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Comparison of Efficacy of Pharmacological Treatments for Chronic Idiopathic Constipation: A Systematic Review and Network Meta-analysis

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chronic idiopathic constipation (CIC)
numbers needed to treat (NNT)
sodium picosulfate (NaP)
polyethylene glycol (PEG)
complete spontaneous bowel movements (CSBM)
spontaneous bowel movements (SBM)
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confidence interval (CI)

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serotonin or 5-hydroxytryptamine (5HT)
normal transit constipation (NTC)
slow transit constipation (STC)
high amplitude propagated contractions (HAPC)

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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 randomized, 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 1 of 4 endpoints.

Data Extraction and Synthesis: Two investigators independently evaluated all full text articles that met inclusion criteria and extracted data for primary and secondary endpoints, risk of bias and quality of evidence.

Outcomes: Primary endpoints were ≥3 complete spontaneous bowel movements (CSBM)/week and increase over baseline by ≥1 CSBM/week. Secondary endpoints 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 endpoint criteria: 9 prucalopride, 3 lubiprostone, 3 linaclotide, 2 tegaserod, 1 each velusetrag, elobixibat, bisacodyl and sodium picosulphate (NaP). All pre-specified endpoints were unavailable in 4 polyethylene glycol studies. Bisacodyl, NaP, prucalopride and velusetrag were superior to placebo for the ≥3 CSBM/week endpoint. No drug was superior at improving the primary endpoints on network meta-analysis. Bisacodyl appeared superior to the other drugs for the secondary endpoint, 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.

SUMMARY BOX

What is already known about this subject?

- Fifty percent of patients with chronic idiopathic constipation (CIC) are not completely satisfied with treatment, especially with fiber and laxatives.
- The number needed to treat (NNT), estimated from placebo-controlled clinical trials in CIC comparing pharmacological therapies to 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 endpoints, 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 (Δb) SBM/week in CIC and in comparison with some of the drugs in Δb 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 nonpharmacological agents like fiber (soluble in preference to nonsoluble fiber and is followed by pharmacological agents if there is no response to fiber.[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 patients with CIC were not completely satisfied with treatment due to lack of efficacy or safety concerns, especially with fiber 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-HT_4 receptor 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 to 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 endpoints were used in individual studies.

The absence of direct comparisons between different drug classes limits comparison of efficacy among treatments to the endpoints currently recommended by the US Food and Drug Administration 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 to placebo using Bayesian network meta-analysis and endpoints 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 (PRISMA) 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 & Other Non-Indexed Citations and Ovid MEDLINE (1946 to present), Ovid EMBASE, Scopus databases (1988 to 2015) and Ovid Cochrane CENTRAL (to March 2015) for all the drugs used for treatment of CIC. An expert librarian (PE) 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, fiber, and randomized 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 (AN 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 randomized, placebo-controlled trials of drugs that are either approved by FDA for CIC or drugs with data available for at least one pre-specified endpoint from phase IIB or III randomized, placebo-controlled trials, and >4 weeks of treatment. Participants included were adults (>18 years of age) who satisfied Rome II or Rome 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 endpoint required by regulatory agencies (specifically, the U.S. Food and Drug Administration) 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 randomized, placebo-controlled trials of linaclotide included this endpoint; therefore, we analyzed different endpoints that addressed

similar outcomes, in order to be consistent in appraising efficacy among studies. The primary endpoints 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 endpoints were continuous, quantitative variables: the change from baseline (Δb) in the number of spontaneous bowel movements (SBM)/week and Δb CSBM/week. Unfortunately, none of the four available PEG trials included the endpoints selected for our network meta-analysis.

Data Extraction and Management

Data extraction from the eligible studies was performed by two independent investigators (AN and SC) for the primary and secondary endpoints. 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 endpoints were extracted as number of responders and non-responders for each primary endpoint and mean and standard deviation for secondary endpoints.

We also collected data about characteristics of the randomized, placebo-controlled trials, such as study center 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 dichotomized outcomes, weighted mean difference (WMD) for continuous outcomes, and related confidence intervals. 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 v5.3 (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 Version 14.0 (StataCorp LP, 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 endpoints. We evaluated effect sizes based on therapeutic dose (standard dose group versus high dose) and study quality for prucalopride (low risk of bias versus 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 (AN and PV) independently assessed the randomization 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 endpoints, 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 randomized, 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, i.e., 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 appraisal. Among the 114 articles, only 18 articles met the inclusion criteria; 96 studies did not meet the inclusion criteria, most often because the endpoints in the trials were different from the selected primary and secondary endpoints, articles did not have original data, or they were nonrandomized studies. The agreement between the investigators (AN and NV) for selection of studies after full text review was high (Kappa 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 endpoints, 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 summarized in Table 1.

There were 9189 patients in the 21 studies: 9 with prucalopride,[13, 14, 15, 16, 17, 18, 19, 20, 21] 3 with lubiprostone,[22, 23, 24] 3 with linaclotide,[25, 26, 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 summarized 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 endpoint are summarized in Figure 3A-D.

