Efficacy and safety of pharmacological therapies for functional constipation in children: a systematic review and meta-analysis

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Summary

Background There has been a substantial increase in studies on functional constipation in children as new therapies are deployed. We aimed to provide an up-to-date, methodologically robust systematic review and meta-analysis on the efficacy and safety of pharmacological therapies for functional constipation in children.

Methods In this systematic review and meta-analysis, we searched PubMed, Medline, Embase, and the Cochrane library from inception to Feb 5, 2025. We included randomised controlled trials that involved children aged 0 years to younger than 18 years with functional constipation treated with pharmacological interventions compared with placebo, no treatment, or other interventions and with at least a 2-week follow-up period. Studies were excluded if there was no definition of functional constipation, children with organic causes for constipation or previous bowel surgery were included, children with faecal incontinence without the presence of constipation were included, or the aim of treatment was faecal disimpaction rather than maintenance therapy. Pairs of authors independently extracted summary data from published reports and critiqued studies. We assessed risk of bias with the Cochrane tool. Meta-analyses estimated risk ratios (RRs) or mean differences, and 95% CIs. Certainty of evidence was established with GRADE. Our main outcomes were treatment success (as defined by study authors), defecation frequency, and withdrawals due to adverse events. This study was registered on PROSPERO (CRD42022368719).

Findings Our search identified 4595 articles, of which 59 randomised controlled trials were included, representing 7045 participants with functional constipation. Interventions included polyethylene glycol (n=36 studies), lactulose (n=18), magnesium oxide or magnesium hydroxide (n=7), picosulfate (n=1), liquid paraffin (n=4), prucalopride (n=1), lubiprostone (n=2), linaclotide (n=3), plecanatide (n=1), enemas (n=2), and domperidone (n=1). Meta-analyses for treatment success showed that polyethylene glycol was probably more effective than placebo (RR 1·74 [95% CI 1·25–2·41], moderate certainty of evidence) and may be more effective than lactulose (1·35 [1·11–1·64], low certainty of evidence). There might be no difference in treatment success for linaclotide compared with placebo (1·21 [0·69–2·13], low certainty of evidence), but linaclotide probably leads to higher defecation frequency per week (mean difference 1·10 [95% CI 0·40–1·80], moderate certainty of evidence). There is low to moderate certainty evidence that prucalopride is not more effective than placebo (RR 1·68 [95% CI 0·77 to 3·68]).

Interpretation Polyethylene glycol is probably more effective than placebo and key comparator therapies and should be considered the standard of first-line care. Future studies should consider polyethylene glycol as an index therapy, and clearly describe methods, patient characteristics, and previous therapeutics.

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Introduction

Paediatric functional constipation is a common problem, with a worldwide prevalence of 9·5%.[1] Functional constipation is characterised by infrequent, hard, and painful stools, often accompanied by faecal incontinence without any underlying organic cause. These symptoms affect social, physical, and emotional functioning of children.[2,3]

Treatment requires a combination of various therapies, starting with non-pharmacological interventions (education, demystification, lifestyle advice, and toilet training).[4] If symptoms persist, polyethylene glycol is recommended as the first-choice laxative by European and North American societies of paediatric gastroenterology and is considered effective and safe for children.[4] Other pharmacological options include alternative osmotic laxatives, stimulant laxatives, lubricants, and enemas. Despite the available treatments, only half of children with functional constipation recover and discontinue laxatives after 6–12 months.[5]

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Research in context

Evidence before this study

We performed scoping searches in PubMed from database inception to Feb 26, 2025, with the search terms "consitpat* AND (child* OR infant* OR pediatr* OR adolescen*) AND (treatment OR therap*)", limiting the search to systematic reviews. No language restrictions were applied. Systematic reviews were considered relevant if they incorporated randomised controlled trials involving children aged 0–18 years with functional constipation treated with any form of pharmacological therapy. All identified systematic reviews focused on a subgroup of pharmacological treatments (eg, polyethylene glycol only) or a subgroup of patients (eg, young children or only those with intractable constipation). Furthermore, only a few reviews assessed certainty of the evidence with the GRADE approach. This finding highlights the current lack of a comprehensive and methodologically robust systematic review assessing efficacy and safety of all available pharmacological therapies for children with functional constipation.

