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TITLE PAGE

Title: Response and Adverse Event Rates with Placebo in Gastroparesis: A Systematic Review and Meta-analysis.

Short title: Meta-analysis: Gastroparesis Response and Adverse Event Rates with Placebo.

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Abbreviations:

CI	confidence interval
FD	functional dyspepsia
GCSI	gastroparesis cardinal symptom index

IBS	irritable bowel syndrome
RCT	randomized controlled trial
SD	standard deviation

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ABSTRACT

Background & Aims: Multiple drugs have been used to treat gastroparesis symptoms, yet their therapeutic benefits are poorly understood partly due to lack of insight into response and adverse event rates with placebo in randomized controlled trials (RCTs). We evaluated these issues systematically in drug trials for gastroparesis.

Methods: We searched the medical literature up to 2nd August 2022 to identify RCTs comparing active drug with placebo in patients with gastroparesis. We assessed placebo response rates according to at least one of the following endpoints: improvement according to a composite outcome, nausea, vomiting, abdominal pain, bloating, or fullness, as well as total adverse events, and adverse events leading to withdrawal. We extracted data as intention-to-treat analyses with dropouts assumed to be treatment failures. We pooled placebo response and adverse event rates using a random effects model and expressed as proportions with 95% confidence intervals (CIs).

Results: Thirty-five studies were eligible. Among 23 trials reporting a composite endpoint of improvement, the pooled placebo response rate was 29.3% (95% CI 23.7%-35.2%). Pooled placebo response rates were higher in idiopathic compared with diabetic gastroparesis (34.2% versus 28.1%), among trials that did not use validated symptom questionnaires (31.2% versus 27.4%), and in RCTs of shorter duration (<4 weeks, 32.6% versus ≥ 9 weeks, 23.2%). Adverse events occurred in 33.8% (95% CI 26.4%-41.8%) of patients with placebo, in 27 trials, and were less common in idiopathic compared with diabetic gastroparesis (17.9% versus 43.4%), trials of shorter duration (<4 weeks, 33.7% versus ≥ 9 weeks, 40.7%), and trials with lower randomization ratios of active drug to placebo (1:1, 26.7% versus 3:1, 50.5%).

Conclusions: This meta-analysis assessed placebo response and adverse event rates in gastroparesis. To accurately assess therapeutic gain, future trials should be a minimum of 8 weeks duration, use validated questionnaires, and distinguish gastroparesis subtypes.

Key words: gastric emptying; gastroparesis; metoclopramide; nausea; placebo response; vomiting

INTRODUCTION

Estimated to affect almost 300 per 100,000 people,[1] gastroparesis is a chronic gastrointestinal sensorimotor disorder characterized by a variety of disruptive symptoms including nausea, vomiting, early satiety, bloating, and abdominal pain.[2, 3] Related to a delay in gastric emptying in the absence of mechanical obstruction, gastroparesis can be diagnosed using a 4-hour solid phase radionuclide gastric emptying scan or a breath test.[4] Despite clear guidelines for diagnosing gastroparesis accurately, overlap of symptoms with other gastrointestinal disorders, including functional dyspepsia (FD), cannabinoid hyperemesis syndrome, and cyclic vomiting syndrome, can make this difficult.[5-7]

There are three well-recognized subtypes of gastroparesis, including idiopathic, diabetic, and postsurgical, all of which impose a substantial burden on both patients and the healthcare system.[8] Studies have reported reduced quality of life among individuals with gastroparesis, compared with healthy individuals.[8, 9] In addition to higher pain scores, a considerable proportion of patients with gastroparesis report impaired ability to engage in work and daily activities due to symptoms.[8, 10] Importantly, a diagnosis of gastroparesis increases the potential for hospitalization and may lead to therapeutic interventions that can be economically burdensome.[1, 8] Despite this, only one drug, metoclopramide, administered either orally or via nasal spray, has been approved by the Food and Drug Administration for its treatment,[11] and only in diabetic gastroparesis. However, a variety of other drugs are used off-label to treat symptoms, with varying reports of efficacy.

A clear understanding of the therapeutic benefits offered by drugs for the treatment of gastroparesis is limited due to unknown effects of the placebo response in randomized controlled trials (RCTs). Accurate interpretation of trials in gastroparesis depends upon a precise understanding of the magnitude of the placebo response rate, which may vary based on subtype and outcome measures. The importance of this issue is reinforced by data documenting high response rates with placebo among patients with other gastrointestinal disorders. For example, according to composite measures of improvement in FD and irritable bowel syndrome (IBS), one-in-three patients respond to

placebo in RCTs.[12-14] Similar placebo response rates have been reported in patients with ulcerative colitis or Crohn's disease.[15, 16]

In tandem with the placebo response, accurate assessment of gastroparesis RCTs requires a thorough evaluation of adverse events, as a variety of non-pharmacological factors can induce negative consequences that may be attributed falsely to a study drug. This phenomenon is reflected in reports of adverse events occurring among participants receiving placebo in numerous studies,[17, 18] also known as the "nocebo" effect.[19, 20] Accordingly, failing to compare the proportion of adverse events experienced by participants in both placebo and experimental trial arms may lead to overestimates of treatment-related adverse events. Similar to inflated placebo response rates, overestimates of treatment-related adverse events can have negative consequences for drug development and approval.[21]

To our knowledge, a systematic assessment of response and adverse event rates with placebo has not been undertaken in the context of gastroparesis. As the first study of its kind, this systematic review and meta-analysis aimed to examine both these issues among RCTs investigating efficacy of drugs for gastroparesis, as well as to characterize factors that may influence these rates. Such investigation is not only essential for clinical decision-making, but also to optimize future clinical trial design for this debilitating condition.

