Gut Online First, published on June 10, 2016 as 10.1136/gutjnl-2016-311835

ORIGINAL ARTICLE

Comparison of efficacy of pharmacological treatments for chronic idiopathic constipation: a systematic review and network meta-analysis

Alfred D Nelson,[1] Michael Camilleri,[1] Sakkarin Chirapongsathorn,[1] Priya Vijayvargiya,[1] Nelson Valentin,[1] Andrea Shin,[2] Patricia J Erwin,[1] Zhen Wang,[3] M Hassan Murad[3]

Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2016-311835).

[1]Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER), Mayo Clinic, Rochester, Minnesota, USA
[2]Indiana University, Indianapolis, Indiana, USA
[3]Mayo Clinic Evidence-Based Practice Center, Mayo Clinic, Rochester, Minnesota, USA

Correspondence to
Professor Michael Camilleri, Mayo Clinic, 200 First St. S.W., Charlton Bldg., Rm. 8-110, Rochester, MN 55905, USA; camilleri.michael@mayo.edu

Received 10 March 2016
Revised 15 April 2016
Accepted 17 May 2016

ABSTRACT

Objective To compare efficacy of pharmacotherapies for chronic idiopathic constipation (CIC) based on comparisons to placebo using Bayesian network meta-analysis.

Data sources We conducted searches (inception to May 2015) of MEDLINE, EMBASE, Scopus and Cochrane Central, as well as original data from authors or drug companies for the medications used for CIC.

Study selection Phase IIB and phase III randomised, placebo-controlled trials (RCT) of ≥4 weeks' treatment for CIC in adults with Rome II or III criteria for functional constipation; trials included at least one of four end points.

Data extraction and synthesis Two investigators independently evaluated all full-text articles that met inclusion criteria and extracted data for primary and secondary end points, risk of bias and quality of evidence.

Outcomes Primary end points were ≥3 complete spontaneous bowel movements (CSBM)/week and increase over baseline by ≥1 CSBM/week. Secondary end points were change from baseline (Δ_b) in the number of SBM/week and Δ_b CSBM/week.

Results Twenty-one RCTs (9189 patients) met inclusion and end point criteria: 9 prucalopride, 3 lubiprostone, 3 linaclotide, 2 tegaserod, 1 each velusetrag, elobixibat, bisacodyl and sodium picosulphate (NaP). All prespecified end points were unavailable in four polyethylene glycol studies. Bisacodyl, NaP, prucalopride and velusetrag were superior to placebo for the ≥3 CSBM/week end point. No drug was superior at improving the primary end points on network meta-analysis. Bisacodyl appeared superior to the other drugs for the secondary end point, Δ_b in number of SBM/week.

Conclusions Current drugs for CIC show similar efficacy. Bisacodyl may be superior to prescription medications for Δ_b in the number of SBM/week in CIC.

Significance of this study

What is already known on this subject?

- Fifty per cent of patients with chronic idiopathic constipation (CIC) are not completely satisfied with treatment, especially with fibre and laxatives.
- The number needed to treat (NNT), estimated from placebo-controlled clinical trials in CIC comparing pharmacological therapies with placebo, have been reported as follows: osmotic and stimulant laxative, NNT 3; lubiprostone, NNT 4 and prucalopride and linaclotide, both NNT 6.
- The absence of direct comparisons between different drug classes limits comparison of efficacy among treatments.

What are the new findings?

- Current drugs for CIC show similar efficacy for primary end points, which were ≥3 complete spontaneous bowel movements (CSBM)/week and increase over baseline by ≥1 CSBM/week.
- Bisacodyl may be superior to prescription medications for change from baseline (Δ_b) SBM/week in CIC and in comparison with some of the drugs in Δ_b CSBM/week.

How might it impact on clinical practice in the foreseeable future?

- Head-to-head trials of active agents are necessary to determine the optimal selection of pharmacological agents for CIC.
- Alternatively, first-line medications for patients with CIC should be according to the pathophysiology in order to increase efficacy, such as prokinetics for patients with documented slow transit constipation in the absence of rectal evacuation disorders.

INTRODUCTION

The estimated global prevalence of chronic idiopathic constipation (CIC) in adults is 14%.[1] It is usually diagnosed using Rome III symptom criteria,[2] is about twice as common in women and more prevalent over 65 years of age, significantly impacts quality of life and constitutes a significant financial burden.[3] Treatment of constipation[4] usually starts with non-pharmacological agents like fibre (soluble in preference to non-soluble fibre) and is followed by pharmacological agents if there is no response to fibre.[5] Polyethylene glycol, an osmotic laxative, increases the mean number of stools per week more effectively than placebo or lactulose in adults with CIC, based on direct meta-analyses.[6] It is estimated that about 50% of

To cite: Nelson AD, Camilleri M, Chirapongsathorn S, *et al*. *Gut* Published Online First: [*please include* Day Month Year] doi:10.1136/gutjnl-2016-311835

patients with CIC were not completely satisfied with treatment due to lack of efficacy or safety concerns, especially with fibre and laxatives (both stimulant and osmotic).

Therefore, this appraisal of the relative efficacy of pharmacotherapies for chronic CIC is clinically relevant. The pharmacological classes of the medications used for CIC are: diphenyl methanes or derivatives (bisacodyl and sodium picosulphate), 5-hydroxytryptamine receptor 4 (5-HT_4) agonists (prucalopride, tegaserod and velusetrag), guanylate cyclase C receptor agonist (linaclotide), chloride channel type 2 opener (lubiprostone) and apical sodium bile acid (also known as ileal bile acid transport) inhibitor (elobixibat).

The numbers needed to treat (NNT), estimated from placebo-controlled clinical trials comparing these medications with placebo in CIC, were reported as follows: osmotic and stimulant laxative, NNT 3; lubiprostone, NNT 4 and prucalopride and linaclotide, both NNT 6.[6] This might suggest differences in efficacy of the different drug classes; however, this assessment was based on failure to respond to therapy, and vastly different end points were used in individual studies.

The absence of direct comparisons between different drug classes limits comparison of efficacy among treatments to the end points currently recommended by the US Food and Drug Administration (FDA) and is consistent with those of European Medicines Agency.[7] Therefore, our aim was to compare the efficacy of drugs for CIC based on results of each drug compared with placebo using Bayesian network meta-analysis and end points consistent with current regulatory agency recommendations.

METHODS

This systematic review and network meta-analysis was performed according to guidance provided by the Cochrane Handbook for Systematic Reviews of Interventions.[8] It is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[9] We followed an a priori established protocol.

Search methods for identification of studies

A thorough database search was done in May 2015, using Ovid MEDLINE In-Process and Other Non-Indexed Citations and Ovid MEDLINE (1946 to present), Ovid EMBASE, Scopus databases (1988–2015) and Ovid Cochrane CENTRAL (to March 2015) for all the drugs used for treatment of CIC. An expert librarian (PJE) conducted the medical literature search with input from the investigators. All the studies for this meta-analysis were identified using a combination of subject headings and free text terms including constipation, chronic constipation, functional constipation, lubiprostone, linaclotide, plecanatide, bisacodyl, sodium picosulfate (NaP), prucalopride, velusetrag, naronapride, polyethylene glycol (PEG), lactulose, elobixibat, fibre and randomised placebo-controlled trial. Terms were searched in the title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word and unique identifier. The search was conducted using combinations of these terms by using 'and/or'. Multiple different combinations of these terms were used. All the abstracts identified using the search strategy were independently evaluated by two investigators (ADN and NV) in order to select studies that were eligible for inclusion. For those studies, full-text articles were requested. Additional studies were added after review of these drugs in the treatment of CIC in clinicaltrials.gov and manual review of the citations in the publications. All the studies were independently identified by two investigators using well-defined inclusion criteria; conflicts were resolved by consensus between the two investigators after discussing with a third investigator (MC) with content expertise.