Primary Endpoints

The data for responder analysis with ≥3 CSBM/week were available for 14 randomized, placebo-controlled trials. All six drugs showed a significant increase in ≥3 CSBM/week when compared to placebo. Among the three $5HT_4$ agonists (prucalopride, velusetrag and tegaserod), prucalopride showed higher efficacy [relative risk (RR)] of 1.85 with a 95% confidence interval (CI) of 1.35 to 2.54 when compared to 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 confidence interval may suggest velusetrag might be less efficacious when compared to 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 endpoint (I^2 = 77.4% P < 0.00001).

For responder analysis with increase over baseline by ≥1 CSBM/week, data were available for 15 randomized, 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 $5HT_4$ 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 to 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 Endpoints

Data for Δ_b CSBM/week were available only for 5 drugs. All the drugs showed superior efficacy when compared to placebo. Bisacodyl had a weighted mean difference (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 7 of the drugs showed superior efficacy relative to placebo. Bisacodyl showed higher efficacy with a WMD of 4.90 when compared to 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%.

Network Meta-analysis

Responder analysis for ≥3 CSBM/week (Table 3A)

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

Responder analysis for increase over baseline by ≥1 CSBM/week (Table 3B)

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

Change in number of CSBM/week compared to baseline (Table 4A)

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

Change in number of SBM/week compared to baseline (Table 4B)

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

Network meta-analysis suggested that bisacodyl is superior when NaP, prucalopride, velusetrag, linaclotide, elobixibat and lubiprostone are compared to bisacodyl. NaP showed superior efficacy when prucalopride and lubiprostone were compared to 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 to placebo, the quality of evidence was moderate or high for all comparisons. However, most head-to-head comparisons were imprecise (i.e., 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 to high and low dose groups for the primary endpoints and for most of the secondary endpoint analyses (Table 6). An exception was that low dose (in contrast to standard or high dose) prucalopride was not effective compared to placebo for the endpoints of ≥3 CSBM/week and Δb SBM/week.

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 randomized, placebo-controlled trials. All the drugs are equally efficacious for the primary endpoints 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 endpoint 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 to 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 randomized, 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 randomized, 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 randomized, 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 (HAPC), 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 fiber, 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 comparisons between active drugs, and the analysis used as primary endpoint the failure to respond to therapy. This appraisal actually combined in non-responder status failure to respond to different endpoints in each trial. In addition, the secondary endpoints 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 endpoints (which are the components of the endpoint currently recommended by FDA), although there is a possible difference in efficacy on secondary endpoints between bisacodyl and other drugs.

Our study has some limitations. There is only one randomized, placebo-controlled trial for 4 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 endpoints in those studies were not uniform or consistent with the inclusion criteria. This particularly applies to the trials with PEG.[47, 48, 49, 50] There is one randomized, placebo-controlled trial directly comparing PEG3350 + electrolytes (PEG3350+E) to prucalopride treatment,[51] but this was a single-center 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 maneuvers to facilitate defecation. Moreover, the primary endpoint 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 randomized, placebo-controlled trial showed non-inferiority of PEG3350 + E 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 to 24 weeks) and safety and adverse events for the drugs were not analyzed 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 confidence interval 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 endpoints 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 endpoints, bisacodyl may be superior to other medications prescribed for CIC; however, bisacodyl is associated with abdominal cramps and diarrhea. 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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Alfred D. Nelson: concept development, data analysis, selection of articles, authorship
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Sakkarin Chirapongsathorn: network meta-analysis, authorship
Priya Vijayvargiya: assessment of study quality, authorship
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Patricia J. Erwin: literature search for systematic review, authorship
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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	2mg, 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	2mg 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	1mg, 2mg, 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	2mg 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	2mg, 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	2mg, 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	1mg 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	2mg 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	15mg, 30mg, 45mg 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	6mg bid	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	2mg, 6mg bid	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	24mcg bid	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	24mcg bid	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	24mcg bid	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 15mgQD	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	10mg 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	10mg 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 600mcg 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	145 or, 290mcg, QD	12	643: 434/209	47.4±14.2	49.3±14.3	87.4	< 3 SBM/week and ≥1 of the following Rome criteria[#] for at least 12 weeks within the preceding 12 months
		LINA		12	633: 418/215	47.2±12.8	47.0±13.5	90.4	
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

*- Rome III criteria which includes straining,

[#]- Part of the Rome III criteria which includes ≥25% straining, incomplete evacuation and hard/lumpy stools,

[$]- 85.32% were male, [¶] 100% were men,

PRU- Prucalopride, VEL- Velusetrag, TEG- Tegaserod, LUBI- Lubiprostone, ELO- Elobixibat, BIS- Bisacodyl, NaP- Sodium Picosulphate, LINA- Linaclotide, MC- Multicenter, SC- Single center, Int- International, I- Intervention, C- Control.

