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TITLE PAGE

Title: Efficacy of Pharmacological Therapies in Chronic Idiopathic Constipation: Systematic Review and Network Meta-analysis.

Short running head: Network Meta-analysis of Pharmacological Therapies in Constipation.

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Abbreviations:

5-HT	5-hydroxytryptamine
b.i.d.	twice daily

CI	confidence interval
CIC	chronic idiopathic constipation
CSBM	complete spontaneous bowel movement
FDA	Food and Drug Administration
MeSH	medical subject heading
o.d.	once daily
PAC-QOL	patient assessment of constipation quality of life
RCT	randomised controlled trial
RR	relative risk
SBM	spontaneous bowel movement

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SUMMARY

Background: There are several pharmacological therapies available for the treatment of chronic idiopathic constipation (CIC), but their relative efficacy is unclear because there have been no head-to-head randomised controlled trials (RCTs). We conducted a network meta-analysis to compare their efficacies in patients with CIC.

Methods: We searched MEDLINE, EMBASE, EMBASE Classic, and the Cochrane central register of controlled trials through June 2019 to identify RCTs assessing the efficacy of pharmacological therapies in adults with CIC. Trials included in the analysis reported a dichotomous assessment of overall response to therapy, and data were pooled using a random effects model. Efficacy and safety of all treatments were reported as a pooled relative risk with 95% CIs to summarise the effect of each comparison tested, and treatments were ranked according to their P-score.

Findings: We identified 33 separate eligible RCTS of pharmacological therapies, containing 17,214 patients. Based on an endpoint of failure to achieve ≥3 complete spontaneous bowel movements (CSBMs) per week, the stimulant diphenyl methane laxatives bisacodyl and sodium picosulfate, at a dose of 10mg once-daily, were ranked first at 4 weeks (RR 0.55; 95% CI 0.48 to 0.63, P-score = 0.99), and prucalopride 2mg once-daily was ranked first at 12 weeks (RR 0.82; 95% CI 0.78 to 0.86, P-score = 0.96). When failure to achieve an increase of ≥1 CSBM per week from baseline was used, again diphenyl methane laxatives at a dose of 10mg once-daily were ranked first at 4 weeks (RR 0.44; 95% CI 0.37 to 0.54, P-score = 0.99), with prucalopride 4mg once-daily ranked first at 12 weeks (RR = 0.74; 95% CI 0.66 to 0.83, P-score 0.79), although linaclotide 290μg once-daily and prucalopride 2mg once-daily performed similarly. Bisacodyl was ranked last in terms of safety for total number of adverse events and abdominal pain.

Interpretation: Almost all pharmacological therapies studied were superior to placebo, according to either failure to achieve ≥3 CSBMs per week or an increase of ≥1 CSBM per week over baseline. Although diphenyl methane laxatives were ranked first for efficacy at 4 weeks, a milder spectrum of patients may have been treated in these trials. Prucalopride was ranked first at 12 weeks, and many of the included trials recruited patients who had previously failed laxatives, suggesting that this drug is likely to be the most efficacious for patients with CIC. However, since treatment duration in most trials was 4 to 12 weeks, the long term relative efficacy of these drugs is unknown.

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RESEARCH IN CONTEXT

Evidence before this study

Chronic idiopathic constipation (CIC) affects as many as 14% of the general population. Randomised controlled trials (RCTs) demonstrate that laxatives and other newer pharmacological therapies are effective for the treatment of CIC. However, there is limited information concerning their relative efficacy. A previous systematic review and network meta-analysis of RCTs was published in 2017, but the literature search was done in 2015, and more RCTs have been published in the intervening 4 years, as well as trials of newer drugs.

Added value of this study

We have conducted a contemporaneous systematic review and network meta-analysis of RCTs reporting the effect of pharmacological therapies in CIC. Analyses according to different efficacy endpoints and duration of therapy were conducted, as well as effect on quality of life and adverse events.

Implications of all the available evidence

Diphenyl methane laxatives were ranked first for efficacy at 4 weeks, when failure to achieve either ≥3 CSBMs per week or an increase of ≥1 CSBM per week over baseline were used to define response to therapy, and were superior to almost all other treatments. However, trials of these drugs may have recruited a milder spectrum of patients, who were not laxative resistant. At 12 weeks of treatment, prucalopride 2mg or 4mg o.d. were ranked first, and appeared superior to several other drugs and dosages. As most RCTs were of 4 to 12 weeks duration, the longer term efficacy of these treatments is unknown.

INTRODUCTION

Chronic idiopathic constipation (CIC) is a chronic functional disorder of the lower gastrointestinal tract, characterised by persistently difficult, infrequent, or incomplete defecation, in the absence of any physiological abnormality. (1) The condition is common; a previous meta-analysis of cross-sectional community-based surveys estimated the prevalence worldwide at 14%. (2) As many as one-in-five people with symptoms compatible with CIC will consult a physician, (3) and the impact on quality of life for patients is comparable with that for organic conditions, such as chronic obstructive pulmonary disease, diabetes, and depression. (4) In a burden of illness study in the USA, constipation accounted for 3 million ambulatory visits and 800,000 emergency room visits. (5) Costs in the USA are estimated to be between $2000 and $7500 per patient per year. (6)

Patients with CIC are often told to increase their dietary fibre intake in order to alleviate symptoms, but randomised controlled trial (RCT) evidence to support this strategy is lacking. (7) Although both osmotic and stimulant laxatives are beneficial for the treatment of CIC, (8) many patients report dissatisfaction with their efficacy and safety. (9) Other pharmacological therapies for the disorder have therefore been developed. Agonists at the 5-hydroxytryptamine-4 (5-HT_4) receptor, such as tegaserod, naronapride, prucalopride, and velusetrag increase colonic motility and transit. (10, 11) Secretagogues such as lubiprostone, linaclotide, and plecanatide are drugs that act by stimulating intestinal fluid secretion, thereby accelerating gastrointestinal transit. (12, 13) Elobixibat is an inhibitor of the ileal bile acid transporter, which leads to delivery of bile acids into the colon, where they are deconjugated and increase colonic motility and secretion. (14) Finally, mizagliflozin and tenapanor are drugs that act on sodium-glucose co-transporters and sodium-hydrogen exchangers, respectively. Both drugs appear to have effects on stool consistency in healthy volunteers. (15, 16)

Many of these pharmacological therapies, including osmotic and stimulant laxatives, have been tested in placebo-controlled trials, but their relative efficacy was unknown, until recently, because head-to-head trials are lacking. A network meta-analysis, published in 2017, (17) attempted to circumvent this limitation in the available evidence by making indirect treatment comparisons between all active therapies tested in placebo-controlled trials, up to March 2015. These included prucalopride, tegaserod, velusetrag, lubiprostone, linaclotide, bisacodyl, sodium picosulfate, and elobixibat. The authors reported that all drugs, except tegaserod and linaclotide, were superior to placebo, but none were superior to each other, when response to therapy was defined as achieving ≥3 complete spontaneous bowel movements (CSBMs) per week. Similarly, all drugs were superior to placebo, except tegaserod and linaclotide, and none were superior to each other, when an increase of ≥1 CSBM per week from baseline was used to define treatment response. Bisacodyl appeared superior to the other drugs for the secondary endpoint, change from baseline in number of bowel movements per week.