Inclusion criteria

This systematic review and network meta-analysis was limited only to randomised, placebo-controlled trials of drugs that are either approved by FDA for CIC or drugs with data available for at least one prespecified end point from phase IIB or III randomised, placebo-controlled trials and >4 weeks of treatment. Participants included were adults (>18 years of age), who satisfied Rome II or III criteria for (chronic) functional constipation.

There were no exclusions based on gender, sample size, medical condition, language limitation or medications that are known to affect colonic transit or minimum follow-up period. All eligible studies were required to have placebo as control intervention.

Outcome assessment

The current recommended end point required by regulatory agencies (specifically, the FDA) for demonstration of efficacy in CIC trials is ≥3 complete spontaneous bowel movements (CSBM)/week and increase over baseline by ≥1 CSBM/week in 9 out of 12 weeks of treatment. However, only randomised, placebo-controlled trials of linaclotide included this end point; therefore, we analysed different end points that addressed similar outcomes, in order to be consistent in appraising efficacy among studies. The primary end points were the proportion of responders, based on ≥3 CSBM)/week or the proportion of responders with increase over baseline by ≥1 CSBM/week. The secondary end points were continuous, quantitative variables: the change from baseline (Δ_b) in the number of spontaneous bowel movements (SBM)/week and Δ_b CSBM/week. Unfortunately, none of the four available PEG trials included the end points selected for our network meta-analysis.

Data extraction and management

Data extraction from the eligible studies was performed by two independent investigators (ADN and SC) for the primary and secondary end points. The authors of the original publications were contacted by email or by phone requesting missing data in the eligible studies. Data were extracted from manuscripts or databases provided by the investigators or drug companies. Data for primary end points were extracted as number of responders and non-responders for each primary end point and mean and SD for secondary end points.

We also collected data about characteristics of the randomised, placebo-controlled trials, such as study centre location (by continents); total number, age and gender of participants in the intervention and control groups; type of intervention; duration of therapy and criteria for a diagnosis of constipation. Finally, data were extracted to appraise study quality, such as method used for analysis of missing data and loss of follow-up in the intervention and control groups.

Statistical analysis

We calculated relative risk for dichotomised outcomes, weighted mean difference (WMD) for continuous outcomes and related CIs. We performed head-to-head comparisons using DerSimonian–Laird random-effects model. We assessed statistical heterogeneity using the I^2 statistic, which represents the proportion of heterogeneity that is not the result of chance, but reflects true differences across study populations and

interventions; $I^2>50\%$ indicates substantial heterogeneity. Direct comparisons were performed using RevMan V.5.3 (The Nordic Cochrane Centre Copenhagen, Denmark).

Network meta-analyses were used to combine effect sizes for all possible comparisons (direct and indirect), regardless of whether they had been compared in trials. In contrast to traditional meta-analyses, which compare one intervention with another one at a time and combine evidence directly from head-to-head clinical trials (if such trials exist), the network meta-analyses allow comparison of all interventions simultaneously. A multivariate meta-regression model developed by White was used.[10] The network meta-analyses were conducted using the 'network' suite in Stata V.14.0 (StataCorp, College Station, TX, USA).[10]

Sensitivity analysis

We examined the effects of the drugs for CIC based on relative risks of the primary and secondary end points. We evaluated effect sizes based on therapeutic dose (standard dose group vs high dose) and study quality for prucalopride (low risk of bias vs high risk of bias) for CIC treatment. We also applied the 'leave-one-out' method by excluding one study of 24 weeks' duration to evaluate the robustness of our findings.

Assessment of risk of bias and publication bias

Risk of bias was assessed using Cochrane Handbook for Assessing the Risk of Bias.[9] Two investigators (ADN and PV) independently assessed the randomisation schedule, allocation concealment, blinding of participants and investigators, blinding of outcome assessment, methods used for missing data, selective reporting, incomplete outcome data, risk of bias for primary and secondary end points and loss of follow-up during the treatment period. Due to the limited number of studies included in the analyses, we were not able to evaluate potential publication bias.[11]

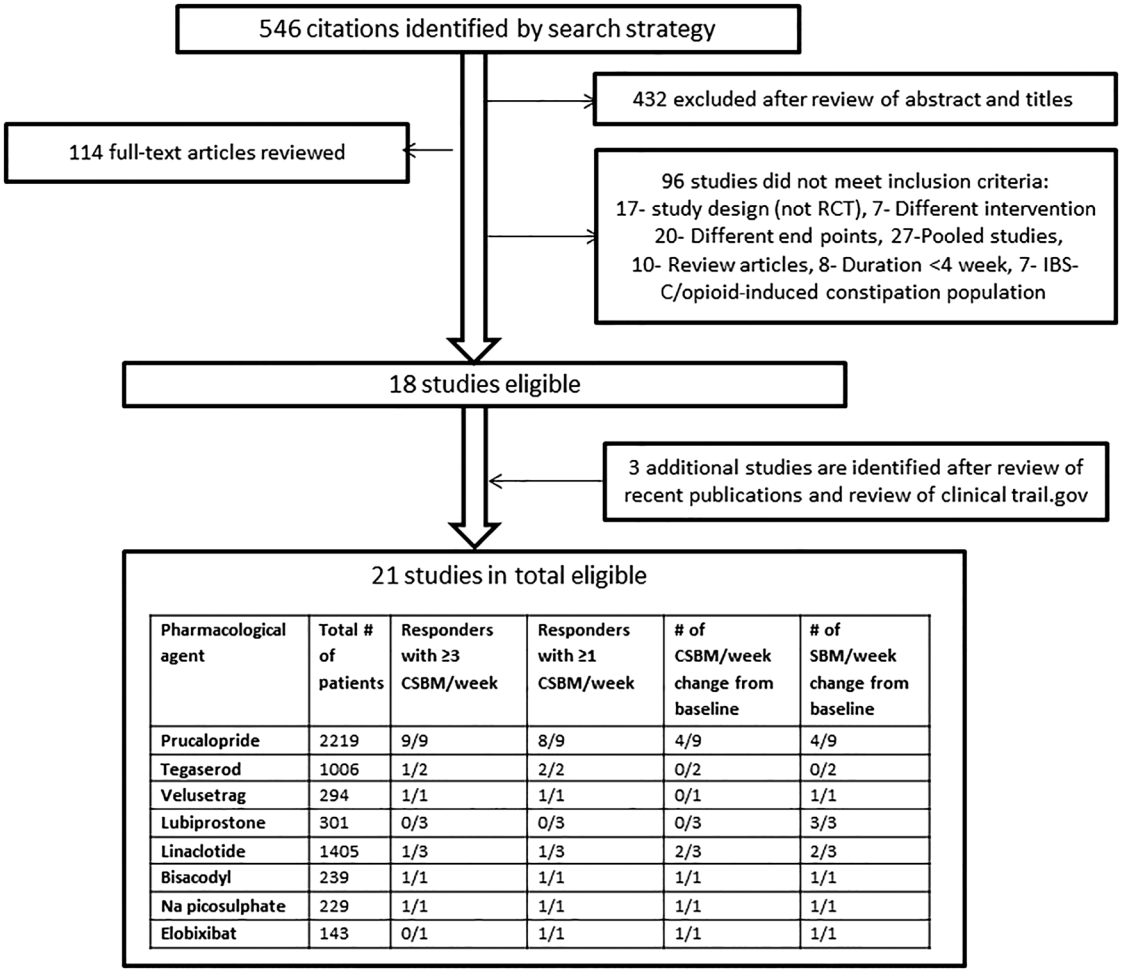
Quality of evidence

We used the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) Approach to rate the quality of evidence for the estimates derived from the network meta-analyses.[12] Since the studies included were only randomised, placebo-controlled trials, the quality of evidence was considered high in the beginning and down rated based on the assessment of risk of bias, inconsistency, indirectness, imprecision and publication bias. The quality of evidence is rated as high, moderate, low and very low. For indirect estimates, the rating usually starts at lowest rating of contributing direct evidence and can be further down rated based on imprecision and indirectness (mainly intransitivity, ie, difference in patient populations between studies involved).