Table 2. Study Quality (CGR=computer generated randomization; Rx=intervention arm, C=control; LOCF=last observation carried forward; PRU=prucalopride, VEL=velusetrag, TEG=tegaserod, LUBI=lubiprostone, ELO=elobixibat, BIS=bisacodyl, NaP=sodium picosulphate, LINA=linaclotide)

Study Identification	Drug	Generation of randomization sequence	Allocation concealment	Double Blind	Lost to follow up	Methods used for missing data	Overall Quality
Camilleri 2008	PRU	Consecutive numbering + block randomization of 3	+	+	5Rx, 3C	Imputation	High
Coremans 2003	PRU	Unclear	Unclear	+	0	-	Mod
Ke 2012	PRU	CGR	+	+	3Rx, 2C	NS	Mod
Mueller-Lissner 2010	PRU	Randomization code generated by sponsor	+	+	0	Considered as non-responders	High
Piessevaux 2015	PRU	Randomization by web-based/voice-response system.	+	+	0	Imputation	Low
Quigley 2009	PRU	Block randomization 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	Randomized using validated computer system	+	+	26Rx, 10C	NS	Mod
Barish 2010	LUBI	Block randomization of four	+	+	4Rx, 1C	LOCF	Mod
Fukudo 2015	LUBI	Method not known	Unclear	+	0	-	Mod
Johanson 2008	LUBI	Block randomization 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	Randomization by statistical programmer not involved in the trial	+	+	10Rx, 5C	Considered as non-responders	High

Table 3. Pooled RR, and 95% confidence intervals (for network meta-analysis) for primary endpoints (p<0.05 is bolded). (Note: For lubiprostone, both of the endpoints are not available +=Superior, -=Inferior).

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

Responders with ≥3 CSBM/week						
Placebo	**2.46 (1.14, 5.31)**	**2.83 (1.27, 6.31)**	**1.84 (1.40, 2.43)**	1.47 (0.7, 3.12)	**4.86 (1.58, 14.99)**	1.96 (0.8, 4.81)
	Bisacodyl	1.15 (0.38, 3.49)	0.75 (0.33, 1.69)	0.59 (0.20, 1.75)	1.97 (0.51, 7.72)	0.79 (0.24, 2.60)
		Sodium picosulphate	0.65 (0.28, 1.52)	0.52 (0.17, 1.56)	1.72 (0.43, 6.84)	0.69 (0.21, 2.31)
			Prucalopride	0.80 (0.36, 1.78)	2.64 (0.83, 8.41)	1.06 (0.41, 2.72)
				Tegaserod	3.30 (0.85, 12.79)	1.33 (0.41, 4.30)
					Velusetrag	0.40 (0.09, 1.70)
						Linaclotide

3B. Responders with ≥1 CSBM per week for the drugs for CIC

Responders with increase over baseline by **≥1 CSBM/week**							
Placebo	**2.04 (1.3, 3.19)**	**2.03 (1.27, 3.23)**	**1.54 (1.30, 1.83)**	1.33 (0.97, 1.83)	**3.1 (1.61, 5.95)**	**1.72 (1.0, 2.96)**	**1.97 (1.09, 3.55)**
	Bisacodyl	0.99 (0.52, 1.9)	0.76 (0.47, 1.22)	0.65 (0.38, 1.13)	1.52 (0.69, 3.35)	0.84 (0.42, 1.71)	0.96 (0.46, 2.02)
		Sodium picosulphate	0.76 (0.46, 1.25)	0.66 (0.37, 1.16)	1.53 (0.69, 3.41)	0.85 (0.42, 1.74)	0.97 (0.46, 2.06)
			Prucalopride	0.86 (0.60, 1.23)	**2.01 (1.02, 3.93)**	1.11 (0.63, 1.97)	1.27 (0.69, 2.35)
				Tegaserod	**2.33 (1.13, 4.80)**	1.29 (0.69, 2.42)	1.48 (0.76, 2.89)
					Velusetrag	0.56 (0.24, 1.30)	0.64 (0.26, 1.53)
						Linaclotide	1.14 (0.51, 2.55)
							Elobixibat

Table 4. Pooled weighted mean difference, and 95% confidence intervals (for network meta-analysis) for Secondary endpoints (p<0.05 is bolded). (Note: Tegaserod both of the endpoints are not available, +=Superior, -=Inferior).

4A. Number of CSBM change from baseline for the drugs for CIC

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

4B. Number of SBM change from baseline for the drugs for CIC

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

Table 5. Quality of Evidence for Responders with ≥1 CSBM

(# -Inconsistency, ## -Severe inconsistency, $ -Indirectness, $$ -Severe indirectness, * - Imprecision, **- Severe imprecision, § -Risk of bias, p<0.05 is bolded)

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

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

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

Drug: Standard dose, Low dose, High dose. Prucalopride: 2mg QD, 1 mg QD, 4mg QD.

Velusetrag: 30mg QD, 15mg QD, 50mg QD. Tegaserod: 6mg bid, 2mg bid, no high dose.

Linaclotide: 145/150mcg QD, 75mcg QD, 290/600mcg QD.

