)} & 455 & 171 & 6.9\% & 0.91 [0.73, 1.13] \\ \text{Total events} & 192 & 83 \\ \text{Heterogeneity: } t^2 = 0.01; \chi^2 = 1.53, df = 1 \ (P = 0.22); f^2 = 35\% \\ \text{Test for overall effect: } Z = 0.87 \ (P = 0.38) \\ 1.2.6 \text{ ABT-}229 \text{ vs placebo} \\ \text{Talley 2000} & 253 & 488 & 47 & 121 & 3.5\% & 1.33 [1.05, 1.70] \\ \text{Subtotal (95\% CI)} & 488 & 121 & 3.5\% & 1.33 [1.05, 1.70] \\ \text{Total events} & 253 & 47 \\ \text{Heterogeneity: } t^2 = 0.04; \chi^2 = 37.24, df = 28 \ (P < 0.00001); f^2 = 91\% \\ \text{Test for overall effect: } Z = 2.36 \ (P < 0.00001) \\ \text{Test for overall effect: } Z = 4.65 \ (P < 0.00001) \\ \text{Test for overall effect: } Z = 4.65 \ (P < 0.00001) \\ \text{Test for overall effect: } Z = 4.65 \ (P < 0.00001) \\ \text{Test for overall effect: } Z = 4.65 \ (P < 0.00001) \\ \text{Test for overall effect: } Z = 4.65 \ (P < 0.00001) \\ \text{Test for overall effect: } Z = 4.65 \ (P < 0.00001) \\ \text{Test for overall effect: } Z = 4.65 \ (P < 0.00001) \\ \text{Test for overall effect: } Z = 4.65 \ (P < 0.00001) \\ \text{Test for subgroup differences; } t^2 = 16.57, df = 57 \ (P = 0.055), f^2 = 69.8\% \\ \end{array}$	Test for overall effect: $Z =$	1 80 (P -	0.07)	0 (7 < 0.0		- 01 /0				
$1.2.4 \text{ Tegaserod 6 mg bid vs placebo}$ Vakil 2008_1 423 685 452 675 4.6% 0.92 [0.85, 1.00] Vakil 2008_2 356 652 420 655 4.6% 0.85 [0.78, 0.33] Vakil 2008_2 356 652 420 655 4.6% 0.89 [0.82, 0.96] Total events 779 872 Heterogeneity: $t^2 = 0.03; t^2 = 1.70, df = 1 (P = 0.19); t^2 = 41\%$ Test for overall effect: $Z = 2.96 (P = 0.03)$ 1.2.5 Mosapride vs placebo Hallerback 2002 171 425 57 141 3.6% 1.00 [0.78, 1.25] Lin 2009 21 30 26 30 3.3% 0.81 [0.61, 1.06] Subtotal (95% Cl) 455 171 6.9% 0.91 [0.73, 1.13] Total events 192 83 Heterogeneity: $t^2 = 0.01; t^2 = 1.53, df = 1 (P = 0.22); t^2 = 35\%$ Test for overall effect: $Z = 0.87 (P = 0.38)$ 1.2.6 ABT-229 vs placebo Talley 200 253 488 47 121 3.5% 1.33 [1.05, 1.70] Subtotal (95% Cl) 488 121 3.5% 1.33 [1.05, 1.70] Subtotal (95% Cl) 5949 4095 100.0% 0.81 [0.74, 0.89] Total events 253 47 Heterogeneity: $t^2 = 0.04; t^2 = 3324, df = 28 (P < 0.00001); t^2 = 91\%$ Test for overall effect: $Z = 2.36 (P = 0.02)$ Total events 3539 3025 Heterogeneity: $t^2 = 0.04; t^2 = 157, df = 28 (P < 0.00001); t^2 = 91\%$ Test for overall effect: $Z = 4.65 (P < 0.00001)$ Test for overall effect: $Z = 4.65 (P < 0.00001)$ Test for overall effect: $Z = 4.65 (P < 0.00001)$ Test for overall effect: $Z = 4.65 (P < 0.00001)$ Test for overall effect: $Z = 4.65 (P < 0.00001)$ Test for overall effect: $Z = 4.65 (P < 0.00001)$ Favours [prokinetic] Favours [placebo]		1.00 (7 =	0.07)							
Vakil 2008_1 423 685 452 675 4.6% 0.92 [0.85, 1.00] Vakil 2008_2 356 652 420 655 4.6% 0.85 [0.78, 0.93] Subtotal (95% CI) 1337 1330 9.2% 0.89 [0.82, 0.96] Total events 779 872 Heterogeneity: $\tau^2 = 0.00; \chi^2 = 1.70, df = 1 (P = 0.19); l^2 = 41\%$ Test for overall effect: $Z = 2.96 (P = 0.03)$ 1.2.5 Mosapride vs placebo Hallerback 2002 171 425 57 141 3.6% 1.00 [0.78, 1.25] Lin 2009 21 30 26 30 3.3% 0.81 [0.61, 1.06] Subtotal (95% CI) 455 171 6.9% 0.91 [0.73, 1.13] Total events 192 83 Heterogeneity: $\tau^2 = 0.01; \chi^2 = 1.53, df = 1 (P = 0.22); l^2 = 35\%$ Test for overall effect: $Z = 0.87 (P = 0.38)$ 1.2.6 ABT-229 vs placebo Talley 2000 253 488 47 121 3.5% 1.33 [1.05, 1.70] Subtotal (95% CI) 488 121 3.5% 1.33 [1.05, 1.70] Total events 253 47 Heterogeneity: not applicable Test for overall effect: $Z = 2.36 (P = 0.02)$ Total (95% CI) 5949 4095 100.0% 0.81 [0.74, 0.89] Total events 3539 3025 Heterogeneity: $\tau^2 = 0.04; \chi^2 = 317.24, df = 28 (P < 0.0001); l^2 = 91\%$ Test for overall effect: $Z = 4.65 (P < 0.0001)$ Test for overall effect: $Z = 0.45; (P < 0.0001)$ Test for overall effect: $Z = 0.45; (P < 0.0001)$ Test for overall effect: $Z = 4.55 (P < 0.00001)$ Test for overall effect: $Z = 4.55 (P < 0.00001)$ Test for overall effect: $Z = 4.55 (P < 0.00001)$ Test for overall effect: $Z = 4.55 (P < 0.00001)$ Test for subgroup differences: $\gamma^2 = 15.57, df = 5 (P = 0.005), l^2 = 69.8\%$	1.2.4 Tegaserod 6 mg bid	vs place	00							