RESULTS

Search results

The search strategy used identified 546 citations and, among these, we identified 114 articles for review for the full-text



Pharmacological agent	Total # of patients	Responders with ≥3 CSBM/week	Responders with ≥1 CSBM/week	# of CSBM/week change from baseline	# of SBM/week change from baseline
Prucalopride	2219	9/9	8/9	4/9	4/9
Tegaserod	1006	1/2	2/2	0/2	0/2
Velusetrag	294	1/1	1/1	0/1	1/1
Lubiprostone	301	0/3	0/3	0/3	3/3
Linaclotide	1405	1/3	1/3	2/3	2/3
Bisacodyl	239	1/1	1/1	1/1	1/1
Na picosulphate	229	1/1	1/1	1/1	1/1
Elobixibat	143	0/1	1/1	1/1	1/1

Figure 1 Flow diagram of included studies identified for systematic review.

Table 1 Study characteristics

Study ID	Location	Drug	Doses tested	Study duration (weeks)	Number total: intervention/ control	Age (I)	Age (C)	Gender, F %	Constipation criteria
Camilleri 2008	USA	PRU	2 or 4 mg QD	12	620: 411/209	48.0±14.3	48.9±13.0	87.1	≤2 CSBM/week for 6 months, and Rome III criteria*
Coremans 2003	Belgium	PRU	4 mg QD	4	53: 27/26	43.8±2.7	47.4±2.9	98.1	≥2 of the following for 6 months: 2 SBM/week and Rome III criteria*
Ke 2012	Asia-Pacific	PRU	2 mg QD	12	501: 249/252	41.4±12.92	41.8±12.9	90	≤2 SBM/week on average, and ≥1 of the following in Rome III criteria†
Mueller-Lissner 2010	Int	PRU	1, 2 or 4 mg QD	4	300: 230/70	76.5±7.7	76±7.4	70.3	≤2 CSBM/week for 6 months and ≥1 of the following in Rome III criteria*
Piessevaux 2015	Europe	PRU	2 mg QD	24	346: 177/169	49.4±15.8	48.3±16.3	14.7‡	≤2 CSBM/week and ≥1 of the following in Rome III criteria* for 6 months
Quigley 2009	USA	PRU	2 or 4 mg QD	12	641: 429/212	48.9±13.9	46.2±13.0	86.6	≤2 CSBM/week for 6 months and ≥1 of the following in Rome III criteria* for 6 months
Tack 2009	Int	PRU	2 or 4 mg QD	12	713: 473/240	44.1±15.1	43.7±15.3	90.8	≤2 CSBM/week for 6 months and ≥1 of the following in Rome III criteria* for 6 months
Emmanuel 2002	UK	PRU	1 mg QD	4	74: 37/37	NA	NA	100	≤2 SBM/week and need to strain at least 25% of the defecation
Yiannnakou 2015	Europe	PRU	2 mg QD	12	370: 184/186	58.4±17.6	58.5±16.3	0§	≤2 CSBM/week for 6 months and ≥1 of the following in Rome III criteria* for 6 months
Goldberg 2010	USA	VEL	15, 30 or 45 mg QD	4	401: 294/107	44.4±11.7	45.4±10.0	92.0	≥18 years of age satisfying Rome 3 criteria functional constipation†
Fried 2007	Int	TEG	6 mg twice daily	12	322: 158/164	51.1±17.1	51.8±17.2	0§	≤3 CSBM/week and ≥1 of the following in Rome III criteria* for 6 months
Kamm 2005	Int	TEG	2 or 6 mg twice daily	12	1264: 848/416	46.3±15.2	46.0±15.6	86.3	≤3 CSBM/week and ≥1 of the following in Rome III criteria* for 6 months
Barish 2010	USA	LUBI	24 μg twice daily	4	237: 119/118	NK	NK	88.2	≤3 SBM/week and ≥1 of the following in Rome III criteria* for 6 months
Fukudo 2015	Japan	LUBI	24 μg twice daily	4	124: 62/62	42.7±16.4	41.5±14.2	88	Rome III criteria†, fewer than 3 defecations per week
Johanson 2008	USA	LUBI	24 μg twice daily	4	244: 120/124	48.0±12.3	49.1±12.9	89.7	≤3 SBM/week and ≥1 of the following in Rome III criteria* for 6 months
Chey 2011	USA	ELO	5, 10 or 15 mg QD	4	190: 143/47	47.6	49.9	89.5	<3 CSBM/week and ≥2 of the following in Rome III criteria†
Kamm 2011	UK	BIS	10 mg QD	4	356: 239/117	55.8±15.9	54.7±15.1	74.7	<3 CSBM/week and ≥1 of the following in Rome III criteria* for 6 months
Mueller-Lissner 2010	Germany	NaP	10 mg QD	4	362: 229/133	50.2±17.2	51.9±16.5	77.7	< 3 CSBM/week on average and ≥1 of the following in Rome III criteria* for 6 months
Lembo 2010	USA	LINA	75, 150, 300 or 600 μg QD	4	307: 239/68	47.6±13.1	46.1±15.6	92	<3 SBM/week and ≥1 of the following in Rome III criteria* at least 12 weeks during the 12 months preceding the study
Lembo 2011	USA	LINA LINA	145 or 290 μg, QD	12 12	643: 434/209 633: 418/215	47.4±14.2 47.2±12.8	49.3±14.3 47.0±13.5	87.4 90.4	<3 SBM/week and ≥1 of the following Rome criteria* for at least 12 weeks within the preceding 12 months
Lacy 2015	USA	LINA		12	487: 314/173	47.9	46.4	92.5	<3 SBM/week and ≥1 of the following Rome criteria* for at least 12 weeks within the preceding 12 months

*Part of the Rome III criteria which includes ≥25% straining, incomplete evacuation and hard/lumpy stools.
†Rome III criteria which includes ≥25% straining, hard/lumpy stools, sensation of incomplete evacuation, anorectal blockage and digital evacuation.
‡85.32% were males.
§100% were men.
BIS, bisacodyl; C, control; CSBM, complete spontaneous bowel movements; ELO, elobixibat; I, intervention; Int, international; LINA, linaclotide; LUBI, lubiprostone; MC, multicenter; NA, not available; NaP, sodium picosulphate; NK, not known; PRU, prucalopride; QD, once daily; SC, single centre; TEG, tegaserod; VEL, velusetrag.

appraisal. Among the 114 articles, only 18 articles met the inclusion criteria; 96 studies did not meet the inclusion criteria, most often because the end points in the trials were different from the selected primary and secondary end points, articles did not have original data, or they were non-randomised studies. The agreement between the investigators (ADN and NV) for selection of studies after full-text review was high (κ statistic 0.86).

