Efficacy and Safety of Drugs for Gastroparesis: Systematic Review and Network Meta-analysis

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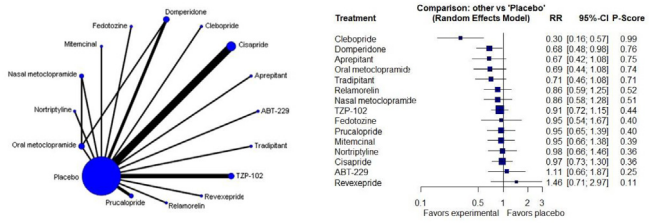
This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e20. Learning Objective: Upon completion of this CME activity, successful learners will be able to understand the relative efficacy and safety of drugs in treating the symptoms of gastroparesis.

Efficacy and Safety of Drugs for Gastroparesis: Systematic Review and Network Meta-analysis.



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In terms of drug classes, only dopamine antagonists and tachykinin-1 antagonists were superior to placebo.

Gastroenterology

See editorial on page 522.

BACKGROUND & AIMS: Although there have been multiple drugs tested in gastroparesis, their relative efficacy and safety are unknown. We evaluated this in a network meta-analysis of randomized controlled trials (RCTs). **METHODS:** We searched the literature to September 7, 2022. We judged the efficacy of drugs based on global symptoms of gastroparesis; individual symptoms, including nausea, vomiting, abdominal pain, bloating, or fullness; and safety according to total adverse events and adverse events leading to withdrawal. We extracted data as intention-to-treat analyses, assuming dropouts to be treatment failures and reporting pooled relative risks (RRs) of not improving with 95% confidence intervals (CIs), ranking drugs according to P-score. **RESULTS:** We identified 29 RCTs (3772 patients). Based on global symptoms, clebopride ranked first for efficacy (RR, 0.30; 95% CI, 0.16–0.57; P-score = .99) followed by domperidone (RR, 0.68; 95% CI, 0.48–0.98; P-score = .76). No other drug was superior to placebo. Only 2 drug classes were efficacious: in rank order, oral dopamine antagonists (RR, 0.58; 95% CI, 0.44–0.77; P-score = .96) and tachykinin-1 antagonists (RR, 0.69; 95% CI, 0.52–0.93; P-score = .83). For individual symptoms, oral metoclopramide ranked first for nausea (RR 0.46; 95% CI, 0.21–1.00; P-score = .95), fullness (RR 0.67; 95% CI, 0.35–1.28; P-score = .86), and bloating (RR 0.53; 95% CI, 0.30–0.93; P-score = .97), based on only 1 small trial. Only prucalopride was more likely to be associated with adverse events than placebo. **CONCLUSIONS:** In a network meta-analysis, oral dopamine antagonists and tachykinin-1 antagonists were more efficacious than placebo for gastroparesis, but confidence in the evidence was low to moderate for most comparisons. There is an unmet need for efficacious therapies for gastroparesis.

Keywords: Gastroparesis; RCT Comparison; Efficacy; Drugs; Safety.

*Authors share co-senior authorship.

Abbreviations used in this paper: **CI, confidence interval; FDA, Food and Drug Administration; GCSI, gastroparesis cardinal symptom index; RCT, randomized controlled trial; RR, relative risk; SD, standard deviation.**

Most current article

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Gastroparesis is a chronic upper gastrointestinal disorder that impacts greatly on quality of life of patients and which is associated with substantial healthcare costs. Treatment of the condition is difficult.

NEW FINDINGS

In a network meta-analysis, versus placebo, clebopride ranked first for efficacy and domperidone second. No other drugs were efficacious. In terms of drug class, oral dopamine antagonists and tachykinin-1 antagonists were superior to placebo.

LIMITATIONS

Few trials were low risk of bias and not all trials confirmed delayed gastric emptying in all participants, so patients with other disorders, such as functional dyspepsia, may have been recruited.

IMPACT

There is a paucity of efficacious drugs for the treatment of gastroparesis. This should be a cause for concern among patients, physicians, pharmaceutical companies, and regulatory agencies.

Gastroparesis is a disorder of upper gastrointestinal motility characterized by delayed gastric emptying of solids associated with symptoms that typically include nausea, vomiting, upper abdominal pain, early satiety or fullness, or bloating, in the absence of any mechanical obstruction of the stomach or duodenum.[1] In patients with such symptoms, delayed gastric emptying can be confirmed by scintigraphy or by stable isotope breath tests, such as the ^{13}C-spirulina breath test.[2] Unfortunately, the symptoms of gastroparesis are not specific and may overlap with other structural or functional disorders, including functional dyspepsia,[3] which can make the diagnosis challenging.[4]

The etiology of gastroparesis is heterogeneous, but there are 3 well-recognized subtypes: diabetic, iatrogenic, occurring due to either upper gastrointestinal surgery or medications, and idiopathic gastroparesis. A population-based study in the United States reported that the most common etiology was diabetic, occurring in almost 60% of patients, and mainly in those with type 2 diabetes, followed by postsurgical in 15%, and idiopathic or drug-induced, each occurring in approximately 10% of patients.[5] However, there is considerable uncertainty around prevalence and incidence estimates from such epidemiological studies. This is because access to gastric emptying tests is limited at the population level, so most studies use inpatient, emergency department, or disease-specific databases to confirm a diagnosis.[6] In a global symptom survey conducted by the Rome Foundation, the prevalence of symptoms compatible with gastroparesis worldwide was 0.9% in all participants, and 1.3% in diabetic individuals.[7] A recent systematic review that included 13 studies,[8] all but 1 of which were conducted in the United States,[9] estimated that the prevalence of gastroparesis, defined by the coexistence of symptoms with evidence of delayed gastric emptying, ranged from 13.8 to 267.7 per 100,000 adults, and incidence from 1.9 to 6.3 per 100,000 person-years. In this study, rates of hospitalization and emergency department attendance appeared to have increased over the past 20 years, and mortality rates were higher than among the general population.[8]

Gastroparesis is, therefore, associated with substantial health care costs.[10,11] Moreover, the condition also negatively affects work productivity and quality of life of patients.[10,12,13] This is reflected by the fact that patients would be willing to accept a median 13.4% risk of sudden death from a hypothetical medication in return for cure of their symptoms.[14] Despite this considerable burden, metoclopramide is the only drug approved by the Food and Drug Administration (FDA) for the treatment of gastroparesis, but any prescription is only recommended for a maximum period of 12 weeks and for people younger than 65.[2] This is because of the potential risk of extrapyramidal side effects, although population-based data suggest this risk is low.[15] The lack of other recommended treatments, and the failure to secure approval and marketing for new drugs for gastroparesis, has led to the off-label use of a variety of other drugs, such as macrolide antibiotics and acetylcholinesterase inhibitors.