Vakil 2008_2 356 652 420 655 4.6% 0.85 [0.78, 0.93] Subtotal (95% CI) 1337 1330 9.2% 0.89 [0.82, 0.96] Total events 779 872 Heterogeneity: $r^2 = 0.00; \chi^2 = 1.70, df = 1 (P = 0.19); l^2 = 41\%$ Test for overall effect: $Z = 2.96 (P = 0.03)$ 1.2.5 Mosapride vs placebo Hallerback 2002 171 425 57 141 3.6% 1.00 [0.78, 1.25] Lin 2009 21 30 26 30 3.3% 0.81 [0.61, 1.06] Subtotal (95% CI) 455 171 6.9% 0.91 [0.73, 1.13] Total events 192 83 Heterogeneity: $r^2 = 0.01; \chi^2 = 1.53, df = 1 (P = 0.22); l^2 = 35\%$ Test for overall effect: $Z = 0.87 (P = 0.38)$ 1.2.6 ABT-229 vs placebo Talley 2000 253 488 47 121 3.5% 1.33 [1.05, 1.70] Subtotal (95% CI) 488 121 3.5% 1.33 [1.05, 1.70] Total events 253 47 Heterogeneity: rot applicable Test for overall effect: $Z = 2.36 (P = 0.02)$ Total events 3539 3025 Heterogeneity: $r^2 = 0.04; \chi^2 = 317.24, df = 28 (P < 0.0001); l^2 = 91\%$ Test for overall effect: $Z = 4.65 (P < 0.0001)$ Test for overall effect: $Z = 1.657, df = 5 (P = 0.005), l^2 = 69.8\%$ Favours [prokinetic] Favours [placebo]	Vakil 2008_1	423	685	452	675	4.6%	0.92 [0.85, 1.00]	-		
Subtotal (95% Cl) 1337 1330 9.2% 0.89 [0.82, 0.96] Total events 779 872 Heterogeneity: $r^2 = 0.00; r^2 = 1.70, df = 1 (P = 0.19); l^2 = 41\%$ Test for overall effect: $Z = 2.96 (P = 0.03)$ 1.2.5 Mosapride vs placebo Hallerback 2002 171 425 57 141 3.6% 1.00 [0.78, 1.25] Lin 2009 21 30 26 30 3.3% 0.81 [0.61, 1.06] Subtotal (95% Cl) 455 171 6.9% 0.91 [0.73, 1.13] Total events 192 83 Heterogeneity: $r^2 = 0.01; r^2 = 1.53, df = 1 (P = 0.22); l^2 = 35\%$ Test for overall effect: $Z = 0.87 (P = 0.38)$ 1.2.6 ABT-229 vs placebo Talley 2000 253 488 47 121 3.5% 1.33 [1.05, 1.70] Subtotal (95% Cl) 488 121 3.5% 1.33 [1.05, 1.70] Total events 253 47 Heterogeneity: not applicable Test for overall effect: $Z = 2.36 (P = 0.02)$ Total events 3539 3025 Heterogeneity: $r^2 = 0.04; r^2 = 31.24, df = 28 (P < 0.00001); l^2 = 91\%$ Test for overall effect: $Z = 4.65 (P < 0.00001)$ Test for overall effect: $Z = 4.65 (P < 0.00001)$ Test for overall effect: $Z = 4.65 (P < 0.00001)$ Test for overall effect: $Z = 4.65 (P < 0.00001)$ Test for overall effect: $Z = 4.65 (P < 0.00001)$ Test for overall effect: $Z = 4.65 (P < 0.00001)$ Test for overall effect: $Z = 4.65 (P < 0.00001)$ Test for subgroup differences: $r^2 = 16.57, df = 5 (P = 0.005), l^2 = 69.8\%$	Vakil 2008_2	356	652	420	655	4.6%	0.85 [0.78, 0.93]			
Total events 779 872 Heterogeneity: $t^2 = 0.00; t^2 = 1.70, df = 1 (P = 0.19); l^2 = 41\%$ Test for overall effect: $Z = 2.96 (P = 0.03)$ 1.2.5 Mosapride vs placebo Hallerback 2002 171 425 57 141 3.6% 1.00 [0.78, 1.25] Lin 2009 21 30 26 30 3.3% 0.81 [0.61, 1.06] Subtotal (95% CI) 455 171 6.9% 0.91 [0.73, 1.13] Total events 192 83 Heterogeneity: $t^2 = 0.01; t^2 = 1.53, df = 1 (P = 0.22); t^2 = 35\%$ Test for overall effect: $Z = 0.87 (P = 0.38)$ 1.2.6 ABT-229 vs placebo Talley 2000 253 488 47 121 3.5% 1.33 [1.05, 1.70] Subtotal (95% CI) 488 121 3.5% 1.33 [1.05, 1.70] Subtotal (95% CI) 488 121 3.5% 1.33 [1.05, 1.70] Total events 253 47 Heterogeneity: not applicable Test for overall effect: $Z = 2.36 (P = 0.02)$ Total (95% CI) 5949 4095 100.0% 0.81 [0.74, 0.89] Total events 3539 3025 Heterogeneity: $t^2 = 0.04; t^2 = 317.24, df = 28 (P < 0.00001); t^2 = 91\%$ Test for overall effect: $Z = 4.65 (P < 0.00001)$ Test for overall effect: $Z = 4.65 (P < 0.00001)$ Test for overall effect: $Z = 1.65, df = 5 (P = 0.005), t^2 = 69.8\%$ Favours [prokinetic] Favours [placebo]	Subtotal (95% CI)		1337		1330	9.2%	0.89 [0.82, 0.96]	◆		
Heterogeneity: $t^2 = 0.00; \chi^2 = 1.70, df = 1 (P = 0.19); l^2 = 41\%$ Test for overall effect: $Z = 2.96 (P = 0.03)$ 1.2.5 Mosapride vs placebo Hallerback 2002 171 425 57 141 3.6% 1.00 [0.78, 1.25] Lin 2009 21 30 26 30 3.3% 0.81 [0.61, 1.06] Subtotal (95% CI) 455 171 6.9% 0.91 [0.73, 1.13] Total events 192 83 Heterogeneity: $t^2 = 0.01; \chi^2 = 1.53, df = 1 (P = 0.22); l^2 = 35\%$ Test for overall effect: $Z = 0.87 (P = 0.38)$ 1.2.6 ABT-229 vs placebo Talley 2000 253 488 47 121 3.5% 1.33 [1.05, 1.70] Subtotal (95% CI) 488 121 3.5% 1.33 [1.05, 1.70] Total events 253 47 Heterogeneity: $t^2 = 0.04; \chi^2 = 37.24, df = 28 (P < 0.0001); l^2 = 91\%$ Test for overall effect: $Z = 0.465 (P < 0.0001)$ Total events 3539 3025 Heterogeneity: $t^2 = 0.04; \chi^2 = 37.24, df = 28 (P < 0.00001); l^2 = 91\%$ Test for overall effect: $Z = 4.65 (P < 0.0001)$ Test for overall effect: $Z = 4.65 (P < 0.00001)$ Test for overall effect: $Z = 1.657, df = 5 (P = 0.005), l^2 = 69.8\%$ Favours [prokinetic] Favours [placebo]	Total events	779		872						
Test for overall effect: $Z = 2.96 (P = 0.03)$ 1.2.5 Mosapride vs placebo Hallerback 2002 171 425 57 141 3.6% 1.00 [0.78, 1.25] Lin 2009 21 30 26 30 3.3% 0.81 [0.61, 1.06] Subtotal (95% Cl) 455 171 6.9% 0.91 [0.73, 1.13] Total events 192 83 Heterogeneity: $r^2 = 0.01; \chi^2 = 1.53, df = 1 (P = 0.22); l^2 = 35\%$ Test for overall effect: $Z = 0.87 (P = 0.38)$ 1.2.6 ABT-229 vs placebo Talley 2000 253 488 47 121 3.5% 1.33 [1.05, 1.70] Subtotal (95% Cl) 488 121 3.5% 1.33 [1.05, 1.70] Subtotal (95% Cl) 488 121 3.5% 1.33 [1.05, 1.70] Total events 253 47 Heterogeneity: not applicable Test for overall effect: $Z = 2.36 (P = 0.02)$ Total (95% Cl) 5949 4095 100.0% 0.81 [0.74, 0.89] Total events 3539 3025 Heterogeneity: $r^2 = 0.04; \chi^2 = 317.24, df = 28 (P < 0.0001); l^2 = 91\%$ Test for overall effect: $Z = 4.65 (P < 0.0001)$ Test for overall effect: $Z = 4.65 (P < 0.0001)$ Test for overall effect: $Z = 4.65 (P < 0.0001)$ Test for overall effect: $Z = 1.65, df = 5 (P = 0.005), l^2 = 69.8\%$ Favours [prokinetic] Favours [placebo]	Heterogeneity: $\tau^2 = 0.00$; χ	$\chi^2 = 1.70,$	df = 1 (P = 0.19)	$I^2 = 41^{\circ}$	%				