However, in the intervening 4 years since the literature search for this network met-analysis was undertaken, (17) there have been further trials conducted of several of the drugs previously studied. In addition, RCTs of plecanatide in CIC have been completed, and prucalopride has been licensed for use in CIC in the USA recently. A reappraisal of the available evidence to support clinical decision-making would seem timely. We have, therefore, conducted a contemporaneous systematic review and network meta-analysis of RCTs of pharmacological therapies in CIC. The Food and Drug Administration (FDA) have made recommendations for the design of treatment trials, and endorsed standardised endpoints that should be used to judge the efficacy of therapies in CIC. As a result, we have been able to conduct a network meta-analysis of RCTs of very similar design, similar

treatment durations and, in many instances, identical efficacy endpoints, in order to examine the relative efficacy and safety of all available pharmacological therapies.

METHODS

Search Strategy and Selection Criteria

We searched MEDLINE (1946 to June 2019), EMBASE and EMBASE Classic (1947 to June 2019), and the Cochrane central register of controlled trials to identify potential studies. In addition, we searched clinicaltrials.gov for unpublished trials, or supplementary data for potentially eligible studies. In order to identify studies published only in abstract form, we hand-searched conference proceedings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week) between 2001 and 2019. Finally, we performed a recursive search, using the bibliographies of all obtained articles.

Randomised controlled trials examining the effect of pharmacological therapies (osmotic or stimulant laxatives, elobixibat, linaclotide, lubiprostone, mizagliflozin, naronapride, plecanatide, prucalopride, tegaserod, tenapanor, or velusetrag) in adult patients (>18 years) with CIC were eligible (Supplementary Table 1). The first period of cross-over RCTs were eligible for inclusion if they provided efficacy data prior to cross-over. The definitions of CIC considered within this network meta-analysis included either a clinician's opinion, or meeting specific symptom-based criteria, for example the Rome criteria. Studies that recruited patients with organic constipation, drug-induced constipation, or highly selected groups of patients (such as elderly patients who were also institutionalised) were ineligible, as were trials that recruited mixed populations of patients with CIC and IBS with constipation, where data were not reported separately for the participants with CIC.

Trials that examined the efficacy of any dose of the drugs of interest, and which compared them with each other, or with placebo, were considered eligible. A minimum treatment duration of 4 weeks was required, and we extracted all endpoints preferentially at 4

weeks, 12 weeks, or both 4 and 12 weeks, if reported, even for RCTs providing efficacy data at other time points. We did this to ensure as much homogeneity as possible between individual trial results, and to avoid overestimating the efficacy of one drug relative to another, as the placebo effect in functional gastrointestinal disorders tends to decrease with time, from average 46% in 1- to 4-week duration trials, 39.8% in 5- to 8-week duration trials, and 34% for trials >8 weeks duration. (18) Studies had to report a dichotomous assessment of response to therapy. We contacted first and senior authors of studies to provide additional information on individual trials, where required.

Two investigators (PL and ACF) conducted the literature search, independently from each other. Studies on CIC were identified with the terms: constipation or gastrointestinal transit (both as medical subject headings (MeSH) and free text terms), or functional constipation, idiopathic constipation, chronic constipation, or slow transit (as free text terms). These were combined using the set operator AND with studies identified with the terms: laxatives, cathartics, anthraquinones, phenolphthaleins, indoles, phenols, lactulose, polyethylene glycol, senna plant, senna extract, bisacodyl, phosphates, dioctyl sulfosuccinic acid, magnesium, magnesium hydroxide, sorbitol, poloxamer, serotonin agonists, receptors, serotonin, 5-HT_4, or receptors, prostaglandin E (both as MeSH terms and free text terms), or the following free text terms: sodium picosulfate, docusate, milk of magnesia, danthron, senna, poloxalkol, elobixibat, A3309, linaclotide, linzess, constella, lubiprostone, amitiza, mizagliflozin, naronapride, plecanatide, trulance, prucalopride, resolor, tegaserod, zelnorm, tenapanor, or velusetrag.

There were no language restrictions. Two investigators (PL 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, in order to assess eligibility independently, according to the pre-defined criteria. We

translated foreign language papers, where required. We resolved disagreements between investigators by discussion.

Data Analysis

We assessed the efficacy of all drugs, compared with each other or with placebo, in CIC in terms of failure to respond to therapy, with the endpoints of interest used to define response reported below. Secondary outcomes included adverse events occurring as a result of therapy (overall numbers of adverse events, as well as adverse events leading to study withdrawal, and individual adverse events, including diarrhoea, headache, abdominal pain, or nausea).

Two investigators (PL and ACF) extracted all data independently onto a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA) as dichotomous outcomes (response or no response to therapy). The included eligible RCTs often reported identical dichotomous endpoints to assess efficacy of the various therapies. We were therefore able to assess this according to the following, which generally conforms to the endpoints studied in the previous network meta-analysis (17): a) the proportion of patients failing to achieve ≥3 CSBMs per week (with or without an increase of ≥1 CSBM per week from baseline); b) the proportion failing to achieve an increase in the number of CSBMs per week from baseline of ≥1; c) the proportion failing to achieve ≥3 spontaneous bowel movements (SBMs) per week; and d) the proportion failing to achieve an improvement in quality of life, according to the patient assessment of constipation quality of life (PAC-QOL). We also extracted the following data for each trial, where available: country of origin, number of centres, criteria used to define CIC, proportion of female patients, proportion of patients who had used laxatives previously, and dose and duration of therapy. We extracted data as intention-to-treat analyses, with dropouts assumed to be treatment failures (i.e. no

response to therapy), wherever trial reporting allowed. If this was not clear from the original article, we planned to perform an analysis on all patients with reported evaluable data.

