Efficacy of drugs in chronic idiopathic constipation: a systematic review and network meta-analysis

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Summary

Background There are several drugs available for the treatment of chronic idiopathic constipation, but their relative efficacy is unclear because there have been no head-to-head randomised controlled trials. We did a network meta-analysis to compare the efficacy of these therapies in patients with chronic idiopathic constipation.

Methods We searched Medline, Embase, Embase Classic, and the Cochrane Central Register of Controlled Trials for randomised controlled trials published from inception to week 3 June, 2019, to identify randomised controlled trials assessing the efficacy of drugs (osmotic or stimulant laxatives, elobixibat, linaclotide, lubiprostone, mizagliflozin, naronapride, plecanatide, prucalopride, tegaserod, tenapanor, or velusetrag) in adults with chronic idiopathic constipation. Participants had to be treated for a minimum of 4 weeks, and we extracted data for all endpoints preferentially at 4 weeks, 12 weeks, or both. Trials included in the analysis reported a dichotomous assessment of overall response to therapy (response or no response to therapy). We pooled the data using a random effects model, and reported efficacy and safety of all treatments as a pooled relative risk (RR) with 95% CIs to summarise the effect of each comparison tested. To rank treatments, we used P-scores, which measure the extent of certainty that a treatment is better than another treatment, averaged over all competing treatments.

Findings We identified 33 eligible randomised controlled trials of drugs, comprising 17 214 patients. Based on an endpoint of failure to achieve three or more complete spontaneous bowel movements (CSBMs) per week, the stimulant diphenyl methane laxatives bisacodyl and sodium picosulfate, at a dose of 10 mg once daily, were ranked first at 4 weeks (RR 0·55, 95% CI 0·48–0·63, P-score 0·99), and prucalopride 2 mg once daily ranked first at 12 weeks (0·82, 0·78–0·86, P-score 0·96). When response to therapy was defined as falilure to achieve an increase of one or more CSBM per week from baseline, diphenyl methane laxatives at a dose of 10 mg once daily ranked first at 4 weeks (0·44, 0·37–0·54, P-score 0·99), with prucalopride 4 mg once daily ranked first at 12 weeks (0·74, 0·66–0·83, P-score 0·79), although linaclotide 290 µg once daily and prucalopride 2 mg once daily had similar efficacy (P-scores of 0·76 and 0·71, respectively). Bisacodyl ranked last in terms of safety for total number of adverse events and abdominal pain (P-score 0·08).

Interpretation Almost all drugs studied were superior to placebo, according to either failure to achieve three or more CSBMs per week or or failure to achieve an increase of one or more CSBM per week over baseline. Although diphenyl methane laxatives ranked first at 4 weeks, patients with milder symptoms might have been included in these trials. Prucalopride ranked first at 12 weeks, and many of the included trials recruited patients who previously did not respond to laxatives, suggesting that this drug is likely to be the most efficacious for patients with chronic idiopathic constipation. However, because treatment duration in most trials was 4–12 weeks, the long-term relative efficacy of these drugs is unknown.

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Introduction

Chronic idiopathic constipation 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] Approximately one in five people with symptoms compatible with chronic idiopathic constipation will consult a physician,[3] and the effect 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,[5] constipation accounted for 3 million ambulatory visits and 800 000 emergency room visits. Costs in the USA are estimated to be between US$2000 and $7500 per patient per year.[6]

Patients with chronic idiopathic constipation are often told to increase their dietary fibre intake to alleviate symptoms, but there is little evidence from randomised controlled trials (RCTs) to support this strategy.[7] Although both osmotic and stimulant laxatives are beneficial for the treatment of chronic idiopathic constipation,[8] many patients report dissatisfaction with their efficacy and

Research in context

Evidence before this study

Chronic idiopathic constipation affects approximately 14% of the general population worldwide. Findings from randomised controlled trials show that laxatives and other newer pharmacological therapies are efficacious for the treatment of chronic idiopathic constipation. However, there is little information about their relative efficacy. A systematic review and network meta-analysis of randomised controlled trials was published in 2017, but the literature search was done in 2015, and more randomised controlled trials of newer drugs have been published in the intervening 4 years.

Added value of this study

We did a contemporaneous systematic review and network meta-analysis of randomised controlled trials reporting the efficacy of drugs in chronic idiopathic constipation. Analyses according to different efficacy endpoints and duration of therapy were done, 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 and were superior to almost all other treatments when failure to achieve an increase of three or more CSBMs per week or an increase of one or more CSBM per week over baseline were used to define response to therapy. However, trials of these drugs might have recruited patients with milder symptoms who were not laxative resistant. At 12 weeks of treatment, prucalopride 2 mg or 4 mg once daily were ranked first. Because most randomised controlled trials were of 4–12 weeks' duration, the longer-term efficacy of these treatments is unknown.

safety.[9] Other drugs for the disorder have therefore been developed. Agonists of the 5-hydroxytryptamine-4 receptor, such as tegaserod, naronapride, prucalopride, and velusetrag, increase colonic motility and transit.[10,11] Secretagogues such as lubiprostone, linaclotide, and plecanatide 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 drugs, including osmotic and stimulant laxatives, have been tested in placebo-controlled trials, but their relative efficacy was unknown until recently, because there are no head-to-head trials. A 2017 network meta-analysis[17] attempted to circumvent this limitation in the available evidence by making indirect treatment comparisons between all active therapies tested in placebo-controlled trials published up to March, 2015. These therapies 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 having three or more complete spontaneous bowel movements (CSBMs) per week. Similarly, all drugs were superior to placebo, except for tegaserod and linaclotide, and none were superior to each other, when an increase of one or more 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 the network meta-analysis was done,[17] there have been further trials of several of the drugs previously studied. In addition, RCTs of plecanatide in chronic idiopathic constipation have been completed, and prucalopride has been licensed for use in patients with chronic idiopathic constipation in the USA. A reappraisal of the available evidence to support clinical decision-making is timely. Therefore, we did a contemporaneous systematic review and network meta-analysis of RCTs of drugs in chronic idiopathic constipation. The US Food and Drug Administration (FDA) has made recommendations for the design of treatment trials and endorsed standardised endpoints that should be used to judge the efficacy of therapies in chronic idiopathic constipation. As a result, we have been able to do a network meta-analysis of RCTs of very similar design, similar treatment durations, and, in many instances, identical efficacy endpoints, to examine the relative efficacy and safety of all available pharmacological therapies.

Methods

Search strategy and selection criteria

We searched Medline (from inception to week 3 June, 2019), Embase, and Embase Classic (from from inception to week 3 June, 2019), and the Cochrane Central Register of Controlled Trials to identify potential studies. Additionally, we searched ClinicalTrials.gov for unpublished trials, and supplementary data for potentially eligible studies. 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 did a recursive search using the bibliographies of all obtained articles.