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Test for overall effect: $Z =$	2.96 (<i>P</i> =	0.03)							
Hallerback 2002 171 425 57 141 3.6% 1.00 [0.78, 1.25] Lin 2009 21 30 26 30 3.3% 0.81 [0.61, 1.06] Subtotal (95% Cl) 455 171 6.9% 0.91 [0.73, 1.13] Total events 192 83 Heterogeneity: $\tau^2 = 0.01; \chi^2 = 1.53, df = 1 (P = 0.22); l^2 = 35\%$ Test for overall effect: $Z = 0.87 (P = 0.38)$ 1.2.6 ABT-229 vs placebo Talley 200 253 488 47 121 3.5% 1.33 [1.05, 1.70] Subtotal (95% Cl) 488 121 3.5% 1.33 [1.05, 1.70] Total events 253 47 Heterogeneity: not applicable Test for overall effect: $Z = 2.36 (P = 0.02)$ Total (95% Cl) 5949 4095 100.0% 0.81 [0.74, 0.89] Total events 3539 3025 Heterogeneity: $\tau^2 = 0.04; \chi^2 = 317.24, df = 28 (P < 0.00001); l^2 = 91\%$ Test for overall effect: $Z = 4.65 (P < 0.00001)$ Test for overall effect: $Z = 4.65 (P < 0.00001)$ Test for subgroup differences: $\tau^2 = 16.57, df = 5 (P = 0.005), l^2 = 69.8\%$ Favours [prokinetic] Favours [placebo]	1.2.5 Macaprida va placet	20								
Halleroack 2002 171 425 57 141 3.6% 1.00 [0.78, 1.25] Lin 2009 21 30 26 30 3.3% 0.81 [0.61, 1.06] Subtotal (95% CI) 455 171 6.9% 0.91 [0.73, 1.13] Total events 192 83 Heterogeneity: $\tau^2 = 0.01; \chi^2 = 1.53, df = 1 (P = 0.22); l^2 = 35\%$ Test for overall effect: $Z = 0.87 (P = 0.38)$ 1.2.6 ABT-229 vs placebo Talley 2000 253 488 47 121 3.5% 1.33 [1.05, 1.70] Subtotal (95% CI) 488 121 3.5% 1.33 [1.05, 1.70] Subtotal (95% CI) 488 121 3.5% 1.33 [1.05, 1.70] Total events 253 47 Heterogeneity: not applicable Test for overall effect: $Z = 2.36 (P = 0.02)$ Total (95% CI) 5949 4095 100.0% 0.81 [0.74, 0.89] Total events 3539 3025 Heterogeneity: $\tau^2 = 0.04; \chi^2 = 317.24, df = 28 (P < 0.00001); l^2 = 91%$ Test for overall effect: $Z = 4.65 (P < 0.00001)$ Test for subgroup differences: $\chi^2 = 16.57, df = 5 (P = 0.005), l^2 = 69.8\%$ Favours [prokinetic] Favours [placebo]	1.2.5 Wosaphue vs place.	174	405			0.00/	4 00 [0 70 4 05]			
Lin 2009 21 30 26 30 3.3% 0.81 [0.61, 1.06] Subtotal (95% CI) 455 171 6.9% 0.91 [0.73, 1.13] Total events 192 83 Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 1.53$, $df = 1$ ($P = 0.22$); $l^2 = 35\%$ Test for overall effect: $Z = 0.87$ ($P = 0.38$) 1.2.6 ABT-229 vs placebo Talley 2000 253 488 47 121 3.5% 1.33 [1.05, 1.70] Subtotal (95% CI) 488 121 3.5% 1.33 [1.05, 1.70] Total events 253 47 Heterogeneity: rot applicable Test for overall effect: $Z = 2.36$ ($P = 0.02$) Total events 3539 3025 Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 317.24$, $df = 28$ ($P < 0.00001$); $l^2 = 91\%$ Test for overall effect: $Z = 4.65$ ($P < 0.00001$) Test for overall effect: $\chi^2 = 16.57$, $df = 5$ ($P = 0.005$), $l^2 = 69.8\%$ Favours [prokinetic] Favours [placebo]	Hallerback 2002	1/1	425	57	141	3.6%	1.00 [0.78, 1.25]	<u>_</u>		
$\begin{array}{c} Contract (c) (c) (c) (c) (c) (c) (c) (c) (c) (c)$	Subtotal (95% CI)	21	30 455	20	30 171	3.3% 6.9%	0.81 [0.61, 1.06]			
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Total events	192	400	83		0.070	0.01 [0.10, 1.10]			
Test for overall effect: $Z = 0.87$ ($P = 0.38$) 1.2.6 ABT-229 vs placebo Talley 2000 253 488 47 121 3.5% 1.33 [1.05, 1.70] Subtal (95% Cl) 488 121 3.5% 1.33 [1.05, 1.70] Total events 253 47 Heterogeneity: not applicable Test for overall effect: $Z = 2.36$ ($P = 0.02$) Total (95% Cl) 5949 4095 100.0% 0.81 [0.74, 0.89] Total events 3539 3025 Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 317.24$, $df = 28$ ($P < 0.00001$); $l^2 = 91\%$ Test for overall effect: $Z = 4.65$ ($P < 0.00001$) Test for overall effect: $\chi^2 = 16.57$, $df = 5$ ($P = 0.05$), $l^2 = 69.8\%$ Favours [prokinetic] Favours [placebo]	Heterogeneity: $\tau^2 = 0.01$:	$\chi^2 = 1.53.$	df = 1 (P = 0.22	$l^2 = 35^{\circ}$	%				
1.2.6 ABT-229 vs placebo Talley 2000 253 488 47 121 3.5% 1.33 [1.05, 1.70] Subtal (95% Cl) 488 121 3.5% 1.33 [1.05, 1.70] Total events 253 47 Heterogeneity: not applicable Test for overall effect: $Z = 2.36$ ($P = 0.02$) Total (95% Cl) 5949 4095 100.0% 0.81 [0.74, 0.89] Total events 3539 3025 Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 317.24$, $df = 28$ ($P < 0.00001$); $l^2 = 91\%$ Test for overall effect: $Z = 4.65$ ($P < 0.00001$) Test for subgroup differences: $\chi^2 = 16.57$, $df = 5$ ($P = 0.05$), $l^2 = 69.8\%$ Favours [prokinetic] Favours [placebo]	Test for overall effect: $Z =$	0.87 (<i>P</i> =	0.38)	,						