We used the Cochrane risk of bias tool (19) to assess this at the study level. Two investigators performed this independently (PL and ACF); we resolved disagreements by discussion. We recorded the method 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.

We performed a network meta-analysis using the frequentist model, with the statistical package "netmeta" (version 0.9-0, https://cran.r-project.org/web/packages/netmeta/index.html) in R (version 3.4.2). This was reported according to the PRISMA extension statement for network meta-analyses, (20) in order to explore indirect treatment comparisons of the efficacy and safety of each medication. Network meta-analysis results usually give a more precise estimate, compared with results from standard, pairwise analyses, (21, 22) and can rank treatments to inform clinical decisions. (23)

We examined the symmetry and geometry of the evidence by producing a network plot with node and connection size corresponding to the number of study subjects and number of studies respectively. We produced comparison adjusted funnel plots to explore publication bias or other small study effects, for all available comparisons versus placebo, using Stata version 14 (Stata Corp., College Station, TX, USA). This is a scatterplot of effect size versus precision, measured via the inverse of the standard error. Symmetry around the effect estimate line indicates the absence of publication bias, or small study effects. (24) We produced a pooled relative risk (RR) with 95% confidence intervals (CIs) to summarise the effect of each comparison tested, using a random effects model as a conservative estimate.

We used a RR of failure to achieve each of the endpoints of interest, where if the RR is less than 1 and the 95% CI does not cross 1, there is a significant benefit of the drug over placebo. As there were no direct comparisons between individual drugs, we were unable to perform consistency modelling to check the correlation between direct and indirect evidence. (25)

We assessed global statistical heterogeneity across all comparisons using the I^2 measure from the "netmeta" statistical package. The I^2 measure ranges between 0% and 100%. Values of 25% to 49%, 50% to 74%, and ≥75% are considered low, moderate, and high levels of heterogeneity, respectively. (26) We ranked treatments according to their P-score, which is a value between 0 and 1. P-scores are based solely on the point estimates and standard errors of the network estimates, and measure the extent of certainty that a treatment is better than another treatment, averaged over all competing treatments. (27) Higher scores indicate a greater probability of the treatment being ranked as best, (27) but the magnitude of the P-score should be considered, as well as the treatment rank. As the mean value of the P-score is always 0.5, if individual treatments cluster around this value they are likely to be of similar efficacy.

Role of the Funding Source

No funding received. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

RESULTS

Trial Assessment and Risk of Bias

The search strategy generated 17,363 citations, 91 of which appeared to be relevant to the systematic review and were retrieved for further assessment (Figure 1). Of these, 59 were excluded for various reasons, leaving 32 eligible articles reporting on 33 separate trials, which contained a total of 17,214 patients, allocated to active therapy or placebo as described in Supplementary Table 2. (28-59) We did not identify any eligible RCTs of mizagliflozin, naronapride, or tenapanor.

Agreement between investigators for trial eligibility was excellent (kappa statistic = 0.83). Detailed characteristics of individual RCTs are provided in Table 1. One elobixibat trial and one trial of tegaserod were only of 8 weeks duration, (45, 49) so we included the data from these trials in our 12-week analysis, but excluded them in a sensitivity analysis. All three RCTs of lubiprostone were of 4 weeks duration, and only reported efficacy according to failure to achieve ≥3 SBMs per week. (52-54) Two of the elobixibat trials were terminated early due to a supply issue with the study medication, but efficacy and safety data at 12 weeks were available from clinicaltrials.gov. (50, 51) Only thirteen RCTs reported specifically that they recruited patients with prior laxative use, (28, 30-34, 41, 43-45, 54, 57, 58) six of which used prucalopride, and four tegaserod. Risk of bias for all included trials is reported in Supplementary Table 3; only seven were at low risk of bias. (34, 40, 42-45, 49) Although many trials did not report a true intention-to-treat analysis, we were able to extract this for all involved studies. No trials made head-to-head comparisons of one drug versus another, meaning that direct evidence was only available in comparison with placebo. As a result, active medications could only be compared with each other using an indirect evidence meta-analysis, relative to the comparison with placebo's effects.

Efficacy

Failure to Achieve ≥3 CSBMs Per Week at 4 Weeks

Sixteen RCTs, including 9466 patients, reported these data at 4 weeks. (28, 29, 31-36, 39-41, 43, 44, 55, 56, 59) There were 6155 patients randomised to active treatment. The network plot is provided in Supplementary Figure 1. When data were pooled there were low levels of statistical heterogeneity (I^2 = 45.5%), and no evidence of publication bias, or other small study effects (Supplementary Figure 2). All treatments were significantly more effective than placebo at 4 weeks, except prucalopride 0.5mg o.d., which is below the minimum approved dose, but the stimulant diphenyl methane laxatives sodium picosulfate and bisacodyl 10mg o.d. were ranked as the most effective (P-score 0.99), in two RCTs (RR 0.55; 95% CI 0.48 to 0.63) (Figure 2). This means that the probability of these drugs being the most effective when all treatments, including placebo, were compared with each other was 99%. After indirect comparison of active treatments, significant differences were seen with: a) stimulant diphenyl methane laxatives compared with all other drugs except linaclotide 500µg o.d.; b) linaclotide 500µg o.d. (P-score 0.91), which is a licensed dose only in Japan, compared with velusetrag 30mg or 50mg o.d., linaclotide 72µg or 145 µg o.d., and tegaserod 2mg or 6mg b.i.d.; and c) both prucalopride 2mg and 4mg o.d. (P-scores 0.67 and 0.64 respectively) compared with tegaserod 2mg or 6mg b.i.d. and linaclotide 72µg o.d. (Supplementary Table 4).