RCTs examining the effect of drugs (osmotic or stimulant laxatives, elobixibat, linaclotide, lubiprostone, mizagliflozin, naronapride, plecanatide, prucalopride, tegaserod, tenapanor, or velusetrag) in adult patients (aged >18 years) with chronic idiopathic constipation were eligible (appendix p 3). The first period of crossover randomised trials were eligible for inclusion if they provided efficacy data before crossover. The definitions of chronic idiopathic constipation considered within this network meta-analysis included either a clinician's opinion, or meeting specific symptom-based criteria (eg, the Rome criteria). Studies that recruited patients with organic constipation, drug-induced constipation, or highly selected groups of patients (such as elderly patients living in institutions) were ineligible, as were trials that recruited mixed populations of patients with chronic idiopathic constipation and irritable bowel syndrome with constipation for which data were not reported separately for the participants with chronic idiopathic constipation.

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. Participants had to be treated for a minimum of 4 weeks, and we extracted data for all endpoints preferentially at 4 weeks, 12 weeks, or both, if reported. including for studies with efficacy data at other timepoints. We used this method to ensure as much homogeneity as possible between individual trial results, and to avoid overestimating the efficacy of one drug relative to another, because the placebo effect in functional gastrointestinal disorders has been shown to decrease with time, from an average of 46% in trials of 1–4 weeks' duration, 39·8% in trials of 5–8 weeks' duration, and 34% for trials that are longer than 8 weeks.[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 when required.

Two investigators (PL and ACF) did the literature search independently from one another. Studies of chronic idiopathic constipation were identified with the terms "constipation" or "gastrointestinal transit" (both as medical subject headings and free text terms), or "functional constipation", "idiopathic constipation", "chronic constipation", or "slow transit" (as free text terms). These terms 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 medical subject headings terms and free text terms), or the 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 independently from one another. They 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 papers that were not in the English language. We resolved disagreements between investigators by discussion.

See Online for appendix

Data analysis

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

Two investigators (PL and ACF) extracted all data independently onto a Microsoft Excel spreadsheet (XP professional edition) as dichotomous outcomes (response or no response to therapy). The included eligible studies often reported identical dichotomous endpoints to assess efficacy of the various therapies. We were therefore able to assess efficacy according to the following criteria, which generally conform to the endpoints studied in the previous network meta-analysis:[17] the proportion of patients who did not have three or more CSBMs per week (with or without an increase of one or more CSBM per week from baseline), the proportion of patients who did not have an increase in the number of CSBMs per week from baseline of more than one, the proportion of patients who did not have three or more spontaneous bowel movements (SBMs) per week, and the proportion of patients who did not have an improvement in quality of life (according to the patient assessment of constipation quality of life). We did two prespecified sensitivity analyses. First, we used the most stringent endpoint reported by some of the trials, which was the proportion of patients who failed to achieve both three or more CSBMs per week and an increase of more than one CSBM from baseline. Second, in the case of trials that reported efficacy endpoints at neither 4 or 12 weeks, but at some point in between, we included these with the 12-week data, but excluded them in a sensitivity analysis

When possible, we extracted the following data from trials: country of origin, number of centres, criteria used to define chronic idiopathic constipation, proportion of female patients, proportion of patients who had used laxatives previously, and dose and duration of therapy. We extracted data for intention-to-treat analyses, with

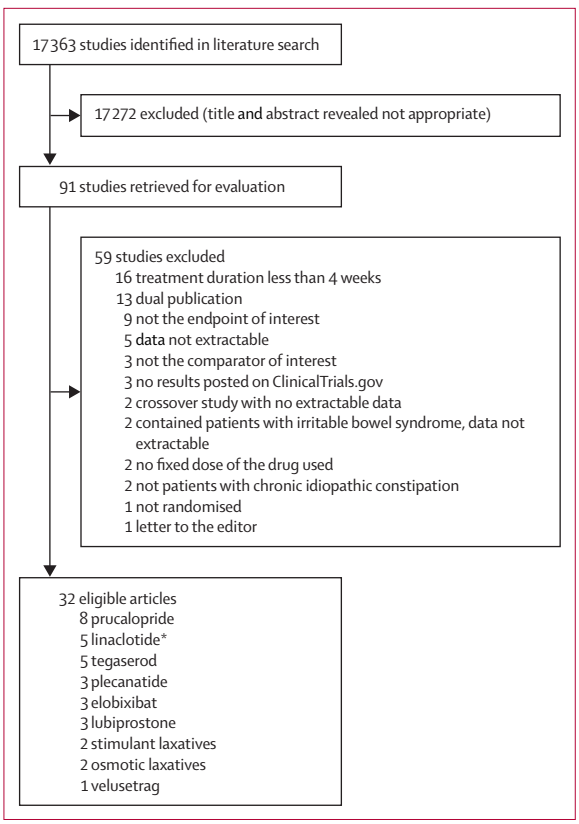

Figure 1: **Study selection**
*Five articles reporting findings from six trials.

dropouts assumed to not have responded to treatment, when trial reporting allowed. If these data were not clear from the original article, we planned to do an analysis on all patients with reported evaluable data.

We used the Cochrane risk of bias tool[19] to assess bias at the study level. Two investigators (PL and ACF) did this independently, and disagreements were resolved by discussion. We recorded the method used to generate the randomisation schedule and conceal treatment allocation, as well as whether masking 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 (appendix pp 5–7).

We did a network meta-analysis using the frequentist model, with the statistical package netmeta (version 0.9–0) in R (version 3.4.2). This study was reported according to the PRISMA extension statement for network meta-analyses[20] to explore indirect treatment comparisons of the efficacy and safety of each drug. Network meta-analysis results usually give a more precise estimate than do 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 size corresponding with the number of study participants and connection size corresponding with the number of studies. 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). Funnel plots are scatterplots of effect size versus precision, measured using the inverse of the standard error. Symmetry around the effect estimate line shows the absence of publication bias, or small study effects.[24] We produced a pooled relative risk (RR) with 95% 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, for which 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. Because there were no direct comparisons between individual drugs, we were unable to do 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 25–49% are considered low, 50–74% are considered moderate, and 75% or more are considered high levels of heterogeneity.[26] We ranked treatments according to their P-score, which is a value between 0 and 1. P-scores are based 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 imply a greater probability of the treatment being as best,[27] but the magnitude of the P-score should be considered, as well as the treatment rank. Because 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

There was no funding source for this study. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

Results

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 studies, 59 were excluded. Overall, we included 32 eligible articles reporting on 33 separate trials. These trials contained 17 214 patients who were allocated to active therapy or placebo (appendix p 4).[28–59] We did not identify any eligible RCTs of mizagliflozin, naronapride, or tenapanor.