$\begin{array}{c c c c c c c c c c c c c c c c c c c $,							
Talley 2000 253 488 47 121 3.5% 1.33 [1.05, 1.70] Subtotal (95% Cl) 488 121 3.5% 1.33 [1.05, 1.70] Total events 253 47 Heterogeneity: not applicable Est for overall effect: $Z = 2.36$ ($P = 0.02$) Image: Comparison of the terogeneity: $\tau^2 = 0.04$; $\chi^2 = 317.24$, $df = 28$ ($P < 0.00001$); $l^2 = 91\%$ Image: Comparison of teroperative in the terogeneity: $\tau^2 = 0.04$; $\chi^2 = 317.24$, $df = 28$ ($P < 0.00001$); $l^2 = 91\%$ Test for overall effect: $Z = 4.65$ ($P < 0.00001$) Image: Comparison of teroperative in the term of term o	1.2.6 ABT-229 vs placebo									
Subtotal (95% CI) 488 121 3.5% $1.33 [1.05, 1.70]$ Total events 253 47 Heterogeneity: not applicable Test for overall effect: $Z = 2.36 (P = 0.02)$ Total (95% CI) 5949 4095 100.0% 0.81 [0.74, 0.89] Total events 3539 3025 Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 317.24$, $df = 28 (P < 0.00001)$; $l^2 = 91\%$ Test for overall effect: $Z = 4.65 (P < 0.00001)$ Test for subgroup differences: $\gamma^2 = 16.57$, $df = 5 (P = 0.005)$, $l^2 = 69.8\%$ Favours [prokinetic] Favours [placebo]	Talley 2000	253	488	47	121	3.5%	1.33 [1.05, 1.70]			
Total events 253 47 Heterogeneity: not applicable Test for overall effect: $Z = 2.36$ ($P = 0.02$) Total (95% CI) 5949 4095 100.0% 0.81 [0.74, 0.89] Total events 3539 3025 Heterogeneity: $\tau^2 = 0.04; \chi^2 = 317.24, df = 28$ ($P < 0.00001$); $I^2 = 91\%$ 0.2 0.5 1 2 5 Test for overall effect: $Z = 4.65$ ($P < 0.00001$) 0.2 0.5 1 2 5 Test for subgroup differences: $\gamma^2 = 16.57, df = 5$ ($P = 0.005$), $I^2 = 69.8\%$ Favours [prokinetic] Favours [placebo]	Subtotal (95% CI)		488		121	3.5%	1.33 [1.05, 1.70]	 ◆		
Heterogeneity: not applicable Test for overall effect: $Z = 2.36 (P = 0.02)$ Total (95% CI) 5949 4095 100.0% 0.81 [0.74, 0.89] Total events 3539 3025 Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 317.24$, $df = 28 (P < 0.00001)$; $l^2 = 91\%$ Test for overall effect: $Z = 4.65 (P < 0.00001)$ Test for subgroup differences: $\chi^2 = 16.57$, $df = 5 (P = 0.005)$, $l^2 = 69.8\%$ Favours [prokinetic] Favours [placebo]	Total events	253		47						
Test for overall effect: $Z = 2.36$ ($P = 0.02$) Total (95% CI) 5949 4095 100.0% 0.81 [0.74, 0.89] Total events 3539 3025 Heterogeneity: $\tau^2 = 0.04; \chi^2 = 317.24, df = 28$ ($P < 0.00001$); $l^2 = 91\%$ 0.2 0.5 1 2 5 Test for overall effect: $Z = 4.65$ ($P < 0.00001$) 0.2 0.5 1 2 5 Test for subgroup differences: $\gamma^2 = 16.57, df = 5$ ($P = 0.005$), $l^2 = 69.8\%$ Favours [prokinetic] Favours [placebo] Favours [placebo]	Heterogeneity: not applica	able								
Total (95% CI) 5949 4095 100.0% 0.81 [0.74, 0.89] Total events 3539 3025 Heterogeneity: $\tau^2 = 0.04; \chi^2 = 317.24, df = 28 (P < 0.00001); l^2 = 91\%$ 1 1 Test for overall effect: $Z = 4.65 (P < 0.00001)$ 0.2 0.5 1 2 5 Test for subgroup differences: $\chi^2 = 16.57, df = 5 (P = 0.005), l^2 = 69.8\%$ Favours [prokinetic] Favours [placebo]	Test for overall effect: $Z = $	2.36 (<i>P</i> =	0.02)							
Total events 3539 3025 Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 317.24$, $df = 28$ ($P < 0.00001$); $I^2 = 91\%$ 0.2 0.5 1 2 5 Test for overall effect: $Z = 4.65$ ($P < 0.00001$) 0.2 0.5 1 2 5 Test for subgroup differences: $\chi^2 = 16.57$, $df = 5$ ($P = 0.005$), $I^2 = 69.8\%$ Favours [prokinetic]	Total (05% CIV		5040		1005	100.0%	0.91 [0.74 .0.90]			
Total events 3039 3029 3029 Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 317.24$, $df = 28$ ($P < 0.00001$); $l^2 = 91\%$ 1 1 1 Test for overall effect: $Z = 4.65$ ($P < 0.00001$) 0.2 0.5 1 2 5 Test for subgroup differences: $\chi^2 = 16.57$, $df = 5$ ($P = 0.005$), $l^2 = 69.8\%$ Favours [prokinetic] Favours [placebo]	Total (30 % CI)	2500	5949	2005	4090	100.0%	0.01 [0.74, 0.89]	•		
Test for overall effect: $Z = 4.65$ ($P = 0.00001$) 0.2 0.5 1 2 5 Test for subgroup differences: $\gamma^2 = 16.57$, $d^f = 5$ ($P = 0.005$), $l^2 = 69.8\%$ Favours [prokinetic] Favours [placebo]	Heterogeneity: $\tau^2 = 0.04$ · π^2	ანაფ / ² = 317 ე	4 df -	3025 28 (P - ∩	000011	$l^2 = 91\%$		· · _ · _ · _ · _ · _ · _ · _		
Test for subgroup differences: $\gamma^2 = 16.57$, df = 5 (P = 0.005), $l^2 = 69.8\%$ Favours [prokinetic] Favours [placebo]	Test for overall effect: $7 - $	4.65 (P <	0.0000	,, _ 0.)		01/0		0.2 0.5 1 2 5		
	Test for subgroup different	Test for subgroup differences: $\gamma^2 = 16.57$, $df = 5$ ($P = 0.005$), $I^2 = 69.8\%$ Favours [prokinetic] Favours [placebo]								