Failure to Achieve ≥3 CSBMs Per Week at 8 to 12 Weeks

Seventeen trials, published in 16 articles, reported these data at 12 weeks, (31-35, 37, 38, 40-43, 46-48, 50, 51) and one RCT at 8 weeks. (45) There were 8827 patients randomised to active treatment, and 4650 to placebo. The network plot is provided in Figure 3. When data

were pooled there were low levels of statistical heterogeneity (I^2 = 34.4%), and no evidence of publication bias, or other small study effects (Supplementary Figure 3). All treatments were significantly more effective than placebo at 8 to 12 weeks, except plecanatide 1mg o.d. and elobixibat 10mg o.d., but prucalopride 2mg o.d. was ranked as the most effective (P-score 0.96), in five RCTs (RR 0.82; 95% CI 0.78 to 0.86) (Figure 4). After indirect comparison of active treatments, significant differences were seen with: a) prucalopride 2mg o.d. and all other treatments except prucalopride 4mg o.d., linaclotide 72µg or 290µg o.d., tegaserod 6mg b.i.d., elobixibat 5mg o.d., and plecanatide 0.3mg o.d.; b) prucalopride 4mg o.d. (P-score 0.90) and plecanatide 6mg o.d., tegaserod 2mg b.i.d., and elobixibat 10mg o.d.; and c) linaclotide 290µg o.d. (P-score 0.77) compared with elobixibat 10mg o.d. (Figure 5). We performed a sensitivity analysis, excluding the trial of tegaserod 6mg b.i.d. that only reported endpoints at 8 weeks, (45) but this did not affect the ranking of tegaserod 6mg b.i.d.

Failure to Achieve ≥3 CSBMs Per Week and an Increase of ≥1 CSBM Per Week from Baseline at 12 Weeks

Eleven of these trials, reported in 10 articles, (35, 37, 38, 40, 42, 46-48, 50, 51) used a more stringent endpoint of failure to achieve ≥3 CSBMs per week and an increase of ≥1 CSBM from baseline. When data from these trials, containing 8129 patients, were pooled in a further sensitivity analysis, prucalopride 2mg o.d. was still ranked first (RR = 0.84; 95% CI 0.75 to 0.93, P-score = 0.88) (Supplementary Figure 4). After indirect comparison, prucalopride 2mg o.d. was only superior to elobixibat 10mg o.d. There was no heterogeneity in this analysis (I^2 = 12.0%).

Failure to Achieve an *Increase of ≥1 CSBM Per Week from Baseline at 4 Weeks*

Nine trials reported data for this endpoint at 4 weeks. (28, 32, 41-44, 55, 56, 59) There were 3645 patients randomised to active treatment, and 1976 to placebo. The network plot is provided in Supplementary Figure 5. When data were pooled there were low levels of statistical heterogeneity (I^2 = 39.6%), but too few studies to assess for evidence of publication bias, or other small study effects. All treatments were significantly more effective than placebo at 4 weeks, but the stimulant diphenyl methane laxatives sodium picosulfate and bisacodyl 10mg o.d. were ranked as the most effective (P-score 0.99), in two RCTs (RR 0.44; 95% CI 0.37 to 0.54) (Supplementary Figure 6). On indirect comparison, stimulant diphenyl methane laxatives were superior to all treatments except prucalopride 1mg o.d., and prucalopride 1mg o.d. (P-score 0.84) was superior to tegaserod 2mg b.i.d. (Supplementary Table 5).

*Failure to Achieve an Increase of ≥1 CSBM Per Week from Baseli*ne at 8 to 12 Weeks

Eleven RCTs, published in 10 articles, reported an increase of ≥1 CSBM per week from baseline at 12 weeks, (31-35, 37, 38, 41-43) and a further two trials at 8 weeks. (45, 49) There were 7997 patients in total, 5097 of whom were randomised to active treatment. The network plot is provided in Supplementary Figure 7. When data were pooled there was moderate global statistical heterogeneity (I^2 = 50.8%), but no evidence of publication bias, or other small study effects (Supplementary Figure 8). All treatments were significantly more effective than placebo at 8 to 12 weeks, but elobixibat 15mg o.d. was ranked as the most effective (P-score 0.91, RR 0.53; 95% CI 0.35 to 0.82), although in only one RCT of 8 weeks duration (Figure 6). After indirect comparison of active treatments, significant differences were seen with both elobixibat 15mg o.d. and prucalopride 4mg o.d. (P-score 0.59), compared with tegaserod 2mg b.i.d. (Figure 7).

In a sensitivity analysis, including only the 11 trials of 12 weeks duration containing 7557 patients, published in 10 articles, (31-35, 37, 38, 41-43) prucalopride 4mg o.d. was ranked first (P-score 0.79), in three RCTs (RR = 0.74; 95% CI 0.66 to 0.83); moderate heterogeneity between studies persisted (I^2 = 54.3%). However, linaclotide 290µg o.d. and prucalopride 2mg o.d. performed similarly (P-scores 0.76 and 0.71 respectively), and there were no significant differences between active therapies after indirect comparison, other than a significant difference between prucalopride 4mg o.d. and tegaserod 2mg b.i.d. Other efficacy data are provided in the Supplementary Materials.

Safety

Twenty-nine trials, published in 28 articles, reported total number of adverse events in 16,419 patients, 10,659 of whom received active treatment. (28, 30-55, 59) There were borderline moderate levels of global statistical heterogeneity (I^2 = 49.5%), but no evidence of publication bias, or other small study effects. When comparing pooled overall adverse events, there were significant differences, compared with placebo, for the following drugs and doses: prucalopride 2mg and 4mg o.d.; plecanatide 3mg o.d., linaclotide 72µg, 145µg, 290µg, and 500µg o.d.; elobixibat 10mg and 15mg o.d.; lubiprostone 24µg b.i.d.; and bisacodyl 10mg o.d. (Supplementary Figure 9). When ranked using a P-score, plecanatide 0.3mg o.d. was the best, and bisacodyl 10mg o.d. the worst, in terms of overall adverse events (P-scores 0.95 and 0.08 respectively). Indirect comparison of active treatments revealed that bisacodyl 10mg o.d. was significantly more likely to lead to adverse events than the following drugs and doses: linaclotide 290µg o.d.; plecanatide 0.3mg, 1mg, 3mg, and 6mg o.d.; prucalopride 2mg and 4mg o.d.; and tegaserod 2mg and 6mg b.i.d. Data concerning withdrawals due to adverse events and individual adverse events are provided in the Supplementary Materials.