Added value of this study

Various pharmacological therapies are included in this systematic review, including novel therapies that, to our knowledge, have not yet been included in any previous systematic review or guideline, such as lubiprostone, prucalopride, and linaclotide. The GRADE approach was used to assess certainty of evidence and to guide current practice. A novel addition to the GRADE approach was the application of predetermined thresholds for evaluating the magnitude of effects, providing a clinically relevant and objective measure of imprecision. Comprehensive analyses showed that polyethylene glycol is more effective than placebo and key comparator treatments. Linaclotide probably leads to higher defecation frequency than placebo and prucalopride is probably not more effective than placebo. Most other therapies provided evidence that was of very low certainty, due to methodological limitations and insufficient information to assess the risk of bias, precluding any evidence-based conclusions. This systematic review provides an up-to-date and methodologically rigorous synthesis of the evidence on all pharmacological treatment options for functional constipation, serving as a valuable resource for policy makers, guideline developers, affected children, and their families and caregivers.

Implications of all the available evidence

This systematic review and meta-analysis suggest that polyethylene glycol is probably more effective than placebo and key comparator therapies and therefore should be considered the standard first-line treatment. Future studies on functional constipation in children should consider polyethylene glycol as an index therapy as this is more clinically relevant, use core outcome sets, and clearly describe methods, patient characteristics, and previous therapeutics.

American Society for Pediatric Gastroenterology, Hepatology and Nutrition guideline on evaluation and treatment of functional constipation was published in 2014.[4] A subsequent 2016 Cochrane systematic review on osmotic and stimulant laxatives for the treatment of functional constipation in children found a lack of high-quality studies to support current practice.[6] Since then, there has been a large increase in publications on this topic, alongside a shift towards the use of the GRADE methods to judge certainty of evidence, particularly regarding imprecision.[7–9] Therefore, the aim of our study is to provide an up-to-date and methodologically robust systematic review of the current literature on the efficacy and safety of pharmacological therapies for functional constipation in children, to guide clinical practice.

Methods

Search strategy and selection criteria

In this systematic review and meta-analysis, we searched PubMed, Medline, Embase, and the Cochrane library from inception to Feb 5, 2025, to identify randomised controlled trials (RCTs) to consider for inclusion (search terms are in the appendix pp 206–211). Unpublished or ongoing studies were identified via ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform, and the metaRegister of Controlled Trials. In parallel with this review, we conducted a systematic review on non-pharmacological treatments, searching the same databases as the present review. As an additional check for potentially missed articles, we made a post-hoc decision to screen for studies comparing non-pharmacological with pharmacological interventions that should have been included in the present pharmacological review. No language restrictions were applied and articles were translated if necessary. References from the reviewed studies were checked for missed studies.

See Online for appendix

After removal of duplicates, pairs of assessors independently screened titles and abstracts through the Covidence tool (Veritas Health Innovation). Disagreements were resolved by a third assessor (MG or VS). Studies were considered eligible if they were an RCT; they included children aged 0 years to younger than 18 years or included a paediatric subgroup; they included children with functional constipation, functional constipation with faecal incontinence, or intractable constipation as defined by study authors; and treatment consisted of a pharmacological intervention with a minimum follow-up of 2 weeks (combination therapies were also included). Studies were excluded if no definition of functional constipation was provided, if children with organic causes for constipation or previous bowel surgery were included, if children with faecal

incontinence without the presence of constipation were included, or if the aim of treatment was faecal disimpaction rather than maintenance therapy. We included RCTs in the meta-analyses when patient demographics and outcomes were sufficiently similar. Included studies had summary estimates extracted from the published papers.