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





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 (12 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; l^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; l^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; *P* 87% and RR 0.75, 95% CI 0.62 to 0.91; *P* 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).

REVIEW ARTICL

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

	Proki	netic	Place	ebo		Risk ratio	Risk ratio		
Study or subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl		
1.4.1 Studies only include	d patients	s with PI	OS subtyp	e					
Lin 2009	21	30	26	30	3.2%	0.81 [0.61, 1.06]			
Ma 2012	44	74	55	71	3.5%	0.77 [0.61, 0.96]			
Matsueda 2010_2	290	346	99	116	4.5%	0.98 [0.90, 1.07]			
Matsueda 2012	383	452	405	445	4.6%	0.93 [0.89, 0.98]	*		
Shen 2014	14	40	22	40	1.8%	0.64 [0.38, 1.06]			
Tack 2011	87	193	53	96	3.4%	0.82 [0.64, 1.04]			
Talley 2000	253	488	47	121	3.4%	1.33 [1.05, 1.70]			
Vakil 2008_1	423	685	452	675	4.5%	0.92 [0.85, 1.00]			
Vakil 2008_2	356	652	420	655	4.5%	0.85 [0.78, 0.93]			
Wang 1995	137	414	145	169	4.1%	0.39 [0.33, 0.45]			
Wong 2014 Subtotal (95% CI)	3	16 3390	4	14 2432	0.4% 37.9%	0.66 [0.18, 2.44] 0.82 [0.70, 0.95]	•		
Total events	2011		1728				•		
Heterogeneity: $\tau^2 = 0.05$: γ	$r^2 = 148.0$	06. d <i>f</i> = 1	0 (P = 0.0)	00001):	l ² = 93%				
Test for overall effect: $Z = 2$	2.61 (<i>P</i> =	0.009)		,					
1 4 2 Studies only include	d natiente	s with F	PS subturn	e					
	e panerita e	17	- 300.yp		1 10/	0 49 [0 24 0 09]			
Me 2012	0	17	22	15	0.7%	0.40 [0.24, 0.90]			
Subtotal (95% CI)	23	45 62		62	3.8%	0.67 [0.48, 0.93]	\bullet		
Total events	29		44				-		
Heterogeneity: $\tau^2 = 0.01$; χ	$r^2 = 1.07$,	df = 1 (1	P = 0.30);	$I^2 = 6\%$,				
Test for overall effect: Z = 2	2.39 (<i>P</i> =	0.02)							
1.4.3 Studies included bot	h subtyp	es (PDS	, EPS)						
De Groot 1997	26	61	35	60	2.6%	0.73 [0.51, 1.05]	— —		
Francois 1987	8	17	14	17	1.6%	0.57 [0.33, 0.99]			
Hallerback 2002	171	425	57	141	3.5%	1.00 [0.79, 1.25]			
Hansen 1998	101	109	99	110	4.5%	1.03 [0.95, 1.12]	t t		
Holtmann 2002	51	59	52	61	4.1%	1.01 [0.88, 1.17]	+-		
Holtmann 2006	174	406	86	142	3.9%	0.71 [0.59, 0.84]			
Kellow 1995	26	30	25	31	3.6%	1.07 [0.86, 1.34]			
Kusunoki 2012	15	21	18	21	2.8%	0.83 [0.60, 1.15]			
Matsueda 2010_1	187	216	94	107	4.5%	0.99 [0.90, 1.08]			
Rosch 1987	27	57	45	57	2.9%	0.60 [0.44, 0.81]			
Talley 2008	195	312	71	104	4.1%	0.92 [0.78, 1.07]			
Talley 2008_1	124	264	226	260	4.2%	0.54 [0.47, 0.62]			
Talley 2008_2	288	315	309	330	4.6%	0.98 [0.93, 1.02]	1		
Yeoh 1997	46	52	47	52	4.2%	0.98 [0.86, 1.12]			
Subtotal (95% CI)		2344		1493	51.1%	0.86 [0.76, 0.97]	\bullet		
Total events	, 1439		1178		2				
Heterogeneity: $\tau^2 = 0.04$; χ	/ ⁻ = 138.4	17, dt = 1	3 (P < 0.0)	00001);	I ⁻ = 91%				
Test for overall effect: $Z = A$	2.52 (P =	0.01)							
1.4.4 Studies did not differ	entiate F	D subty	be						
AI-Quorain 1995	22	48	47	50	2.9%	0.49 [0.36, 0.67]			
Champion 1997	43	83	26	40	2.9%	0.80 [0.59, 1.08]			
Teixeria 2000	9	22	11	16	1.4%	0.60 [0.33, 1.09]			
Subtotal (95% CI)		153		106	7.2%	0.62 [0.44, 0.87]	\bullet		
Total events	74		84						
Heterogeneity: $\tau^2 = 0.05$; χ	² = 4.81,	df = 2 (<i>I</i>	^D < 0.09);	$I^2 = 58^{\circ}$	%				
Test for overall effect: $Z = 2.74$ ($P = 0.006$)									
Total (95% CI)		5949		4093	100.0%	0.81 [0.75, 0.89]	•		
Total events	3553		3034						
Heterogeneity: $\tau^2 = 0.04$:	² = 313.2	24, $df = 2$	29 (<i>P</i> < 0.0	00001):	l ² = 91%		-+ + + +		
Test for overall effect: $Z = 4$	4.72 (<i>P</i> =	0.0000	1)	/,			0.2 0.5 1 2 5		
Test for subgroup difference	ces: $\chi^2 = -$	Favours [prokinetic] Favours [placebo]							

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; l^2 87%, p < 0.0001; NNT 8, 95% CI 5 to 19 and RR 0.87, 95% CI 0.80 to 0.95; l^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).

