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**TITLE PAGE**

**Title:** Systematic Review and Network Meta-analysis: Efficacy of Drugs for Functional Dyspepsia.

**Running head:** Drugs for Functional Dyspepsia: Network Meta-analysis.

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**Abbreviations:**

| | |
|---|---|
| 5-HT | 5-hydroxytryptamine |
| CI | confidence interval |

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|---|---|
| EPS | epigastric pain syndrome |
| FD | functional dyspepsia |
| GRADE | Grading of Recommendations, Assessment, Development and Evaluation |
| *H. pylori* | *Helicobacter pylori* |
| $H_2RA$ | histamine-$_2$ receptor antagonist |
| PDS | postprandial distress syndrome |
| PPI | proton pump inhibitor |
| RCT | randomised controlled trial |
| SNRI | serotonin norepinephrine reuptake inhibitor |
| SSRI | selective serotonin reuptake inhibitor |
| SUCRA | surface under the cumulative ranking curve |
| TCA | tricyclic antidepressant |
| RR | relative risk |

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**SUMMARY**

**Background:** Functional dyspepsia (FD) is a relapsing and remitting condition affecting between 5% and 10% of people. Efficacious therapies are available, but their relative efficacy is unknown.

**Aim:** We performed a systematic review and network meta-analysis to try to resolve this uncertainty.

**Methods:** We searched the medical literature through July 2020 for randomised controlled trials (RCTs) assessing efficacy of drugs for adults with FD, compared with each other, or placebo. Trials reported a dichotomous assessment of symptom status after completion of therapy. We pooled data using a random effects model. Efficacy was reported as a pooled relative risk (RR) of remaining symptomatic, with a 95% confidence interval (CI) to summarise efficacy of each comparison tested. Relative ranking was assessed with surface under the cumulative ranking curve (SUCRA) probabilities.

**Results:** We identified 71 eligible RCTs (19,243 participants). Tricyclic antidepressants (TCAs) were ranked second for efficacy (RR of remaining symptomatic = 0.71; 95% CI 0.58 to 0.87, SUCRA 0.87), and first when only low risk of bias trials were included. Most RCTs that used TCAs recruited patients who were refractory to other drugs included in the network. Although sulpiride or levosulpiride were ranked first for efficacy (RR = 0.49; 95% CI 0.36-0.69, SUCRA 0.99), trial quality was low, and only 86 patients received active therapy. TCAs were more likely to cause adverse events than placebo.

**Conclusions:** TCAs, histamine-$_2$ receptor antagonists, standard- and low-dose proton pump inhibitors, sulpiride or levosulpiride, itopride, and acotiamide, were all more efficacious than placebo for FD.

## INTRODUCTION

Functional dyspepsia (FD) is a chronic disorder of the gastroduodenum, and is considered a disorder of gut-brain interaction. [1] The condition is diagnosed using the Rome IV criteria, [2] which include epigastric pain or burning, early satiety, and/or postprandial fullness, in the presence of a structurally normal upper gastrointestinal endoscopy. Patients are subgrouped according to symptoms, with those reporting only epigastric pain or burning classed as having epigastric pain syndrome (EPS), those with early satiety or postprandial fullness have postprandial distress syndrome (PDS), and those with both types of symptoms have overlap of EPS and PDS. The rationale for this is to help select therapy although, to date, there is little evidence that these subgroups define a particular group of patients with a different prognosis or different response to treatment.

The condition affects between 5% and 10% of the world's population at any one point in time, [3] and has a relapsing and remitting natural history. This means it is difficult to treat, and therefore FD represents a considerable burden to both individuals and society as a whole. Patients with FD demonstrate increased health care usage, higher prescription medicine costs, low mood and somatoform-type behaviour, reduced quality of life, higher rates of absenteeism, and reduced productivity at work. [4-10] In one study, almost 50% of patients would accept a mean 12.7% risk of death in return for a 99% chance of cure of symptoms from a hypothetical medication. [11] The economic impact of FD in the USA has been estimated to be in excess of $18 billion per year. [12]

In the absence of *Helicobacter pylori* (*H. pylori*) infection, efficacious treatment options for FD include acid suppressing drugs, such as proton pump inhibitors (PPIs) or histamine-$_2$ receptor antagonists ($H_2$RAs), central neuromodulators, including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), or antipsychotics, such as levosulpiride, or prokinetics. The latter include drugs acting on dopamine receptors, including domperidone, mosapride, or itopride, 5-hydroxytryptamine (5-HT) receptor

agonists, such as tegaserod or buspirone, or the acetylcholinesterase inhibitor acotiamide. Central neuromodulators also have peripheral effects on gastrointestinal motility that stem from their agonism or antagonism of receptors with an affinity for various neurotransmitters, including 5-HT, dopamine $D_2$, histamine, and acetylcholine receptors, which is the rationale for their use in functional dyspepsia. For example, the intestinal enterochromaffin cells contain 90% of the body's total stores of 5-HT, [13,14] which is integral to gastrointestinal motility, and antagonism of $D_2$ receptors in the myenteric plexus promotes gastric emptying, pyloric relaxation, and increased lower oesophageal sphincter tone, [15] which may explain the beneficial effects of antipsychotic drugs.

There have been numerous randomised controlled trials (RCTs) of these different drugs versus placebo, and many have demonstrated efficacy in trial-based systematic reviews and meta-analyses. [16-19] However, there have been few head-to-head trials of one drug versus another, so the relative efficacy of available treatment options for FD is unclear. In addition, which treatment option should be preferred in patients with EPS or PDS is uncertain. We conducted a systematic review and network meta-analysis in an attempt to resolve this uncertainty.

## METHODS

This systematic review was performed according to an *a priori* established protocol, published on the PROSPERO international prospective register of systematic reviews (registration number CRD42020182093), and is reported according to the PRISMA extension statement for systematic reviews incorporating network meta-analyses. [20]

### Search Strategy and Study Selection

We searched MEDLINE (1946 to July 2020), EMBASE, EMBASE Classic (1947 to July 2020), and the Cochrane central register of controlled trials to identify potential studies. In order to identify studies published only in abstract form, conference proceedings (Digestive Disease Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week) between 2010 and 2019 were hand-searched. Finally, we performed a recursive search, using the bibliographies of all obtained articles.