The protocol was registered on PROSPERO on Oct 25, 2022 (CRD42022368719). Protocol deviations are reported in the appendix (p 212). This study adhered to PRISMA reporting guidelines.

Data analysis

Main outcomes were treatment success (as defined by the study authors), defecation frequency, and withdrawals attributed to adverse events (unexplained withdrawals were included to represent a worst-case scenario for safety). Secondary outcomes were painful defecation, stool consistency, quality of life, faecal incontinence, abdominal pain, school attendance, serious adverse events, total adverse events, and compliance to or tolerability of treatment.

Pairs of authors (AdG and AJT or AA and SL) carried out data extraction independently for all included studies, extracting summary estimates reported in the paper and using a predesigned data extraction template. The variables for which data were extracted are listed in the appendix (pp 8–29). Data on race and ethnicity were not extracted. Disagreements were resolved through consensus with a third author (MG or VS). Risk of bias was assessed with the Cochrane risk of bias tool, evaluating random sequence generation, allocation concealment, masking of participants and personnel, masking of outcome assessors, attrition, selective reporting, and other bias.[10] Each study and domain was judged as low, high, or unclear risk of bias.

We used the GRADE framework to judge the certainty of evidence for all primary and secondary outcomes. Magnitude of effect size thresholds for the outcome measures were used to objectively assess imprecision of the results (appendix pp 1–2).[11]

Dichotomous outcomes were expressed as risk ratios (RRs) with 95% CIs, and continuous outcomes expressed as mean differences (MDs) with 95% CIs. In cases in which studies measured the same continuous outcome with varied methods, standardised mean differences (SMDs) were used to evaluate outcomes. We used the Mantel–Haenszel method and random effects model to pool estimates for the RRs and the inverse variance method and random effects model for the means. Heterogeneity was quantified through χ^2 tests and I^2 statistics, as recommended in the Cochrane handbook.[12]

Given the large number of comparisons, we made a post-hoc decision to present only the results of some comparisons, based on the number of included studies and participants per comparison, certainty of the evidence, magnitude of effect, and clinical relevance. Of those comparisons, figures are shown for outcomes with at least a low certainty of evidence and that include more than one study in the meta-analysis.

We conducted sensitivity analysis to consider the effect of risk of bias, fixed and random effects, and heterogeneity. Analyses were done in Review Manager (version 5.4).

Role of the funding source

There was no funding source for this study.