Given there is a substantial unmet need for patients with gastroparesis, detailed understanding of the efficacy of available drugs is important, to improve outcomes for patients. To our knowledge, there has been no synthesis of the evidence of the efficacy and safety of licensed or unlicensed drugs for gastroparesis. We, therefore, conducted a systematic review and network meta-analysis of randomized controlled trials (RCTs) assessing the efficacy and safety of all drugs tested in patients with gastroparesis, defined according to typical symptoms, with or without evidence of delayed gastric emptying.

Methods

Search Strategy and Study Selection

We searched MEDLINE (1946 to September 7, 2022), EMBASE and EMBASE Classic (1947 to September 7, 2022), and the Cochrane central register of controlled trials. Furthermore, we searched clinicaltrials.gov for unpublished trials or supplementary data for potentially eligible RCTs. We searched conference proceedings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week) between 2001 and 2022 to identify trials published only in abstract form. Finally, we performed a recursive search using the bibliographies of all eligible articles.

We considered RCTs examining the efficacy of any active drug compared with either another drug or placebo in patients 16 years or older with gastroparesis of any etiology (Supplementary Table 1).We excluded trials assessing the efficacy of devices or endoscopic or surgical interventions, and only included crossover trials if efficacy data related to the first phase, before crossover, were available. We defined gastroparesis as the presence of typical symptoms including nausea, vomiting, upper abdominal pain, early satiety or fullness, or bloating, with or without evidence of delayed gastric emptying on radiographic, radionuclide, isotope breath testing, or

wireless motility capsule. We required a minimum treatment duration of 7 days. Furthermore, we only included studies reporting an assessment of response to therapy in terms of improvement in global gastroparesis symptoms and/or individual symptoms of gastroparesis including nausea, vomiting, abdominal pain, bloating, or fullness. We contacted the first and senior authors of studies if additional information or data were required.

Two investigators (Maria Rosa Ingrosso and Alexander C. Ford) conducted independent literature searches. We identified studies on gastroparesis using the terms: *gastroparesis* or *gastric emptying* (both as medical subject headings and free text terms), or *delayed* adj5 *gastric emptying* (as a free text term). We used the set operator AND to combine these 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 headings or free text terms). We applied no language restrictions. Two investigators (Maria Rosa Ingrosso and Alexander C. Ford) evaluated all abstracts independently. We obtained full texts of all potentially eligible papers and evaluated them according to our eligibility criteria, using predesigned forms. We translated foreign language articles, where necessary. We examined both clinicaltrials.gov as well as secondary publications, if multiple papers were associated with one trial, to obtain data for as many endpoints of interest as possible. We resolved disagreements between investigators by discussion.

Outcome Assessment

The primary endpoint was the efficacy of all drugs vs each other, or placebo, in terms of failure to achieve an improvement in global gastroparesis symptoms. This could be via either adequate relief of, or improvement in, global symptoms or using a composite endpoint, such as an improvement in the gastroparesis cardinal symptom index (GCSI). Secondary endpoints included efficacy in terms of failure to improve individual symptoms of gastroparesis, including nausea, vomiting, abdominal pain, bloating, or fullness. Other secondary outcomes assessed, where reported, included number of patients experiencing at least 1 drug-related adverse event as well as the number of study withdrawals due to adverse events.

Data Extraction

Two investigators (Maria Rosa Ingrosso and Alexander C. Ford) extracted data from all eligible studies independently from each other onto a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA) as dichotomous outcomes (global gastroparesis symptoms improved or not improved, individual symptoms of gastroparesis, including nausea, vomiting, etc, improved or not improved). If studies assessed response to therapy according to dichotomous endpoints, for example a 50% improvement in the GCSI score or an improvement of $\geq$2 on a gastroparesis symptom severity rating scale being achieved or not achieved, we extracted these data. Otherwise, if investigators reported mean symptom scores at baseline and mean scores at the end of treatment, along with a standard deviation (SD), we imputed dichotomous responder and nonresponder data, according to the methodology described by Furukawa et al.[16] For example, a 50% improvement in GCSI score is determined from the following formula: number of participants in each treatment arm at final follow-up $\times$ normal SD. The latter corresponds to (50% of the baseline mean GCSI score – follow-up mean GCSI score)/follow-up SD. We resolved any disagreements between the 2 investigators by discussion.

In addition, for all included trials we extracted the following data, where available: country of origin, number of centers, setting (primary, secondary, or tertiary care), proportion of female patients, criteria used to diagnose gastroparesis, etiology of gastroparesis, dose and treatment schedule of active drug and placebo, and duration of treatment. We extracted data in accordance with intention-to-treat principles, assuming all dropouts were treatment failures. However, if the number of patients randomized originally in each treatment arm was unclear, we performed an analysis in all patients with evaluable data. To assess the safety and tolerability of treatments, we analyzed data using the safety population, which included patients receiving at least 1 dose of the study drug, where available.

Quality Assessment and Risk of Bias

We used the Cochrane risk of bias tool to assess this at the study level.[17] Two investigators (Maria Rosa Ingrosso and Alexander C. Ford) performed this independently, resolving any disagreements by discussion. We recorded the method used to generate the randomization schedule and to conceal treatment allocation, as well as whether blinding was implemented for participants, study personnel, and personnel involved in outcomes assessment, whether there was evidence of incomplete outcomes data, and whether there was evidence of selective reporting of outcomes.