Eligible RCTs examined the efficacy of various drugs for FD in adult participants (≥18 years) including the first period of cross-over trials, prior to cross-over to the second treatment (Table 1). Trials had to compare drugs for FD with each other, or with placebo. Duration of therapy had to be ≥2 weeks. The diagnosis of FD could only be made after a normal upper gastrointestinal endoscopy and was based on either a physician's opinion or accepted symptom-based diagnostic criteria. Subjects were required to be followed up for ≥2 weeks, and studies had to report either a global assessment of FD symptom resolution or improvement, resolution or improvement of epigastric pain or discomfort, or resolution or improvement of early satiety or postprandial fullness, after completion of therapy, preferably as reported by the patient, but if this was not recorded then as documented by the investigator or via questionnaire data. Where studies did not report these types of dichotomous data but were otherwise eligible for inclusion in the systematic review, we attempted to contact the

original investigators in order to obtain further information. Ethical approval for this evidence synthesis was not required.

Two investigators (CJB and ACF) conducted the literature search independently from each other. The search strategy used is detailed in the Supplementary Materials. There were no language restrictions. Two investigators (SKV and ACF) evaluated all abstracts identified by the search for eligibility, again independently from each other. We obtained all potentially relevant papers, and evaluated them in more detail, using pre-designed forms, to assess eligibility independently, according to the pre-defined criteria. We translated foreign language papers, where required. We resolved disagreements between investigators by discussion.

**Outcome Assessment**

The primary outcome assessed was the efficacy of all drugs in FD, in terms of global FD symptoms, epigastric pain or discomfort, early satiety, or postprandial fullness not improving, or not resolving, after completion of therapy. Secondary outcomes included adverse events occurring as a result of therapy (total numbers of adverse events, as well as adverse events leading to study withdrawal, if reported).

**Data Extraction**

Two investigators (SKV and ACF) extracted all data independently onto a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA) as dichotomous outcomes (global FD symptoms unimproved or unresolved, epigastric pain or discomfort unimproved or unresolved, early satiety unimproved or unresolved, or postprandial fullness unimproved or unresolved). For all included studies, we also extracted the following data for each trial, where available: country of origin, criteria used to define FD, drug used and dosage prescribed, duration of therapy, and primary outcome measure used to define symptom improvement or

resolution following therapy. For PPIs we classed doses <20mg as low-dose, doses of ≥20mg to ≤30mg as standard-dose, and doses of >30mg as high-dose. Data were extracted as intention-to-treat analyses, with all dropouts assumed to be treatment failures (*i.e.* symptomatic at final point of follow-up), wherever trial reporting allowed this.

**Quality Assessment and Risk of Bias**

Risk of bias assessment was performed at the study level, by two investigators (SKV and ACF) independently, using the Cochrane risk of bias tool. [21] We resolved disagreements by discussion. We recorded the methods used to generate the randomisation schedule and conceal treatment allocation, as well as whether blinding was implemented for participants, personnel, and 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**

For direct comparisons, we performed a standard pairwise meta-analysis using a DerSimonian and Laird random effects model to estimate pooled relative risk (RR) and 95% confidence intervals (CIs), summarising the efficacy of each active and control intervention tested (Supplementary Figures 1a to 1d). [22] If a direct comparison was based on two or more studies, we assessed heterogeneity between trials using the $I^2$ statistics; an $I^2$ estimate ≥50% was interpreted as evidence of substantial levels of heterogeneity. [23] We applied a random-effects network meta-analysis using a consistency model within a frequentist approach to incorporate indirect with direct comparisons. [24] We evaluated network inconsistency using a global inconsistency test by fitting design-by-treatment in the inconsistency model, [25,26] and also using the loop-specific approach by estimating the inconsistency factor, and the corresponding 95% CIs, as the absolute difference between direct and indirect estimates for one of the comparisons in the loop (Supplementary Tables

1a and 1b). [25] We used the node splitting method to explore within-network inconsistency, separating evidence into direct and indirect. [27] We used surface under the cumulative ranking curve (SUCRA), which estimates the probabilities for all treatments to obtain a treatment hierarchy. [28] We reported the relative ranking of interventions on efficacy and safety outcomes as their SUCRA, ranging from 1, indicating that the treatment has a high likelihood of being best, to 0, which indicates the treatment has a high likelihood of being worst. We used a RR of remaining symptomatic at the final point of follow-up; where if the RR is less than 1 and the 95% CI does not cross 1, there is a significant benefit of one intervention over another. We examined for small study effects using a comparison-adjusted funnel plot. [24,28] For statistical analysis and graph generation we used Stata version 15.1 (StataCorp, College Station, TX, USA).

In our primary analysis, we pooled data for the risk of symptoms not improving at the final point of follow-up in each study for all included RCTs using an intention-to-treat analysis. However, we also performed an additional analysis including only trials that reported likelihood of symptoms not resolving. We conducted subgroup analyses according to duration of therapy (<8 weeks versus ≥8 weeks), geographical region (trials conducted in the East versus the West), criteria used to define FD (clinical criteria versus the symptom-based Rome criteria), and FD subtype (EPS versus PDS). In the latter case, there were very few RCTs that recruited only patients with EPS or only patients with PDS. However, many studies mandated only the presence of epigastric pain or burning, or only the presence of early satiety and/or postprandial fullness for trial entry but allowed coexistence of other symptoms. We therefore classified these trials as containing patients with EPS and overlap, or patients with PDS and overlap, respectively. To assess the robustness of our findings, we performed sensitivity analyses including omission of small sized trials (<25th percentiles), [29] trials with inadequate concealment of allocation, and trials with unclear or high risk of bias.

**GRADE Summary of Evidence**

We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, adapted to network meta-analysis, to rate the quality of evidence. [30] In this method, direct evidence from trials rated as high quality can be downgraded based on the risk of bias, indirectness, imprecision, inconsistency (or heterogeneity), and/or publication bias to levels of moderate, low, or very low quality. The lower confidence rating of the two direct comparisons that contribute as first-order loops to the indirect estimate constitutes the confidence rating of the indirect evidence. The rating of the indirect evidence can be downgraded further for imprecision or intransitivity (dissimilarity between studies in terms of clinical or methodological characteristics). If only direct or indirect evidence is available for a given comparison, the network quality rating is based on that estimate. If both direct and indirect evidence is available, we used the higher of the two quality ratings as the rating for the network meta-analysis estimate.

## RESULTS

The search strategy generated 11,425 citations, 83 of which we retrieved for further assessment as they appeared to be relevant (Supplementary Figure 2). Of these, 67 articles were eligible for inclusion, [31-97] which reported on 71 separate RCTs comprising 19,243 participants. Of these, 12,535 received a drug for FD and 6708 a placebo, allocated as described in Supplementary Table 2. Seven trials were published in abstract form only. [42,44,49,66,67,87,94] Agreement between investigators for eligibility of newly identified trials was good (Kappa statistic = 0.79).