METHODS

Search Strategy and Selection Criteria

We searched MEDLINE (1946 to 2nd August 2022), EMBASE and EMBASE Classic (1947 to 2nd August 2022), and the Cochrane central register of controlled trials, as well as clinicaltrials.gov for unpublished trials or supplementary data for potentially eligible RCTs. We hand-searched conference proceedings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week) between 2007 and 2022 to identify trials published only as abstracts. Finally, we used bibliographies of all obtained articles to perform a recursive search.

Placebo-controlled trials examining the efficacy of any active drug in adults (≥18 years) with gastroparesis of any etiology were eligible (Table 1). We did not consider trials of devices or endoscopic or surgical interventions. The first period of cross-over RCTs were eligible if they provided efficacy data prior to cross-over. We considered definitions of gastroparesis that included confirmation of delayed gastric emptying on radionuclide or breath testing, or those with typical symptoms felt to meet a diagnosis clinically. We required a minimum treatment duration of 1 week. Studies had to report assessment of response to therapy, using either a composite endpoint for improvement, such as the gastroparesis cardinal symptom index (GCSI), improvement in individual symptoms of gastroparesis, including nausea, vomiting, abdominal pain, bloating, or fullness, improvement in gastric emptying rate, or adverse event rates.

Two investigators (JW and ACF) conducted the literature search, independently from each other. We identified studies on gastroparesis with the terms: *gastroparesis* or *gastric emptying* (both as medical subject heading and free text terms), or *delayed* adj5 *gastric emptying* (as a free text term). We combined these using the set operator AND with studies identified with the terms: *metoclopramide*, *domperidone*, *prucalopride*, *velusetrag*, *relamorelin*, *amitriptyline*, *nortriptyline*, *imipramine*, *desipramine*, *ghrelin agonist*, *5-HT4 agonist*, *5HT4 agonist*, *5 HT4 agonist*, *tradipitant*,

aprepitant, *TACR1 antagonist*, *neurokinin-1 receptor antagonist*, *neurokinin 1 receptor antagonist*, *NKR1 antagonist*, *dopamine receptor antagonist*, *revexepride*, *mitemcinal*, *motilin agonist*, *itopride*, *mosapride*, *renzapride*, *erythromycin*, *azithromycin*, or *clarithromycin* (as medical subject heading or free text terms). We did not apply language restrictions. Two investigators (MRI and ACF) evaluated all abstracts identified by the search for eligibility, again independently from each other. We obtained all papers that appeared relevant, evaluating them in more detail against our eligibility criteria, using pre-designed forms. We translated foreign language papers, where required. We resolved disagreements between investigators (MRI and ACF) by discussion.

Outcome Assessment

The primary outcome was the magnitude of the placebo response rate, in terms of the proportion of patients achieving a composite endpoint of improvement in gastroparesis symptoms (e.g., an improvement in GCSI), as well as adverse event rates with placebo. Secondary outcomes included assessing placebo response rate according to improvement in individual symptoms of gastroparesis, such as nausea, vomiting, abdominal pain, bloating, or fullness, improvement in the rate of gastric emptying, and rates of withdrawal due to adverse events with placebo.

Data Extraction

Two investigators (MRI and ACF) extracted all data independently onto a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA) as dichotomous outcomes (gastroparesis symptoms improved or not improved, nausea improved or not improved, adverse events experienced or not experienced, etc.) in the placebo arms of the included RCTs. Where studies reported a dichotomous assessment of response to therapy according to these endpoints, for example a 50% improvement in the GCSI score being achieved or not achieved, we extracted these data from the article. For studies reporting mean symptom scores at baseline together

with follow-up mean symptom scores and standard deviation (SD) for these endpoints for each intervention arm, we imputed dichotomous responder and non-responder data using methodology previously described by Furukawa *et al*.[22, 23] For example, a 50% improvement in GCSI score is derived from the formula: number of participants in each treatment arm at final follow-up x normal standard distribution. The latter corresponds to (50% of the baseline mean GCSI score – follow-up mean GCSI score) / follow-up SD. We contacted first and senior authors of studies to provide additional data for individual trials, where required. We resolved any discrepancies by consensus.

We also extracted the following data for each trial, where available: country of origin, etiology of gastroparesis, whether delayed gastric emptying was confirmed in all patients, the proportion of female patients, duration of treatment, dosing schedule of placebo, and whether randomization to active drug or placebo was 1:1. We extracted all efficacy data as intention-to-treat analyses, with placebo dropouts assumed to be treatment failures, wherever trial reporting allowed this. If this was not clear from the original article, we performed an analysis on all patients with reported evaluable data. We extracted all adverse events data with placebo with the denominators consisting of the safety populations reported; that is all patients receiving at least one dose of the placebo.