Data Synthesis and Statistical Analysis

We performed a network meta-analysis using a frequentist approach to incorporate direct and indirect comparisons, with the statistical package "netmeta" (version 0.9-0, https://cran.rproject.org/web/packages/netmeta/index.html) in R (version 4.0.2). We report this according to the PRISMA extension statement for network meta-analyses.[18] Network meta-analysis results can provide a more accurate effect estimate than pairwise meta-analysis,[19,20] and can be used to rank drugs for a particular outcome and, therefore, inform clinical decisions.[21]

For each analysis, we summarized the structure of the network of drugs by producing a network plot, which is a diagram consisting of nodes, representing drugs, and connections, showing available direct comparisons between pairs of drugs. Node size reflects the number of patients randomized to that drug, whereas connection size depends on number of trials comparing 2 drugs. In addition, we created comparison adjusted funnel plots to examine publication bias or other small study effects, using Stata version 16 (Stata Corp., College Station, TX). This is a scatterplot of effect size vs precision, measured via the inverse of the standard error. Symmetry around the effect estimate line indicates absence of publication bias, or small study effects.[22] We used a random effects model to pool data to give a more conservative estimate of the efficacy of drugs in gastroparesis.[23] We expressed efficacy as a pooled relative risk (RR) of global and/or individual gastroparesis symptoms not improving, with 95% confidence intervals (CIs). This approach is the most

stable, compared with an RR of improvement, or using the odds ratio, for some meta-analyses.[24] We also pooled adverse events data with RRs and 95% CIs. We assessed global statistical heterogeneity using the τ^2 measure from the "netmeta" statistical package. τ^2 is an estimate of between-trial variance, with values of τ^2 of 0.04, 0.16, and 0.36 considered to represent low, moderate, and high levels of heterogeneity, respectively.[25]

One of the aims of a network meta-analysis is to guide clinicians in prescribing the most efficacious therapy. Therefore, we ranked all therapies according to their P-score. P-scores are based solely on point estimates and standard errors from the network estimates and measure the mean extent of certainty that one drug is better than another, averaged over all competing drugs.[26] Higher scores indicate a greater probability of the drug being ranked as best,[26] but the magnitude of the P-score should be considered, as well as the rank. The mean value of the P-score is always 0.5 so if individual drugs cluster around this value they are likely to be similarly efficacious. However, it is also important to take the RR and corresponding 95% CI for each comparison into account when interpreting the results, rather than relying on rankings alone.[27] We conducted subgroup analyses, including only RCTs that confirmed delayed gastric emptying in all patients, according to etiology of gastroparesis (diabetic or idiopathic/mixed populations), and excluding trials that incorporated a prerandomization run-in period, as the latter may underestimate placebo response and inflate response to active therapy.

For our primary endpoint of failure to achieve improvement in global gastroparesis symptoms, we used the Confidence in Network Meta-Analysis (CINeMA) framework to evaluate confidence in the direct and indirect treatment estimates from the network,[28,29] which is endorsed by the Cochrane Collaboration. This includes the Risk of Bias from Missing Evidence in Network Meta-Analysis tool for evaluation of reporting bias.[30]

Results

The search identified 3146 unique citations. Of these, we discarded 2987 based on the title and abstract. We obtained 159 citations for further examination; 130 were ineligible (Supplementary Figure 1), leaving 29 eligible RCTs, containing 3772 patients. Of these, 26 trials were published in full,[31–56] and there were a further 3 RCTs available on clinicaltrials.gov (NCT03285308, NCT03426345, and NCT02210000). Assignment of patients to drug class or placebo, as well as individual drug, is detailed in Supplementary Table 2. Agreement between investigators for study eligibility was excellent (kappa statistic = 0.86). Detailed characteristics of individual RCTs are provided in Supplementary Table 3. Among trials that confirmed delayed gastric emptying among all participants, a variety of thresholds were used to define this. Three RCTs used a placebo run-in period,[33,38,51] and 1 trial only randomized responders to single-blind domperidone.[39] We included these trials in our primary analysis but excluded them in subgroup analyses. Risk of bias of trials is provided in Supplementary Table 4. Only 4 trials were at low risk of bias across all domains.[45,47,53,55] Availability of, and licensed indications for, the drugs studied is provided in Supplementary Table 5.

Effect on Global Gastroparesis Symptoms

Twenty-five RCTs,[31,33–53,55,56] involving 2967 patients, reported data for this endpoint. The network plot is provided in Figure 1*A*. When we pooled data, there was low heterogeneity ($\tau^2 = 0.0329$). The funnel plot did not suggest any evidence of publication bias or other small study effects (Supplementary Figure 2). Clebopride ranked first for efficacy (RR of global gastroparesis symptoms not improving = 0.30; 95% CI, 0.16–0.57; P-score = .99) (Figure 1*B*), meaning that the probability of clebopride being the most efficacious drug was 99%. The second most efficacious drug was domperidone (RR, 0.68; 95% CI, 0.48–0.98; P-score = .76). None of the other drugs were superior to placebo. After direct and indirect comparisons, clebopride was superior to all drugs, except aprepitant (Table 1). Using the CINeMA framework to evaluate confidence in the results of this

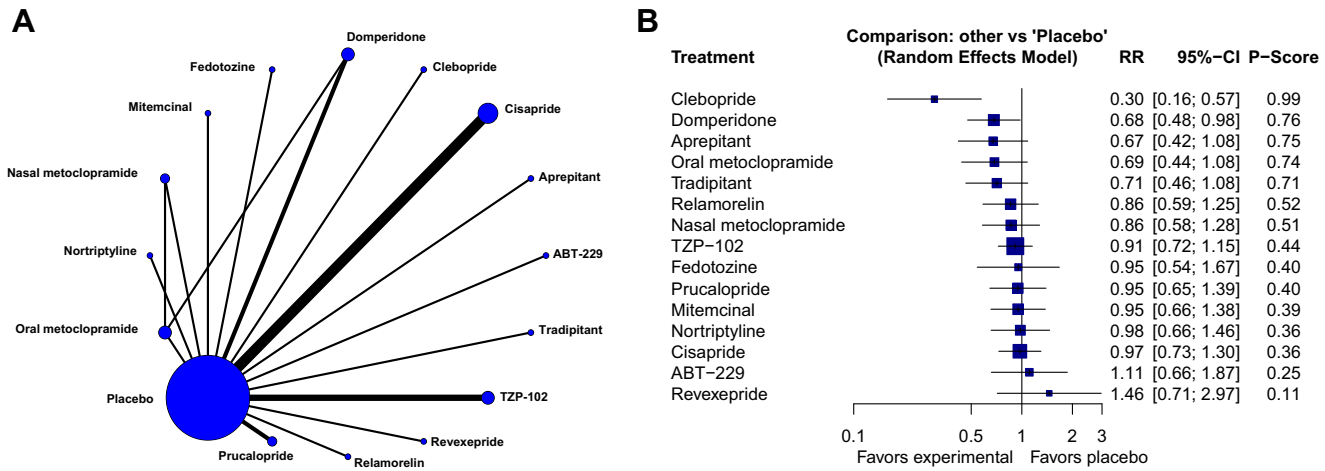

Figure 1. (*A*) Network plot for failure to achieve an improvement in global gastroparesis symptoms: all RCTs. *Circle* (node) size is proportional to the number of study participants assigned to receive each intervention. The *line width* (connection size) corresponds to the number of studies comparing the individual interventions. (*B*) Forest plot for failure to achieve an improvement in global gastroparesis symptoms: all RCTs. The P-score is the probability of each intervention being ranked as best in the network.