Three studies which were not identified by the search strategy were added by the investigators. We contacted the authors and drug sponsors of these studies for additional information regarding the primary and secondary end points, and their responses were added to the analysis.

Figure 1 shows the schematic diagram of study selection for the systematic review and meta-analysis; in total, 21 studies were eligible. The study characteristics are summarised in table 1.

There were 9189 patients in the 21 studies: 9 with prucalopride,[13–21] 3 with lubiprostone,[22–24] 3 with linaclotide,[25–27] 2 with tegaserod,[28 29] 1 each with velusetrag,[30] elobixibat,[31] bisacodyl[32] and sodium (Na) picosulphate.[33] The number of drugs, sample size of each drug and the number of clinical trials included in the network meta-analysis are represented in the form of a network diagram (figure 2).

The risk of bias of the included studies is summarised in table 2. Overall, quality was high in 11, moderate in 9 and low in 1 study. Downgrading of quality was based most often on unstated details regarding blinding, allocation concealment or management of missing data.

Direct meta-analysis

The results of the direct meta-analysis for each primary and secondary end point are summarised in figure 3A–D.

Primary end points

The data for *responder analysis with ≥3 CSBM/week* were available for 14 randomised, placebo-controlled trials. All six drugs showed a significant increase in ≥3 CSBM/week when compared with placebo. Among the three 5-HT_4 agonists (prucalopride, velusetrag and tegaserod), prucalopride showed higher efficacy (relative risk (RR)) of 1.85 with a 95% CI of 1.35 to 2.54 when compared with placebo and with significant heterogeneity of 80.8% (p=0.0001). Velusetrag had an RR of 4.86 (95% CI 2.02 to 11.71); the wider CI may suggest velusetrag might be less efficacious when compared with prucalopride. Stimulant laxatives, bisacodyl and NaP showed approximately similar efficacy. For linaclotide, RR was 1.96 (95% CI 1.12 to 3.44). There was significant heterogeneity between studies of all the drugs appraised using this end point (I^2=77.4%, p<0.00001).

For *responder analysis with* increase over baseline by *≥1 CSBM/week*, data were available for 15 randomised, placebo-controlled trials; all 7 of the drugs were superior to placebo. Stimulant laxatives (bisacodyl and NaP) and elobixibat showed approximately similar efficacy. Prucalopride showed superior efficacy among the 5-HT_4 agonists, but the heterogeneity between studies was significant (I^2=74.5%, p=0.0001). Even though the RR for velusetrag was 3.10, which is relatively high when compared with the RR for prucalopride, the 95% CI with velusetrag was wide (1.83 to 5.24) and overlapped that of prucalopride. Given the overlapping 95% CI for the two drugs and the significant heterogeneity in the efficacy of prucalopride, the data show overall similar efficacy for prucalopride and velusetrag.

Secondary end points

Data for Δ_b *CSBM/week* were available only for five drugs. All the drugs showed superior efficacy when compared with placebo. Bisacodyl had a WMD of 3.20 (95% CI 2.66 to 3.74). Elobixibat and NaP had similar efficacy. For linaclotide, the WMD was 1.57, with heterogeneity I^2 of 0%; this WMD was greater than that of prucalopride, which was 0.90 and was also associated with significant heterogeneity I^2 of 76.8%.

For the Δ_b *SBM/week*, all seven of the drugs showed superior efficacy relative to placebo. Bisacodyl showed higher efficacy with a WMD of 4.90 when compared with NaP (3.20). Velusetrag, elobixibat and linaclotide showed similar efficacy with a mean difference (MD) in the absolute number of Δ_b *SBM/week* of ~2.08. For prucalopride, the WMD was 2.03, with significant heterogeneity of 63.9%. For lubiprostone, WMD was 1.91 with an I^2 of 23.4%.

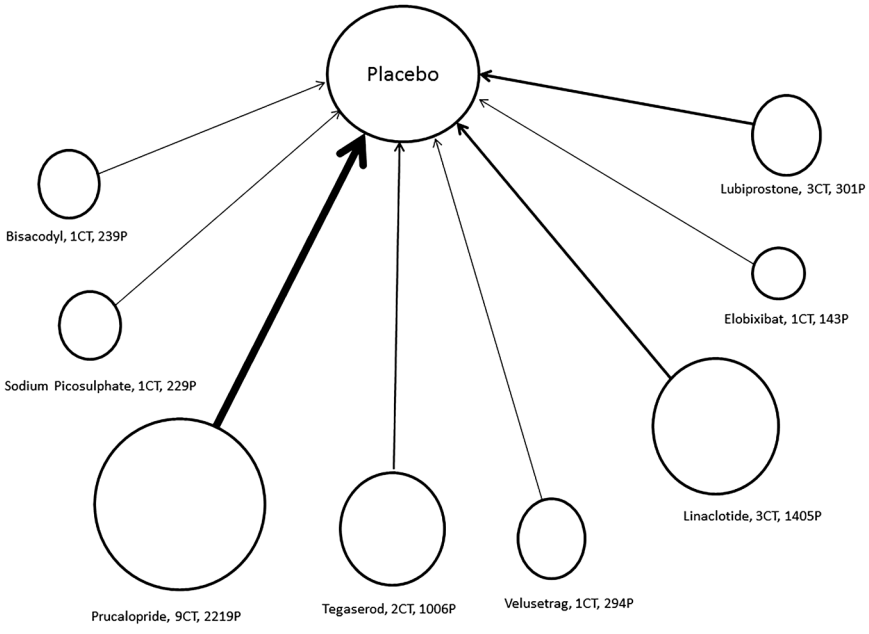


Figure 2 Network diagram. CT, clinical trials; P, patients.

Table 2 Study quality

Study identification	Drug	Generation of randomisation sequence	Allocation concealment	Double blind	Lost to follow-up	Methods used for missing data	Overall quality
Camilleri 2008	PRU	Consecutive numbering+block randomisation of three	+	+	5Rx, 3C	Imputation	High
Coremans 2003	PRU	Unclear	Unclear	+	0	–	Mod
Ke 2012	PRU	CGR	+	+	3Rx, 2C	NS	Mod
Mueller-Lissner 2010	PRU	Randomisation code generated by sponsor	+	+	0	Considered as non-responders	High
Piessevaux 2015	PRU	Randomisation by web-based/voice-response system	+	+	0	Imputation	Low
Quigley 2009	PRU	Block randomisation of three	+	+	5Rx, 2C	Imputation	High
Tack 2009	PRU	Random allocation sequence by the investigator	Unclear	+	5Rx, 1C	Considered as non-responders	High
Emmanuel 2002	PRU	Method not known	Unclear	+	0Rx, 1C	NS	Mod
Yiannnakou 2015	PRU	Central interactive web-based response system	+	+	2Rx, 0C	Imputation	Mod
Goldberg 2010	VEL	Telephonic interactive voice-response system using a permuted block algorithm	+	+	NK	LOCF	High
Fried 2007	TEG	Validated system that automated the random assignment by sponsor	+	+	0	–	High
Kamm 2005	TEG	Randomised using validated computer system	+	+	26Rx, 10C	NS	Mod
Barish 2010	LUBI	Block randomisation of four	+	+	4Rx, 1C	LOCF	Mod
Fukudo 2015	LUBI	Method not known	Unclear	+	0	–	Mod
Johanson 2008	LUBI	Block randomisation of four	+	+	1Rx, 2C	LOCF	Mod
Chey 2011	ELO	CGR by sponsor	+	+	1Rx, 0C	NS	Mod
Kamm 2011	BIS	CGR	+	+	0	–	High
Mueller-Lissner 2010	NaP	CGR	+	+	0	–	High
Lembo 2010	LINA	CGR using a block size of 5	+	+	3Rx, 0C	Observed-cases approach	Mod
Lembo 2011	LINA	CGR using a block size of 6	+	+	29Rx, 4C		High
Lacy 2015	LINA	Randomisation by statistical programmer not involved in the trial	+	+	10Rx, 5C	Considered as non-responders	High