Agreement between investigators for trial eligibility was good (κ 0·83). Detailed characteristics of individual RCTs are provided in the table. One trial of elobixibat and one trial of tegaserod were only of 8 weeks' duration;[45,49]

	Country and number of centres	Diagnostic criteria used to define CIC	Endpoints used to define symptom improvement following therapy	Total number of patients	Proportion of female patients‡	Number of patients with previous laxative use (%)	Number of patients assigned to active drug, dose, schedule, and duration of therapy
Miner (1999)[29]*	Not stated	Rome II criteria	≥3 CSBMs per week at 4 weeks	229	Not stated	Not reported	Prucalopride 0·5 mg (n=42), 1 mg (n=48), 2 mg (n=47), or 4 mg (n=46), once daily, for 4 weeks
Coremans (2003)[30]	Belgium, one site	Rome II, <3 SBMs per week	≥3 SBMs per week at 4 weeks	53	98·1%	53 (100%)	Prucalopride 4 mg (n=27), once daily, for 4 weeks
Camilleri (2008)[31]	USA, 38 sites	Rome II, <3 CSBMs per week	≥3 CSBMs per week at 4 and 12 weeks; increase of ≥1 CSBM per week from baseline at 12 weeks	628	87·9%	602 (95·9%)	Prucalopride 2 mg (n=210), or 4 mg (n=205), once daily, for 12 weeks
Quigley (2009)[32]	USA, 41 sites	Rome II, <3 CSBMs per week	≥3 CSBMs per week at 4 and 12 weeks; increase of ≥1 CSBM per week from baseline at 4 and 12 weeks	641	86·6%	630 (98·3%)	Prucalopride 2 mg (n=214), or 4 mg (n=215), once daily, for 12 weeks
Tack (2009)[33]	Multinational, number of sites not stated	Rome II, <3 CSBMs per week	≥3 CSBMs per week at 4 and 12 weeks; increase of ≥1 CSBM per week from baseline at 12 weeks	716	90·8%	677 (94·6%)	Prucalopride 2 mg (n=238), or 4 mg (n=238), once daily, for 12 weeks
Muller-Lissner (2010)[28]	Multinational, 48 sites	Rome II, <3 CSBMs per week	≥3 CSBMs per week at 4 weeks; increase of ≥1 CSBM per week from baseline at 4 weeks	303	70·0%	252 (83·2%)	Prucalopride 1 mg (n=76), 2 mg (n=75), or 4 mg (n=80), once daily, for 4 weeks
Ke (2012)[34]	Multinational, 46 sites	Rome II, <3 SBMs per week	≥3 CSBMs per week at 4 and 12 weeks; increase of ≥1 CSBM per week from baseline at 12 weeks	501	89·8%	360 (71·8%)	Prucalopride 2 mg (n=249), once daily, for 12 weeks
Yiannakou (2015)[35]	Multinational, 66 sites	Rome III, <3 CSBMs per week	≥3 CSBMs per week and an increase of ≥1 CSBM per 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 per week from baseline at 12 weeks	374	0%	Not reported	Prucalopride 2 mg (n=187), once daily, for 12 weeks
Lembo (2010)[36]	USA, 57 sites	Rome II, <3 SBMs per week	≥3 CSBMs per week and an increase of ≥1 CSBM per week from baseline at 4 weeks; ≥3 SBMs per week and an increase of ≥1 SBM per week from baseline at 4 weeks	310	92·0%	Not reported	Linaclotide 72 µg (n=59), 145 µg (n=57), 290 µg (n=62), or 600 µg (n=63), once daily, for 4 weeks
Lembo (2011)[37]	USA and Canada, 108 sites	Rome II, <3 SBMs per week	≥3 CSBMs per week and an increase of ≥1 CSBM per week from baseline at 12 weeks; increase of ≥1 CSBM per week from baseline at 12 weeks	633	90·4%	Not reported	Linaclotide 145 µg (n=213), or 290 µg (n=205), once daily, for 12 weeks
Lembo (2011)[37]	USA, 105 sites	Rome II, <3 SBMs per week	≥3 CSBMs per week and an increase of ≥1 CSBM per week from baseline at 12 weeks; increase of ≥1 CSBM per week from baseline at 12 weeks	643	87·4%	Not reported	Linaclotide 145 µg (n=217), or 290 µg (n=217), once daily, for 12 weeks
Lacy (2015)[38]	USA and Canada, 141 sites	Rome II, <3 SBMs per week, an average bloating score of ≥5·0 on a scale of 0–10	≥3 CSBMs per week and an increase of ≥1 CSBM per week from baseline at 12 weeks; ≥3 CSBMs per week at 4 and 12 weeks; increase of ≥1 CSBM per week from baseline at 12 weeks	487	91·6%	Not reported	Linaclotide 145 µg (n=154), or 290 µg (n=160), once daily, for 12 weeks

(Table continues on next page)