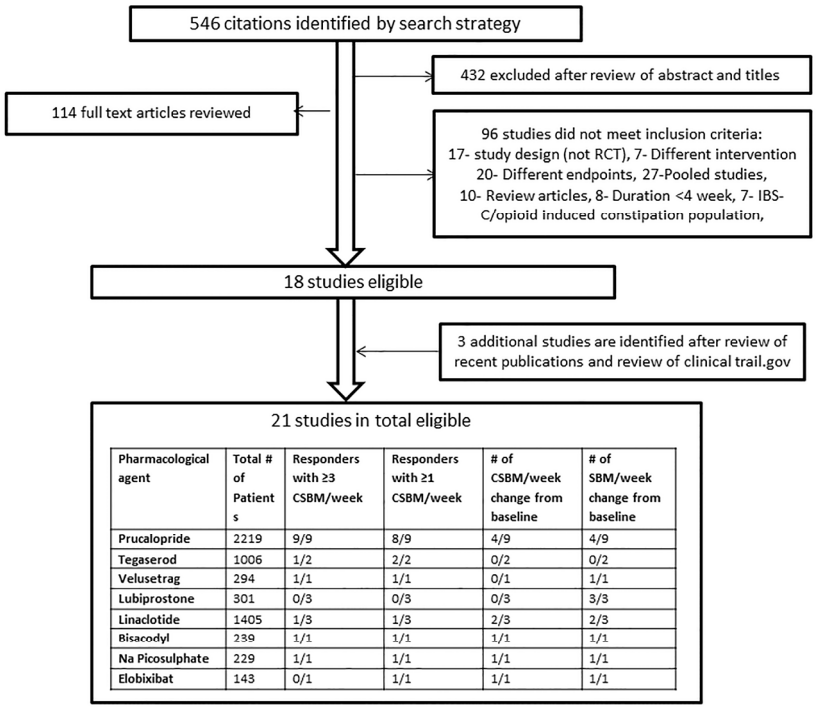
Elobixibat: 10mg QD, 5mg QD, 15mg QD. Lubiprostone: 24mcg bid, no low and high dose.

FIGURE LEGENDS

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

Figure 2: Network diagram (CT=clinical trials, P=patients)

Figure 3: Comparisons between treatment vs. placebo of primary endpoints, ≥3 CSBM/week (panel A) or increase over baseline by >1 CSBM/week (panel B), and secondary endpoints, change in CSBM from baseline (panel C) and change in SBM from baseline (panel D).



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.
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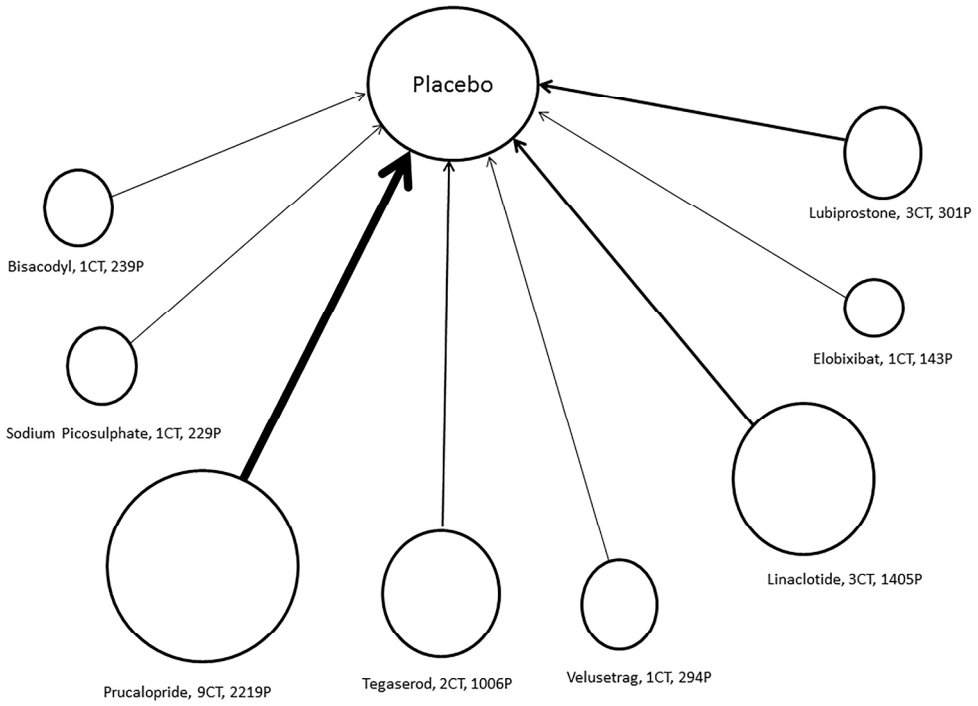