	Proki	notio	Place	obo		Dick ratio	Pick ratio	
Study or subaroup	Events	Total	Events	Total	Weiaht	M-H. Random, 95% Cl	M-H. Random, 95% Cl	
1.5.1 Western countries					J	,,		
Champion 1997	43	83	26	40	3.0%	0.80[0.59, 1.08]		
De Groot 1997	26	61	35	60	2.6%	0.73 [0.51, 1.05]		
De Nutte 1989	6	17	11	15	1.2%	0.48 [0.24, 0.98]		
Erançois 1987	8	17	14	17	1.2%	0.57 [0.33, 0.99]		
Hallerback 2002	171	425	57	141	3.6%	1 00 [0 79 1 25]		
Hansen 1998	101	109	99	110	4.6%	1 03 [0 95 1 12]	+	
Holtmann 2002	51	59	52	61	4.0%	1 01 [0 88 1 17]	<u> </u>	
Holtmann 2006	174	406	86	142	4.0%	0 71 [0 59 0 84]		
Kellow 1995	26	30	25	31	3.7%	1 07 [0.86, 1.34]		
Rosch 1987	27	57	45	57	3.0%	0.60 [0.44, 0.81]		
Tack 2011	87	103	53	96	3.5%	0.82 [0.64, 1.04]		
Talley 2000	253	/88	17	121	3.5%	1 33 [1 05 1 70]		
Talley 2000	105	212	71	104	1.0%			
Talley 2000	104	264	226	260	4.2 /0	0.52 [0.76, 1.07]		
Talley 2008_1	000	204	220	200	4.3 /0	0.04 [0.47, 0.02]	1	
Tailey 2006_2	200	315	309	330	4.7%	0.96 [0.93, 1.02]		
	9	22	11	10	1.5%	0.60 [0.33, 1.09]		
Vakii 2008_1	423	685	452	6/5	4.6%	0.92 [0.85, 1.00]		
Vakii 2008_2 Subtotal (95% CL)	356	052 /105	420	0001	4.6%	0.85 [0.78, 0.93]	<u> </u>	
Tatal aventa	0000	4195	0000	2931	02.0%	0.65 [0.77, 0.94]	•	
Hotorogonoitur $-^2 - 0.02$	2368 ² = 122	90 df-	2039	00001), 1 ² _ 070/			
Helefogeneity. $\tau = 0.03$,	χ = 133	.09, u/ =	17 (F < 0	J.00001), 1 = 01%			
l est for overall effect: Z	= 3.19 (<i>P</i>	= 0.001)					
1.5.2 Asia								
Al-Quorain 1995	22	48	47	50	3.0%	0.49 [0.36, 0.67]		
Kusunoki 2012	15	21	18	21	2.9%	0.83 [0.60, 1.15]	— <u> </u>	
Lin 2009	21	30	26	30	3.3%	0.81 [0.61 1.06]		
Ma 2012	53	119	79	120	3.5%	0.68 [0.53, 0.86]		
Matsueda 2010 1	187	216	94	107	4.6%	0.99 [0.90, 1.08]	+	
Matsueda 2010_2	290	346	99	116	4.6%	0.98 [0.90, 1.07]		
Matsueda 2012	383	452	405	445	4 7%	0.93 [0.89, 0.98]	+	
Shen 2014	14	40	22	40	1.8%	0.64 [0.38, 1.06]		
Wang 1995	137	414	145	169	4.2%	0.39 [0.33, 0.45]		
Wong 2014	107	16	145	1/1	0.4%	0.66 [0.18, 2.44]		
Yeoh 1997	46	52	47	52	4.3%	0.98 [0.86, 1.12]		
Subtotal (95% CI)	40	1754	47	1164	37.4%	0.75 [0.62, 0.91]	•	
Total evants	1171		986				•	
Heterogeneity: $r^2 = 0.08^{\circ}$	2 - 101	82 df-	10 (P < 1	00001	12 - 95%			
Test for overall effect: Z	= 2.97 (<i>P</i>	= 0.003)		,, = 5576			
Total (95% CI)		5949		4095	100.0%	0.81 [0.74, 0.89]	•	
Total events	3539		3025				Ť	
Heterogeneity: $\tau^2 = 0.04$	$\sqrt{2} = 317$	24 df-	28 (P - 1) / ² _ 01%			
Test for overall of feed Z_{-4} (B_{-2} (C_{-0} (
TESTIOL OVERALI ELLER /	= 4 65 (P		20 (/ < \ 01)), / _ 91/6	1	0.2 0.5 1 2 5	

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

	Prokir	Prokinetics		Placebo		Risk ratio		Ri	k ratio	
Study or subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% (CI	M-H, Rai	ndom, 95% CI	
1.6.1 High RoB					-					
Champion 1997	43	83	26	40	3.0%	0.80 [0.59, 1.08]			<u> </u>	
Ma 2012	53	119	79	120	3.5%	0.68 [0.53, 0.86]				
Wang 1995	137	414	145	169	4.2%	0.39 [0.33, 0.45]				
Yeah 1997	46	52	47	52	4.3%	0.98 [0.86, 1.12]			- - -	
Subtotal (95% CI)		668		381	15.1%	0.67 [0.39, 1.15]				
Total events	279		297							
Heterogeneity: $\tau^2 = 0.29$	$\gamma^2 = 98.59$	df = 3(P)	$< 0.00001) \cdot l^2$	= 97%						
Test for overall effect: Z	(= 1.46 (<i>P</i> =	0.14)	,,							
1.6.2 Unclear RoB										
Al-Quorain 1995	22	48	47	50	3.0%	0.49 [0.36, 0.67]				
De Groot 1997	26	61	35	60	2.6%	0.73 [0.51, 1.05]			—	
De Nutte 1989	6	17	11	15	1.2%	0.48 [0.24, 0.98]			_	
Francois 1987	8	17	14	17	1.7%	0.57 [0.33, 0.99]		<u> </u>	_	
Hallerback 2002	171	425	57	141	3.6%	1.00 [0.79, 1.25]		-	<u> </u>	
Hansen 1998	101	109	99	110	4.6%	1.03 [0.95, 1.12]			+	
Holtmann 2002	51	59	52	61	4.2%	1.01 [0.88, 1.17]			+	
Kellow 1995	26	30	25	31	3.7%	1.07 [0.86, 1.34]				
Kusunoki 2012	15	21	18	21	2.9%	0.83 [0.60, 1.15]				
Lin 2009	21	30	26	30	3.3%	0.81 [0.61, 1.06]				
Matsueda 2010_1	187	216	94	107	4.6%	0.99 [0.90, 1.08]			+	
Matsueda 2010_2	290	346	99	116	4.6%	0.98 [0.90, 1.07]			+	
Rosch 1987	27	57	45	57	3.0%	0.60 [0.44, 0.81]				
Shen 2014	14	40	22	40	1.8%	0.64 [0.38, 1.06]				
Tack 2011	87	193	53	96	3.5%	0.82 [0.64, 1.04]			<u> </u>	
Talley 2000	253	488	47	121	3.5%	1.33 [1.05, 1.70]				
Talley 2008	195	312	71	104	4.2%	0.92 [0.78, 1.07]		-		
Talley 2008_1	124	264	226	260	4.3%	0.54 [0.47, 0.62]				
Talley 2008_2	288	315	309	330	4.7%	0.98 [0.93, 1.02]			4	
Teixeira 2000	9	22	11	16	1.5%	0.60 [0.33, 1.09]			+	
Wong 2014	3	16	4	14	0.4%	0.66 [0.18, 2.44]		· · ·		
Subtotal (95% CI)		3086		1797	67.0%	0.84 [0.76, 0.93]				
Total events	1924		1365							
Heterogeneity: $\tau^2 = 0.04$	$k; \chi^2 = 150.2$	7, df = 20 (<i>P</i> < 0.00001);	l ² = 87%						
16.2 Low PoP	- 0.02 (7 -	0.0003)								
Holtmann 2006	174	406	86	142	4.0%	0.71 [0.59. 0.84]				
Mateuada 2012	383	452	405	445	4.7%	0.93 [0.89, 0.98]			-	
Vakil 2009 1	423	685	452	675	4.6%	0.92 [0.85, 1.00]				
Vakii 2008_1	356	652	420	655	4.6%	0.85 [0.78, 0.93]		_	-	
Subtotal (95% CI)		2195		1917	17.9%	0.87 [0.80, 0.95]			•	
Total events	1336		1363							
Heterogeneity: $\tau^2 = 0.01$ Test for overall effect: Z	; χ ² = 12.32 ζ = 3.09 (<i>P</i> =	, d <i>f</i> = 3 (<i>P</i> = 0.002)	= 0.006); <i>I</i> ² = 7	76%						
Total (95% CI)		5949		4095	100.0%	0.81 [0.74, 0.89]		•	•	
Total events	3539		3025							
Heterogeneity: $\tau^2 = 0.04$	l; χ ² = 317.2	4, df = 28 (P < 0.00001);	$I^2 = 91\%$					+ +	<u>_</u>
Test for overall effect: Z	= 4.65 (<i>P</i> <	0.0001)					0.2	0.5	1 2	5
Test for subaroup differe	ences: $\gamma^2 = \frac{1}{2}$	1.07. df = 2	$(P = 0.59), I^2$	= 0%			Favo	ours [prokinetic]	Favours [pl	acebo]