	Country and number of centres	Diagnostic criteria used to define CIC	Endpoints used to define symptom improvement following therapy	Total number of patients	Proportion of female patients‡	Number of patients with previous laxative use (%)	Number of patients assigned to active drug, dose, schedule, and duration of therapy
(Continued from previous page)							
Fukudo (2019)[39]	Japan, 39 sites	Rome III, <3 SBMs per week	≥3 CSBMs per week and an increase of ≥1 CSBM per week from baseline at 4 weeks; ≥3 SBMs per week and an increase of ≥1 SBM per week from baseline at 4 weeks	186	82·3%	Not reported	Linaclotide 500 µg (n=95), once daily, for 4 weeks
Schoenfeld (2018)[40]	USA, 105 sites	Rome III, <3 SBMs per week	≥3 CSBMs per week and an increase of ≥1 CSBM per week from baseline at 4 and 12 weeks	1223	77·0%	Not reported	Linaclotide 72 µg (n=411), or 145 µg (n=411), once daily, for 12 weeks
Johanson (2004)[41]	Multinational, 105 sites	Rome II, <3 CSBMs per week	≥3 CSBMs per week at 4 and 12 weeks; increase of ≥1 CSBM per week from baseline at 4 and 12 weeks	1348	90·0%	Recruited previous laxative users but numbers not reported	Tegaserod 2 mg (n=450), 6 mg (n=451), twice daily, for 12 weeks
Kamm (2005)[43]	Multinational, 128 sites	Rome II, <3 CSBMs per week	≥3 CSBMs per week at 4 and 12 weeks; increase of ≥1 CSBM per week from baseline at 4 and 12 weeks	1264	86·3%	730 (57·8%)	Tegaserod 2 mg (n=417), 6 mg (n=431), twice daily, for 12 weeks
Fried (2007)[42]	Multinational, 100 sites	Rome II, <3 CSBMs per week	≥3 CSBMs per week and an increase of ≥1 CSBM per week from baseline at 12 weeks; increase of ≥1 CSBM per week from baseline at 4 and 12 weeks	322	0%	Not reported	Tegaserod 6 mg (n=158), twice daily, for 12 weeks
Lin (2007)[44]	China, 15 sites	Rome II, <3 CSBMs per week	≥3 CSBMs per week at 4 weeks; increase of ≥1 CSBM per week from baseline at 4 weeks	607	78·4%	217 (35·7%)	Tegaserod 6 mg (n=304), twice daily, for 4 weeks
On Chan (2007)[45]	Hong Kong, one site	Rome II, <3 CSBMs per week	≥3 CSBMs per week at 8 weeks; increase of ≥1 CSBM per week from baseline at 8 weeks	250	90·4%	133 (53·2%)	Tegaserod 6 mg (n=125), twice daily, for 8 weeks
Miner (2013)[48]	USA, 121 sites	Rome III, <3 CSBMs per week	≥3 CSBMs per week and an increase of ≥1 CSBM per week from baseline at 12 weeks	951	86·4%	Not reported	Plecanatide 0·3 mg (n=238), 1 mg (n=238), or 3 mg (n=238), once daily, for 12 weeks
DeMicco (2017)[47]	USA, 162 sites	Rome III, <3 CSBMs per week	≥3 CSBMs per week and an increase of ≥1 CSBM per week from baseline at 12 weeks	1402	74·8%	Not reported	Plecanatide 3 mg (n=467), or 6 mg (n=469), once daily, for 12 weeks
Miner (2017)[46]	USA and Canada, 164 sites	Rome III, <3 CSBMs per week	≥3 CSBMs per week and an increase of ≥1 CSBM per week from baseline at 12 weeks	1389	80·8%	Not reported	Plecanatide 3 mg (n=474), or 6 mg (n=457), once daily, for 12 weeks
Chey (2011)[49]	USA, 45 sites	Rome III, <3 CSBMs per week	Increase of ≥1 CSBM per week from baseline at 8 weeks	190	89·5%	Not reported	Elobixibat 5 mg (n=48), 10 mg (n=47), or 15 mg (n=48) once daily, for 8 weeks
NCT01833065	Multinational, 97 sites	Rome III, <3 SBMs per week	≥3 CSBMs per week and an increase of ≥1 CSBM per week from baseline at 12 weeks	329	84·7%	Not reported	Elobixibat 5 mg (n=100), or 10 mg (n=118), once daily, for 12 weeks
NCT01827592	Multinational, 94 sites	Rome III, <3 SBMs per week	≥3 CSBMs per week and an increase of ≥1 CSBM per week from baseline at 12 weeks	376	83·5%	Not reported	Elobixibat 5 mg (n=126), or 10 mg (n=126), once daily, for 26 week†

(Table continues on next page)

	Country and number of centres	Diagnostic criteria used to define CIC	Endpoints used to define symptom improvement following therapy	Total number of patients	Proportion of female patients‡	Number of patients with previous laxative use (%)	Number of patients assigned to active drug, dose, schedule, and duration of therapy
(Continued from previous page)							
Johanson (2008)[52]	USA, 20 sites	Rome II, <3 SBMs per week	≥3 SBMs per week at 4 weeks	244	89·7%	Not reported	Lubiprostone 24 µg (n=120), twice daily, for 4 weeks
Barish (2010)[53]	Not stated, 20 sites	Rome II, <3 SBMs per week	≥4 SBMs per week at 4 weeks	237	88·2%	Not reported	Lubiprostone 24 µg (n=119), twice daily, for 4 weeks
Fukudo (2015)[54]	Japan, 11 sites	Rome III, <3 SBMs per week	≥4 SBMs per week at 4 weeks	124	87·9%	75 (60·5%)	Lubiprostone 24 µg (n=62), twice daily, for 4 weeks
Mueller-Lissner (2010)[56]	Germany, 45 sites	Rome III, <3 CSBMs per week	≥3 CSBMs per week at 4 weeks; increase of ≥1 CSBM per week from baseline at 4 weeks	367	77·7%	Not reported	Sodium picosulfate (dulcolax) 10 mg (n=233), once daily, for 4 weeks
Kamm (2011)[55]	UK, 27 sites	Rome III, <3 CSBMs per week	≥3 CSBMs per week at 4 weeks; increase of ≥1 CSBM per week from baseline at 4 weeks	368	74·7%	Not reported	Bisacodyl (dulcolax) 10 mg (n=247), once daily, for 4 weeks
Corazziari (1996)[58]	Italy, 6 sites	Rome I criteria, <2 SBMs per week	≥3 SBMs per week at 8 weeks	48	77·1%	29 (60·4%)	Polyethylene glycol 17·5 g (n=25), twice daily, for 8 weeks
Corazziari (2000)[57]	Italy, 5 sites	Rome I criteria, <2 SBMs per week	≥3 SBMs per week at 12 weeks	70	82·9%	Recruited previous laxative users but numbers not reported	Polyethylene glycol 17·5 g (n=33), twice daily, for 20 weeks†
Goldberg (2010)[59]	USA, 49 sites	Rome III, <3 SBMs per week	≥3 CSBMs per week and an increase of ≥1 CSBM per week from baseline at 4 weeks; ≥3 CSBMs per week at 4 weeks; increase of ≥1 CSBM per week from baseline at 4 weeks; ≥3 SBMs per week at 4 weeks	401	92·0%	Not reported	Velusetrag 15 mg (n=101), 30 mg (n=96), or 50 mg (n=97), once daily, for 4 weeks

CIC=chronic idiopathic constipation. CSBM=complete spontaneous bowel movement. SBM=spontaneous bowel movement. *Full information not reported in published article, but obtained after correspondence with the authors. †Data extracted at 12 weeks for this analysis. ‡Proportion of female patients relative to total number of patients was extracted.

Table: **Characteristics of randomised controlled trials of pharmacological therapies versus placebo in patients with chronic idiopathic constipation**

therefore, we included data from those 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 three or more SBMs per week.[52–54] Two of the elobixibat trials were terminated early because of a supply issue with the study medication, but efficacy and safety data at 12 weeks were available from ClinicalTrials.gov.[50,51] Only 13 RCTs had reported specifically that they recruited patients who has used laxatives previously,[28,30–34,41,43–45,54,57,58] six of which used prucalopride, and four used tegaserod. Risk of bias for all included trials is reported in the appendix (pp 5–7); 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 these data for all included studies. No trials made head-to-head comparisons of one drug versus another, meaning that direct evidence was available only 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.