Data Synthesis and Statistical Analysis

We pooled the proportion of patients assigned to placebo achieving each of the symptom endpoints to give a pooled placebo response rate for all RCTs, as well as the proportion of patients randomized to placebo experiencing adverse events or withdrawals due to adverse events. We used a random effects model to provide conservative estimates, according to the methodology of DerSimonian and Laird.[17] We assessed heterogeneity between studies using both the χ^2 test, with a P value <0.10 defining a significant degree of heterogeneity, and the I^2 statistic, which ranges between 0% and 100%. We considered values of 25% to 49%, 50% to 74%, and ≥75% to represent low,

moderate, and high levels of heterogeneity, respectively.[18] We used StatsDirect version 3.2.7 (StatsDirect Ltd, Sale, Cheshire, England) to generate Forest plots of pooled placebo response and adverse event rates, with 95% confidence intervals (CIs). For our primary endpoint of placebo response rate, we performed subgroup analyses according to etiology of gastroparesis, whether delayed gastric emptying was confirmed in all individuals, whether the questionnaire used to define response was validated or unvalidated, year of the study, treatment duration, dosing schedule of the placebo, and whether randomization to active drug or placebo was 1:1. We also excluded trials that used a placebo run-in period in a sensitivity analysis. For adverse event rates with placebo, we performed subgroup analyses according to etiology of gastroparesis, whether delayed gastric emptying was confirmed in all participants, year of the study, treatment duration, dosing schedule of the placebo, and whether randomization to active drug or placebo was 1:1.

RESULTS

The search strategy generated 3124 citations, 152 of which appeared to be relevant. Thirty-five of these fulfilled eligibility criteria (Figure 1). Of these, 29 articles were published in full,[24-52] and there were a further six trials available on clinicaltrials.gov (NCT03285308, NCT03426345, NCT02210000, NCT1262898, NCT02025751, NCT02025725). One article reported two separate trials,[37] and efficacy and adverse events data were reported for one trial in two separate papers.[41, 49] Agreement between investigators for study eligibility was excellent (kappa statistic = 0.88). Detailed characteristics of individual RCTs are provided in Table 2.

Placebo Response Rates

In total, there were 22 articles, reporting on 23 separate trials, providing placebo response rates according to a composite endpoint of improvement in gastroparesis symptoms in 1011 patients.[25-29, 31-34, 36-40, 43-45, 48-52] The pooled placebo response rate in all studies was 29.3% (95% CI 23.7% to 35.2%) (Figure 2a), with significant heterogeneity (I^2 = 72.0%). Subgroup analyses according to trial characteristics are provided in Table 3. Pooled placebo response rates were generally lower in diabetic gastroparesis, RCTs that confirmed delayed gastric emptying in all participants, rather than relying on typical symptoms in a proportion of, or all, patients, trials that used a validated questionnaire to define response, RCTs with a treatment duration ≥9 weeks, and trials in which randomization to active drug or placebo was 1:1 or 2:1. Placebo response increased stepwise with each increase in dosing schedule. There was no consistent effect of study year. Heterogeneity was moderate to high in most analyses. Three trials used a placebo run-in period.[29, 49, 52] Excluding these three studies in a sensitivity analysis led to only a slight increase in the pooled placebo response rate for the composite endpoint of improvement in gastroparesis symptoms (31.3%; 95% CI 24.8% to 38.0%, I^2 = 72.9%). The pooled placebo response rate in the three trials that used a placebo run-in period was, however, lower (20.7%; 95% CI 15.0% to 27.1%, I^2 = 0%).

Placebo response rates for nausea were provided by 10 trials, [24, 29, 33, 37, 38, 40, 45, 50] (NCT03285308, NCT03426345) vomiting by six trials,[24, 29, 38, 49](NCT03285308, NCT03426345) abdominal pain by eight trials,[26, 29, 33, 37, 38, 40](NCT03285308, NCT03426345) bloating by eight trials,[24, 29, 33, 37, 38, 40](NCT03285308, NCT03426345) and fullness by 10 trials.[24, 26, 29, 33, 37, 38, 40](NCT03285308, NCT03426345, NCT02210000) Pooled placebo response rates for individual symptoms were broadly similar and are provided in Table 4. There were high levels of heterogeneity in all analyses. The symptom with the lowest pooled placebo response rate was vomiting (30.8%; 95% CI 20.7% to 41.9%) and the highest nausea (35.1%; 95% CI 25.1% to 45.9%).

A subgroup analysis of studies reporting gastric emptying test results at baseline and at trial conclusion in participants receiving placebo were examined to assess the effect of placebo on quantitative measures of gastric emptying. A total of 15 studies reported these data,[26, 29, 32, 34, 35, 37, 38, 40, 42-44, 46, 49, 52] (NCT01262898) but due to differences in reporting a formal meta-analysis was not possible. However, none of the trials reported a significant change in gastric emptying rate among patients receiving placebo.

Adverse Event Rates with Placebo

Total adverse events were provided by 27 studies,[24-31, 35, 37-39, 41-43, 45-47, 50-52](NCT03285308, NCT03426345, NCT02210000, NCT1262898, NCT02025751, NCT02025725) containing 1366 patients. Overall, the pooled adverse event rate with placebo was 33.8% (95% CI 26.4% to 41.8%) (Figure 2b), with high heterogeneity between studies (I^2 = 88.3%). Pooled adverse event rates with placebo according to trial characteristics are provided in Table 5. Heterogeneity was high in almost all analyses. Adverse event rates with placebo were generally higher in RCTs in diabetic patients, trials that did not confirm delayed gastric emptying in all patients, RCTs ≥9 weeks duration, trials with once or twice daily dosing, and RCTs in which randomization to active drug or placebo was >1:1. Again, there was no consistent effect of study year. Withdrawals due to adverse events were

reported by 28 trials.[24-27, 29, 31, 33, 35-39, 42, 44-52](NCT03285308, NCT03426345, NCT02210000, NCT1262898, NCT02025751, NCT02025725) containing 1573 patients. The pooled rate of withdrawal due to adverse events with placebo across all these RCTs was 3.7% (95% CI 2.7% to 4.9%) with borderline low heterogeneity between studies (I^2 = 20.4%).