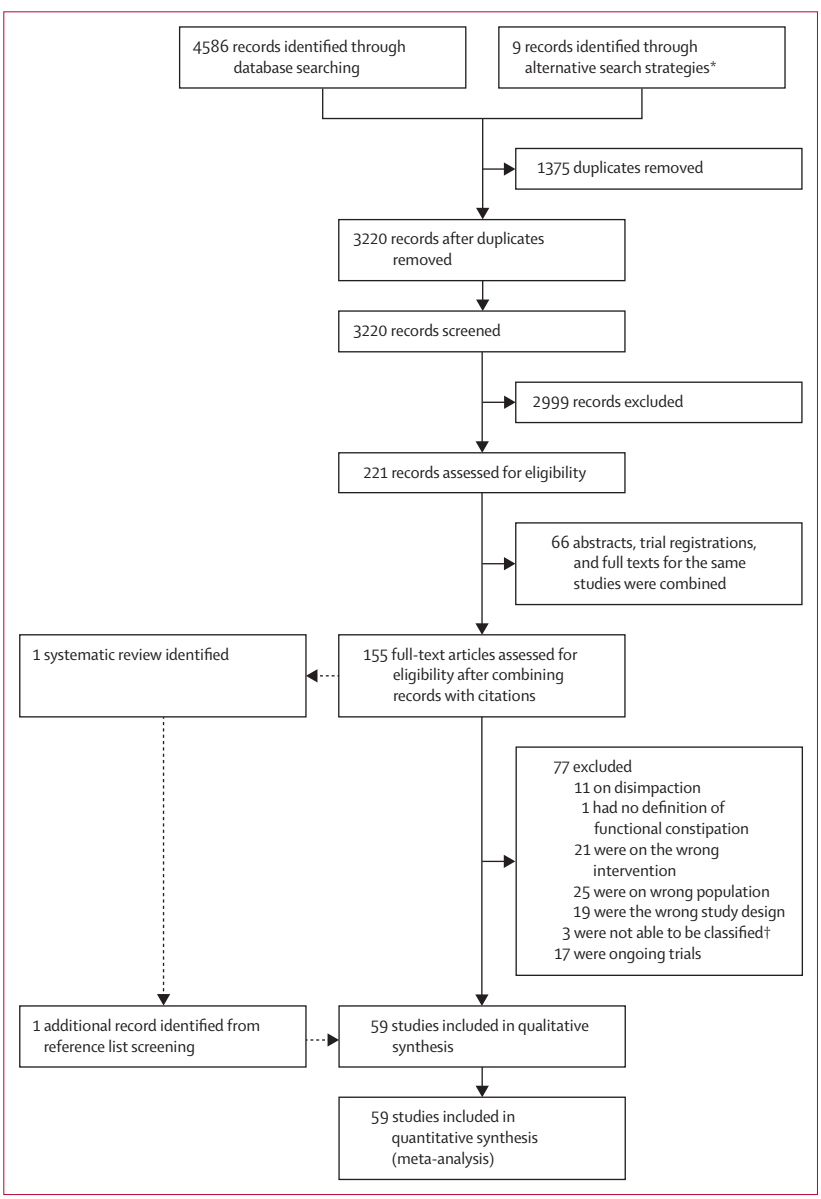

Figure 1: **PRISMA flow chart**

*These studies resulted from a search in the same databases on non-pharmacological therapies for children with functional constipation, which was done for another systematic review. However, as these studies compared non-pharmacological therapies to pharmacological treatments, they were also eligible for this systematic review. †Studies were not able to be classified as eligible or ineligible when additional information had been requested from the authors but was not received in time for inclusion.

Results

We found a total of 4586 articles through our initial search (figure 1). A further nine studies were identified through searching the same databases for non-pharmacological therapies and were eligible for inclusion, as these studies compared a non-pharmacological treatment to a pharmacological treatment. After removing 1375 duplicates, 3220 records remained for title and abstract screening, of which 2999 were excluded. After combining records for the same studies, 155 full-text articles were assessed for eligibility. 77 studies were excluded for various reasons (figure 1; appendix pp 3–5). One systematic review yielded an additional study. 17 ongoing trials were identified, and three studies could not be classified as additional information requested from authors was not received in time for inclusion (appendix pp 6–7).

59 studies fulfilled the inclusion criteria and were included (figure 1; appendix pp 8–29, 213–215). The included RCTs consisted of 7045 children aged 0 years to younger than 18 years with functional constipation, of whom 3382 (48%) were female and 3663 (52%) were male. The year of publication ranged from 1995 to 2025: one (2%) study was published before 2000, 14 (24%) studies between 2000 and 2009, 24 (41%) studies between 2010 and 2019, and 20 (34%) studies in 2020 or later. 22 (37%) studies were done in the Middle East, 15 (25%) in Europe, 11 (19%) in Asia, 5 (8%) in North America, 3 (5%) in South America, 2 (3%) in both North America and Europe, and 1 (2%) in Africa. Most studies (n=44, 75%) were done in tertiary care centres. Follow-up ranged from 4 weeks to 12 months and length of treatment period ranged from 2 weeks to 12 months. Most studies (n=48, 81%) used Rome criteria (II, III, IV) for diagnosis. Studied interventions included polyethylene glycol (n=36 studies), lactulose (n=18), magnesium hydroxide or magnesium oxide (n=7), picosulfate (n=1), liquid paraffin (n=4), prucalopride (n=1), lubiprostone (n=2), linaclotide (n=3), plecanatide (n=1), enemas (n=2), and domperidone (n=1). In total, 37 different comparative groups were studied, including non-pharmacological treatments (eg, dietary fibre, herbal medicine, and probiotics) and placebo. No RCTs were identified for commonly used laxatives such as bisacodyl, senna, or docusate. Study characteristics, the complete results for all comparisons, outcome definitions by authors, and all summary of findings tables (including forest plots) can be found in the appendix (pp 8–146).