Figure 2. Network diagram (CT=clinical trials, P=patients)
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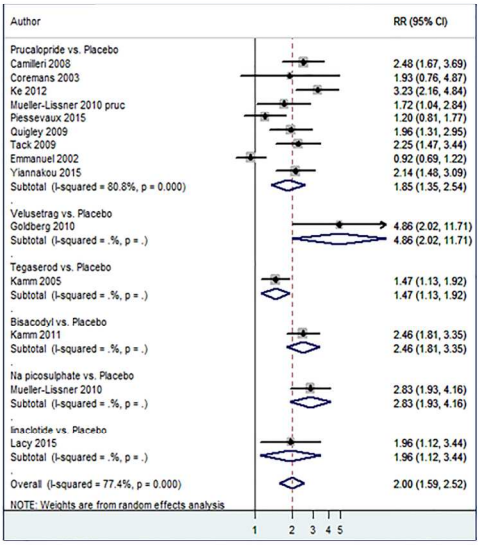

Figure 3A. Comparisons between treatment vs. placebo of primary endpoints, ≥3 CSBM/week (panel A) or increase over baseline by >1 CSBM/week (panel B), and secondary endpoints, change in CSBM from baseline (panel C) and change in SBM from baseline (panel D).
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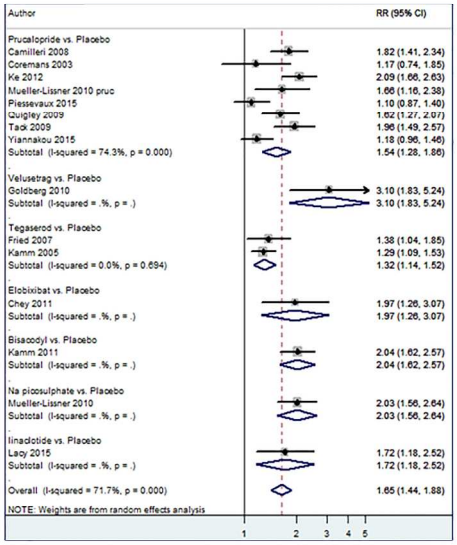

Figure 3B. Comparisons between treatment vs. placebo of primary endpoints, ≥3 CSBM/week (panel A) or increase over baseline by >1 CSBM/week (panel B), and secondary endpoints, change in CSBM from baseline (panel C) and change in SBM from baseline (panel D).
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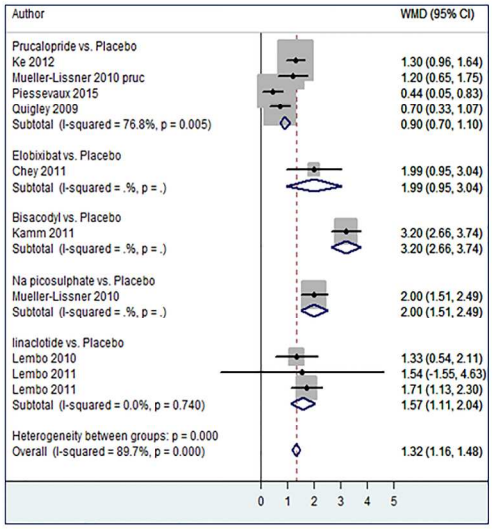

Figure 3C. Comparisons between treatment vs. placebo of primary endpoints, ≥3 CSBM/week (panel A) or increase over baseline by >1 CSBM/week (panel B), and secondary endpoints, change in CSBM from baseline (panel C) and change in SBM from baseline (panel D).
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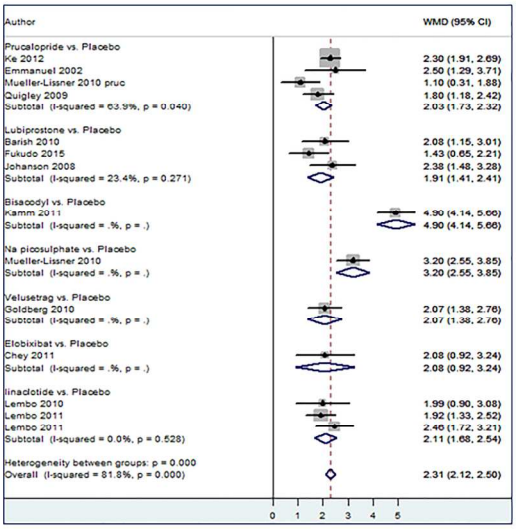

Figure 3D. Comparisons between treatment vs. placebo of primary endpoints, ≥3 CSBM/week (panel A) or increase over baseline by >1 CSBM/week (panel B), and secondary endpoints, change in CSBM from baseline (panel C) and change in SBM from baseline (panel D).
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Comparison of Efficacy of Pharmacological Treatments for Chronic Idiopathic Constipation: A Systematic Review and Network Meta-analysis

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Key words: bisacodyl, elobixibat, linaclotide, lubiprostone, picosulfate, polyethylene glycol, prucalopride, tegaserod, velusetrag

Abbreviations:
chronic idiopathic constipation (CIC)
numbers needed to treat (NNT)
sodium picosulfate (NaP)
polyethylene glycol (PEG)
complete spontaneous bowel movements (CSBM)
spontaneous bowel movements (SBM)
weighted mean difference (WMD)
confidence interval (CI)

serotonin or 5-hydroxytryptamine (5HT)
normal transit constipation (NTC)
slow transit constipation (STC)
high amplitude propagated contractions (HAPC)

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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 randomized, 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 1 of 4 endpoints.