Risk of bias items for all included trials are reported in Supplementary Table 3. In total, 20 RCTs, reported in 18 articles, [40,46,47,58,65,68-73,77,80-83,85,96] were judged as low risk of bias across all domains. Detailed characteristics of individual RCTs, including the comparisons made, are provided in Supplementary Table 4. Eleven RCTs compared $H_2$RAs with placebo, [31-41] six trials, reported in five articles, compared acotiamide with placebo, [42-46] five RCTs, reported in four articles, compared itopride with placebo, [47-49,94] six trials compared itopride with domperidone, [50-55] four RCTs, reported in three articles, compared standard-dose and low-dose PPIs both with each other and with placebo, [56-58] four trials compared high-dose PPIs with placebo, [59-62] three RCTs compared standard-dose PPIs with placebo, [63-65] three trials compared low-dose PPIs with placebo, [66-68] three RCTs compared TCAs with placebo, [69,70,96] three trials compared 5-$HT_{1A}$-receptor agonists with placebo, [71-73] three RCTs compared antipsychotic drugs with placebo, [74-76] two trials, reported in one article, compared tegaserod with placebo, [77] two RCTs compared $H_2$RAs and 5-$HT_{1A}$-receptor agonists both with each other and with mosapride, [78,79] one trial compared SSRIs with placebo, [80] one RCT compared SNRIs with placebo, [81] one trial compared TCAs and SSRIs both with each other and with placebo, [82] one RCT compared mirtazapine with placebo, [83] one trial compared mosapride with placebo, [84] one trial compared high-dose, standard-dose, and low-dose PPIs with each other and with placebo, [85] one RCT compared standard-dose and low-dose PPIs, and $H_2$RAs with each other and with placebo, [86] one trial compared standard-dose PPIs with $H_2$RAs, [87] one RCT compared TCAs with high-dose

PPIs, [97] one RCT compared high-dose PPIs with mosapride, [88] one trial compared standard-dose PPIs with mosapride, [89] one RCT compared low-dose PPIs with itopride, [90] one trial compared $H_2$RAs with mosapride, [91] one RCT compared itopride with mosapride, [92] one trial compared mosapride with domperidone, [93] and one RCT compared SSRIs with mirtazapine. [95]

## Efficacy

*Failure to Achieve an Improvement in FD Symptoms*

All 71 RCTs provided dichotomous data for likelihood of symptoms not improving. [31-97] The network plot is provided in Figure 1. Network meta-analysis suggested that, compared with placebo, antipsychotics (sulpiride or levosulpiride) were ranked first (RR of symptoms not improving = 0.49; 95% CI 0.36 to 0.69, SUCRA 0.99) (Figure 2), followed by TCAs (RR = 0.71; 95% CI 0.58 to 0.87, SUCRA 0.87). There was also a statistically significant effect observed for $H_2$RAs (RR = 0.81; 95% CI 0.73 to 0.90, SUCRA 0.72), standard-dose PPIs (RR = 0.84; 95% CI 0.77 to 0.91, SUCRA 0.65) and low-dose PPIs (RR = 0.86; 95% CI 0.79 to 0.94, SUCRA, 0.54), compared with placebo. The results of network meta-analyses were similar to those obtained using standard pairwise meta-analyses (Supplementary Figure 1a). When we assessed comparative efficacy, antipsychotics were superior to all other agents, except TCAs and mirtazapine (Table 2). $H_2$RAs and PPIs (low- and standard-dose) were comparable with each other.

Antipsychotics remained superior to placebo in subgroup analyses based on duration of treatment (<8 weeks), geographical region (trials conducted in both the East and the West, although in the latter instance the 95% CI crossed 1), and when only studies using a clinical diagnosis of FD were included, but not in the analysis based on the trials that only included patients with either EPS or overlap (Supplementary Tables 5 and 6). TCAs were ranked first in studies of ≥8 weeks duration, and in studies that included patients with either EPS or overlap. No drugs were found to be

associated with any improvement in symptoms in subgroup analysis based on trials that only included patients with PDS or overlap. Antipsychotics remained superior to placebo when we performed sensitivity analyses excluding trials with small sample sizes (Supplementary Table 6). Since, all three trials compared antipsychotics with placebo were considered to be at unclear risk of bias, we were not able to include antipsychotics in the sensitivity analysis based on low risk of bias trials; hence, TCAs were ranked first. When including only studies that used the Rome criteria to diagnose FD, there were no data for antipsychotics; acotiamide was ranked first. Overall, the results from sensitivity analyses were robust for the main analysis for $H_2$RAs, standard-dose, and low-dose PPIs.

*Failure to Achieve Resolution of FD Symptoms*

Thirty RCTs, reported in 28 articles, [32,34-37,39,40,46,48,52,54,56-60,64,66,75,78,79,81,85-87,89,90,93] provided dichotomous data for likelihood of symptoms not resolving. The network plot is provided in Figure 3. Network meta-analysis suggested that, compared with placebo, standard-dose PPIs were ranked first (RR of symptoms not resolving = 0.86; 95% CI 0.80 to 0.93, SUCRA 0.81) (Figure 4), followed by antipsychotics (RR = 0.84; 95% CI 0.65 to 1.08, SUCRA 0.78), high-dose PPIs (RR = 0.88; 95% CI 0.77 to 0.99, SUCRA, 0.74), $H_2$RAs (RR = 0.88; 95% CI 0.81 to 0.96, SUCRA, 0.73), and low-dose PPIs (RR = 0.89; 95% CI 0.83 to 0.96, SUCRA, 0.68) (Table 3). TCAs were not included in the analysis because no trials reported this endpoint. The results of network meta-analyses were similar to those obtained using standard pairwise meta-analyses (Supplementary Figure 1b). When we assessed comparative efficacy, different doses of PPIs and $H_2$RAs were superior to 5-$HT_{1A}$-receptor agonists and domperidone (Table 3), but not to any other treatments, or each other.

Standard-dose PPIs remained superior to placebo in subgroup analyses based on the duration of treatment (≥8 weeks), geographical region (trials conducted in the West), and when we included only studies that used either a clinical diagnosis of FD or the Rome criteria to diagnose FD

(Supplementary Tables 7 and 8). However, $H_2$RAs were ranked first, followed by standard-dose PPIs, in a subgroup analysis based on a duration of treatment <8 weeks. Only $H_2$RAs were found to be associated with resolution of dyspepsia symptoms in a subgroup analysis including only trials from the East. In sensitivity analyses, standard-dose PPIs remained superior to placebo when trials with small sample sizes were excluded (Supplementary Table 8).