DISCUSSION

This network meta-analysis demonstrated that the diphenyl methane laxatives sodium picosulfate and bisacodyl were ranked first for efficacy at 4 weeks, when failure to achieve either ≥3 CSBMs per week or an increase of ≥1 CSBM per week over baseline were used as the endpoint to define response to therapy. These laxatives appeared superior to all other drugs, except linaclotide 500μg o.d. and prucalopride 1mg o.d. when using failure to achieve ≥3 CSBMs per week or an increase of ≥1 CSBM per week over baseline, respectively. At 12 weeks of treatment, prucalopride 2mg or 4mg o.d. were ranked first, and appeared superior to several other drugs and dosages. At 8 to 12 weeks, elobixibat 15mg o.d. was ranked first using failure to achieve an increase of ≥1 CSBM per week over baseline. Sensitivity analyses using the more stringent endpoint of failure to achieve ≥3 CSBMs per week and an increase of ≥1 CSBM per week over baseline did not change the bottom line of the meta-analysis at 12 weeks; prucalopride 2mg o.d. was still ranked first for efficacy. In terms of safety, bisacodyl 10mg o.d. was ranked worst based on overall adverse events, and stimulant diphenyl methane laxatives as a class were the most likely to lead to abdominal pain, whereas velusetrag 50mg o.d. was the most likely to lead to either diarrhoea or dropout due to adverse events.

We described our search strategy, eligibility criteria, and data extraction processes in detail. In addition, the literature search, eligibility assessment, and data extraction were undertaken independently by two reviewers, with any discrepancies resolved by consensus. We used an intention-to-treat analysis, with all dropouts assumed to have failed therapy, and pooled data with a random effects model, in order to reduce the likelihood that any beneficial effect of pharmacological therapies in CIC has been overestimated. Heterogeneity was low in the majority of our analyses,

presumably because we pooled data according to identical endpoints at the same time points, wherever possible. We conducted analyses according to duration of therapy, type of drug and dosage used, and criteria used to define response to therapy. We also performed a sensitivity analysis using the more stringent endpoint recommended by the FDA to judge efficacy in treatment trials in CIC. Our results generally confirm those of the prior network meta-analysis, (17) but they update the list of drugs tested to all those that are relevant in 2019, and demonstrate significant differences in efficacy between individual drugs. Finally, we extracted and pooled data for total and individual adverse events, to ensure that the relative safety of these therapies, as well as their efficacy, could be judged.

There are several limitations of this network meta-analysis. Only seven of the eligible and included trials were at low risk of bias, (34, 40, 42-45, 49) and most RCTs were conducted in referral populations, meaning that the relative efficacy of these drugs in patients in primary care is unclear. There were no eligible head-to-head trials of one active drug versus another, meaning estimates of relative efficacy based on indirect comparisons. We did identify one RCT of polyethylene glycol versus prucalopride, but this trial was ineligible, as it did not use a fixed dose of prucalopride. (60) Another open-label trial of tegaserod versus polyethylene glycol did not report efficacy data using any of our endpoints of interest. (61) A RCT of prucalopride versus placebo was not able to be included as it used a variable dose of prucalopride, based on age. (62) In terms of newer drugs, we identified three RCTs of plecanatide, (46-48) but there were no eligible studies of either mizagliflozin or tenapanor. We did identify one trial of mizagliflozin, but this included a mixed population of patients with CIC and irritable bowel syndrome with constipation. (63) Two of the RCTs of elobixibat were not fully published, and had been terminated

early due to a supply issue with the active drug. (50, 51) Although we identified further published trials of elobixibat, these were ineligible as the treatment duration was only 2 weeks. (64, 65) The trials of lubiprostone were conducted over only 4 weeks and did not report efficacy according to either ≥3 CSBMs per week, or an increase of ≥1 CSBM per week over baseline, (52-54) meaning the relative efficacy of this drug according to FDA-recommended endpoints is unclear. The use of CSBMs as an outcome measure in treatment trials in CIC only captures one aspect of symptoms that patients' experience, and does not address other troublesome symptoms, such as straining at stool, sensation of incomplete evacuation or blockage, abdominal pain, and bloating. The effect of the drugs studied in this network meta-analysis on these is unknown. Finally, it is important to point out that there was no standardised reporting of adverse events, unlike for efficacy data, which may mean making comparisons of safety between individual treatments is less valid.

Although diphenyl methane laxatives and prucalopride were ranked first for efficacy at 4 and 12 weeks in this network meta-analysis, it is worth pointing out that very few trials mentioned whether the patients they recruited had been unresponsive to, or dissatisfied with, laxatives previously. The majority of trials that did report this information involved either prucalopride or tegaserod. As a result, the potentially milder spectrum of patients treated in the trials of stimulant diphenyl methane laxatives may have led to an overestimation of their efficacy, versus other therapies, at 4 weeks. In addition, the trials of linaclotide that reported data at 4 weeks used a more stringent endpoint of failure to achieve ≥3 CSBMs per week and an increase of ≥1 CSBM from baseline. (36, 39, 40) There is also the possibility that, because tegaserod, lubiprostone, and prucalopride were tested in CIC before linaclotide and plecanatide, patients in the more recent trials of these latter two agents had already

failed treatment with tegaserod, lubiprostone, or prucalopride. This would imply that a more treatment-resistant group of patients was studied in the trials of linaclotide and plecanatide. However, as these RCTs did not report the proportion of patients who had previously received treatment with other drugs for CIC, this point is speculative and, we suspect, unlikely, as the availability of tegaserod in the USA has been limited for the last 10 years, and prucalopride has only just received FDA-approval for the treatment of CIC.

Given the lack of head-to-head trials of individual drugs, all the conclusions in this network meta-analysis are derived from data based on indirect treatment comparisons. Network meta-analysis allows credible ranking systems of the likely efficacy and safety of different treatments to be developed in order to inform clinical decisions, even in the absence of trials making direct comparisons. (23) The results of our study are therefore still likely to be important for both patients and policy makers, in order to help inform treatment decisions for CIC. It is at least 5 years since national guidelines for the management of CIC were published in the USA. (66, 67) The American College of Gastroenterology monograph made strong recommendations for the use of osmotic or stimulant laxatives, 5-HT_4 agonists, and secretagogues in CIC, based on a mixture of low, moderate, and high quality evidence, but did not discuss their relative efficacy. (67) The American Gastroenterological Association technical review on CIC highlighted that “traditional” drug therapies may be as effective as newer pharmacological agents, but emphasised the lack of available evidence to allow judgements concerning the relative efficacy of pharmacological therapies to be made. (66) The information contained in this network meta-analysis should allow these evidence-based recommendations to be updated.