DISCUSSION

The power of placebo cannot be underestimated as treatment with placebo can both induce symptom relief and provoke adverse effects.[53] As therapeutic gain is used to calculate the number needed to treat, an absolute measure that helps to inform drug development and approval processes, placebo response rates influence the perceived efficacy of therapeutic interventions. Accordingly, response to placebo in RCTs can impact clinicians' willingness to use therapeutic agents to improve patients' quality of life. For example, it has been proposed that many phase III clinical trial failures that result in study termination and drug discontinuation are due to high placebo response rates, with consequent low estimates of therapeutic gain.[54] However, as a variety of procedural and disease-specific factors affect the placebo response, including chosen endpoints, disease etiology, and the number of treatment arms, among others, evaluations of therapeutic gain in trials may underestimate the true efficacy of experimental treatments.[54] As a result, a clear understanding of placebo response and adverse event rates is essential to understand efficacy of both new and developing drugs.

The importance of investigating the placebo response and adverse event rates in gastroparesis trials is highlighted by reports of substantial placebo response rates in other gastrointestinal disorders. Among patients with disorders of gut-brain interaction, including FD and IBS, pooled placebo response rates are highly variable, estimated to range between 6% to 73% in FD and between 3% and 83% in IBS.[12, 14, 55] The power of placebo is further underlined by considerable response rates to placebo even among patients with organic gastrointestinal disorders, such as Crohn's disease and ulcerative colitis.[15, 16] However, despite a high placebo response in all of these gastrointestinal conditions, the finding of substantial variability in response rates, when stratified according to trial protocol and disease characteristics, suggests that careful and strategic trial design is critical to assess the therapeutic benefits of experimental drugs accurately.

This systematic review and meta-analysis of 23 trials, which included a total of 1011 patients, estimated a pooled placebo response rate of almost 30% according to a composite endpoint of

improvement in gastroparesis symptoms. Subgroup analyses revealed several trial characteristics that influenced this, including gastroparesis etiology, use of validated symptom questionnaires, treatment duration, ratio of randomization to active drug or placebo, dosing schedule, and whether delayed gastric emptying was confirmed in trial participants. A placebo run-in period did appear to reduce this, but only three trials used this design and, therefore, firm conclusions cannot be drawn regarding this issue. Other than gastroparesis etiology, in which diabetic gastroparesis demonstrated lower placebo response rates than idiopathic, other factors identified as influencing placebo response rates involved modifiable elements of trial design. Several potential hypotheses exist for why patients with idiopathic gastroparesis may respond differently to placebo than participants with diabetic gastroparesis. As it may be difficult to distinguish gastroparesis from FD, it is plausible that study participants identified as having idiopathic gastroparesis more closely align with patients with disorders of gut-brain interaction, and this may explain the higher placebo response rates reported among these individuals. Furthermore, in patients with fibromyalgia, the duration of exposure to pain symptoms over the course of their disease was negatively associated with placebo response.[56] Similarly, it could be hypothesized that individuals with diabetic gastroparesis experience these "chronification" effects,[56] with associated lower placebo response rates resulting from exposure to chronic symptoms of comorbid conditions. Additionally, differences in manifestations and severity of symptoms among patients with diabetic, versus idiopathic, gastroparesis may also play a role in the differences seen.[57]

Elements associated with lower placebo response rates included the use of gastric emptying studies to confirm delayed emptying in all trial participants, the use of validated questionnaires to assess symptom response, a treatment duration ≥9 weeks, a dosing schedule of once or twice daily, compared with three or four times daily, a randomization ratio for active drug versus placebo of less than 3:1, and a placebo run-in period. Although confirmation of delayed gastric emptying prior to study participant inclusion serves to minimize confounding in trial results, Food and Drug

Administration guidance for the evaluation of drugs for the treatment of gastroparesis no longer recommend the use of gastric emptying as a primary endpoint.[58] However, this guidance did support the identification of trial populations with a clinical diagnosis of gastroparesis based on symptoms, exclusion of other etiologies, and the presence of delayed gastric emptying. In addition, although patient-reported assessments of signs and symptoms are considered adequate outcome measures, this meta-analysis suggests that the use of validated tools to confirm a diagnosis of gastroparesis prior to trial participation remains important, especially given the overlap of gastroparesis with FD.[6] Findings related to dosing schedules and randomization ratios for placebo are supported by similar findings from studies investigating the placebo response in patients with other gastrointestinal disorders.[59-61] Accordingly, previous studies have demonstrated that more frequent dosing, as well as trials with greater active treatment to placebo ratios, may enhance the placebo effect as patients have a greater expectancy of receiving the experimental drug and at a sufficient dose. Furthermore, as patient and clinician optimism regarding the likelihood of experiencing persistent benefit from a new treatment may wane with time, longer trials frequently confer lower placebo response rates.[62]

This systematic review and meta-analysis also investigated adverse event rates with placebo, another important consideration when assessing experimental interventions in RCTs. Inclusion of 27 studies involving a total of 1366 patients revealed a pooled adverse event rate with placebo of 33.8%. Although no other study has examined adverse events with placebo in patients with gastroparesis systematically, to our knowledge, this rate is similar to pooled adverse event rates with placebo in patients with IBS.[7] Subgroup analyses revealed higher pooled adverse event rates with placebo among patients with diabetic, compared with mixed or idiopathic, gastroparesis and in studies that did not confirm delayed gastric emptying at inclusion. Although speculative, it is plausible that patients with complex illnesses, including diabetes, experience a variety of symptoms that are easily misinterpreted as side effects of treatment with a new medication. Adverse event rates were also higher among patients participating in RCTs with treatment duration ≥9 weeks, with placebo dosing

once or twice per day, and with randomization ratios for active drug versus placebo of greater than 1:1.