## Safety

### *Adverse Events*

In terms of total numbers of adverse events, these data were provided by 38 trials, reported in 37 articles. [31,34,37,39-41,43,45-47,50-55,64-66,69,71-76,79,80,82,83,85,86,88-90,92,93] The network plot is provided in Supplementary Figure 3. When comparing total numbers of adverse events, there was a significant difference, compared with placebo, only for TCAs (RR = 1.56; 95% CI 1.07 to 2.26) (Supplementary Figure 4). When ranked, 5-$HT_{1A}$-receptor agonists were best (SUCRA 0.84), and antipsychotics worst (SUCRA 0.13), in terms of total number of adverse events. The results of network meta-analysis were similar to those obtained using standard pairwise meta-analyses (Supplementary Figure 1c). When we assessed comparative safety, TCAs were also more likely to lead to adverse events than $5HT_{1A}$-receptor agonists, acotiamide, and $H_2$RAs (Supplementary Table 9).

### *Adverse Events Leading to Withdrawal*

There were 42 RCTs, reported in 41 separate articles, [31,32,34,36,37,39,43,46,47,51,54,55,57-61,65,69-77,79-84,86,88,90-93,96,97] reporting adverse events leading to withdrawal. The network plot is provided in Supplementary Figure 5. When comparing total numbers of adverse events leading to withdrawal, there was a significant difference, compared with placebo, only for tegaserod (SUCRA 0.25), SSRIs (SUCRA 0.18), and SNRIs (SUCRA 0.05) (Supplementary Figure 6). When we assessed

comparative safety, SNRIs were also more likely to lead to adverse events requiring withdrawal than 5-$HT_{1A}$-receptor agonists, low-, standard-, and high-dose PPIs, itopride, or acotiamide (Supplementary Table 10).

**Network Consistency and Small Study Effects**

For all outcomes, the test of global inconsistency using the 'design-by-treatment' interaction model (Supplementary Table 1a), and inconsistency using the loop-specific approach (Supplementary Table 1b), demonstrated no evidence of inconsistency within any network comparisons. We did not find any evidence of small study effects based on comparison-adjusted funnel plot asymmetry (Supplementary Figures 7a to 7d).

**GRADE Summary of Evidence**

Overall, the quality of evidence based on applying GRADE criteria to findings from the network meta-analysis was generally rated as very low to moderate quality (Supplementary Table 11). We had moderate confidence in estimates supporting the use of TCAs and standard-dose PPIs, compared with placebo, in terms of FD symptoms not improving, and low confidence in estimates supporting the use of antipsychotics, $H_2$RAs, and low-dose PPIs, compared with placebo. The evidence for treatments compared with placebo, in terms of FD symptoms not resolving, was graded as very low to low quality. Adverse events associated with TCAs, compared with placebo, had moderate confidence in estimates based on GRADE criteria, applied only to direct estimates.

## DISCUSSION

This systematic review and network meta-analysis included data from 71 RCTs, containing over 19,000 participants. It has demonstrated that antipsychotics, TCAs, $H_2$RAs, standard- and low-dose PPIs, itopride, and acotiamide, were all more efficacious than placebo, in terms of likelihood of symptoms not improving. In this analysis, antipsychotics were ranked first, and were superior to all other treatments, except TCAs, which were ranked second, and mirtazapine. However, this was based on only three small RCTs, containing 172 patients. In addition, when only low risk of bias trials were included in the analysis, or trials of longer duration, TCAs were ranked first. In terms of resolution of symptoms, fewer trials examined this endpoint, and some drugs were not studied, but high-, standard-, and low-dose PPIs, and $H_2$RAs were all more efficacious than placebo in terms of likelihood of symptoms not resolving. Standard-dose PPIs were ranked first, with antipsychotics second, although the 95% CIs versus placebo crossed 1, and high-dose PPIs were third. Antipsychotics were ranked first when only low risk of bias RCTs were included, and standard-dose PPIs were again first when only trials of 8 weeks or more duration were considered. TCAs were the only drug more likely to cause adverse events than placebo, although these were no more likely to lead to withdrawal. Withdrawal due to adverse events was more likely with tegaserod, SSRIs, and SNRIs.

We were able to make indirect comparisons between 19,243 participants from the 71 RCTs included in this network meta-analysis. The trials themselves took place in a wide variety of settings, and countries, meaning the results of our study are likely to be generalisable to many patients with FD. We used an intention-to-treat analysis, with all trial dropouts assumed to be symptomatic, and performed subgroup analysis varying the definition of response to treatment, and sensitivity analyses according to characteristics of the eligible trials, as well as the participants. We contacted authors of studies to obtain supplementary data, and translated foreign language article, to maximise the number

of trials that were eligible for inclusion. Finally, we undertook extensive assessment for network inconsistency, and did not identify any in any of our analyses.

Weaknesses include variability between individual trials, in terms of the population studied, study setting, criteria used to define FD, duration of treatment, and the endpoint used to define symptom response. Some studies were conducted prior to the Rome criteria becoming the gold standard for the diagnosis of FD. These older trials, which mainly used $H_2$RAs, recruited patients whose symptom profiles would no longer be considered commensurate with FD, including reflux-predominant dyspepsia, [32,33,39,40] which may explain why these drugs ranked relatively highly. *H. pylori* status was not reported at all in some trials, while others stated specifically that they recruited patients who were *H. pylori*-negative following successful eradication therapy, but whose symptoms were persistent. A previous trial-based meta-analysis demonstrated no difference in efficacy of PPIs according to *H. pylori* status. [16] Overlap between FD and other functional gastrointestinal disorders, such as IBS, was allowed in some RCTs, [32,36,47,65,70] but not others. [48,58,59,61,86] This may mean that it is not appropriate to combine data from them in a meta-analysis. Few trials recruited patients only with EPS, or only with PDS. Our sensitivity analyses according to FD subtype were therefore based on trials that mandated only the presence of epigastric pain or burning, or only the presence of early satiety and/or postprandial fullness for trial entry but allowed coexistence of other symptoms. This means that these analyses are based on patients with EPS or overlap, or patients with PDS or overlap, rather than EPS alone or PDS alone. Only 20 of the RCTs we identified were at low risk of bias across all domains, meaning the efficacy of some of these drugs may have been overestimated, although we undertook sensitivity analyses according to risk of bias of individual trials. The majority of studies were conducted in secondary or tertiary care, with very few based solely in primary care. This may mean that the results of the network are not generalisable to patients with FD consulting in this setting. Finally, unlike previous Cochrane reviews on this topic, [17,18] we did not include RCTs of some prokinetic drugs, such as cisapride or metoclopramide. However, the former has been

withdrawn in many countries due to adverse cardiac events, and the latter has had its use restricted to short courses of therapy in Europe, due to extra-pyramidal side effects. Only one small RCT of metoclopramide, versus domperidone or levosulpiride, [98] was eligible for inclusion in the Cochrane systematic review, but this did not report dichotomous symptom data, and would therefore have been ineligible for this network meta-analysis, according to our inclusion criteria.