BIS, bisacodyl; C, control; CGR, computer-generated randomisation; ELO, elobixibat; LINA, linaclotide; LOCF, last observation carried forward; LUBI, lubiprostone; NaP, sodium picosulphate; NS, not significant; PRU, prucalopride; Rx, intervention arm; TEG, tegaserod; VEL, velusetrag.

Network meta-analysis

Responder analysis for ≥3 CSBM/week

Except for tegaserod, all the other drugs (bisacodyl, NaP, prucalopride, velusetrag, linaclotide and elobixibat) showed superior efficacy compared with placebo, but none of the drugs showed superior efficacy when compared with each other in the network meta-analysis (table 3A).

Responder analysis for increase over baseline by ≥1 CSBM/week

Apart from tegaserod and linaclotide, all the drugs (bisacodyl, NaP, prucalopride and velusetrag) showed superior efficacy when compared with placebo, but none of the drugs showed superior efficacy when compared with each other in the network meta-analysis, with the exception of velusetrag which appears superior when compared with prucalopride and tegaserod (table 3B).

Change in number of CSBM/week compared with baseline

Bisacodyl, NaP, prucalopride, linaclotide and elobixibat showed superior efficacy on the Δ_b CSBM/week when compared with placebo. On a network meta-analysis, bisacodyl was superior to NaP, prucalopride and linaclotide. Bisacodyl did not show significant efficacy over elobixibat using this end point. NaP showed superior efficacy when compared with prucalopride (table 4A).

Change in number of SBM/week compared with baseline

When compared with placebo on a network meta-analysis, bisacodyl, NaP, prucalopride, velusetrag, linaclotide, elobixibat and lubiprostone treatment showed superior increase in Δ_b SBM/week (table 4B).

Network meta-analysis suggested that bisacodyl is superior when NaP, prucalopride, velusetrag, linaclotide, elobixibat and lubiprostone are compared with bisacodyl. NaP showed superior efficacy when prucalopride and lubiprostone were compared with NaP.

Quality of evidence

We applied the GRADE approach to the main outcome of ≥1 CSBM/week because it had the largest number of included trials. In terms of direct estimates of drugs compared with placebo, the quality of evidence was moderate or high for all comparisons. However, most head-to-head comparisons were imprecise (ie, their CIs were wide and overlapped the null effect). Therefore, the quality of evidence of head-to-head comparisons was mostly low (table 5).

Sensitivity analysis

We conducted sensitivity analyses based on dose of medication (for all drugs for which at least two doses were studied) and risk of bias (for prucalopride). Results were consistent between standard therapeutic dose group compared with high-dose and low-dose groups for the primary end points and for most of the secondary end point analyses (table 6). An exception was that low-dose (in contrast to standard or high dose) prucalopride was not effective compared with placebo for the end points of ≥3 CSBM/week and Δ_b SBM/week.

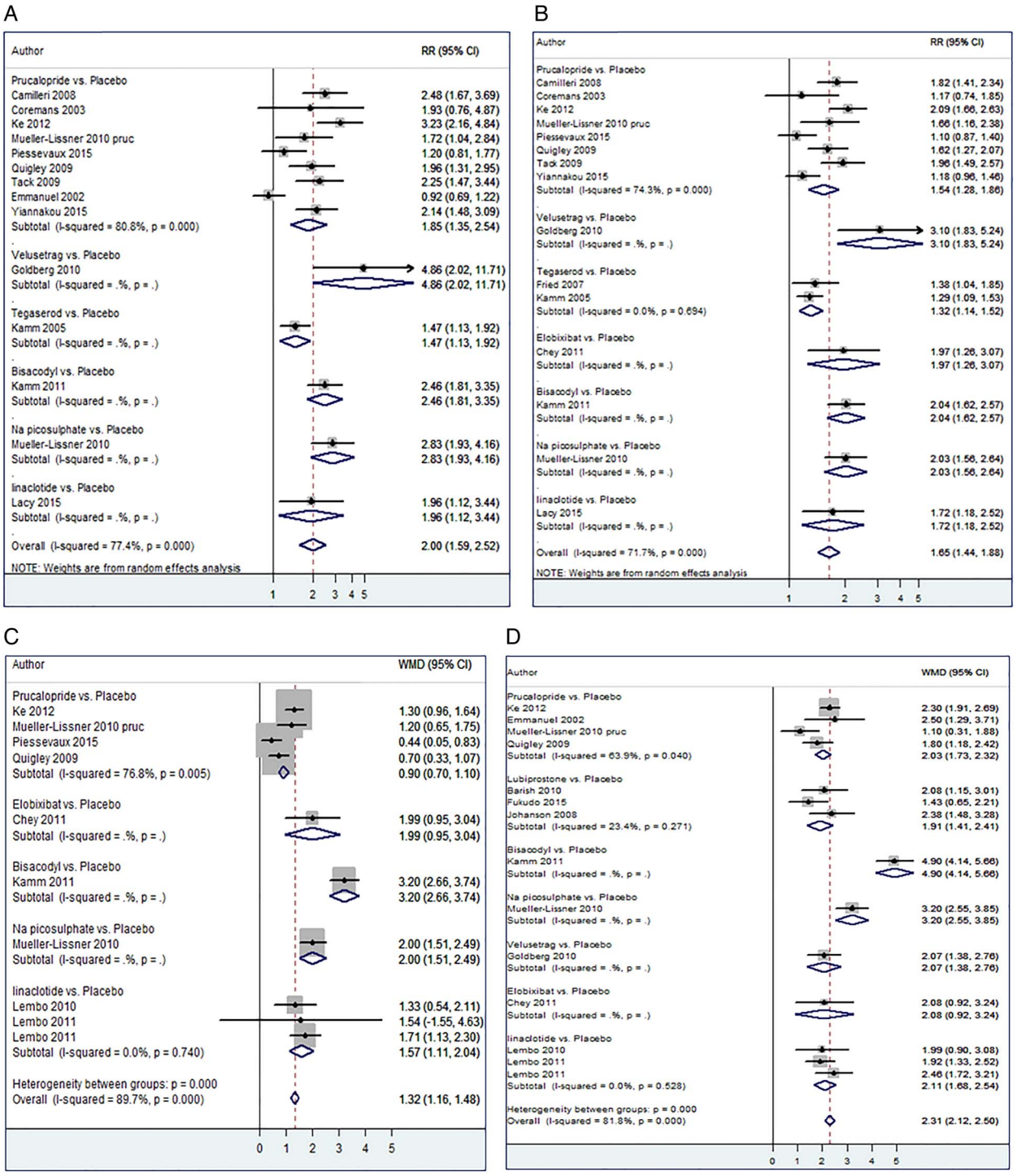


Figure 3 Comparisons between treatment versus placebo of primary end points, ≥3 complete spontaneous bowel movements (CSBM)/week (A) or increase over baseline by >1 CSBM/week (B), and secondary end points, change in CSBM from baseline (C) and change in SBM from baseline (D). I^2 values and p values can only be calculated for each drug where there are ≥2 studies.