There are several limitations of this study. First, moderate to high levels of heterogeneity existed among pooled trial data throughout most of our analyses, which challenges the strength of pooled placebo response and adverse event rates. Second, inconsistencies in reporting of trial design and outcomes reduced the number of trials that could be included in several subgroup analyses, most notably of patients with idiopathic gastroparesis and of studies that only used presence of typical symptoms as inclusion criteria, with only five studies and one study, respectively. Additionally, this meta-analysis did not evaluate other interventions used for the management of gastroparesis, including botulinum toxin or endoscopic myotomy. Despite these limitations, this study also has several strengths. Notably, this is the first meta-analysis, to our knowledge, of placebo response and adverse event rates in RCTs for gastroparesis despite similar studies having been conducted in a variety of other gastrointestinal disorders. Furthermore, the search strategy utilized in this systematic review and meta-analysis was comprehensive, including both published studies and unpublished clinical trial data. Conservative estimates were also used to prevent overestimation of placebo response and adverse event rates.

In summary, our study demonstrates that clinical response and adverse event rates with placebo in gastroparesis trials are substantial. This information is critical to future clinical trial design as a high placebo response can negate a potentially positive therapeutic response to a drug. Moving forward, several aspects of trial design should be optimized to minimize the effects of placebo in trials. To improve future drug development endeavors for gastroparesis, RCTs should utilize a study duration longer than 8 weeks, separate diabetic from mixed or idiopathic gastroparesis, confirm delayed gastric emptying objectively prior to trial inclusion, and utilize validated questionnaires to assess symptoms throughout the course of clinical trials.

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TABLES

Table 1. Eligibility Criteria.

Randomized controlled trials.
Adults (≥18 years) with gastroparesis of any etiology.
Compared any active drug with placebo.
Minimum duration of therapy of 1 week.
Dichotomous assessment of response to therapy in terms of effect on composite gastroparesis symptom scores, individual symptom scores, or adverse events, or withdrawals due to adverse events, or continuous data in the form of effect on composite gastroparesis symptom scores or individual symptom scores.*

*Preferably patient-reported, but if this was not available then as assessed by a physician or questionnaire data.

Table 2. Characteristics of Randomized Placebo-controlled Trials in Gastroparesis.

Study	Country and Etiology of Gastroparesis	Criteria Used to Define Gastroparesis	Endpoint(s) Provided	Total Number of Patients (% female)	Number of Patients Assigned to Placebo, Dosing Schedule, and Duration of Treatment	Active Drug (Randomization Ratio to Placebo)
Perkel 1980 [25]	USA, mixed	All patients had abnormal radiologic Barium study	Composite endpoint, adverse events, withdrawal due to adverse events	47 (80)	23 patients received placebo q.i.d.* for 3 weeks	Metoclopramide (1:1)
McCallum 1983 [24]	USA, diabetic	All patients had abnormal radioisotope-labeled test meal or radiologic Barium study	Nausea, vomiting, bloating, fullness, adverse events, withdrawal due to adverse events	44 (64)	24 patients received placebo q.i.d. for 3 weeks	Metoclopramide (1:1)
Bavestrello 1985 [52]	Chile, idiopathic	All patients had abnormal radiologic Barium study	Composite endpoint, adverse events, withdrawal due to adverse events	94 (not reported)	48 patients received placebo t.i.d.† for 12 weeks	Clebopride (1:1)

Corinaldesi 1987 [26]	Italy, idiopathic	All patients had abnormal gastric emptying study	Composite endpoint, abdominal pain, fullness, adverse events, withdrawal due to adverse events	12 (58)	6 patients received placebo t.i.d. for 2 weeks	Cisapride (1:1)
Horowitz 1987 [27]	Australia, diabetic	All patients had abnormal gastric emptying study	Composite endpoint, adverse events, withdrawal due to adverse events	20 (60)	10 patients received placebo q.i.d. for 4 weeks	Cisapride (1:1)
Davis 1988 [28]	USA, idiopathic	All patients had abnormal gastric emptying study	Composite endpoint, adverse events	16 (94)	7 patients received placebo q.i.d. for 6 weeks	Domperidone (1:1)
Jian 1989 [51]	France, idiopathic	All patients had typical symptoms, 46% had abnormal gastric emptying study	Composite endpoint, adverse events, withdrawal due to adverse events	28 (64)	13 patients received placebo t.i.d. for 6 weeks	Cisapride (1:1)
Richards 1993 [29]	USA, mixed	All patients had abnormal gastric emptying study	Composite endpoint, nausea, vomiting, abdominal pain, bloating, fullness, adverse events, withdrawal due to adverse events	39 (95)	20 patients received placebo t.i.d. for 6 weeks	Cisapride (1:1)

Melga 1997 [30]	Italy, diabetic	All patients had abnormal gastric emptying study	Adverse events	40 (57.5)	20 patients received placebo t.i.d. for 26 weeks	Levosulpiride (1:1)
Silvers 1998 [31]	USA, diabetic	All patients had typical symptoms, 46% had abnormal gastric emptying study	Composite endpoint, adverse events, withdrawal due to adverse events	208 (68)	103 patients received placebo q.i.d. for 4 weeks	Domperidone (1:1)
Jones 2000 [32]	Australia, diabetic	All patients had abnormal gastric emptying study	Composite endpoint	31 (76)	16 patients received placebo t.i.d. for 2 weeks	Fedotozine (1:1)
Talley 2001 [33]	USA and Canada, diabetic	All patients had typical symptoms, 29% had abnormal C^{13} octanoic acid breath test	Composite endpoint, nausea, abdominal pain, bloating, fullness, withdrawal due to adverse events	269 (66)	48 patients received placebo b.i.d.± for 4 weeks	ABT-229 (4:1)
Braden 2002 [34]	Germany, diabetic	All patients had abnormal C^{13} octanoic acid breath test	Composite endpoint	19 (74)	10 patients received placebo t.i.d. for 52 weeks	Cisapride (1:1)