Table 1. League Table for Failure to Achieve an Improvement in Global Gastroparesis Symptoms: All RCTs

CLE													**0.30 (0.16–0.57)**			
0.44 (0.21–0.93)	DOM		0.92 (0.58–1.46)										0.72 (0.48–1.08)			
0.45 (0.20–1.00)	1.01 (0.56–1.83)	APR											0.67 (0.42–1.08)			
0.44 (0.20–0.96)	0.99 (0.67–1.47)	0.98 (0.51–1.89)	Oral MET			1.97 (0.38–10.32)							**0.48 (0.23–0.99)**			
0.43 (0.20–0.92)	0.96 (0.55–1.67)	0.95 (0.50–1.80)	0.97 (0.52–1.80)	TRA									0.71 (0.46–1.08)			
0.35 (0.17–0.74)	0.80 (0.47–1.34)	0.79 (0.43–1.44)	0.80 (0.45–1.44)	0.83 (0.47–1.46)	REL								0.86 (0.59–1.25)			
0.35 (0.17–0.74)	0.79 (0.47–1.33)	0.78 (0.42–1.45)	0.80 (0.45–1.42)	0.82 (0.46–1.47)	0.99 (0.58–1.71)	Nasal MET							0.91 (0.61–1.36)			
0.33 (0.17–0.65)	0.75 (0.49–1.14)	0.74 (0.43–1.25)	0.75 (0.45–1.25)	0.78 (0.48–1.26)	0.94 (0.60–1.46)	0.94 (0.60–1.49)	TZP-102						0.91 (0.72–1.15)			
0.32 (0.14–0.74)	0.72 (0.37–1.40)	0.71 (0.34–1.48)	0.72 (0.35–1.48)	0.75 (0.37–1.51)	0.90 (0.46–1.77)	0.91 (0.46–1.80)	0.96 (0.52–1.76)	FED					0.95 (0.54–1.67)			
0.32 (0.15–0.67)	0.72 (0.42–1.22)	0.71 (0.39–1.31)	0.72 (0.40–1.31)	0.75 (0.42–1.33)	0.90 (0.53–1.55)	0.91 (0.53–1.57)	0.96 (0.62–1.51)	1.00 (0.51–1.98)	PRU				0.95 (0.65–1.39)			
0.32 (0.15–0.67)	0.72 (0.43–1.20)	0.71 (0.39–1.30)	0.72 (0.40–1.30)	0.75 (0.42–1.31)	0.90 (0.53–1.53)	0.91 (0.53–1.56)	0.96 (0.62–1.49)	1.00 (0.51–1.97)	1.00 (0.58–1.70)	MIT			0.95 (0.66–1.38)			
0.31 (0.14–0.66)	0.70 (0.41–1.19)	0.69 (0.37–1.28)	0.70 (0.38–1.28)	0.72 (0.40–1.30)	0.87 (0.50–1.52)	0.88 (0.50–1.54)	0.93 (0.59–1.48)	0.97 (0.49–1.94)	0.97 (0.56–1.68)	0.97 (0.56–1.68)	NOR		0.98 (0.66–1.46)			
0.31 (0.15–0.63)	0.70 (0.44–1.11)	0.69 (0.40–1.21)	0.71 (0.41–1.20)	0.73 (0.44–1.22)	0.88 (0.55–1.42)	0.89 (0.54–1.44)	0.94 (0.65–1.36)	0.98 (0.52–1.84)	0.97 (0.60–1.57)	0.98 (0.61–1.56)	1.01 (0.61–1.65)	CIS	0.97 (0.73–1.30)			
0.30 (0.16–0.57)	**0.68 (0.48–0.98)**	0.67 (0.42–1.08)	0.69 (0.44–1.08)	0.71 (0.46–1.08)	0.86 (0.59–1.25)	0.86 (0.58–1.28)	0.91 (0.72–1.15)	0.95 (0.54–1.67)	0.95 (0.65–1.39)	0.95 (0.66–1.38)	0.98 (0.66–1.46)	0.97 (0.73–1.30)	PLA	0.90 (0.54–1.52)	0.69 (0.34–1.40)	
0.27 (0.12–0.62)	0.61 (0.33–1.16)	0.61 (0.30–1.23)	0.62 (0.31–1.23)	0.64 (0.33–1.25)	0.77 (0.41–1.47)	0.78 (0.41–1.49)	0.82 (0.47–1.46)	0.86 (0.40–1.85)	0.86 (0.45–1.63)	0.86 (0.45–1.63)	0.88 (0.46–1.70)	0.88 (0.48–1.59)	0.90 (0.54–1.52)	ABT-229		
0.21 (0.08–0.54)	0.47 (0.21–1.04)	0.46 (0.20–1.09)	0.47 (0.20–1.10)	0.49 (0.21–1.12)	0.59 (0.26–1.32)	0.59 (0.26–1.33)	0.63 (0.30–1.33)	0.65 (0.26–1.62)	0.65 (0.29–1.46)	0.65 (0.29–1.46)	0.67 (0.30–1.52)	0.67 (0.31–1.44)	0.69 (0.34–1.40)	0.76 (0.32–1.84)	REV	

NOTE. RR with 95% CIs in parentheses. Comparisons, column vs row, should be read from left to right, and are ordered relative to their overall efficacy. The intervention in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Direct comparisons are provided above the drug labels, and indirect comparisons are below. Bold values denote a statistically significant difference.
APR, aprepitant; CIS, cisapride; CLE, clebopride; DOM, domperidone; FED, fedotozine; MET, metoclopramide; MIT, mitemcinal; NOR, nortriptyline; PLA, placebo; PRU, prucalopride; REL, relamorelin; REV, revexepride; TRA, tradipitant.