16 RCTs, including 9466 patients, reported data for failure to achieve three or more CSBMs per week at 4 weeks.[28,29,31–36,39–41,43,44,55,56,59] 6155 (65%) patients were randomly assigned to active treatment. The network plot is provided in the appendix p 12. When data were pooled there was low statistical heterogeneity (I^2=45·5%) and no evidence of publication bias or other small study effects (appendix p 13). All treatments were significantly more effective than placebo at 4 weeks, except for prucalopride 0·5 mg once daily, which is less than the minimum approved dose, but the stimulant diphenyl methane laxatives sodium picosulfate and bisacodyl 10 mg once daily were ranked first in two RCTs (RR 0·55, 95% CI 0·48–0·63; figure 2). The probability of these drugs being the most efficacious when all treatments, including placebo, were compared with each other was 99%. After indirect comparison of active treatments, there were significant differences with: stimulant diphenyl methane

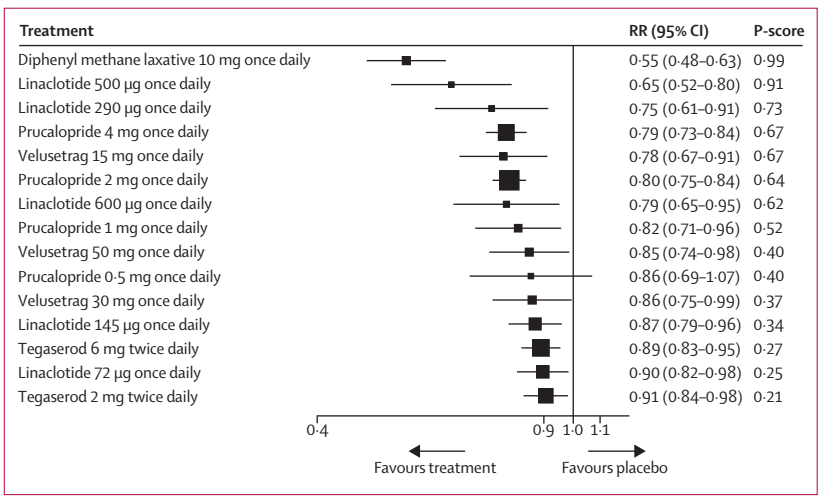

Figure 2: **Forest plot for failure to achieve three or more complete spontaneous bowel movements per week at 4 weeks**
Diphenyl methane laxatives were bisacodyl and sodium picosulfate.

laxatives compared with all other drugs except for linaclotide 500 µg once daily; linaclotide 500 µg once daily, which is a licensed dose only in Japan, compared with velusetrag 30 mg or 50 mg once daily, linaclotide 72 µg or 145 µg once daily, and tegaserod 2 mg or 6 mg twice daily; and both prucalopride 2 mg and 4 mg once daily compared with tegaserod 2 mg or 6 mg twice daily and linaclotide 72 µg once daily (appendix p 8).

17 trials, published in 16 articles, reported data for failure to achieve three or more CSBMs per week at 12 weeks,[31–35,37,38,40–43,46–48,50,51] and one RCT reported this outcome at 8 weeks.[45] Of 13477 patients, 8827 (65·5%) were randomly assigned to active treatment and 4650 (34·5%) to placebo. The network plot is provided in figure 3. When data were pooled there was low statistical heterogeneity (I^2=34·4%), and no evidence of publication bias or other small study effects (appendix p 14). All treatments were significantly more effective than placebo at 8–12 weeks, except for plecanatide 1 mg once daily and

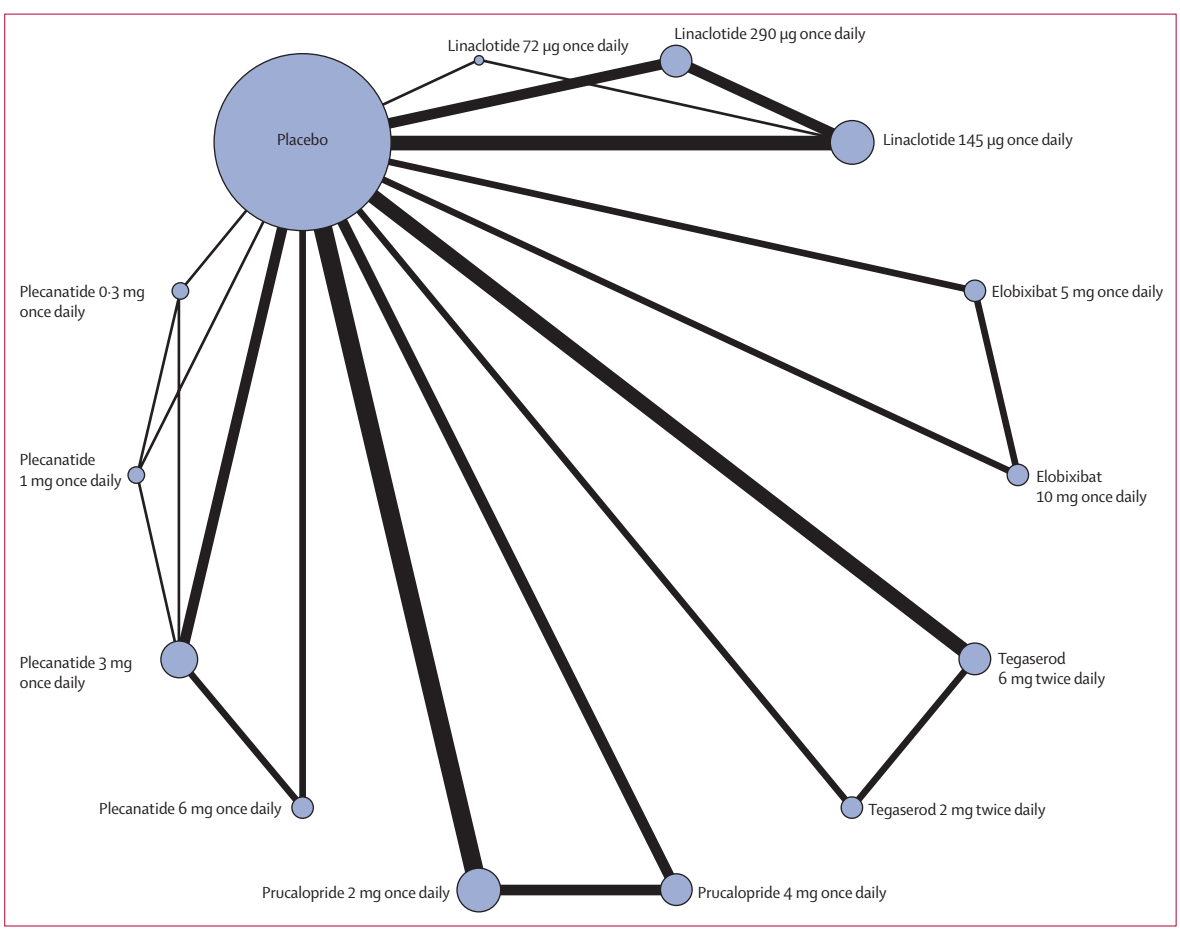

Figure 3: **Network plot for failure to achieve three or more complete spontaneous bowel movements per week at 8–12 weeks**