McCallum 2007a [35]	USA and Canada, mixed	All patients had abnormal gastric emptying study	Adverse events, withdrawal due to adverse events	106 (76)	22 patients received placebo b.i.d. for 4 weeks	Mitemcinal (2:1)
McCallum 2007b [36]	USA, diabetic	All patients had typical symptoms, 49% had abnormal gastric emptying study	Composite endpoint, withdrawal due to adverse events	392 (64.5)	131 patients received placebo b.i.d. for 12 weeks	Mitemcinal (2:1)
Ejskjaer 2013 [38]	Multinational, diabetic	All patients had abnormal breath test	Composite endpoint, nausea, vomiting, abdominal pain, bloating, fullness, adverse events, withdrawal due to adverse events	92 (65)	26 patients received placebo o.d.‡ for 4 weeks	TZP-102 (3:1)
McCallum 2013a [37]	Multinational, diabetic	All patients had abnormal C^{13} spirulina breath test	Composite endpoint, nausea, abdominal pain, bloating, fullness, adverse events, withdrawal due to adverse events	201 (72)	66 patients received placebo o.d. for 12 weeks	TZP-102 (2:1)

McCallum 2013b [37]	USA and Poland, diabetic	All patients had prior abnormal gastric emptying documented or had abnormal C^{13} spirulina breath test at study entry	Composite endpoint	87 (77)	43 patients received placebo t.i.d. for 4 weeks	TZP-102 (1:1)
Parkman 2013 [48]	USA, idiopathic	All patients had abnormal gastric emptying study	Composite endpoint, withdrawal due to adverse events	130 (89)	65 patients received placebo o.d. for 12 weeks	Nortriptyline (1:1)
Parkman 2015 [39]	USA, diabetic	All patients had typical symptoms	Composite endpoint, adverse events, withdrawal due to adverse events	285 (71)	95 patients received placebo q.i.d. for 4 weeks	Metoclopramide (2:1)
Bharucha 2016 [40]	USA, diabetic	All patients had abnormal gastric emptying study	Composite endpoint, nausea, abdominal pain, bloating, fullness,	20 (90)	9 patients received placebo weekly for 8 weeks	Hemin (1:1)
Lembo 2016 [42]	USA, diabetic	All patients had abnormal C^{13} spirulina breath test	Adverse events, withdrawal due to adverse events	204 (67)	69 patients received placebo b.i.d. for 4 weeks	Relamorelin (2:1)

Tack 2016 [43]	Multinational, mixed	All patients had typical symptoms, 40% had abnormal C^{13} octanoic acid breath test	Composite endpoint, adverse events	92 (60)	24 patients received placebo t.i.d. for 4 weeks	Revexepride (3:1)
Camilleri 2017 [49] **and Camilleri 2020** [41]	Multinational, diabetic	All patients had abnormal C^{13} spirulina breath test	Composite endpoint, vomiting, adverse events, withdrawal due to adverse events	393 (62)	104 patients received placebo b.i.d. for 12 weeks	Relamorelin (3:1)
Pasricha 2018 [50]	USA, mixed	All patients had typical symptoms, 57% had abnormal gastric emptying study	Composite endpoint, nausea, adverse events, withdrawal due to adverse events	126 (80)	63 patients received placebo o.d. for 4 weeks	Aprepitant (1:1)
Abell 2021 [47]	USA, diabetic	All patients had prior abnormal gastric emptying documented or had this confirmed at study entry	Adverse events, withdrawal due to adverse events	21 (100)	11 patients received placebo b.i.d. for 4 weeks	Sepiapterin (1:1)
Andrews 2021 [44]	Canada, mixed	All patients had abnormal gastric emptying study	Composite endpoint, withdrawal due to adverse events	15 (60)	6 patients received placebo o.d. for 4 weeks	Prucalopride (1:1)

Carlin 2021 [45]	USA, mixed	All patients had prior abnormal gastric emptying documented or had abnormal breath test at study entry	Composite endpoint, nausea, adverse events, withdrawal due to adverse events	152 (90)	75 patients received placebo b.i.d. for 4 weeks	Tradipitant (1:1)
Kuo 2021 [46]	USA, mixed	All patients had prior abnormal gastric emptying documented	Adverse events, withdrawal due to adverse events	51 (78)	12 patients received placebo b.i.d. for 1 week	Trazpiroben (3:1)
NCT03285308	Multinational, diabetic	All patients had abnormal breath test	Nausea, vomiting, abdominal pain, bloating, fullness, adverse events, withdrawal due to adverse events	336 (66)	165 patients received placebo b.i.d. for 12 weeks	Relamorelin (1:1)
NCT03426345	Multinational, diabetic	All patients had abnormal breath test	Nausea, vomiting, abdominal pain, bloating, fullness, adverse events, withdrawal due to adverse events	311 (73)	155 patients received placebo b.i.d. for 12 weeks	Relamorelin (1:1)
NCT02210000	USA, diabetic	All patients had abnormal C^{13} breath test	Fullness, adverse events, withdrawal due to adverse events	114 (32)	57 patients received placebo o.d. for 12 weeks	Camicinal (1:1)