When analysis was restricted to prucalopride studies at low risk of bias, four trials[13 16 18 19] were included and, for the two primary responder analyses, we noted that for ≥3 CSBM/week, the RR was 2.12 (1.71, 2.63) and, for increase over baseline by ≥1 CSBM/week, the RR was 1.76 (1.54, 2.02); both had heterogeneity of 0%.

A third sensitivity analysis assessed whether any one study with a markedly different duration[17] had a dominant effect on the pooled RR or heterogeneity. We found that this single study did not markedly affect the summary estimate for the prucalopride studies. Thus, including the study resulted in RRs for ≥3 CSBM/week and for increase over baseline by ≥1 CSBM/week of 1.85 (I^2 80.8%) and 1.54 (I^2 74.3%), respectively; excluding the study, the RRs were 1.96 (I^2 81.8%) and 1.63 (I^2 66.4%), respectively.

DISCUSSION

Our study has shown that each drug used in the treatment of CIC is superior to placebo, based on the published randomised, placebo-controlled trials. All the drugs are equally efficacious

Table 3 Pooled relative risk (RR) and 95% CIs (for network meta-analysis) for primary end points

Responders with ≥3 CSBM/week

(A) Responders with ≥3 CSBM per week for the drugs for CIC

Placebo	**2.46 (1.14 to 5.31)**	**2.83 (1.27 to 6.31)**	**1.84 (1.40 to 2.43)**	1.47 (0.7 to 3.12)	**4.86 (1.58 to 14.99)**	1.96 (0.8 to 4.81)
	Bisacodyl	1.15 (0.38 to 3.49)	0.75 (0.33 to 1.69)	0.59 (0.20 to 1.75)	1.97 (0.51 to 7.72)	0.79 (0.24 to 2.60)
		Sodium picosulphate	0.65 (0.28 to 1.52)	0.52 (0.17 to 1.56)	1.72 (0.43 to 6.84)	0.69 (0.21 to 2.31)
			Prucalopride	0.80 (0.36 to 1.78)	2.64 (0.83 to 8.41)	1.06 (0.41 to 2.72)
				Tegaserod	3.30 (0.85 to 12.79)	1.33 (0.41 to 4.30)
					Velusetrag	0.40 (0.09 to 1.70)
						Linaclotide

Responders with increase over baseline by ≥1 CSBM/week

(B) Responders with ≥1 CSBM per week for the drugs for CIC

Placebo	**2.04 (1.3 to 3.19)**	**2.03 (1.27 to 3.23)**	**1.54 (1.30 to 1.83)**	1.33 (0.97 to 1.83)	**3.1 (1.61 to 5.95)**	**1.72 (1.0 to 2.96)**	**1.97 (1.09 to 3.55)**
	Bisacodyl	0.99 (0.52 to 1.9)	0.76 (0.47 to 1.22)	0.65 (0.38 to 1.13)	1.52 (0.69 to 3.35)	0.84 (0.42 to 1.71)	0.96 (0.46 to 2.02)
		Sodium picosulphate	0.76 (0.46 to 1.25)	0.66 (0.37 to 1.16)	1.53 (0.69 to 3.41)	0.85 (0.42 to 1.74)	0.97 (0.46 to 2.06)
			Prucalopride	0.86 (0.60 to 1.23)	**2.01 (1.02 to 3.93)**	1.11 (0.63 to 1.97)	1.27 (0.69 to 2.35)
				Tegaserod	**2.33 (1.13 to 4.80)**	1.29 (0.69 to 2.42)	1.48 (0.76 to 2.89)
					Velusetrag	0.56 (0.24 to 1.30)	0.64 (0.26 to 1.53)
						Linaclotide	1.14 (0.51 to 2.55)
							Elobixibat

For lubiprostone, both of the end points are not available.
p Values <0.05 are in bold.
CIC, chronic idiopathic constipation; CSBM, complete spontaneous bowel movements.

Table 4 Pooled weighted mean difference, and 95% CIs (for network meta-analysis) for secondary end points

# of CSBM/week change from baseline

(A) Number of CSBM change from baseline for the drugs for CIC

Placebo	**3.2 (2.37 to 4.03)**	**2.0 (1.19 to 2.81)**	**0.9 (0.52 to 1.28)**	**1.55 (0.90 to 2.19)**	**1.99 (0.77 to 3.22)**
	Bisacodyl	**−1.2 (−2.36 to -0.04)**	**−2.3 (−3.22 to -1.38)**	**−1.65(−2.70 to −0.60)**	−1.21 (−2.69 to 0.28)
		Sodium picosulphate	**−1.10 (−1.99 to −0.21)**	−0.45 (−1.48 to 0.58)	−0.01 (−1.47 to 1.46)
			Prucalopride	0.65 (−0.10 to 1.40)	1.09 (−0.19 to 2.38)
				Linaclotide	0.44 (−0.94 to 1.83)
					Elobixibat

# of SBM/week change from baseline

(B) Number of SBM change from baseline for the drugs for CIC

Placebo	**4.9 (3.90 to 5.90)**	**3.20 (2.28 to 4.12)**	**1.93 (1.45 to 2.40)**	**2.07 (1.12 to 3.01)**	**2.13 (1.54 to 2.71)**	**2.08 (0.76 to 3.41)**	**1.93 (1.30 to 2.55)**
	Bisacodyl	**−1.7 (−3.05 to −0.35)**	**−2.97 (−4.07 to −1.87)**	**−2.83 (−4.20 to −1.46)**	**−2.77 (−3.93 to −1.62)**	**−2.82 (−4.48 to −1.16)**	**−2.97 (−4.14 to −1.79)**
		Sodium picosulphate	**−1.27 (−2.30 to −0.24)**	−1.13 (−2.45 to 0.18)	−1.07 (−2.16 to 0.01)	−1.12 (−2.73 to 0.49)	**−1.27 (−2.38 to -0.16)**
			Prucalopride	0.14 (−0.92 to 1.20)	0.2 (−0.55 to 0.95)	0.15 (−1.26 to 1.56)	0 (−0.79 to 0.79)
				Velusetrag	0.06 (−1.05 to 1.17)	0.01 (−1.61 to 1.64)	−0.14 (−1.27 to 0.99)
					Linaclotide	−0.04 (−1.49 to 1.40)	−0.2 (−1.05 to 0.66)
						Elobixibat	−0.15 (−1.62 to 1.31)
							Lubiprostone

Note: Tegaserod both of the end points are not available.
p Values <0.05 are in bold.
+, positive pooled RR; −, negative pooled RR (inferior efficacy); CIC, chronic idiopathic constipation; CSBM, complete spontaneous bowel movements; SBM, spontaneous bowel movements.