elobixibat 10 mg once daily, but prucalopride 2 mg once daily was ranked first (P-score=0·96) in five RCTs (RR 0·82, 95% CI 0·78–0·86; figure 4). After indirect comparison of active treatments, there were significant differences with: prucalopride 2 mg once daily and all other treatments except for prucalopride 4 mg once daily, linaclotide 72 µg or 290 µg once daily, tegaserod 6 mg twice daily, elobixibat 5 mg once daily, and plecanatide 0·3 mg once daily; prucalopride 4 mg once daily compared with plecanatide 6 mg once daily, tegaserod 2 mg twice daily, and elobixibat 10 mg once daily; and linaclotide 290 µg once daily compared with elobixibat 10 mg once daily (figure 5). We did a sensitivity analysis, excluding the trial of tegaserod 6 mg twice daily that only reported endpoints at 8 weeks,[45] but this did not affect the ranking of tegaserod 6 mg twice daily (data not shown).

11 of the included trials, reported in ten articles,[35,37,38,40,42,46–48,50,51] used a more stringent endpoint of failure to achieve three or more CSBMs per week and an increase of more than one CSBM from baseline. When data from these trials, comprising 8129 patients, were pooled in a further sensitivity analysis, prucalopride 2 mg once daily was still ranked first (RR 0·84, 95% CI 0·75–0·93, P-score 0·88; appendix p 15). After indirect comparison, prucalopride 2 mg once daily was superior only to elobixibat 10 mg once daily. There was no heterogeneity in this analysis (I^2=12·0%).

Nine trials reported data for achieve an increase of one or more CSBM per week from baseline at 4 weeks.[28,32,41–44,55,56,59] Of 5621 patients, 3645 (65%) were randomly assigned to active treatment, and 1976 (35%) to placebo. The network plot is provided in the appendix p 16. When data were pooled there was low 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 10 mg once daily were ranked first (P-score 0·99) in two RCTs (RR 0·44, 95% CI 0·37–0·54; appendix p 17). On indirect comparison, stimulant diphenyl methane laxatives were superior to all treatments except for prucalopride 1 mg once daily, and prucalopride 1 mg once daily (P-score 0·84) was superior to tegaserod 2 mg twice daily (appendix p 9).

11 RCTs, published in ten articles, reported an increase of one or more 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 (64%) of whom were randomly assigned to active treatment. The network plot is provided in the appendix (p 18). 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 (appendix p 19). All treatments were significantly more effective than placebo at 8–12 weeks, but elobixibat 15 mg once daily was ranked first (P-score 0·91, RR 0·53,95% CI 0·35–0·82), although in only one RCT of 8 weeks duration (figure 6). After indirect comparison of active treatments, there were significant differences with both elobixibat 15 mg once daily and prucalopride 4 mg once daily (P-score 0·59), compared with tegaserod 2 mg twice daily (figure 7).

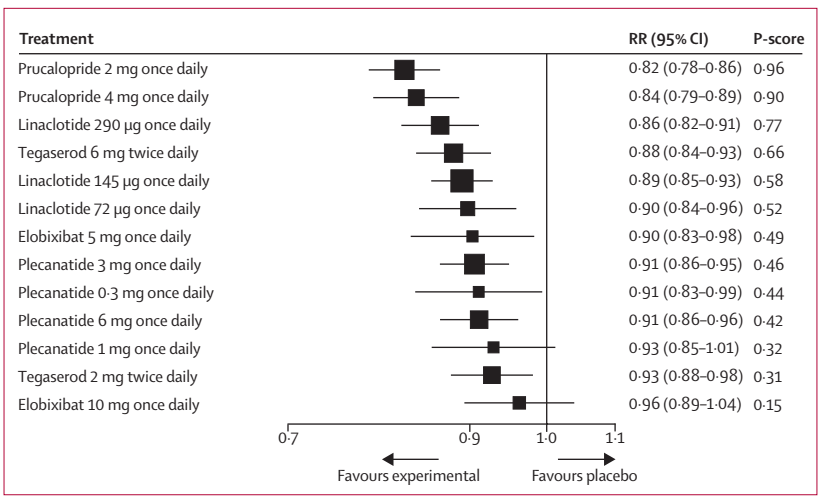

Figure 4: **Forest plot for failure to achieve three or more complete spontaneous bowel movements per week at 8–12 weeks**

In a sensitivity analysis, including only the 11 trials of 12 weeks' duration containing 7557 patients, published in ten articles,[31–35,37,38,41–43] prucalopride 4 mg once daily was ranked first (P-score 0·79) in three RCTs (RR 0·74, 95% CI 0·66–0·83); moderate heterogeneity between studies persisted (I^2=54·3%). However, linaclotide 290 µg once daily and prucalopride 2 mg once daily had similar P-scores (0·76 and 0·71, respectively), and there were no significant differences between active therapies after indirect comparison, except for a significant difference between prucalopride 4 mg once daily and tegaserod 2 mg twice daily. Other efficacy data are provided in the appendix p 1.

29 trials, published in 28 articles, reported the total number of adverse events in 16 419 patients, 10 659 (65%) 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 2 mg and 4 mg once daily, plecanatide 3 mg once daily; linaclotide 72 µg, 145 µg, 290 µg, and 500 µg once daily; elobixibat 10 mg and 15 mg once daily; lubiprostone 24 µg twice daily; and bisacodyl 10 mg once daily (appendix p 20). When ranked using a P-score, plecanatide 0·3 mg once daily was ranked first, and bisacodyl 10 mg once daily was ranked last in terms of overall adverse events (P-scores 0·95 and 0·08, respectively). Indirect comparison of active treatments revealed that bisacodyl 10 mg once daily was significantly