Our findings, in terms of the efficacy of individual drugs versus placebo, echo those of previous systematic reviews and meta-analyses in this field. However, our network allowed us to make comparisons between individual drugs and perform sensitivity analyses according to various trial and patient characteristics. In terms of improvement in symptoms, when only low risk of bias studies were included TCAs were ranked first, with itopride ranked second. When studies with a duration of treatment of 8 weeks or more were included, again TCAs ranked first, followed by mirtazapine, although the 95% CIs crossed 1, and standard-dose PPIs were ranked third. Among studies conducted in the East, antipsychotics ranked first, followed by $H_2$RAs, and TCAs. In studies conducted in Western countries, antipsychotics, TCAs, and mirtazapine were ranked first, second, and third, although in all instance 95% CIs crossed 1, with high-dose PPIs ranked fourth. Finally, in patients with EPS and overlap, TCAs ranked first, whereas for PDS and overlap acotiamide had the highest SUCRA rank, although again the 95% CIs crossed 1, and it should be pointed out that the majority of trials of acotiamide only recruited patients with PDS. We also examined the effect on resolution of symptoms, although given the fluctuating nature of FD, [4] and its background prevalence in the community, [99] whether this represents true "cure" of symptoms in the trials that reported this information is debatable. We were also able to rank therapies based on incidence of total adverse events, and adverse events leading to withdrawal, which has not been studied before. TCAs were the only drug more likely to lead to adverse events than placebo, although this did not translate into significantly higher dropout rates.

Although this network meta-analysis provides some evidence to aid selection of therapies in patients with FD, future studies should focus on strengthening this evidence, which may help to refine clinical guidelines for management of the condition. Of note is that there was moderate confidence in estimates of the efficacy of TCAs, which were ranked second in our primary analysis, and first when only low risk of bias trials were included. This is despite the fact that four of the five trials recruited patients whose symptoms were refractory to acid suppression therapy, prokinetics, or both. [69,70,82,96] These were the only RCTs to report consistently that patients had to have failed other therapies to be eligible for inclusion, although we believe that patients with refractory symptoms would be less likely to be recruited into trials of drugs used first-line for FD, such as PPIs or $H_2$RAs. This is in keeping with the literature for the management of other functional gastrointestinal disorders, where central neuromodulators have effects on gastrointestinal motility and function via actions on peripheral dopamine, noradrenaline, and serotonin receptors, [100-102] such as irritable bowel syndrome. [103,104] This suggests that earlier use of these drugs may be beneficial, and that large head-to-head studies of TCAs versus conventional therapies, such as PPIs, are required in primary care. Uninvestigated dyspepsia is highly prevalent in this setting, and 80% of patients with dyspepsia will have a normal endoscopy, [105] and therefore be labelled as having FD. Non-invasive management strategies for uninvestigated dyspepsia include testing for, and treating, *H. pylori*, or empirical PPI. [106] Given that most patients with uninvestigated dyspepsia in primary care will have FD, pragmatic trials of a TCA versus one or other of these management strategies may also be warranted.

In summary, we found antipsychotics, TCAs, $H_2$RAs, standard- and low-dose PPIs, itopride, and acotiamide, to be more efficacious than placebo for FD, in terms of likelihood of symptoms not improving, with antipsychotics ranked first and TCAs second. When likelihood of symptoms not resolving was examined in a subgroup analysis, high-, standard-, and low-dose PPIs, and $H_2$RAs were all more efficacious than placebo, with standard-dose PPIs ranked first. Adverse events were significantly more common with TCAs than with placebo, but these drugs were ranked first when

only low risk of bias trials were included, and most RCTs that used these drugs recruited patients refractory to other therapies. Given that there was moderate confidence in estimates of the efficacy of TCAs in FD, consideration should be given to using them earlier in the disease course, and definitive head-to-head trials of these drugs versus more widely accepted treatments for FD, or versus other management strategies for uninvestigated dyspepsia, should be conducted in primary care. Finally, there is a need for RCTs examining the efficacy of combined approaches for FD, such as acid suppression therapy and a central neuromodulator.

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**AUTHOR CONTRIBUTIONS**

Study concept and design: ACF, PM, CJB, YY, SKV, KK, NC, SM, and YYL conceived and drafted the study. ACF, CJB, YY, SKV, KK, and NC analysed, and interpreted the data. ACF, SKV, and NC drafted the manuscript. All authors have approved the final draft of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

**DECLARATION OF INTERESTS**

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**ETHICS COMMITTEE APPROVAL**

Not required.