Table 5 Quality of evidence for responders with ≥1 CSBM

Comparison	Direct	Quality of evidence	Indirect	Quality of evidence	Network	Quality of evidence
Bisacodyl vs placebo	**2.04 (1.62 to 2.57)**	High	–	–	**2.04 (1.3 to 3.19)**	High
NaP vs placebo	**2.03 (1.56 to 2.64)**	High	–	–	**2.03 (1.27 to 3.23)**	High
Prucalopride vs placebo	**1.54 (1.28 to 1.86)**	Moderate*	–	–	**1.54 (1.30 to 1.83)**	Moderate*
Tegaserod vs placebo	**1.32 (1.14 to 1.52)**	High	–	–	1.33 (0.97 to 1.83)	High
Velusetrag vs placebo	**3.1 (1.83 to 5.24)**	High	–	–	**3.1 (1.61 to 5.95)**	High
Linaclotide vs placebo	**1.72 (1.18 to 2.52)**	High	–	–	**1.72 (1.0 to 2.96)**	High
Elobixibat vs placebo	**1.97 (1.26 to 3.07)**	Moderate*	–	–	**1.97 (1.09 to 3.55)**	Moderate*
NaP vs bisacodyl	–	–	0.99 (0.52 to 1.9)	High	0.99 (0.52 to 1.9)	Low†
Prucalopride vs bisacodyl	–	–	0.76 (0.47 to 1.22)	Moderate	0.76 (0.47 to 1.22)	Very low†
Tegaserod vs bisacodyl	–	–	0.65 (0.38 to 1.13)	High	0.65 (0.38 to 1.13)	Low†
Velusetrag vs bisacodyl	–	–	1.52 (0.69 to 3.35)	High	1.52 (0.69 to 3.35)	Low†
Linaclotide vs bisacodyl	–	–	0.84 (0.42 to 1.71)	High	0.84 (0.42 to 1.71)	Low†
Elobixibat vs bisacodyl	–	–	0.96 (0.46 to 2.02)	Moderate	0.96 (0.46 to 2.02)	Very Low†
Prucalopride vs NaP	–	–	0.76 (0.46 to 1.25)	Moderate	0.76 (0.46 to 1.25)	Very low†
Tegaserod vs NaP	–	–	0.66 (0.37 to 1.16)	High	0.66 (0.37 to 1.16)	Low†
Velusetrag vs NaP	–	–	1.53 (0.69 to 3.41)	High	1.53 (0.69 to 3.41)	Low†
Linaclotide vs NaP	–	–	0.85 (0.42 to 1.74)	High	0.85 (0.42 to 1.74)	Low†
Elobixibat vs NaP	–	–	0.97 (0.46 to 2.06)	Moderate	0.97 (0.46 to 2.06)	Very low†
Tegaserod vs prucalopride	–	–	0.86 (0.60 to 1.23)	Moderate	0.86 (0.60 to 1.23)	Very Low†
Velusetrag vs prucalopride	–	–	**2.01 (1.02 to 3.93)**	Moderate	**2.01 (1.02 to 3.93)**	Low‡
Linaclotide vs prucalopride	–	–	1.11 (0.63 to 1.97)	Moderate	1.11 (0.63 to 1.97)	Very Low†
Elobixibat vs prucalopride	–	–	1.27 (0.69 to 2.35)	Moderate	1.27 (0.69 to 2.35)	Very low†
Velusetrag vs tegaserod	–	–	**2.33 (1.13 to 4.80)**	High	**2.33 (1.13 to 4.80)**	Moderate‡
Linaclotide vs tegaserod	–	–	1.29 (0.69 to 2.42)	High	1.29 (0.69 to 2.42)	Low†
Elobixibat vs tegaserod	–	–	1.48 (0.76 to 2.89)	Moderate	1.48 (0.76 to 2.89)	Very Low†
Linaclotide vs velusetrag	–	–	0.56 (0.24 to 1.30)	High	0.56 (0.24 to 1.30)	Low†
Elobixibat vs velusetrag	–	–	0.64 (0.26 to 1.53)	Moderate	0.64 (0.26 to 1.53)	Very low†
Elobixibat vs linaclotide	–	–	1.14 (0.51 to 2.55)	Moderate	1.14 (0.51 to 2.55)	Very low†

*Risk of bias.
†Severe imprecision.
p Values <0.05 are in bold.
CSBM, complete spontaneous bowel movements.

for the primary end points of responder analysis with ≥3 CSBM/week and increase over baseline by ≥1 CSBM/week, in the network meta-analysis. Bisacodyl may be superior to all the other drugs in the secondary end point of Δ_b SBM/week and in comparison with some of the drugs in Δ_b CSBM/week.

There are, however, limitations in this appraisal of relatively greater efficacy of bisacodyl. There is only one bisacodyl trial with only 4 weeks of treatment compared with other drugs which provided treatment for 12 or 24 weeks. Confirmation of superiority of any of these pharmacotherapies requires direct comparisons of the active interventions using randomised, placebo-controlled trials. A network meta-analysis has distinct features in the absence of trials of direct comparisons of treatments, and may inform judicious selection of treatment. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) recommends use of multiple treatment meta-analyses in synthesis of data, even with nodal networks, as it allows for more statistically sound assessment of comparative efficacy.[34]

Typically, patients in these randomised, placebo-controlled trials fulfilled Rome II or III criteria for constipation after exclusion of medical and structural conditions.[35] These symptom-based criteria do not differentiate groups, based on the pathophysiology causing CIC. Based on a study of symptoms and pathophysiology in 1411 patients, subgroups of CIC were identified, based on pathophysiology: normal transit constipation (NTC) in ~70%, dyssynergic defecation in ~25% and slow transit constipation (STC) in ~4.5%.[36] In fact, epidemiological studies also have shown that about one-third of people in the community who experience constipation endorse symptoms consistent with dyssynergic defecation.[4] With a preponderance of CIC patients being female and having NTC, the similar efficacy to all the classes of drugs for the treatment of CIC is not surprising.

Prior randomised, placebo-controlled trials included in this analysis did not subgroup patients according to pathophysiology; hence, we are unable to report efficacy in subgroups of CIC. It is conceivable that patients with STC might respond better to treatment with agents that have significant effects on colonic motor function. Several of the agents evaluated in this network meta-analysis accelerate colonic transit, including intestinal secretagogues (lubiprostone,[37] linaclotide,[38] and the bile acid transport inhibitor, elobixibat[39]) and prokinetic agents (prucalopride,[40] tegaserod,[41] and bisacodyl[42]). However, among all these drugs, only prucalopride[43] and bisacodyl have been shown to increase the number of high amplitude propagated contractions, which are highly propulsive in the colon.[44] Lubiprostone did not induce colonic high amplitude contractions.[45]

A recent consensus monograph, based on meta-analysis of treatments of CIC, gave strong recommendation for treatment with fibre, osmotic laxatives (PEG, lactulose), stimulant laxatives (NaP and bisacodyl), prucalopride, linaclotide and lubiprostone.[46] However, the quality of evidence was considered moderate in some of the trials, there were no direct

Table 6 Sensitivity analysis based on dose of medication (for primary end points NS if RR's 95% CI overlaps 1, for secondary end points NS if RR's 95% CI overlaps 0)