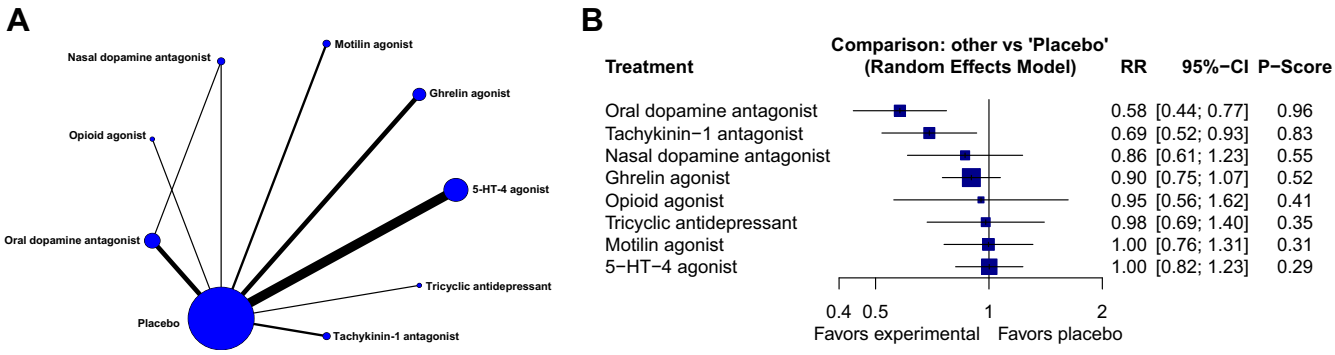

Figure 2. (*A*) Network plot for failure to achieve an improvement in global gastroparesis symptoms: according to drug class. *Circle* (node) size is proportional to the number of study participants assigned to receive each intervention. The *line width* (connection size) corresponds to the number of studies comparing the individual interventions. (*B*) Forest plot for failure to achieve an improvement in global gastroparesis symptoms: according to drug class. The P-score is the probability of each intervention being ranked as best in the network.

endpoint, most direct and indirect comparisons across the network were rated as either low or moderate confidence (Supplementary Table 6).

We excluded the 3 trials with a placebo run-in,[33,38,51] as well as a trial in which only responders to single-blind domperidone were randomized.[39] There were 21 RCTs, recruiting 2233 patients, in this analysis, and domperidone ranked first (RR, 0.48; 95% CI, 0.25–0.90; P-score = .93), with oral metoclopramide second (RR, 0.54; 95% CI, 0.30–0.96; P-score = .87) (Supplementary Figure 3). None of the other drugs were superior to placebo. Heterogeneity between studies was low ($\tau^2 = 0.0331$). After direct and indirect comparison, domperidone was superior to ABT-229 and revexepride, and oral metoclopramide was superior to revexepride (Supplementary Table 7).

Given the fact that most drugs were not efficacious, we performed an analysis according to class of drug to assess whether there were particular drug classes that appeared promising and should be prioritized for future assessment. The network plot is provided in Figure 2*A*. One of these trials compared 2 different oral dopamine antagonists and was excluded from this analysis.[40] Therefore, 24 RCTs, recruiting 2872 patients, were analyzed. When we pooled data, there was low heterogeneity ($\tau^2 = 0.0246$). Oral dopamine antagonists ranked first (RR, 0.58; 95% CI, 0.44–0.77; P-score = .96), followed by tachykinin-1 antagonists (RR, 0.69; 95% CI, 0.52–0.93; P-score = .83) (Figure 2*B*), but none of the other drug classes were superior to placebo. After direct and indirect comparison, oral dopamine antagonists were superior to all drugs, except tachykinin-1 antagonists, nasal dopamine antagonists, and opioid agonists, whereas tachykinin-1 antagonists were only superior to 5-HT_4 agonists (Table 2).

There were 16 trials that confirmed delayed gastric emptying among all participants[31,33–36,38,41,43,45–47,51,53,55,56]; these 16 trials recruited 1381 patients. In this analysis, only clebopride, which ranked first (RR, 0.30; 95% CI, 0.16–0.57; P-score = .95), and metoclopramide, which ranked third (RR, 0.48; 95% 0.23–0.98), were more efficacious than placebo, with low heterogeneity between studies ($\tau^2 = 0.0299$) (Supplementary Figure 4). When only the 13 trials recruiting a total of 785 patients with diabetic gastroparesis were included in the analysis,[35,39–46,48,49,51] none of the active drugs was superior to placebo (Supplementary Figure 5), with low heterogeneity between studies ($\tau^2 = 0.0108$). When the 12 RCTs recruiting patients with idiopathic or mixed etiology gastroparesis were included,[31,33,34,36–38,47,50,52,53,55,56] which contained 785 participants, clebopride ranked first (RR, 0.30; 95% CI, 0.15–0.61; P-score = .93) (Supplementary Figure 6). None of the other active drugs were superior to placebo.

Effect on Individual Symptoms of Gastroparesis

There were too few studies in any of these analyses to assess for evidence of publication bias. Nine RCTs,[32,38,42,45,46,52,56] (NCT03285308 and NCT03426345) containing 1559 patients, provided extractable dichotomous data in terms of failure to improve nausea. When data were pooled, there was no heterogeneity ($\tau^2 = 0$). Oral metoclopramide ranked first for efficacy (RR, 0.46; 95% CI, 0.21–1.00; P-score = .95) (Figure 3), but this was based on 1 small trial and the CI reached 1.0. Tradipitant ranked second (RR, 0.77; 95% CI, 0.65–0.91; P-score = .76) and TZP-102 performed similarly in third place (RR, 0.78; 95% CI, 0.63–0.95; P-score = .74). After direct and indirect comparison, oral metoclopramide was superior to ABT-229, and both tradipitant and TZP-102 were superior to relamorelin, but there were no other significant differences between active drugs (Table 3).