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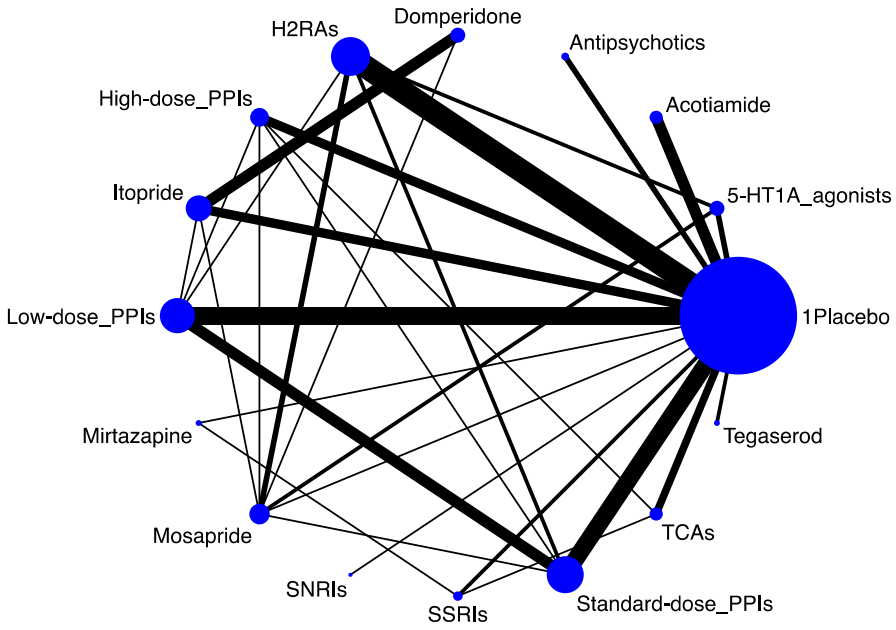
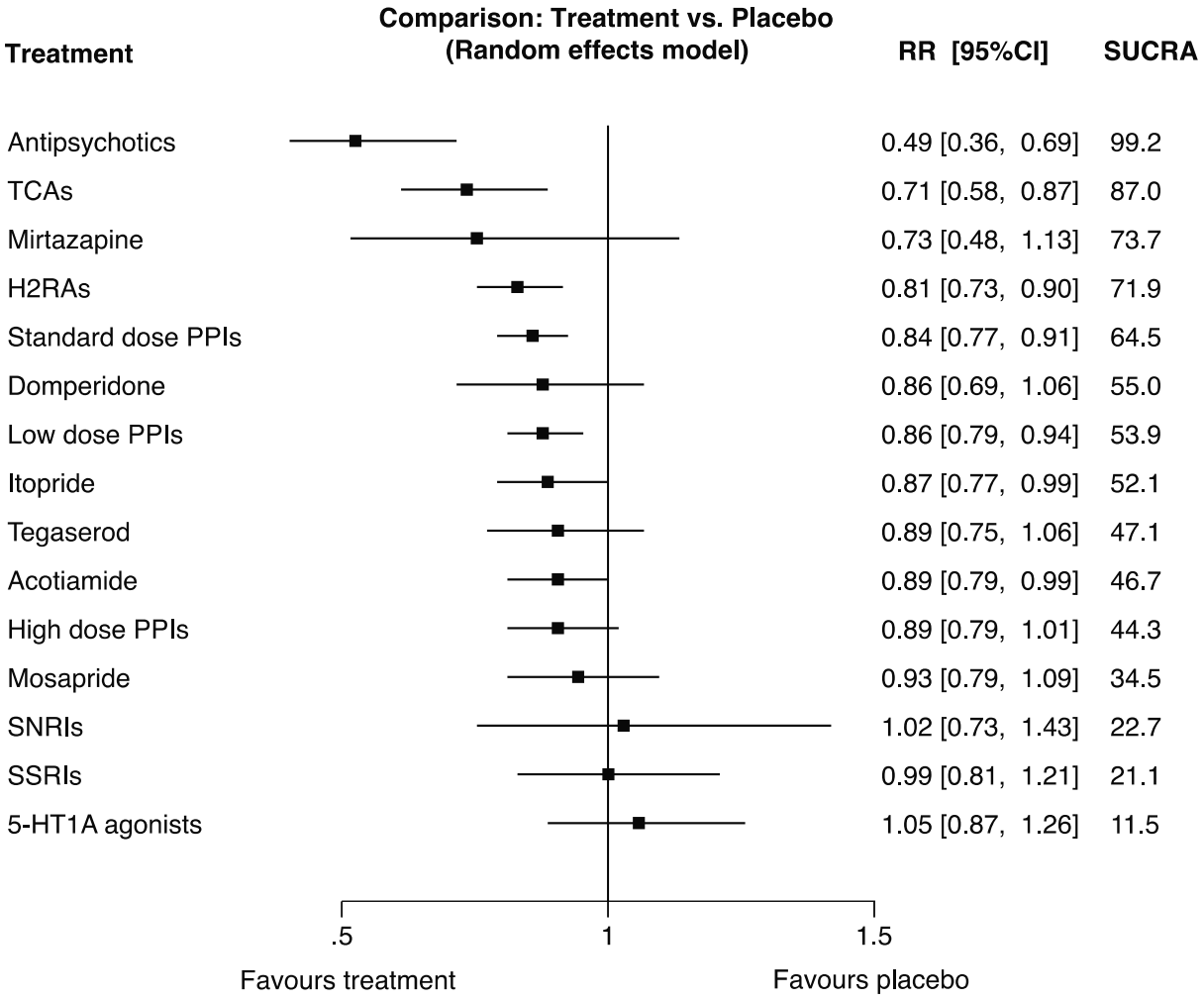
**Figure 1. Network Plot for Failure to Achieve an Improvement in FD Symptoms.**



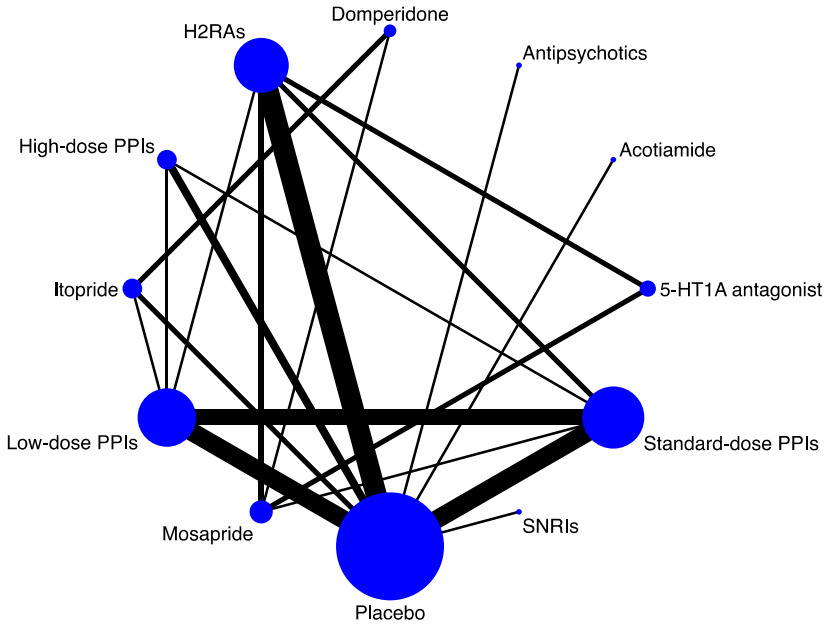

Note: 71 separate studies, containing 19,243 participants. Circle (node) size is proportional to the number of study participants assigned to receive each intervention. The line width (connection size) corresponds to the number of studies comparing the individual treatments.