Drug	Responders with ≥3 CSBM			Responders with increase over baseline by ≥1 CSBM			Δ_b CSBM/week			Δ_b SBM/week		
	Standard	Low	High	Standard	Low	High	Standard	Low	High	Standard	Low	High
Bisacodyl vs Placebo	2.46 (1.81 to 3.35)	–	–	2.04 (1.62 to 2.57)	–	–	3.2 (2.66 to 3.74)	–	–	4.90 (4.14 to 5.66)	–	–
NaP vs Placebo	2.83 (1.93 to 4.16)	–	–	2.03 (1.56 to 2.64)	–	–	2.0 (1.51 to 2.49)	–	–	3.20 (2.55 to 3.85)	–	–
Prucalopride vs Placebo	2.04 (1.59 to 2.62)	1.31 (0.56 to 3.04)	2.23 (1.74 to 2.85)	1.54 (1.24 to 1.92)	1.81 (1.23 to 2.66)	1.71 (1.45 to 2.01)	0.88 (0.49 to 1.28)	1.30 (0.76 to 1.84)	0.9 (0.42 to 1.38)	1.58 (0.72 to 2.44)	1.85 (0.79 to 2.91)	1.63 (0.46 to 2.81)
Tegaserod vs Placebo	1.75 (1.32 to 2.33)	1.18 (0.86 to 1.62)	–	1.41 (1.18 to 1.69)	1.17 (0.96 to 1.42)	–	–	–	–	–	–	–
Velusetrag vs Placebo	4.09 (1.59 to 10.51)	5.57 (2.24 to 13.86)	4.9 (1.93 to 12.43)	2.49 (1.38 to 4.46)	3.33 (1.91 to 5.80)	3.5 (2.01 to 6.10)	–	–	–	1.90 (1.23 to 2.57)	2.20 (1.55 to 2.85)	2.10 (1.35 to 2.85)
Linaclotide vs Placebo	1.92 (1.03 to 3.57)	–	2.0 (1.08 to 3.69)	1.64 (1.07 to 2.51)	–	1.81 (1.19 to 2.73)	1.45 (1.09 to 1.82)	1.02 (0.22 to 1.82)	1.70 (1.39 to 2.01)	1.83 (1.18 to 2.48)	–	2.26 (1.84 to 2.68)
Elobixibat vs Placebo	–	–	–	2.25 (1.42 to 3.58)	1.74 (1.06 to 2.87)	2.25 (1.42 to 3.58)	1.46 (0.54 to 2.38)	1.42 (0.25 to 2.59)	3.09 (2.05 to 4.13)	1.79 (0.72 to 2.86)	1.18 (−0.06 to 2.42)	3.27 (2.11 to 4.43)
Lubiprostone vs placebo	–	–	–	–	–	–	–	–	–	1.92 (1.35 to 2.49)	–	–

Drug: standard dose, low dose, high dose. Prucalopride: 2 mg QD, 1 mg QD, 4 mg QD.
Velusetrag: 30 mg QD, 15 mg QD, 50 mg QD. Tegaserod: 6 mg twice daily, 2 mg twice daily, no high dose.
Linaclotide: 145/150 µg QD, 75 µg QD, 290/600 µg QD.
Elobixibat: 10 mg QD, 5 mg QD, 15 mg QD. Lubiprostone: 24 µg twice daily, no low and high dose.
CSBM, complete spontaneous bowel movements; RR, relative risk; QD, once daily.
Bold indicates p Values < 0.05.

comparisons between active drugs and the analysis used as primary end point the failure to respond to therapy. This appraisal actually combined in non-responder status failure to respond to different end points in each trial. In addition, the secondary end points evaluated did not differentiate SBM from CSBM. Despite these methodological differences, our direct and network meta-analyses confirm the general conclusion of the prior report regarding the efficacy of each intervention relative to placebo with reference to the primary end points (which are the components of the end point currently recommended by the FDA), although there is a possible difference in efficacy on secondary end points between bisacodyl and other drugs.

Our study has some limitations. There is only one randomised, placebo-controlled trial for four of the drugs included in the meta-analysis (NaP, bisacodyl, velusetrag and elobixibat), and osmotic laxatives such as PEG, lactulose, and magnesium salts were not included, since the end points in those studies were not uniform or consistent with the inclusion criteria. This particularly applies to the trials with PEG.[47–50] There is one randomised, placebo-controlled trial directly comparing PEG3350+electrolytes with prucalopride treatment,[51] but this was a single-centre study conducted in a controlled environment on patients many of whom had features suggesting evacuation disorder at baseline: ~50% reported sensation of anal blockage and 15% manual manoeuvres to facilitate defecation. Moreover, the primary end point was the proportion of patients having ≥3 SCBMs during the last week of treatment in a 4-week trial, rather than the entire treatment period, and the randomised, placebo-controlled trial showed non-inferiority of PEG3350 +electrolytes to prucalopride, consistent with our general conclusion that the approved pharmacotherapies for CIC have similar efficacy.

Other limitations in our network meta-analysis are the variability in the duration of treatment (4–24 weeks) and safety and adverse events for the drugs were not analysed in our study. Another limitation is that, in many of these pivotal clinical trials, bisacodyl is often used as the rescue medication, and the impact of this on the 'placebo' arms could not be appraised as it is not reported in detail in the trials. It is also conceivable that the high number of prucalopride trials impacted the relative assessment of efficacy by reducing the width of the CI of the RR; therefore, we have interpreted cautiously the RR differences between prucalopride and velusetrag, which was the only medication identified as less efficacious than prucalopride in the statistical analysis.

Strengths in our study design and network meta-analysis include trials with similar patient population, comparators, outcome assessments and trial design; application of the GRADE approach to provide an objective and transparent assessment of the quality of evidence for evaluating comparative efficacy of these agents[52] and the inclusion of the responder analyses as well as secondary end points, which are very relevant in view of differences in baseline SBM and CSBM between studies.[53]

In conclusion, network meta-analysis shows that current pharmacotherapies for CIC have similar efficacy. Based on secondary end points, bisacodyl may be superior to other medications prescribed for CIC; however, bisacodyl is associated with abdominal cramps and diarrhoea. In the future, head-to-head trials of active agents are necessary to determine the efficacy and adverse effects in order to facilitate optimal selection of pharmacological agents for CIC instead of the current choice based on failure of prior drugs.

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Acknowledgements We thank Dr Fabio Cataldi and Dr Debra Silberg (Shire Pharmaceuticals, Turnhout, Belgium), the late Dr Hans Graffner (Albireo, Göteborg, Sweden), Dr Sabine Niedermeier (Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany), Dr Peter Lichtlen (Sucampo AG, Bethesda, Maryland, USA), Dr Fukudo Shin (Tohoku University, Sendai, Japan), Dr Michael A Kamm (University of Melbourne, Melbourne, Australia) and Dr Stefan Mueller-Lissner (Lehrkrankenhaus der Charité, Universitätsmedizin, Berlin, Germany) for providing access to clinical trial data for medications reviewed in this article.

Contributors ADN and MC: concept development, data analysis, selection of articles, authorship. SC and ZW: network meta-analysis, authorship. PV: assessment of study quality, authorship. NV: selection of articles to be included after the literature search, authorship. AS: analysis of data on 5-HT_4 agonists, authorship. PJE: literature search for systematic review, authorship. MHM: systematic review and network meta-analysis, authorship.

Funding MC is supported by grant R01-DK92179 from National Institutes of Health for studies on lower functional GI disorders.

Competing interests MC received grants for research on pharmacodynamics of prucalopride, velusetrag, elobixibat, linaclotide and lubiprostone in the past decade. MC serves as an advisor to Albireo, Rhythm and Theravance, with compensation for his time serving as an advisor paid to his employer, Mayo Clinic, not to himself personally.

Provenance and peer review Not commissioned; externally peer reviewed.

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Alfred D Nelson, Michael Camilleri, Sakkarin Chirapongsathorn, Priya Vijayvargiya, Nelson Valentin, Andrea Shin, Patricia J Erwin, Zhen Wang and M Hassan Murad

Gut published online June 10, 2016