Prucalopride 2 mg once daily												
0·98 (0·92–1·05)	Prucalopride 4 mg once daily											
0·95 (0·89–1·02)	0·97 (0·89–1·05)	Linaclotide 290 µg once daily										
0·93 (0·87–1·00)	0·95 (0·88–1·03)	0·98 (0·91–1·06)	Tegaserod 6 mg twice daily									
0·92 (0·87–0·99)	0·94 (0·87–1·01)	0·97 (0·91–1·03)	0·99 (0·92–1·06)	Linaclotide 145 µg once daily								
0·92 (0·84–1·00)	0·93 (0·85–1·02)	0·96 (0·89–1·05)	0·98 (0·90–1·07)	0·99 (0·93–1·06)	Linaclotide 72 µg once daily							
0·91 (0·83–1·00)	0·93 (0·83–1·03)	0·96 (0·86–1·06)	0·97 (0·88–1·08)	0·99 (0·90–1·08)	0·99 (0·89–1·11)	Elobixibat 5 mg once daily						
0·91 (0·85–0·97)	0·92 (0·86–1·00)	0·95 (0·89–1·02)	0·97 (0·91–1·04)	0·98 (0·92–1·05)	0·99 (0·91–1·08)	1·00 (0·90–1·10)	Plecanatide 3 mg once daily					
0·90 (0·82–1·00)	0·92 (0·83–1·02)	0·95 (0·86–1·05)	0·97 (0·87–1·07)	0·98 (0·89–1·08)	0·98 (0·88–1·10)	0·99 (0·88–1·12)	0·99 (0·91–1·09)	Plecanatide 0·3 mg once daily				
0·90 (0·84–0·97)	0·92 (0·85–0·99)	0·95 (0·88–1·02)	0·97 (0·90–1·04)	0·98 (0·91–1·05)	0·98 (0·90–1·07)	0·99 (0·90–1·10)	0·99 (0·94–1·05)	1·00 (0·91–1·10)	Plecanatide 6 mg once daily			
0·88 (0·80–0·98)	0·90 (0·81–1·00)	0·93 (0·84–1·03)	0·95 (0·86–1·05)	0·96 (0·87–1·05)	0·97 (0·87–1·08)	0·97 (0·86–1·10)	0·97 (0·89–1·06)	0·98 (0·89–1·08)	0·98 (0·89–1·08)	Plecanatide 1 mg once daily		
0·89 (0·82–0·96)	0·90 (0·83–0·98)	0·93 (0·86–1·01)	0·95 (0·89–1·01)	0·96 (0·89–1·03)	0·97 (0·89–1·06)	0·97 (0·88–1·08)	0·98 (0·91–1·05)	0·98 (0·88–1·09)	0·98 (0·91–1·06)	1·00 (0·90–1·11)	Tegaserod 2 mg once daily	
0·85 (0·78–0·93)	0·87 (0·79–0·96)	0·90 (0·82–0·98)	0·91 (0·83–1·00)	0·92 (0·85–1·01)	0·93 (0·84–1·03)	0·94 (0·86–1·02)	0·94 (0·86–1·03)	0·95 (0·84–1·06)	0·95 (0·86–1·04)	0·97 (0·86–1·08)	0·96 (0·88–1·06)	Elobixibat 10 mg once daily
0·82 (0·78–0·86)	0·84 (0·79–0·89)	0·86 (0·82–0·91)	0·88 (0·84–0·93)	0·89 (0·85–0·93)	0·90 (0·84–0·96)	0·90 (0·83–0·98)	0·91 (0·86–0·95)	0·91 (0·83–0·99)	0·91 (0·86–0·96)	0·93 (0·85–1·01)	0·93 (0·88–0·98)	0·96 (0·89–1·04)

Placebo

Figure 5: **Relative efficacy of treatments for failure to achieve three or more complete spontaneous bowel movements per week at 8–12 weeks**
Data are relative risk (95% CI). Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall effectiveness. The treatment in the top-left position is ranked as most efficacious according to the network meta-analysis of indirect effects. Boxes highlighted in green show significant differences.

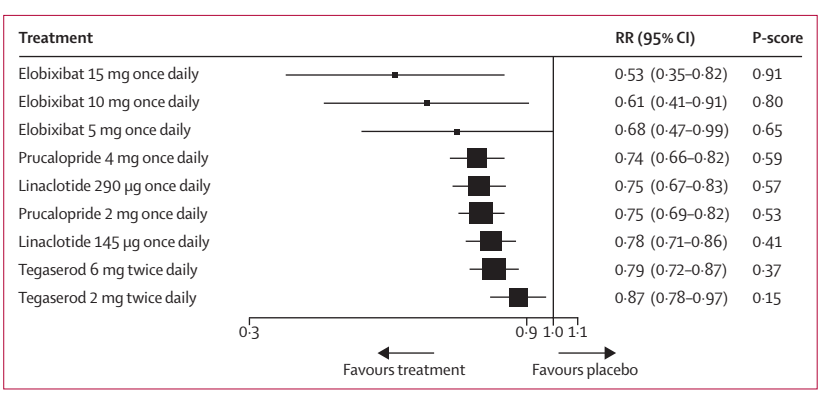

Figure 6: **Forest plot for failure to achieve an increase of one or more complete spontaneous bowel movements from baseline at 8–12 weeks**

more likely to lead to adverse events than linaclotide 290 µg once daily; plecanatide 0·3 mg, 1 mg, 3 mg, and 6 mg once daily; prucalopride 2 mg and 4 mg once daily; and tegaserod 2 mg and 6 mg twice daily (appendix p 21). Data about withdrawals due to adverse events and individual adverse events are provided in the appendix pp 1–2.

Discussion

This network meta-analysis shows that the diphenyl methane laxatives sodium picosulfate and bisacodyl were ranked first at 4 weeks, when either failure to achieve three or more CSBMs per week or faiure to achieve an increase of one or more CSBM per week over baseline were used as the endpoint to define response to therapy. These laxatives seemed superior to all other drugs except linaclotide 500 µg once daily for the outcome of failure to achieve three or more CSBMs per week, and prucalopride 1 mg once daily for the outcome of failure to achieve an increase of one or more CSBM per week over baseline. At 12 weeks of treatment, prucalopride 2 mg or 4 mg once daily were ranked first, and appeared superior to several other drugs and doses. At 8–12 weeks, elobixibat 15 mg once daily was ranked first when using failure to achieve an increase of one or more CSBM per week over baseline. Sensitivity analyses using the more stringent endpoint of failure to achieve three or more CSBMs per week and an increase of one or more CSBM per week over baseline did not change the main result of the meta-analysis at 12 weeks: prucalopride 2 mg once daily was still ranked first for efficacy. In terms of safety, bisacodyl 10 mg once daily was ranked last on the basis of overall adverse events, and stimulant diphenyl methane laxatives as a class were the most likely to lead to abdominal pain, whereas velusetrag 50 mg once daily was the most likely to lead to diarrhoea or dropout due to adverse events.