**Figure 2. Forest Plot for Failure to Achieve an Improvement in FD Symptoms.**



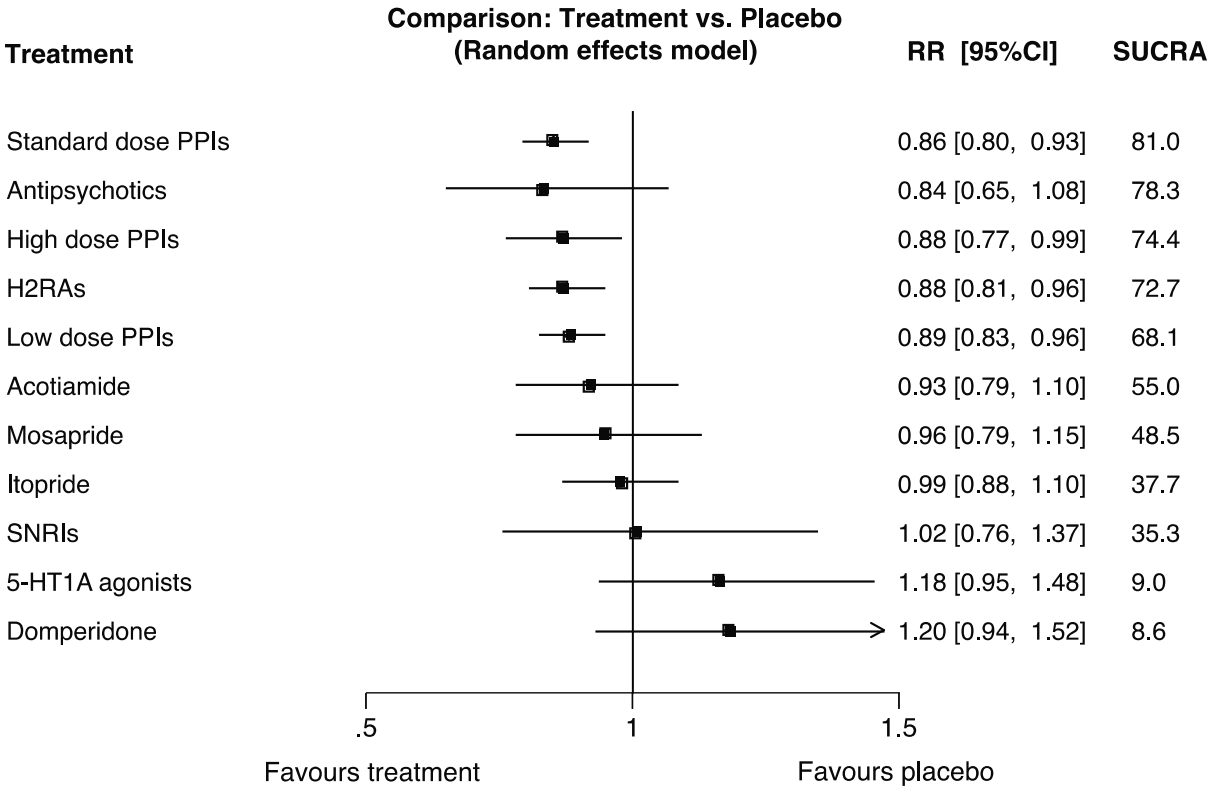

Note: Treatments are reported in order of efficacy ranking according to SUCRA. The SUCRA is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.

**Figure 3. Network Plot for Failure to Achieve Resolution of FD Symptoms.**




Note: 30 separate studies, containing 9,841 participants. 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 treatments.

**Figure 4. Forest Plot for Failure to Achieve Resolution of FD Symptoms.**




Note: Treatments are reported in order of efficacy ranking according to SUCRA. The SUCRA is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.

**Table 1. Eligibility Criteria.**

| |
|---|
| Randomised controlled trials. |
| Adults (participants aged ≥18 years). |
| Diagnosis of FD based on either a clinician's opinion, or meeting specific diagnostic criteria*, supplemented by negative upper gastrointestinal endoscopy. |
| Compared drugs for FD with each other or with placebo. |
| Minimum duration of therapy 2 weeks. |
| Minimum duration of follow-up 2 weeks. |
| Dichotomous assessment of response to therapy in terms of effect on FD symptom resolution or improvement, resolution or improvement of epigastric pain or discomfort, or resolution or improvement of early satiety or postprandial fullness.† |

*Rome I, II, III, or IV criteria.

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

**Table 2. Summary Treatment Effects from the Network Meta-analysis for Failure to Achieve an Improvement in FD Symptoms.**