In summary, this systematic review and network meta-analysis has demonstrated that almost all drugs and dosages were superior to placebo, according to either failure to achieve ≥3 CSBMs per week or an increase of ≥1 CSBM per week over baseline, both at 4 weeks and at 8 to 12 weeks. However, the stimulant laxatives bisacodyl and sodium picosulfate were ranked first at 4 weeks, and were superior to almost all other drugs, including prucalopride, which was ranked first at 12 weeks. However, these trials may have recruited a milder spectrum of patients than those of other drugs. With regard to safety, bisacodyl 10mg o.d. was most likely to cause adverse events, and diphenyl methane laxatives the most likely to cause abdominal pain. Diarrhoea was more common with all drugs, other than tegaserod 2mg b.i.d., and diphenyl methane laxatives were more likely to cause diarrhoea than tegaserod, linaclotide, or prucalopride at the most commonly used doses. Although this information may assist clinicians and patients with CIC in making therapy-related choices, it is important to point out that the summary RRs were similar for many of the lower-ranked drugs, suggesting there is little to choose between them in terms of efficacy. In addition, the relatively short duration of treatment in many of the included trials means the longer-term effects of these drugs on symptoms in CIC, and their safety, are unknown.

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AUTHORS CONTRIBUTIONS

PL, MC, NEB, EMMQ, CJB, and ACF conceived and drafted the study. PL and ACF collected all data. CJB, ACF, and NEB analysed and interpreted the data. CJB, ACF,

and NEB drafted the manuscript. All authors commented on drafts of the paper. All authors have approved the final draft of the manuscript.

DECLARATION OF INTERESTS

Pavit Luthra: none. Michael Camilleri: has received research funding from Allergan and serves as a consultant to Ironwood, Allergan, Shire and Takeda with remuneration to his employer, Mayo Clinic, not to himself. Nicholas E. Burr: none. Eamonn M.M. Quigley: has acted as a consultant for Allergan, Ironwood, Salix, Synergy, and Vibrant, and received research funding from Vibrant and 4D Pharma. Christopher J. Black: none. Alexander C. Ford: has acted as a consultant for, and received researching funding from, Almirall.

ETHICS COMMITTEE APPROVAL

Not required.

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Table 1. Characteristics of Randomised Controlled Trials of Pharmacological Therapies Versus Placebo in Chronic Idiopathic Constipation.

Study	Country and Number of Centres	Diagnostic Criteria Used to Define CIC	Dichotomous Endpoints Used to Define Symptom Improvement Following Therapy	Number of Patients (% Female)	Number of Patients with Previous Laxative Use (%)	Number of Patients Assigned to Active Drug, Dosage, Schedule, and Duration of Therapy
Miner 1999 (29)*	Not stated	Rome II criteria	≥3 CSBMs† per week at 4 weeks	229 (not stated)	Previous laxative use not reported	42, 48, 47, and 46 patients received prucalopride 0.5mg, 1mg, 2mg, or 4mg o.d.§ respectively for 4 weeks
Coremans 2003 (30)	Belgium, 1 site	Rome II and <3 SBMs‡/week	≥3 SBMs per week at 4 weeks	53 (98.1)	53 (100%) previous laxative use	27 patients received prucalopride 4mg o.d. for 4 weeks
Camilleri 2008 (31)	USA, 38 sites	Rome II and <3 CSBMs/week	≥3 CSBMs per week at 4 and 12 weeks Increase of ≥1 CSBM/week from baseline at 12 weeks	628 (87.9)	602 (95.9%) previous laxative use	210 and 205 patients received prucalopride 2mg or 4mg o.d. respectively for 12 weeks
Quigley 2009 (32)	USA, 41 sites	Rome II and <3 CSBMs/week	≥3 CSBMs per week at 4 and 12 weeks Increase of ≥1 CSBM/week from baseline at 4 and 12 weeks	641 (86.6)	630 (98.3%) previous laxative use	214 and 215 patients received prucalopride 2mg or 4mg o.d. respectively for 12 weeks
Tack 2009 (33)	Multinational, number of sites not stated	Rome II and <3 CSBMs/week	≥3 CSBMs per week at 4 and 12 weeks Increase of ≥1 CSBM/week from baseline at 12 weeks	716 (90.8)	677 (94.6%) previous laxative use	238 and 238 patients received prucalopride 2mg or 4mg o.d. respectively for 12 weeks
Muller-Lissner 2010a (28)	Multinational, 48 sites	Rome II and <3 CSBMs/week	≥3 CSBMs per week at 4 weeks Increase of ≥1 CSBM/week from baseline at 4 weeks	303 (70.0)	252 (83.2%) previous laxative use	76, 75, and 80 patients received prucalopride 1mg, 2mg, or 4mg o.d. respectively for 4 weeks
Ke 2012 (34)	Multinational, 46 sites	Rome II and <3 SBMs/week	≥3 CSBMs per week at 4 and 12 weeks Increase of ≥1 CSBM/week from baseline at 12 weeks	501 (89.8)	360 (71.8%) previous laxative use	249 patients received prucalopride 2mg o.d. for 12 weeks

Yiannakou 2015 (35)	Multinational, 66 sites	Rome III and <3 CSBMs/week	≥3 CSBMs/week and an increase of ≥1 CSBM/week from baseline at 12 weeks ≥3 CSBMs per week at 4 and 12 weeks ≥3 SBMs per week at 12 weeks Increase of ≥1 CSBM/week from baseline at 12 weeks	374 (0)	Previous laxative use not reported	187 patients received prucalopride 2mg o.d. for 12 weeks
Lembo 2010 (36)	USA, 57 sites	Rome II and <3 SBMs/week	≥3 CSBMs/week and an increase of ≥1 CSBM/week from baseline at 4 weeks ≥3 SBMs/week and an increase of ≥1 SBM/week from baseline at 4 weeks	310 (92.0)	Previous laxative use not reported	59, 57, 62, and 63 patients received linaclotide 72µg, 145µg, 290µg, or 600µg o.d. respectively for 4 weeks
Lembo 2011a (37)	USA and Canada, 108 sites	Rome II and <3 SBMs/week	≥3 CSBMs/week and an increase of ≥1 CSBM/week from baseline at 12 weeks Increase of ≥1 CSBM/week from baseline at 12 weeks	633 (90.4)	Previous laxative use not reported	213 and 205 patients received linaclotide 145µg or 290µg o.d. respectively for 12 weeks
Lembo 2011b (37)	USA, 105 sites	Rome II and <3 SBMs/week	≥3 CSBMs/week and an increase of ≥1 CSBM/week from baseline at 12 weeks Increase of ≥1 CSBM/week from baseline at 12 weeks	643 (87.4)	Previous laxative use not reported	217 and 217 patients received linaclotide 145µg or 290µg o.d. respectively for 12 weeks
Lacy 2015 (38)	USA and Canada, 141 sites	Rome II, <3 SBMs/week, and an average bloating score of ≥5.0 on a scale of 0-10	≥3 CSBMs/week and an increase of ≥1 CSBM/week from baseline at 12 weeks ≥3 CSBMs per week at 4 and 12 weeks Increase of ≥1 CSBM/week from baseline at 12 weeks	487 (91.6)	Previous laxative use not reported	154 and 160 patients received linaclotide 145µg or 290µg o.d. respectively for 12 weeks