Data Extraction and Synthesis: Two investigators independently evaluated all full text articles that met inclusion criteria and extracted data for primary and secondary endpoints, risk of bias and quality of evidence.

Outcomes: Primary endpoints were ≥3 complete spontaneous bowel movements (CSBM)/week and increase over baseline by ≥1 CSBM/week. Secondary endpoints 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 endpoint criteria: 9 prucalopride, 3 lubiprostone, 3 linaclotide, 2 tegaserod, 1 each velusetrag, elobixibat, bisacodyl and sodium picosulphate (NaP). All pre-specified endpoints were unavailable in 4 polyethylene glycol studies. Bisacodyl, NaP, prucalopride and velusetrag were superior to placebo for the ≥3 CSBM/week endpoint. No drug was superior at improving the primary endpoints on network meta-analysis. Bisacodyl appeared superior to the other drugs for the secondary endpoint, 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.

SUMMARY BOX

What is already known about this subject?

- Fifty percent of patients with chronic idiopathic constipation (CIC) are not completely satisfied with treatment, especially with fiber and laxatives.
- The number needed to treat (NNT), estimated from placebo-controlled clinical trials in CIC comparing pharmacological therapies to 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 endpoints, 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 (Δb) SBM/week in CIC and in comparison with some of the drugs in Δb 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 nonpharmacological agents like fiber (soluble in preference to nonsoluble fiber and is followed by pharmacological agents if there is no response to fiber.[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 patients with CIC were not completely satisfied with treatment due to lack of efficacy or safety concerns, especially with fiber 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-HT_4 receptor 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 to 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 endpoints were used in individual studies.

The absence of direct comparisons between different drug classes limits comparison of efficacy among treatments to the endpoints currently recommended by the US Food and Drug Administration 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 to placebo using Bayesian network meta-analysis and endpoints 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 (PRISMA) 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 & Other Non-Indexed Citations and Ovid MEDLINE (1946 to present), Ovid EMBASE, Scopus databases (1988 to 2015) and Ovid Cochrane CENTRAL (to March 2015) for all the drugs used for treatment of CIC. An expert librarian (PE) 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, fiber, and randomized 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 (AN 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 randomized, placebo-controlled trials of drugs that are either approved by FDA for CIC or drugs with data available for at least one pre-specified endpoint from phase IIB or III randomized, placebo-controlled trials, and >4 weeks of treatment. Participants included were adults (>18 years of age) who satisfied Rome II or Rome 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 endpoint required by regulatory agencies (specifically, the U.S. Food and Drug Administration) 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 randomized, placebo-controlled trials of linaclotide included this endpoint; therefore, we analyzed different endpoints that addressed

similar outcomes, in order to be consistent in appraising efficacy among studies. The primary endpoints 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 endpoints were continuous, quantitative variables: the change from baseline (Δb) in the number of spontaneous bowel movements (SBM)/week and Δb CSBM/week. Unfortunately, none of the four available PEG trials included the endpoints selected for our network meta-analysis.

Data Extraction and Management

Data extraction from the eligible studies was performed by two independent investigators (AN and SC) for the primary and secondary endpoints. 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 endpoints were extracted as number of responders and non-responders for each primary endpoint and mean and standard deviation for secondary endpoints.

We also collected data about characteristics of the randomized, placebo-controlled trials, such as study center 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 dichotomized outcomes, weighted mean difference (WMD) for continuous outcomes, and related confidence intervals. 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 v5.3 (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 Version 14.0 (StataCorp LP, 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 endpoints. We evaluated effect sizes based on therapeutic dose (standard dose group versus high dose) and study quality for prucalopride (low risk of bias versus 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 (AN and PV) independently assessed the randomization 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 endpoints, 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 randomized, 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, i.e., 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 appraisal. Among the 114 articles, only 18 articles met the inclusion criteria; 96 studies did not meet the inclusion criteria, most often because the endpoints in the trials were different from the selected primary and secondary endpoints, articles did not have original data, or they were nonrandomized studies. The agreement between the investigators (AN and NV) for selection of studies after full text review was high (Kappa 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 endpoints, 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 summarized in Table 1.

There were 9189 patients in the 21 studies: 9 with prucalopride,[13, 14, 15, 16, 17, 18, 19, 20, 21] 3 with lubiprostone,[22, 23, 24] 3 with linaclotide,[25, 26, 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 summarized 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 endpoint are summarized in Figure 3A-D.

Primary Endpoints

The data for responder analysis with ≥3 CSBM/week were available for 14 randomized, placebo-controlled trials. All six drugs showed a significant increase in ≥3 CSBM/week when compared to placebo. Among the three $5HT_4$ agonists (prucalopride, velusetrag and tegaserod), prucalopride showed higher efficacy [relative risk (RR)] of 1.85 with a 95% confidence interval (CI) of 1.35 to 2.54 when compared to 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 confidence interval may suggest velusetrag might be less efficacious ~~, was considered inferior~~ when compared to prucalopride ~~since the CI is wide~~. 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 endpoint (I^2 = 77.4% P < 0.00001).