NCT01262898	Multinational, diabetic	All patients had abnormal C^{13} breath test	Adverse events, withdrawal due to adverse events	79 (59.5)	21 patients received placebo o.d. for 4 weeks	Camicinal (3:1)
NCT02025751	USA, diabetic	All patients had prior abnormal gastric emptying documented	Adverse events, withdrawal due to adverse events	53 (0)	27 patients received placebo q.i.d. for 4 weeks	Metoclopramide (1:1)
NCT02025725	USA, diabetic	All patients had prior abnormal gastric emptying documented	Adverse events, withdrawal due to adverse events	205 (100)	103 patients received placebo q.i.d. for 4 weeks	Metoclopramide (1:1)

*Four times daily.

†Three times daily.

±Twice daily.

‡Once daily.

Table 3. Pooled Placebo Response Rates for Composite Endpoint for Improvement in Gastroparesis Symptoms.

	Number of trials	Number of patients receiving placebo	Pooled placebo response rate (%)	95% CI	I^2 (%)	P value for χ^2*
All studies	23	1011	29.3	23.7 – 35.2	72.0	<0.001
Gastroparesis etiology						
Diabetic	12	661	28.1	20.8 – 36.0	75.9	<0.001
Mixed	6	211	31.6	18.8 – 46.1	75.7	0.001
Idiopathic	5	139	34.2	19.2 – 51.1	68.0	0.014
Criteria used to define gastroparesis						
Gastric emptying studies/breath testing	17	547	23.6	19.1 – 28.5	32.1	0.10
Typical symptoms or gastric emptying studies/breath testing	5	369	42.2	26.9 – 58.3	89.2	<0.001
Typical symptoms only	1	95	34.7	25.3 – 45.2	N/A	N/A
Criteria used to define symptomatic response						
Validated questionnaire (e.g., GCSI)	11	576	27.4	20.7 – 34.6	69.1	0.004
Non-validated questionnaire/adequate relief/improvement in symptoms	12	435	31.2	21.8 – 41.4	75.2	<0.001

Year of the study						
1980-1989	6	107	31.8	18.6 – 46.7	54.6	0.051
1990-1999	2	123	25.7	4.2 – 57.1	86.8	0.0059
2000-2009	4	205	32.5	12.9 – 56.1	87.9	<0.001
2010-2019	9	495	27.9	20.1 – 36.4	74.0	<0.001
2020 onwards	2	81	22.7	14.4 – 32.4	0	0.45
Treatment duration						
1 – 4 weeks	13	538	32.6	24.2 – 41.7	76.0	<0.001
5 – 8 weeks	4	49	29.4	7.4 – 58.3	77.1	0.0045
≥9 weeks	6	424	23.2	19.3 – 27.3	0	0.66
Dosing schedule of the placebo†						
o.d.±	5	226	25.1	16.8 – 34.5	53.8	0.07
b.i.d.‡	4	358	29.8	16.4 – 45.3	89.2	<0.001
t.i.d.⁑	8	180	31.8	17.8 – 47.7	78.2	<0.001
q.i.d.⁋	5	238	35.5	29.6 – 41.7	0	0.54
Randomization ratio for active drug versus placebo						
1:1	16	517	26.9	21.4 – 32.9	46.3	0.0022
2:1	3	292	28.7	19.8 – 38.4	68.3	0.043
≥3:1	4	202	37.4	13.9 – 64.7	92.8	<0.001

*χ^2 for inconsistency between study results

†One trial administered weekly dosing

±Once daily.

‡Twice daily.

⁑Three times daily.

⁋Four times daily.

Table 4. Pooled Placebo Response Rates for Improvement in Individual Gastroparesis Symptoms.

	Number of trials	Number of patients receiving placebo	Pooled placebo response rate (%)	95% CI	I^2 (%)	P value for χ^2*
Nausea	10	647	35.1	25.1 – 45.9	85.8	<0.001
Vomiting	6	482	30.8	20.7 – 41.9	80.4	<0.001
Abdominal pain	8	494	34.8	24.1 – 46.5	81.2	<0.001
Bloating	8	511	31.5	20.7 – 43.4	84.6	<0.001
Fullness	10	574	32.9	21.4 – 45.5	87.8	<0.001

*χ^2 for inconsistency between study results

Table 5. Pooled Adverse Event Rates with Placebo in Gastroparesis.

	Number of trials	Number of patients receiving placebo	Pooled adverse event rate (%)	95% CI	I^2 (%)	P value for χ^2*
All studies	27	1366	33.9	26.4 – 41.8	88.3	<0.001
Gastroparesis etiology						
Diabetic	16	1050	43.4	35.3 – 51.7	85.0	<0.001
Mixed	7	242	21.7	10.4 – 35.7	81.2	<0.001
Idiopathic	4	74	17.9	7.6 – 31.4	32.4	0.22
Criteria used to define gastroparesis						
Gastric emptying studies/breath testing	21	1002	30.5	22.4 – 39.2	86.9	<0.001
Typical symptoms or gastric emptying studies/breath testing	5	269	42.8	22.2 – 64.9	91.9	<0.001
Typical symptoms only	1	95	55.8	45.2 – 66.0	N/A	N/A