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 Prokinetic compared to placebo for functional dyspepsia

Patient or population: Functional dyspepsia

Setting: Out-patients

Intervention: Prokinetic

Comparison: Placebo

Outcomes	Anticipated absolu	te effects ^a (95% CI)	Relative effect (95% CI)	No of participants	Certainty of	Comments	
	Risk with placebo	Risk with Prokinetic		(studies)	(GRADE)		
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 ${}^{\scriptscriptstyle b,c,d,e}$		
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 ${}^{\text{b,c,e,f,i}}$		

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

^aThe 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)

^bDowngraded 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

°One study was open-labeled design

^aDowngraded one level due to serious inconsistency: significant heterogeneity without plausible explanations

Downgraded one level due to other considerable in publication bias: the funnel plot was asymmetrical, probably from small study effect

^fOne study was considered to be high risk of bias

Downgraded one level due to serious inconsistency: significant heterogeneity with some possible explanations

^hDowngraded two levels due to imprecision (95% Cl of pooled data included no effect and small number of included trials)

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 eff	ects ^a (95% CI)	Relative effect	No. of participants	Certainty of the	Comments
	Risk with domperidone 10 mg tid	Risk with Other prokinetics	(95% CI)	(studies)	evidence (GRADE)	
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}	
CRADE Working Group grade	s of avidance					

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

^aThe 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).

^bDowngraded 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)

^cDowngraded two levels due to imprecision (95% Cl of pooled data included no effect and small number of included trials)

^dDowngraded one level due to imprecision (there were lesser events than 300 and wide 95% Cl)

^eDowngraded one level due to imprecision (95% CI of pooled data was very close to no effect)

Moayyedi; drafting the manuscript, Rapat Pittayanon, Yuhong Yuan, Brian E. Lacy, Christopher N. Andrews and Paul Moayyedi. All authors have approved the final draft submitted.

Financial support: None

Potential competing interests: None

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 welltolerated (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.

REFERENCES

- Ford AC, Forman D, Bailey AG, et al. Initial poor quality of life and new onset of dyspepsia: results from a longitudinal 10-year follow-up study. Gut. 2007;56:321–7.
- Tack J, Masaoka T, Janssen P. Functional dyspepsia. Curr Opin Gastroenterol. 2011;27:549–57.
- Stanghellini V, Chan FK, Hasler WL, et al. Gastroduodenal Disorders. Gastroenterology. 2016;150:1380–92.
- Sarnelli G, Caenepeel P, Geypens B, et al. Symptoms associated with impaired gastric emptying of solids and liquids in functional dyspepsia. Am J Gastroenterol. 2003;98:783–8.
- 5. Bisschops R, Karamanolis G, Arts J, et al. Relationship between symptoms and ingestion of a meal in functional dyspepsia. Gut. 2008;57:1495–503.
- Talley NJ, Vakil NB, Moayyedi P. American gastroenterological association technical review on the evaluation of dyspepsia. Gastroenterology. 2005;129:1756–80.
- 7. Moayyedi P, Soo S, Deeks J, et al. Pharmacological interventions for nonulcer dyspepsia. Cochrane Database Syst Rev 2006:CD001960.
- Talley NJ, Vakil N. Practice Parameters Committee of the American College of G. Guidelines for the management of dyspepsia. Am J Gastroenterol. 2005;100:2324–37.
- Moayyedi PM, Lacy BE, Andrews CN, et al. ACG and CAG Clinical Guideline: Management of Dyspepsia. Am J Gastroenterol. 2017; 112:988–1013.
- 10. Tack J, Talley NJ, Camilleri M, et al. Functional gastroduodenal disorders. Gastroenterology. 2006;130:1466–79.
- 11. Talley NJ, Stanghellini V, Heading RC, et al. Functional gastroduodenal disorders. Gut. 1999;45(Suppl 2):II37–42.
- 12. Laird NM, Ware JH. Random-effects models for longitudinal data. Biometrics. 1982;38:963–74.
- Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924–6.