Fukudo 2019 (39)	Japan, 39 sites	Rome III and <3 SBMs/week	≥3 CSBMs/week and an increase of ≥1 CSBM/week from baseline at 4 weeks ≥3 SBMs/week and an increase of ≥1 SBM/week from baseline at 4 weeks	186 (82.3)	Previous laxative use not reported	95 patients received linaclotide 500μg o.d. for 4 weeks
Schoenfeld 2018 (40)	USA, 105 sites	Rome III and <3 SBMs/week	≥3 CSBMs/week and an increase of ≥1 CSBM/week from baseline at 4 and 12 weeks	1223 (77.0)	Previous laxative use not reported	411 and 411 patients received linaclotide 72μg or 145μg o.d. respectively for 12 weeks
Johanson 2004 (41)	Multinational, 105 sites	Rome II and <3 CSBMs/week	≥3 CSBMs per week at 4 and 12 weeks Increase of ≥1 CSBM/week from baseline at 4 and 12 weeks	1348 (90.0)	Recruited previous laxative users but numbers not reported	450 and 451 patients received tegaserod 2mg or 6mg b.i.d.± respectively for 12 weeks
Kamm 2005 (43)	Multinational, 128 sites	Rome II and <3 CSBMs/week	≥3 CSBMs per week at 4 and 12 weeks Increase of ≥1 CSBM/week from baseline at 4 and 12 weeks	1264 (86.3)	730 (57.8%) previous laxative use	417 and 431 patients received tegaserod 2mg or 6mg b.i.d. respectively for 12 weeks
Fried 2007 (42)	Multinational, 100 sites	Rome II and <3 CSBMs/week	≥3 CSBMs/week and an increase of ≥1 CSBM/week from baseline at 12 weeks Increase of ≥1 CSBM/week from baseline at 4 and 12 weeks	322 (0)	Previous laxative use not reported	158 patients received tegaserod 6mg b.i.d. for 12 weeks
Lin 2007 (44)	China, 15 sites	Rome II and <3 CSBMs/week	≥3 CSBMs per week at 4 weeks Increase of ≥1 CSBM/week from baseline at 4 weeks	607 (78.4)	217 (35.7%) previous laxative use	304 patients received tegaserod 6mg b.i.d. for 4 weeks
On Chan 2007 (45)	Hong Kong, 1 site	Rome II and <3 CSBMs/week	≥3 CSBMs per week at 8 weeks Increase of ≥1 CSBM/week from baseline at 8 weeks	250 (90.4)	133 (53.2%) previous laxative use	125 patients received tegaserod 6mg b.i.d. for 8 weeks
Miner 2013 (48)	USA, 121 sites	Rome III and <3 CSBMs/week	≥3 CSBMs/week and an increase of ≥1 CSBM/week from baseline at 12 weeks	951 (86.4)	Previous laxative use not reported	238, 238, and 238 patients received plecanatide 0.3mg, 1mg, or 3mg o.d. respectively for 12 weeks
DeMicco 2017 (47)	USA, 162 sites	Rome III and <3 CSBMs/week	≥3 CSBMs/week and an increase of ≥1 CSBM/week from baseline at 12 weeks	1402 (74.8)	Previous laxative use not reported	467 and 469 patients received plecanatide 3mg or 6mg o.d. respectively for 12 weeks

Miner 2017 (46)	USA and Canada, 164 sites	Rome III and <3 CSBMs/week	≥3 CSBMs/week and an increase of ≥1 CSBM/week from baseline at 12 weeks	1389 (80.8)	Previous laxative use not reported	474 and 457 patients received plecanatide 3mg or 6mg o.d. respectively for 12 weeks
Chey 2011 (49)	USA, 45 sites	Rome III and <3 CSBMs/week	Increase of ≥1 CSBM/week from baseline at 8 weeks	190 (89.5)	Previous laxative use not reported	48, 47, and 48 patients received elobixibat 5mg, 10mg, or 15mg o.d. respectively for 8 weeks
NCT01833065 (50)	Multinational, 97 sites	Rome III and <3 SBMs/week	≥3 CSBMs/week and an increase of ≥1 CSBM/week from baseline at 12 weeks	329 (84.7)	Previous laxative use not reported	100 and 118 patients received elobixibat 5mg or 10mg o.d. respectively for 12 weeks
NCT01827592 (51)	Multinational, 94 sites	Rome III and <3 SBMs/week	≥3 CSBMs/week and an increase of ≥1 CSBM/week from baseline at 12 weeks	376 (83.5)	Previous laxative use not reported	126 and 126 patients received elobixibat 5mg or 10mg o.d. respectively for 26 weeks‖
Johanson 2008 (52)	USA, 20 sites	Rome II and <3 SBMs/week	≥3 SBMs per week at 4 weeks	244 (89.7)	Previous laxative use not reported	120 patients received lubiprostone 24µg b.i.d. for 4 weeks
Barish 2010 (53)	Not stated, 20 sites	Rome II and <3 SBMs/week	≥4 SBMs per week at 4 weeks	237 (88.2)	Previous laxative use not reported	119 patients received lubiprostone 24µg b.i.d. for 4 weeks
Fukudo 2015 (54)	Japan, 11 sites	Rome III and <3 SBMs/week	≥4 SBMs per week at 4 weeks	124 (87.9)	75 (60.5%) previous laxative use	62 patients received lubiprostone 24µg b.i.d. for 4 weeks
Mueller-Lissner 2010b (56)	Germany, 45 sites	Rome III and <3 CSBMs/week	≥3 CSBMs/week at 4 weeks Increase of ≥1 CSBM/week from baseline at 4 weeks	367 (77.7)	Previous laxative use not reported	233 patients received sodium picosulfate (Dulcolax) 10mg o.d. for 4 weeks
Kamm 2011 (55)	UK, 27 sites	Rome III and <3 CSBMs/week	≥3 CSBMs/week at 4 weeks Increase of ≥1 CSBM/week from baseline at 4 weeks	368 (74.7)	Previous laxative use not reported	247 patients received bisacodyl (Dulcolax) 10mg o.d. for 4 weeks
Corazziari 1996 (58)	Italy, 6 sites	Rome I criteria and <2 SBMs/week	≥3 SBMs/week at 8 weeks	48 (77.1)	29 (60.4%) previous laxative use	25 patients received polyethylene glycol 17.5g b.i.d. for 8 weeks
Corazziari 2000 (57)	Italy, 5 sites	Rome I criteria and <2 SBMs/week	≥3 SBMs/week at 12 weeks	70 (82.9)	Recruited previous laxative users but numbers not reported	33 patients received polyethylene glycol 17.5g b.i.d. for 20 weeks‖