Fullness was assessed in 9 RCTs,[32,34,38,42,45,46] (NCT03285308, NCT03426345, and NCT02210000) recruiting 1410 patients. Although oral metoclopramide ranked first (RR, 0.67; 95% CI, 0.35–1.28; P-score = .86) (Supplementary Figure 7), the CI crossed 1. TZP-102 ranked second (RR, 0.78; 95% CI, 0.65–0.94; P-score = .85) but none of the other drugs were superior to placebo. There was no heterogeneity detected ($\tau^2 = 0$). After direct and indirect comparison, TZP-102 was superior to camicinal, but there were no other significant differences (Supplementary Table 8).

Seven trials, containing 1287 patients, reported data on improvement in bloating[32,38,42,45,46] (NCT03285308 and NCT03426345). In this analysis, oral metoclopramide

Table 2. League Table for Failure to Achieve an Improvement in Global Gastroparesis Symptoms: According to Drug Class

Oral dopamine antagonist		1.97 (0.38–10.22)							**0.56 (0.42–0.75)**
0.84 (0.56–1.25)	Tachykinin-1 antagonist								**0.69 (0.52–0.93)**
0.67 (0.43–1.05)	0.80 (0.51–1.27)	Nasal dopamine antagonist							0.91 (0.63–1.30)
0.65 (0.46–0.90)	0.77 (0.55–1.09)	0.96 (0.65–1.43)	Ghrelin agonist						0.90 (0.75–1.07)
0.61 (0.33–1.11)	0.73 (0.40–1.34)	0.91 (0.48–1.72)	0.94 (0.54–1.65)	Opioid agonist					0.95 (0.56–1.62)
0.59 (0.37–0.94)	0.71 (0.45–1.12)	0.88 (0.53–1.46)	0.92 (0.61–1.37)	0.97 (0.51–1.85)	Tricyclic antidepressant				0.98 (0.69–1.40)
0.58 (0.39–0.86)	0.70 (0.47–1.04)	0.87 (0.56–1.35)	0.90 (0.65–1.25)	0.96 (0.53–1.74)	0.98 (0.63–1.54)	Motilin agonist			1.00 (0.76–1.31)
0.58 (0.41–0.82)	**0.69 (0.49–0.99)**	0.86 (0.57–1.30)	0.90 (0.68–1.18)	0.95 (0.54–1.68)	0.98 (0.65–1.48)	1.00 (0.71–1.40)	5-HT-4 agonist		1.00 (0.82–1.23)
0.58 (0.44–0.77)	**0.69 (0.52–0.93)**	0.86 (0.61–1.23)	0.90 (0.75–1.07)	0.95 (0.56–1.62)	0.98 (0.69–1.40)	1.00 (0.76–1.31)	1.00 (0.82–1.23)	Placebo	

NOTE. RR with 95% CIs in parentheses. Comparisons, column vs row, should be read from left to right, and are ordered relative to their overall efficacy. The intervention in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Direct comparisons are provided above the drug labels, and indirect comparisons are below. Bold values denote a statistically significant difference.

ranked first (RR, 0.53; 95% CI, 0.30–0.93; P-score = .97), although again this was based on 1 small trial and the CIs were wide (Supplementary Figure 8), but none of the other drugs were more efficacious than placebo. No heterogeneity was detected between studies ($\tau^2 = 0$). After direct and indirect comparison, oral metoclopramide was superior to relamorelin and cisapride (Supplementary Table 9).

Seven RCTs[34,38,42,45,46] (NCT03285308 and NCT03426345), containing 1256 patients, assessed efficacy according to improvement in abdominal pain. Six trials[32,38,45,51] (NCT03285308 and NCT03426345), containing 1162 patients, assessed the efficacy of drugs in terms of improvement in vomiting. None of the drugs was more efficacious than placebo in either of these analyses (Supplementary Figures 9 and 10).

Adverse Events

Twenty RCTs[31–39,45,46,49,50,52–54,56] (NCT03285308, NCT03426345, and NCT02210000), recruiting 2639 patients, reported total numbers of adverse events. There was no heterogeneity between studies ($\tau^2 = 0$). Camicinal (RR, 0.77; 95% CI, 0.55–1.08; P-score = .93) and prucalopride (RR, 2.96; 95% CI, 1.24–7.07; P-score = .10) were the least and most likely drug to be associated with adverse events, respectively (Figure 4). Prucalopride, oral metoclopramide, and aprepitant were more likely to be associated with adverse events than placebo. After direct and indirect comparisons, camicinal and TZP-102 were less likely to be associated with adverse events than tradipitant, aprepitant, oral metoclopramide, or prucalopride (Supplementary Table 10). In addition, domperidone was less likely to be associated with adverse events than aprepitant, oral metoclopramide, or prucalopride, and nasal metoclopramide and relamorelin were less likely to be associated with adverse events than prucalopride.

Finally, 23 trials[31–35,37–40,42,44–49,52,54–56] (NCT03285308, NCT03426345, and NCT02210000), including 3501 patients, reported withdrawals because of adverse events. Camicinal was the least likely drug to be associated with withdrawals due to adverse events (RR, 0.20; 95% CI, 0.02–1.92; P-score = .87), and nortriptyline most likely (RR, 3.33; 95% CI, 0.76–14.60; P-score = .16), but there were no significant differences between any individual drug and placebo (Supplementary Figure 11). Heterogeneity between studies was moderate ($\tau^2 = 0.1654$). After direct and indirect comparison, camicinal and ABT-229 were less likely to be associated with withdrawal because of adverse events than nortriptyline, and ABT-229 was less likely to be associated with withdrawals because of adverse events than relamorelin (Supplementary Table 11).

Discussion

We conducted a systematic review and network meta-analysis of drugs used to treat gastroparesis as, to our knowledge, a contemporaneous synthesis of evidence for treatment of the condition is unavailable. We incorporated data from 29 separate RCTs, containing almost 4000 patients. With global gastroparesis symptoms as the endpoint

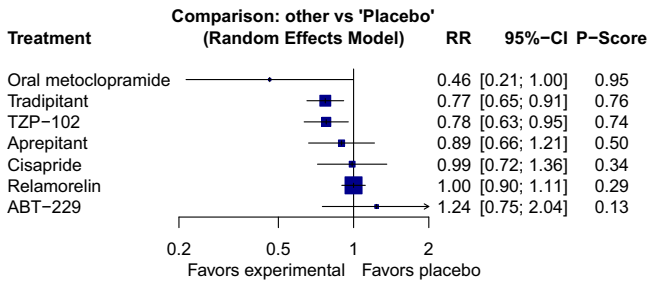

Figure 3. Forest plot for failure to achieve an improvement in nausea. The P-score is the probability of each intervention being ranked as best in the network.