We described our search strategy, eligibility criteria, and data extraction processes in detail. Additionally, the literature search, eligibility assessment, and data extraction were done independently by two reviewers, and any discrepancies were resolved by consensus. We used an intention-to-treat analysis, with all dropouts assumed to

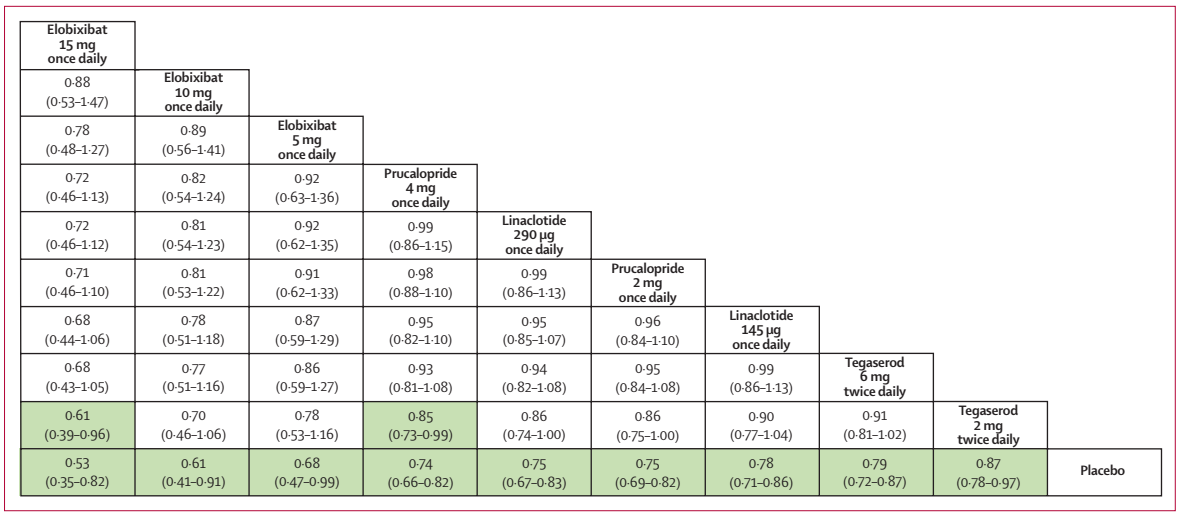

Figure 7: **Relative efficacy of treatments for failure to achieve three or more complete spontaneous bowel movements per week at 8–12 weeks**
Data are relative risk (95% CI). Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall effectiveness. The treatment in the top-left position is ranked as most efficacious after the network meta-analysis of indirect effects. Boxes highlighted in green show significant differences.

not have benefited from therapy, and pooled data with a random effects model to reduce the likelihood that any beneficial effect of pharmacological therapies in chronic idiopathic constipation has been overestimated. Heterogeneity was low in most of our analyses, presumably because we pooled data according to identical endpoints at the same time points when possible. We did analyses according to duration of therapy, type of drug and doses used, and criteria used to define response to therapy. We also did a sensitivity analysis using the more stringent endpoint recommended by the US FDA to judge efficacy in treatment trials in chronic idiopathic constipation. Our results generally confirm those of the previous network meta-analysis,[17] but they update the list of drugs tested to all those that are relevant in 2019, and show 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 our 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 done 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; therefore, estimates of relative efficacy are based on indirect comparisons. Although we identified one RCT of polyethylene glycol versus prucalopride, this trial was ineligible because 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] An RCT of prucalopride versus placebo was not included because 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 mizagliflozin or tenapanor. Although we identified one trial of mizagliflozin, it included a mixed population of patients with chronic idiopathic constipation and irritable bowel syndrome with constipation.[63] Two of the RCTs of elobixibat were not fully published and had been terminated early because of a supply issue with the active drug.[50,51] Although we identified further published trials of elobixibat, these were ineligible because treatment duration was only 2 weeks.[64,65] The trials of lubiprostone were done over 4 weeks only and did not report failure to achieve three or more CSBMs per week, or failure to achieve an increase of one or more CSBM per week over baseline;[52–54] therefore, 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 chronic idiopathic constipation captures only 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 symptoms is unknown. Finally, it is important to point out that there was no standardised reporting of adverse events, unlike for efficacy data, which might mean that 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 our network meta-analysis, very few trials mentioned whether the patients they recruited had been unresponsive to, or dissatisfied with, laxatives previously. Most 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 might have led to an overestimation of their efficacy, versus other therapies, at 4 weeks. Additionally, the trials of linaclotide that reported data at 4 weeks used a more stringent endpoint of failure to

achieve three or more CSBMs per week and an increase of one or more CSBM from baseline.[36,39,40] There is also the possibility that, because tegaserod, lubiprostone, and prucalopride were tested in chronic idiopathic constipation before linaclotide and plecanatide, patients in the more recent trials of linaclotide and plecanatide had already not responded to 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, because these RCTs did not report the proportion of patients who had previously received treatment with other drugs for chronic idiopathic constipation, this point is speculative and, we suspect, unlikely, because the availability of tegaserod in the USA has been limited for the past 10 years and prucalopride has only just received FDA approval for the treatment of chronic idiopathic constipation.

Because of the absence 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 probable efficacy and safety of different treatments to be developed 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 to help inform treatment decisions for chronic idiopathic constipation. It is at least 5 years since national guidelines for the management of chronic idiopathic constipation 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-hydroxytryptamine-4 agonists, and secretagogues in chronic idiopathic constipation, based on a mixture of evidence of low, moderate, and high quality, but did not discuss their relative efficacy.[67] The American Gastroenterological Association technical review on chronic idiopathic constipation highlighted that traditional drug therapies might be as effective as newer pharmacological agents, but emphasised that there was insufficient available evidence to allow judgments 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 shown that almost all drugs and dosages were superior to placebo, according to either failure to achieve three or more CSBMs per week or failure to achieve an increase of one CSBM per week over baseline, both at 4 weeks and at 8–12 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 might have recruited a milder spectrum of patients than those of other drugs. With regard to safety, bisacodyl 10 mg once daily was most likely to cause adverse events, and diphenyl methane laxatives were the most likely to cause abdominal pain. Diarrhoea was more common with all drugs, except for tegaserod 2 mg twice daily, 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 chronic idiopathic constipation in making therapy-related choices, the summary RRs were similar for many of the lower- drugs, suggesting there is little to choose between them in terms of efficacy. Additionally, the relatively short duration of treatment in many of the included trials means the longer-term effects of these drugs on symptoms in chronic idiopathic constipation, and their safety, are unknown.

Contributors

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

MC has received research funding from Allergan; and is a consultant to Ironwood, Allergan, Shire, and Takeda with remuneration to his employer, Mayo Clinic, not to himself. EMMQ has been a consultant for Allergan, Ironwood, Salix, Synergy, and Vibrant; and has received research funding from Vibrant and 4D Pharma. ACF has been a consultant for Almirall and has received researching funding from Almirall. All other authors declare no competing interests.

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