For responder analysis with increase over baseline by ≥1 CSBM/week, data were available for 15 randomized, 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 $5HT_4$ 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 to 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 Endpoints

Data for Δ_b CSBM/week were available only for 5 drugs. All the drugs showed superior efficacy when compared to placebo. Bisacodyl had a weighted mean difference (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 7 of the drugs showed superior efficacy relative to placebo. Bisacodyl showed higher efficacy with a WMD of 4.90 when compared to 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%.

Network Meta-analysis

Responder analysis for ≥3 CSBM/week (Table 3A)

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

Responder analysis for increase over baseline by ≥1 CSBM/week (Table 3B)

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

Change in number of CSBM/week compared to baseline (Table 4A)

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

Change in number of SBM/week compared to baseline (Table 4B)

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

Network meta-analysis suggested that bisacodyl is superior when NaP, prucalopride, velusetrag, linaclotide, elobixibat and lubiprostone are compared to bisacodyl. NaP showed superior efficacy when prucalopride and lubiprostone were compared to 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 to placebo, the quality of evidence was moderate or high for all comparisons. However, most head-to-head comparisons were imprecise (i.e., 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 to high and low dose groups for the primary endpoints and for most of the secondary endpoint analyses (Table 6). An exception was that low dose (in contrast to standard or high dose) prucalopride was not effective compared to placebo for the endpoints of ≥3 CSBM/week and Δb SBM/week.

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 randomized, placebo-controlled trials. All the drugs are equally efficacious for the primary endpoints 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 endpoint 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 to 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 randomized, 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 randomized, 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 randomized, 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 (HAPC), 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 fiber, 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 comparisons between active drugs, and the analysis used as primary endpoint the failure to respond to therapy. This appraisal actually combined in non-responder status failure to respond to different endpoints in each trial. In addition, the secondary endpoints 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 endpoints (which are the components of the endpoint currently recommended by FDA), although there is a possible difference in efficacy on secondary endpoints between bisacodyl and other drugs.

Our study has some limitations. There is only one randomized, placebo-controlled trial for 4 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 endpoints in those studies were not uniform or consistent with the inclusion criteria. This particularly applies to the trials with PEG.[47, 48, 49, 50] There is one randomized, placebo-controlled trial directly comparing PEG3350 + electrolytes (PEG3350+E) to prucalopride treatment,[51] but this was a single-center 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 maneuvers to facilitate defecation. Moreover, the primary endpoint 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 randomized, placebo-controlled trial showed non-inferiority of PEG3350 + E 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 to 24 weeks) and safety and adverse events for the drugs were not analyzed 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 confidence interval 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 endpoints 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 endpoints, bisacodyl may be superior to other medications prescribed for CIC; however, bisacodyl is associated with abdominal cramps and diarrhea. 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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Authors' contributions:
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Michael Camilleri: concept development, data analysis, selection of articles, authorship
Sakkarin Chirapongsathorn: network meta-analysis, authorship
Priya Vijayvargiya: assessment of study quality, authorship
Nelson Valentin: selection of articles to be included after the literature search, authorship
Andrea Shin: analysis of data on $5HT_4$ agonists, authorship
Patricia J. Erwin: literature search for systematic review, authorship
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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	2mg, 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	2mg 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	1mg, 2mg, 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	2mg 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	2mg, 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	2mg, 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	1mg 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	2mg 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	15mg, 30mg, 45mg 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	6mg bid	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	2mg, 6mg bid	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	24mcg bid	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	24mcg bid	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	24mcg bid	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 15mgQD	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	10mg 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	10mg 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 600mcg 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	145 or, 290mcg, QD	12	643: 434/209	47.4±14.2	49.3±14.3	87.4	< 3 SBM/week and ≥1 of the following Rome criteria[#] for at least 12 weeks within the preceding 12 months
		LINA		12	633: 418/215	47.2±12.8	47.0±13.5	90.4	
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

*- Rome III criteria which includes straining,

[#]- Part of the Rome III criteria which includes ≥25% straining, incomplete evacuation and hard/lumpy stools,

[$]- 85.32% were male, [¶] 100% were men,

PRU- Prucalopride, VEL- Velusetrag, TEG- Tegaserod, LUBI- Lubiprostone, ELO- Elobixibat, BIS- Bisacodyl, NaP- Sodium Picosulphate, LINA- Linaclotide, MC- Multicenter, SC- Single center, Int- International, I- Intervention, C- Control.