of interest, only clebopride and domperidone were significantly more efficacious than placebo, ranking first and second, respectively. Most comparisons across this network were rated as either low or moderate confidence. Given the lack of efficacy of most individual drugs, we performed an analysis according to drug class. In this drug class analysis, only oral dopamine antagonists and tachykinin-1 antagonists were superior to placebo. We also performed a subgroup analysis including only the 16 RCTs that confirmed delayed gastric emptying in all patients; in this subgroup analysis, only clebopride and oral metoclopramide were more efficacious than placebo. In patients with diabetic gastroparesis, none of the drugs studied were superior to placebo, but clebopride ranked first and was more efficacious than placebo in patients with idiopathic or mixed etiology gastroparesis. When evaluating the effects of drugs on individual symptoms of gastroparesis, oral metoclopramide ranked first for nausea, fullness, and bloating, but this was based on only 1 small trial and the CIs were either wide or not significant. Tradipitant and TZP-102, a ghrelin agonist, were both more efficacious than placebo for nausea, and ranked second and third, respectively, and TZP-102 was superior to placebo and ranked second for fullness. None of the drugs studied were more efficacious than placebo for either vomiting or abdominal pain. Finally, camicinal, a motilin agonist, was the drug that was least likely to be associated with adverse events or withdrawals due to adverse events, whereas prucalopride was significantly more likely to be associated with adverse events than placebo, and nortriptyline the most likely to be associated with withdrawals, although not significantly more so than placebo.

We used rigorous and reproducible methodology for this systematic review and network meta-analysis with the literature search, eligibility judging, and data extraction performed independently by 2 investigators. We also used an intention-to-treat analysis, assuming all dropouts were treatment failures, and a random effects model, in order not to overestimate the efficacy of therapies. We searched clinicaltrials.gov for unpublished RCTs, contacted trial authors to obtain supplementary data, and imputed dichotomous responder data to maximize number of eligible studies. Heterogeneity between studies was low or absent in almost all analyses and there was no evidence of publication bias or other small study effects in our primary analysis.

Table 3. League Table for Failure to Achieve an Improvement in Nausea

Oral MET						0.46 (0.21–1.00)	
0.60 (0.27–1.32)	TRA					**0.77 (0.65–0.91)**	
0.59 (0.27–1.32)	0.99 (0.76–1.29)	TZP-102				**0.78 (0.63–0.95)**	
0.52 (0.23–1.18)	0.86 (0.61–1.22)	0.87 (0.60–1.25)	APR			0.89 (0.66–1.21)	
0.47 (0.20–1.08)	0.78 (0.54–1.12)	0.79 (0.54–1.15)	0.91 (0.58–1.41)	CIS		0.99 (0.72–1.36)	
0.46 (0.21–1.01)	**0.77 (0.63–0.94)**	**0.78 (0.62–0.98)**	0.90 (0.65–1.24)	0.99 (0.70–1.38)	REL	1.00 (0.90–1.11)	
0.46 (0.21–1.00)	**0.77 (0.65–0.91)**	**0.78 (0.63–0.95)**	0.89 (0.66–1.21)	0.99 (0.72–1.36)	1.00 (0.90–1.11)	PLA	0.81 (0.49–1.33)
0.37 (0.15–0.94)	0.62 (0.37–1.06)	0.63 (0.37–1.08)	0.72 (0.40–1.30)	0.80 (0.44–1.44)	0.81 (0.48–1.35)	0.81 (0.49–1.33)	ABT-229

NOTE. RR with 95% CIs in parentheses. Comparisons, column vs row, should be read from left to right, and are ordered relative to their overall efficacy. The intervention in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Direct comparisons are provided above the drug labels, and indirect comparisons are below. Bold values denote a statistically significant difference.
APR, aprepitant; CIS, cisapride; MET, metoclopramide; PLA, placebo; REL, relamorelin; TRA, tradipitant.

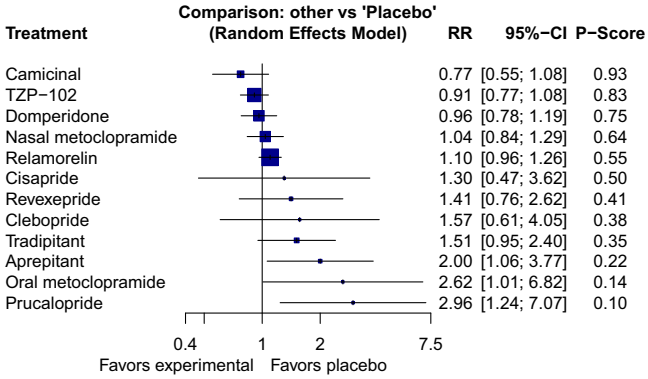

Figure 4. Forest plot for adverse events. The P-score is the probability of each intervention being ranked as best in the network.

One of the core assumptions in any network meta-analysis relates to transitivity, where indirect comparisons between drugs assume that any patient included in the network could, theoretically, have been recruited to any of the trials and assigned to any of the drugs. This assumption can be jeopardized by underlying differences between RCTs. Given the 40-year timespan over which patients were recruited to these trials, there is the potential that a trial conducted in the 1980s may have recruited a less refractory patient population than a trial performed more recently. However, given the limited efficacy of most drugs we studied, we suspect this is unlikely. Nevertheless, there may be other differences relating to design of trials, including criteria for response, method of diagnosis of gastroparesis, and patient population, that affect transitivity, as these differences are not protected by randomization.

We had identified these issues and addressed some of them a priori. Hence, our analysis in only patients with confirmed delayed gastric emptying, which again demonstrated efficacy of dopamine antagonists, and similar conclusions were reached in analyzing only trials recruiting patients with idiopathic or a mixed etiology gastroparesis. It could still be argued that, particularly given the different etiologies of gastroparesis studied, combining the results of these RCTs in a meta-analysis is inappropriate. However, given that when we pooled data according to etiology separately none of the drugs studied were more efficacious than placebo in diabetic gastroparesis, and only clebopride was superior to placebo in idiopathic or mixed etiology gastroparesis, it is only by pooling trials together that any efficacy signals emerge at all. Access to individual patient-level data may allow more detailed analysis according to etiology to be conducted, but given the timespan of studies, this would be challenging.