Goldberg 2010 (59)	USA, 49 sites	Rome III and <3 SBMs/week	≥3 CSBMs/week and an increase of ≥1 CSBM/week from baseline at 4 weeks ≥3 CSBMs/week at 4 weeks Increase of ≥1 CSBM/week from baseline at 4 weeks ≥3 SBMs per week at 4 weeks	401 (92.0)	Previous laxative use not reported	101, 96, and 97 patients received velusetrag 15mg, 30mg, or 50mg o.d. respectively for 4 weeks

*Full information not reported in published article, but obtained after correspondence with the authors

†CSBM; complete spontaneous bowel movement

§o.d.; once-daily

‡SBM; spontaneous bowel movement

±b.i.d.; twice-daily

‖Data extracted at 12 weeks for the purpose of this analysis

FIGURES

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

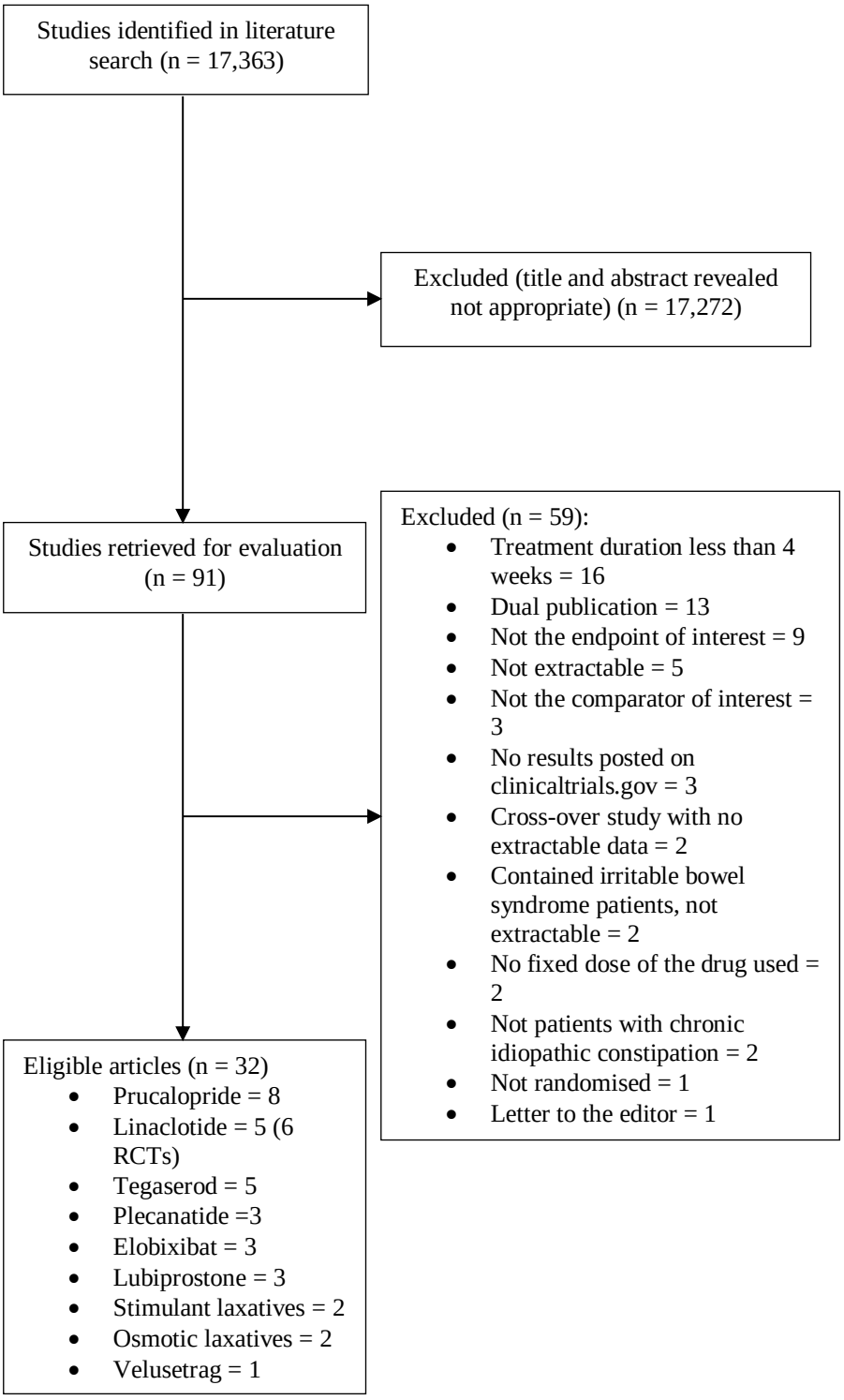

Figure 2. Forest Plot for Failure to Achieve ≥3 CSBMs Per Week at 4 Weeks.

Figure 3. Network Plot for Failure to Achieve ≥3 CSBMs Per Week at 8 to 12 Weeks.

Figure 4. Forest Plot for Failure to Achieve ≥3 CSBMs Per Week at 8 to 12 Week

Figure 5. League Ranking of Results for Failure to Achieve ≥3 CSBMs Per Week at 8 to 12 Weeks.

Figure 6. Forest Plot for Failure to Achieve an Increase of ≥1 CSBM Per Week from Baseline at 8 to 12 Weeks.

Figure 7. League Ranking of Results for Failure to Achieve an Increase of ≥1 CSBM Per Week from Baseline at 8 to 12 Weeks.