Table 2. Study Quality (CGR=computer generated randomization; Rx=intervention arm, C=control; LOCF=last observation carried forward; PRU=prucalopride, VEL=velusetrag, TEG=tegaserod, LUBI=lubiprostone, ELO=elobixibat, BIS=bisacodyl, NaP=sodium picosulphate, LINA=linaclotide)

Study Identification	Drug	Generation of randomization sequence	Allocation concealment	Double Blind	Lost to follow up	Methods used for missing data	Overall Quality
Camilleri 2008	PRU	Consecutive numbering + block randomization of 3	+	+	5Rx, 3C	Imputation	High
Coremans 2003	PRU	Unclear	Unclear	+	0	-	Mod
Ke 2012	PRU	CGR	+	+	3Rx, 2C	NS	Mod
Mueller-Lissner 2010	PRU	Randomization code generated by sponsor	+	+	0	Considered as non-responders	High
Piessevaux 2015	PRU	Randomization by web-based/voice-response system.	+	+	0	Imputation	Low
Quigley 2009	PRU	Block randomization 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	Randomized using validated computer system	+	+	26Rx, 10C	NS	Mod
Barish 2010	LUBI	Block randomization of four	+	+	4Rx, 1C	LOCF	Mod
Fukudo 2015	LUBI	Method not known	Unclear	+	0	-	Mod
Johanson 2008	LUBI	Block randomization 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	Randomization by statistical programmer not involved in the trial	+	+	10Rx, 5C	Considered as non-responders	High

Table 3. Pooled RR, and 95% confidence intervals (for network meta-analysis) for primary endpoints (p<0.05 is bolded). (Note: For lubiprostone, both of the endpoints are not available +=Superior, -=Inferior).

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

Responders with ≥3 CSBM/week						
Placebo	**2.46 (1.14, 5.31)**	**2.83 (1.27, 6.31)**	**1.84 (1.40, 2.43)**	1.47 (0.7, 3.12)	**4.86 (1.58, 14.99)**	1.96 (0.8, 4.81)
	Bisacodyl	1.15 (0.38, 3.49)	0.75 (0.33, 1.69)	0.59 (0.20, 1.75)	1.97 (0.51, 7.72)	0.79 (0.24, 2.60)
		Sodium picosulphate	0.65 (0.28, 1.52)	0.52 (0.17, 1.56)	1.72 (0.43, 6.84)	0.69 (0.21, 2.31)
			Prucalopride	0.80 (0.36, 1.78)	2.64 (0.83, 8.41)	1.06 (0.41, 2.72)
				Tegaserod	3.30 (0.85, 12.79)	1.33 (0.41, 4.30)
					Velusetrag	0.40 (0.09, 1.70)
						Linaclotide

3B. Responders with ≥1 CSBM per week for the drugs for CIC

Responders with increase over baseline by **≥1 CSBM/week**							
Placebo	**2.04 (1.3, 3.19)**	**2.03 (1.27, 3.23)**	**1.54 (1.30, 1.83)**	1.33 (0.97, 1.83)	**3.1 (1.61, 5.95)**	**1.72 (1.0, 2.96)**	**1.97 (1.09, 3.55)**
	Bisacodyl	0.99 (0.52, 1.9)	0.76 (0.47, 1.22)	0.65 (0.38, 1.13)	1.52 (0.69, 3.35)	0.84 (0.42, 1.71)	0.96 (0.46, 2.02)
		Sodium picosulphate	0.76 (0.46, 1.25)	0.66 (0.37, 1.16)	1.53 (0.69, 3.41)	0.85 (0.42, 1.74)	0.97 (0.46, 2.06)
			Prucalopride	0.86 (0.60, 1.23)	**2.01 (1.02, 3.93)**	1.11 (0.63, 1.97)	1.27 (0.69, 2.35)
				Tegaserod	**2.33 (1.13, 4.80)**	1.29 (0.69, 2.42)	1.48 (0.76, 2.89)
					Velusetrag	0.56 (0.24, 1.30)	0.64 (0.26, 1.53)
						Linaclotide	1.14 (0.51, 2.55)
							Elobixibat

Table 4. Pooled weighted mean difference, and 95% confidence intervals (for network meta-analysis) for Secondary endpoints (p<0.05 is bolded). (Note: Tegaserod both of the endpoints are not available, +=Superior, -=Inferior).

4A. Number of CSBM change from baseline for the drugs for CIC

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

4B. Number of SBM change from baseline for the drugs for CIC

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

Table 5. Quality of Evidence for Responders with ≥1 CSBM

(# -Inconsistency, ## -Severe inconsistency, $ -Indirectness, $$ -Severe indirectness, * - Imprecision, **- Severe imprecision, § -Risk of bias, p<0.05 is bolded)

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

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

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

Drug: Standard dose, Low dose, High dose. Prucalopride: 2mg QD, 1 mg QD, 4mg QD.

Velusetrag: 30mg QD, 15mg QD, 50mg QD. Tegaserod: 6mg bid, 2mg bid, no high dose.

Linaclotide: 145/150mcg QD, 75mcg QD, 290/600mcg QD.

Elobixibat: 10mg QD, 5mg QD, 15mg QD. Lubiprostone: 24mcg bid, no low and high dose.

FIGURE LEGENDS

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

Figure 2: Network diagram (CT=clinical trials, P=patients)

Figure 3: Comparisons between treatment vs. placebo of primary endpoints, ≥3 CSBM/week (panel A) or increase over baseline by >1 CSBM/week (panel B), and secondary endpoints, change in CSBM from baseline (panel C) and change in SBM from baseline (panel D).