- al-Quorain A, Larbi EB, al-Shedoki F. A double-blind, randomized, placebo-controlled trial of cisapride in Saudi Arabs with functional dyspepsia. Scand J Gastroenterol. 1995;30:531–4.
- Champion MC, MacCannell KL, Thomson AB, et al. A double-blind randomized study of cisapride in the treatment of nonulcer dyspepsia. The Canadian Cisapride Nud Study Group. Can J Gastroenterol. 1997;11:127–34.
- de Groot GH, de Both PS. Cisapride in functional dyspepsia in general practice. A placebo-controlled, randomized, double-blind study. Aliment Pharmacol Ther. 1997;11:193–9.
- De Nutte N, Van Ganse W, Witterhulghe M, et al. Relief of epigastric pain in nonulcer dyspepsia: controlled trial of the promotility drug cisapride. Clin Ther. 1989;11:62–8.
- Hansen JM, Bytzer P, Schaffalitzky de Muckadell OB. Placebo-controlled trial of cisapride and nizatidine in unselected patients with functional dyspepsia. Am J Gastroenterol. 1998;93:368–74.
- Holtmann G, Gschossmann J, Mayr P, et al. A randomized placebocontrolled trial of simethicone and cisapride for the treatment of patients with functional dyspepsia. Aliment Pharmacol Ther. 2002;16:1641–8.
- Kellow JE, Cowan H, Shuter B, et al. Efficacy of cisapride therapy in functional dyspepsia. Aliment Pharmacol Ther. 1995;9:153–60.
- 21. Rosch W. Cisapride in non-ulcer dyspepsia. Results of a placebo-controlled trial. Scand J Gastroenterol. 1987;22:161–4.
- 22. Yeoh KG, Kang JY, Tay HH, et al. Effect of cisapride on functional dyspepsia in patients with and without histological gastritis: a double-blind placebo-controlled trial. J Gastroenterol Hepatol. 1997;12:13–8.
- Wang B, Liang X, Jia B. [A controlled multi-centre clinical trial on cisapride in treatment of functional dyspepsia]. Zhonghua Nei Ke Za Zhi. 1995;34:180–4.
- 24. Franciois I, De Nutte N. Nonulcer dyspepsia: effect of the gastrointestinal prokinetic drug cisapride. Curr Ther Res. 1987;41:891–8.
- Teixeira CR, Kurban A, C. A., Denical IP, et al. Randomized, double-blind study of functional dyspepsia with cisapride, trimebutine and placebo relationship with variation of the gastric emptying time. Rev Bras Med. 2000;57(7):729–35.
- Kusunoki H, Haruma K, Manabe N, et al. Therapeutic efficacy of acotiamide in patients with functional dyspepsia based on enhanced postprandial gastric accommodation and emptying: randomized controlled study evaluation by real-time ultrasonography. Neurogastroenterol Motil. 2012;24:540–5. e250-1
- 27. Matsueda K, Hongo M, Tack J, et al. Clinical trial: dose-dependent therapeutic efficacy of acotiamide hydrochloride (Z-338) in patients with functional dyspepsia 100 mg t.i.d. is an optimal dosage. Neurogastroenterol Motil. 2010;22:618–e173.
- Matsueda K, Hongo M, Tack J, et al. A placebo-controlled trial of acotiamide for meal-related symptoms of functional dyspepsia. Gut. 2012;61:821–8.
- Tack J, Stanghellini V, Holtmann G, et al. Efficacy and safety study of acotiamide (Z-338) in european patients with functional dyspepsia. Gastroenterology. 2011;140:S805.
- Talley NJ, Tack J, Kowalski D, et al. A novel acetylcholine esterase inhibitor acotiamide hydrochloride (YM443) in functional dyspepsia: efficacy in a randomized, double-blind, placebo-controlled dose ranging Trial. Gastroenterology. 2008;134:A157–A8.
- Talley NJ, Tack J, Ptak T, et al. Itopride in functional dyspepsia: results of two phase III multicentre, randomised, double-blind, placebo-controlled trials. Gut. 2008;57:740–6.
- 32. Holtmann G, Talley NJ, Liebregts T, et al. A placebo-controlled trial of itopride in functional dyspepsia. N Engl J Med. 2006;354:832–40.

- Ma TT, Yu SY, Li Y, et al. Randomised clinical trial: an assessment of acupuncture on specific meridian or specific acupoint vs. sham acupuncture for treating functional dyspepsia. Aliment Pharmacol Ther. 2012;35:552–61.
- Shen Y, Fang N, Yang C. Azintamide combined with itopride hydrochloride for treatment of functional dyspepsia. World Chin J Dig. 2014;22:2993–6.
- 35. Wong Z, Daud UN, Naidu J, et al. Randomised, double-blind placebo controlled trial assessing the efficacy of itopride in postprandial distress syndrome (PDS): a pilot study. J Gastroenterol Hepatol. 2014;29:124–5.
- Vakil N, Laine L, Talley NJ, et al. Tegaserod treatment for dysmotility-like functional dyspepsia: results of two randomized, controlled trials. Am J Gastroenterol. 2008;103:1906–19.
- 37. Hallerback BI, Bommelaer G, Bredberg E, et al. Dose finding study of mosapride in functional dyspepsia: a placebo-controlled, randomized study. Aliment Pharmacol Ther. 2002;16:959–67.
- Lin J, Ren M, Peng X, et al. Short-term efficacy of mosapride dispersible tablet on postprandial distress syndrome. Chin J Gastroenterol. 2009;14:488–90.
- 39. Talley NJ, Verlinden M, Snape W, et al. Failure of a motilin receptor agonist (ABT-229) to relieve the symptoms of functional dyspepsia in patients with and without delayed gastric emptying: a randomized doubleblind placebo-controlled trial. Aliment Pharmacol Ther. 2000;14:1653–61.
- Li YH, Gong PL, Hou XH, et al. Itopride in treatment of 104 patients with functional dyspepsia: a randomized, double-blind controlled clinical trial. Zhongguo Xinyao Yu Linchuang Zazhi. 2005;7:524–8.
- Mo JZ, Li DG, Jiang JH, et al. A multi-center clinical trial of itopride hydrochloride in the treatment of functional dyspepsia Zhongguo Xinyao Zazhi. 2003;12:467–9.
- 42. Sun J, Zhang CL, Chu Y, et al. A multi-center, double-blind, randomized and controlled trial of itopride hydrochloride in treatment of functional dyspepsia. Shanghai Yixue. 2003;26:227–9.
- Zhou LY, Li BQ, Lin SR, et al. A multicenter clinicnal trial on Itopride Hydrochloride for treatment of functional dyspepsia. Chin J Clin Pharmacol. 2000;16:403–7.
- Zhu CQ, Mao YM, Zeng MD, et al. A clinical study of hydrochloride itopride in the treatment of functional dyspepsia. Zhongguo Yaoke Daxue Xuebao. 2005;6:580–3.
- 45. Choi MG, Rhee PL, Park H, et al. Randomized, controlled, multi-center trial: comparing the safety and efficacy of DA-9701 and itopride hydrochloride in patients with functional dyspepsia. J Neurogastroenterol Motil. 2015;21:414–22.
- 46. Du Y, Su T, Song X, et al. Efficacy and safety of cinitapride in the treatment of mild to moderate postprandial distress syndrome-predominant functional dyspepsia. J Clin Gastroenterol. 2014;48:328–35.
- Chen SY, Wang JY, Zhu CW, et al. [A randomized controlled Multi-center clinical trial on mosapride in the treatment of functional dyspepsia]. Zhonghua Liu Xing Bing Xue Za Zhi. 2004;25:165–8.
- Amarapurkar DN, Rane P. Randomised, double-blind, comparative study to evaluate the efficacy and safety of ganaton (itopride hydrochloride) and mosapride citrate in the management of functional dyspepsia. J Indian Med Assoc. 2004;102:735–7. 60
- Thumshirn M, Fruehauf H, Stutz B, et al. Clinical trial: effects of tegaserod on gastric motor and sensory function in patients with functional dyspepsia. Aliment Pharmacol Ther. 2007;26: 1399–407.
- 50. Miwa H, Kusano M, Arisawa T, et al. Evidence-based clinical practice guidelines for functional dyspepsia. J Gastroenterol. 2015;50:125–39.