Despite recently updated guidelines for the management of gastroparesis,[2] the condition remains a challenging one to diagnose and treat. The field has become confused by reports of overlap between gastroparesis and functional dyspepsia,[3] and tests to distinguish between the 2, such as scintigraphy or breath testing, are not available in a primary care setting. Consequently, patients with milder gastroparesis symptoms may be misdiagnosed. The results of our meta-analysis seem to confirm the efficacy of dopamine antagonists for gastroparesis. This is in line with the results of recent RCTs of metoclopramide,[48,49] as well a dynamic cohort study, which demonstrated that domperidone use was associated with improvements in the GCSI, individual symptoms, and quality of life.[57] However, the long-term use of both these drugs has been discouraged in many countries because of their potential side effects. Metoclopramide, both in oral and nasal spray formulations, is the only FDA-recommended drug for gastroparesis, but the risk of central nervous system side effects in some patients, including extrapyramidal effects like tardive dyskinesia, means its use is limited to a maximum period of 12 weeks. The risk of this has been estimated to be in the order of 1% to 10% previously, but a recent literature review reported a much lower risk of 0.1% per 1000 patient years.[15] Domperidone has been the subject of an alert because of an increased risk of QT interval prolongation on the electrocardiogram, but pharmacoepidemiologic data suggest this is rare, with ventricular arrhythmia occurring in 0.02% of patients prescribed the drug.[58] Although our meta-analysis suggests clebopride, another dopamine antagonist, is an efficacious drug for gastroparesis, ranking first for effect on global symptoms, this was in a single RCT recruiting only 94 patients and the drug is not available in many countries, including the United States. In addition, evidence from the Spanish health care system suggests that this drug may be more likely to cause extrapyramidal side effects than metoclopramide.[59]

The tachykinin-1 antagonists aprepitant and tradipitant ranked third and fifth, respectively, for global gastroparesis symptoms, but were no more efficacious than placebo. However, when we studied effect on global symptoms according to drug class, these drugs were more efficacious than placebo and ranked second, suggesting they may be a promising treatment for gastroparesis. A further phase III trial of tradipitant in gastroparesis has been conducted (NCT04028492), but it is yet to be published. However, preliminary reports suggest that the drug was not superior to placebo.[60] Although 5-HT_4 agonists did not appear to be efficacious, trials of another drug in this class, velusetrag, are ongoing, and prucalopride was superior to placebo in a crossover trial included in our meta-analysis.[53] A parallel group trial of the latter drug may, therefore, be warranted, although adverse events, most of which related to diarrhea, were significantly more likely with the drug.

Our findings can be used to make some practical recommendations, which are consistent with advice from regulatory agencies. Metoclopramide should be used at a maximum dosage of 10 mg before each meal and 10 mg at bedtime, either as liquid or tablets, for a duration of only 3 months. The nasal preparation also could be used, although pharmacokinetics are similar to the liquid formula. Domperidone at a dosage of 10 mg 4 times per day could be used under special guidance provided by the FDA, with a precautionary measurement of the QT interval on electrocardiogram before prescription. If this is prolonged greater

than 450 ms, its prescription is precluded. Although not approved for the treatment of gastroparesis, a prescription of aprepitant 80 mg daily for 3 days could be considered to abort a cycle of emesis, where available. In patients with concomitant chronic idiopathic constipation, treatment with prucalopride 1 to 2 mg per day may also benefit symptoms of gastroparesis. Other approaches to managing symptoms could include the use of antiemetic drugs to address nausea and vomiting. However, recent guidelines stress that these have little effect on gastric emptying.[2] Although there is anecdotal evidence of efficacy of granisetron and ondansetron in gastroparesis,[61,62] a search of the literature for RCTs of antiemetic drugs revealed 1 trial of a single injection of haloperidol in the emergency department, with 1 hour of follow-up,[63] and another RCT of ondansetron conducted in patients with functional dyspepsia with impaired gastric accommodation, but not abnormal gastric emptying.[64] Neither of these trials would have been eligible for inclusion according to our eligibility criteria.

Limitations include the fact that only 4 RCTs were low risk of bias across all domains,[45,47,53,55] meaning that efficacy of many of the drugs studied may have been overestimated.[65] Some RCTs used a run-in period, which again may have overestimated response to active drug, although we excluded these trials in a subgroup analysis. Gastric emptying studies were not performed in all trials, which may mean that patients with functional dyspepsia or other disorders of gut-brain interaction were recruited in some RCTs, but an analysis restricted to only those studies that confirmed delayed gastric emptying in all participants yielded similar findings to our primary analysis. On a similar note, even among trials that did confirm delayed gastric emptying, thresholds used were not standardized and, in most cases, investigators did not use the recommended criteria of $>10\%$ retention at 4 hours.[66] Furthermore, a variety of measures were used to assess treatment response, owing to the absence of FDA-recommended endpoints for treatment trials in gastroparesis, and different time points to assess the efficacy of therapies. Finally, although the meta-analysis included data from 3772 patients, the number of trials of each drug was relatively small, and even where individual drugs were more efficacious than placebo, often CIs were wide or approached unity. This was compounded by small total participant numbers for some individual trials, meaning they were probably underpowered to detect any significant benefit of drug over placebo. We attempted to circumvent this by performing an analysis according to drug class to better prioritize future efforts to identify efficacious drugs. Nevertheless, further trials of existing drug classes, or RCTs of novel agents, need to be adequately powered.

In summary, this systematic review and network meta-analysis highlights the paucity of efficacious drugs for the treatment of gastroparesis. Although dopamine antagonists appeared to be superior to placebo, there were few trials of each drug, many were more than 20 years old, and efficacy was modest. Tachykinin-1 antagonists may also be efficacious but, beyond these 2 drug classes, there is a limited pipeline of new therapies. This should be a cause for concern among patients, physicians, pharmaceutical companies, and regulatory agencies. Given the fact that there has been a large expansion in novel therapies for other gastrointestinal conditions, such as inflammatory bowel disease, which are highly profitable for industry, developing new drugs for a condition like gastroparesis may be viewed as a high-risk strategy. Nevertheless, there is a clear unmet need for efficacious therapies for patients with gastroparesis.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org and at https://doi.org/10.1053/j.gastro.2022.12.014.

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