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Anti-psychotics** | | | | | | | | | | | | | | |
| 0.70 (0.47,1.03) | **TCAs** | | | | | | | | | | | | | |
| 0.67 (0.39,1.16) | 0.97 (0.60,1.55) | **Mirtazapine** | | | | | | | | | | | | |
| 0.61 (0.43,0.86) | 0.87 (0.70,1.09) | 0.90 (0.58,1.41) | **$H_2$RAs** | | | | | | | | | | | |
| 0.59 (0.42,0.83) | 0.85 (0.68,1.06) | 0.88 (0.56,1.36) | 0.97 (0.86,1.10) | **Standard-dose PPIs** | | | | | | | | | | |
| 0.58 (0.39,0.85) | 0.83 (0.62,1.11) | 0.85 (0.53,1.39) | 0.95 (0.75,1.20) | 0.97 (0.77,1.23) | **Domperidone** | | | | | | | | | |
| 0.57 (0.41,0.81) | 0.82 (0.66,1.02) | 0.85 (0.55,1.32) | 0.94 (0.83,1.07) | 0.97 (0.88,1.07) | 0.99 (0.79,1.25) | **Low-dose PPIs** | | | | | | | | |
| 0.57 (0.40,0.81) | 0.81 (0.64,1.03) | 0.84 (0.54,1.32) | 0.93 (0.79,1.09) | 0.96 (0.83,1.12) | 0.99 (0.83,1.17) | 0.99 (0.86,1.15) | **Itopride** | | | | | | | |
| 0.56 (0.38,0.81) | 0.80 (0.61,1.04) | 0.83 (0.52,1.32) | 0.92 (0.75,1.12) | 0.94 (0.78,1.15) | 0.97 (0.73,1.28) | 0.97 (0.80,1.18) | 0.98 (0.79,1.22) | **Tegaserod** | | | | | | |
| 0.56 (0.39,0.79) | 0.80 (0.63,1.01) | 0.83 (0.53,1.30) | 0.92 (0.79,1.07) | 0.94 (0.82,1.09) | 0.97 (0.76,1.24) | 0.97 (0.84,1.13) | 0.98 (0.83,1.17) | 1.00 (0.81,1.23) | **Acotiamide** | | | | | |
| 0.55 (0.39,0.79) | 0.80 (0.63,1.00) | 0.82 (0.52,1.29) | 0.91 (0.78,1.07) | 0.94 (0.81,1.09) | 0.96 (0.75,1.23) | 0.97 (0.84,1.12) | 0.98 (0.82,1.17) | 0.99 (0.80,1.23) | 0.99 (0.84,1.18) | **High-dose PPIs** | | | | |
| 0.53 (0.37,0.77) | 0.76 (0.59,0.98) | 0.79 (0.50,1.25) | 0.88 (0.73,1.05) | 0.90 (0.76,1.07) | 0.93 (0.72,1.20) | 0.93 (0.78,1.11) | 0.94 (0.77,1.14) | 0.96 (0.76,1.21) | 0.96 (0.79,1.16) | 0.96 (0.80,1.15) | **Mosapride** | | | |
| 0.48 (0.30,0.78) | 0.70 (0.47,1.03) | 0.72 (0.42,1.24) | 0.80 (0.56,1.13) | 0.82 (0.58,1.16) | 0.84 (0.57,1.25) | 0.85 (0.60,1.20) | 0.85 (0.60,1.22) | 0.87 (0.60,1.27) | 0.87 (0.61,1.24) | 0.87 (0.61,1.25) | 0.91 (0.63,1.32) | **SNRIs** | | |
| 0.50 (0.34,0.73) | 0.71 (0.55,0.92) | 0.74 (0.46,1.18) | 0.82 (0.65,1.02) | 0.84 (0.68,1.05) | 0.87 (0.65,1.16) | 0.87 (0.70,1.08) | 0.88 (0.69,1.11) | 0.89 (0.69,1.17) | 0.89 (0.71,1.13) | 0.90 (0.71,1.14) | 0.94 (0.73,1.21) | 1.03 (0.70,1.52) | **SSRIs** | |
| 0.49 (0.36,0.69) | 0.71 (0.58,0.87) | 0.73 (0.48,1.13) | 0.81 (0.73,0.90) | 0.84 (0.77,0.91) | 0.86 (0.69,1.06) | 0.86 (0.79,0.94) | 0.87 (0.77,0.99) | 0.89 (0.75,1.06) | 0.89 (0.79,0.99) | 0.89 (0.79,1.01) | 0.93 (0.79,1.09) | 1.02 (0.73,1.43) | 0.99 (0.81,1.21) | **Placebo** |
| 0.47 (0.32,0.69) | 0.68 (0.51,0.89) | 0.70 (0.44,1.12) | 0.77 (0.63,0.95) | 0.80 (0.65,0.98) | 0.82 (0.62,1.08) | 0.82 (0.67,1.01) | 0.83 (0.66,1.04) | 0.84 (0.66,1.09) | 0.85 (0.68,1.05) | 0.85 (0.68,1.06) | 0.88 (0.71,1.10) | 0.97 (0.66,1.43) | 0.95 (0.72,1.24) | 0.95 (0.79,1.15) | **5-$HT_{1A}$ agonists** |

Treatments are reported in order of efficacy ranking according to SUCRA. Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right. The treatment in the top left position is ranked as best after the network meta-analysis of indirect effects. Boxes shaded green denote a statistically significant difference.

$H_2$RAs; histamine-$_2$ receptor antagonists, PPIs; proton pump inhibitors, SNRIs; serotonin norepinephrine reuptake inhibitors, SSRIs; selective serotonin reuptake inhibitors, TCAs; tricyclic antidepressants.

**Table 3. Summary Treatment Effects from the Network Meta-analysis for Failure to Achieve Resolution of FD Symptoms.**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Standard-dose PPIs** | | | | | | | | | | | |
| 1.03 (0.79,1.34) | **Anti-psychotics** | | | | | | | | | | |
| 0.99 (0.86,1.13) | 0.96 (0.73,1.27) | **High-dose PPIs** | | | | | | | | | |
| 0.98 (0.88,1.08) | 0.95 (0.73,1.24) | 0.99 (0.86,1.15) | **$H_2$RAs** | | | | | | | | |
| 0.97 (0.89,1.05) | 0.94 (0.72,1.22) | 0.98 (0.85,1.12) | 0.99 (0.89,1.10) | **Low-dose PPIs** | | | | | | | |
| 0.93 (0.77,1.12) | 0.90 (0.67,1.22) | 0.94 (0.76,1.16) | 0.95 (0.79,1.15) | 0.96 (0.80,1.15) | **Acotiamide** | | | | | | |
| 0.90 (0.75,1.09) | 0.88 (0.64,1.20) | 0.91 (0.73,1.14) | 0.92 (0.76,1.12) | 0.93 (0.77,1.13) | 0.97 (0.76,1.25) | **Mosapride** | | | | | |
| 0.88 (0.77,1.00) | 0.85 (0.65,1.12) | 0.89 (0.75,1.05) | 0.90 (0.78,1.03) | 0.91 (0.80,1.03) | 0.94 (0.77,1.16) | 0.97 (0.79,1.19) | **Itopride** | | | | |
| 0.85 (0.63,1.15) | 0.82 (0.56,1.21) | 0.86 (0.62,1.18) | 0.87 (0.64,1.17) | 0.88 (0.65,1.18) | 0.91 (0.65,1.28) | 0.94 (0.66,1.33) | 0.97 (0.71,1.32) | **SNRIs** | | | |
| 0.86 (0.80,0.93) | 0.84 (0.65,1.08) | 0.88 (0.77,0.99) | 0.88 (0.81,0.96) | 0.89 (0.83,0.96) | 0.93 (0.79,1.10) | 0.96 (0.79,1.15) | 0.99 (0.88,1.10) | 1.02 (0.76,1.37) | **Placebo** | | |
| 0.73 (0.58,0.92) | 0.71 (0.51,1.00) | 0.74 (0.57,0.95) | 0.75 (0.60,0.93) | 0.75 (0.60,0.95) | 0.79 (0.59,1.04) | 0.81 (0.66,0.98) | 0.83 (0.65,1.06) | 0.86 (0.60,1.25) | 0.84 (0.68,1.06) | **5-$HT_{1A}$ agonists** | |
| 0.72 (0.57,0.92) | 0.70 (0.50,0.99) | 0.73 (0.56,0.95) | 0.74 (0.58,0.94) | 0.75 (0.58,0.95) | 0.78 (0.58,1.04) | 0.80 (0.62,1.02) | 0.82 (0.65,1.03) | 0.85 (0.58,1.24) | 0.83 (0.66,1.06) | 0.99 (0.74,1.33) | **Domperidone** |

Treatments are reported in order of efficacy ranking according to SUCRA. Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right. The treatment in the top left position is ranked as best after the network meta-analysis of indirect effects. Boxes shaded green denote a statistically significant difference.

$H_2$RAs; histamine-$_2$ receptor antagonists, PPIs; proton pump inhibitors, SNRIs; serotonin norepinephrine reuptake inhibitors.