Year of the study						
1980-1989	7	134	13.0	6.4 – 21.5	37.2	0.14
1990-1999	3	143	18.0	1.5 – 70.7	96.8	<0.001
2000-2009	1	22	54.5	32.2 – 75.6	N/A	N/A
2010-2019	11	654	46.9	36.8 – 57.2	85.3	<0.001
2020 onwards	5	413	38.4	29.1 – 48.1	66.6	0.018
Treatment duration						
1 – 4 weeks	17	717	33.7	24.0 – 44.1	87.0	<0.001
5 – 8 weeks	3	40	16.6	4.3 – 48.8	79.8	0.0071
≥9 weeks	7	609	40.7	27.8 – 54.3	90.8	<0.001
Dosing schedule of the placebo						
o.d.†	4	166	52.5	24.5 – 79.6	92.8	<0.001
b.i.d.±	8	608	42.1	35.9 – 48.4	51.6	0.044
t.i.d.‡	7	197	19.4	3.8 – 43.1	92.0	<0.001
q.i.d.⁑	8	395	28.3	14.2 – 45.1	90.7	<0.001
Randomization ratio for active drug versus placebo						
1:1	19	993	26.7	17.9 – 36.7	90.4	<0.001
2:1	3	186	50.9	42.7 – 59.2	20.1	0.29
≥3:1	5	187	50.5	36.3 – 64.7	67.9	0.014

*χ^2 for inconsistency between study results

†Once daily.

±Twice daily.

‡Three times daily.

⁑Four times daily.

FIGURES

Figure 1. Flow Diagram of Assessment of Studies Identified in the Systematic Review.

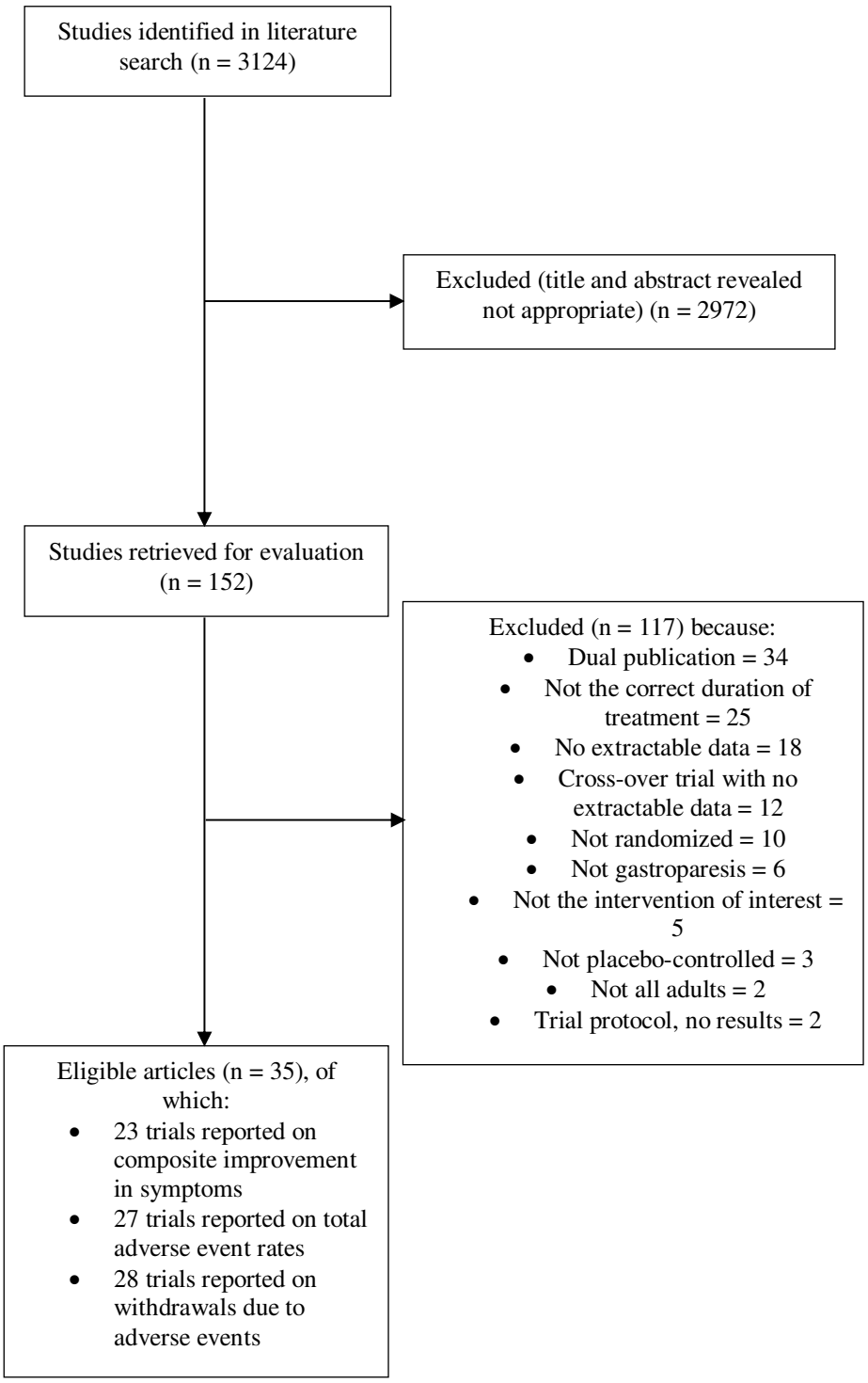

Figure 2a. Forest Plot of Pooled Placebo Response Rates for Composite Endpoint for Improvement in Gastroparesis Symptoms in All Included Studies.

Figure 2b. Forest Plot of Pooled Adverse Event Rates with Placebo in Gastroparesis in All Included Studies.