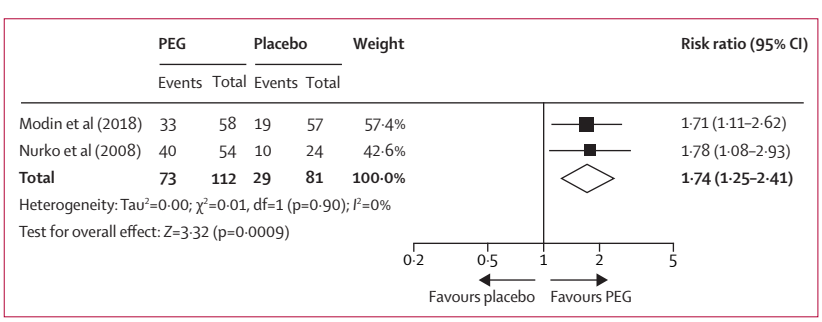

Figure 2: **Forest plot of treatment success for PEG versus placebo**
PEG=polyethylene glycol.

Complete details of the risk of bias outcomes with supporting statements and a summary are available in the appendix (pp 147–205). 42 (71%) of 59 studies clearly explained randomisation methods and were rated as low risk of bias. 17 (29%) studies were rated as having an unclear risk of bias due to insufficient information. Allocation concealment was rated low risk in 25 (42%) studies and unclear in 34 (58%) studies. In 32 (54%) studies, both performance and detection bias were rated as high risk of bias, mostly related to an open-label study design. Both performance and detection bias were rated low risk in 21 (36%) studies and unclear in four (7%) studies. Attrition bias was rated high risk in seven (12%) studies due to substantial imbalanced attrition or no explanation for dropouts, unclear risk in 18 (31%) studies, and low risk in 34 (58%) studies. In nine (15%) studies, key efficacy or safety outcomes were not reported or not reported per protocol and rated as high risk for selective reporting. 27 (46%) studies were rated unclear risk for selective reporting, predominately due to unavailable protocols or trial registrations. 23 (39%) studies were rated as low risk for selective reporting.

Three RCTs compared polyethylene glycol with placebo (n=269 children, aged 2–16 years). Two studies were used in our meta-analysis for treatment success (figure 2; appendix pp 30–35). Due to serious risk of bias, there was moderate certainty of evidence that polyethylene glycol leads to higher treatment success than placebo (n=193 children, treatment success in 73 [65%] of 112 children in the polyethylene glycol group *vs* 29 [36%] of 81 in the placebo group, RR 1·74 [95% CI 1·25–2·41], number needed to treat=4, large effect size magnitude; figure 2; appendix p 57). Owing to risk of bias, inconsistency, and imprecision, GRADE assessment showed there was very low certainty evidence regarding defecation frequency, and therefore no conclusion could be drawn. Cumulatively, four (4%) of 112 withdrawals reported in the polyethylene glycol group were due to adverse events and three (4%) of 81 withdrawals were due to adverse events in the placebo group. GRADE assessment showed very low certainty of evidence due to risk of bias, inconsistency, and very serious imprecision, and therefore no conclusion could be drawn about withdrawals due to adverse events.

Eight RCTs compared polyethylene glycol with lactulose (n=868 children, aged 6 months to 18 years). Five studies reported data on treatment success and were included in meta-analysis (figure 3A; appendix pp 30–35). Due to risk of bias and imprecision, GRADE assessment showed low certainty evidence that polyethylene glycol could be more effective in achieving treatment success than lactulose (n=585 children, treatment success in 207 [72%] of 288 children in polyethylene glycol group *vs* 151 [51%] of 297 in lactulose

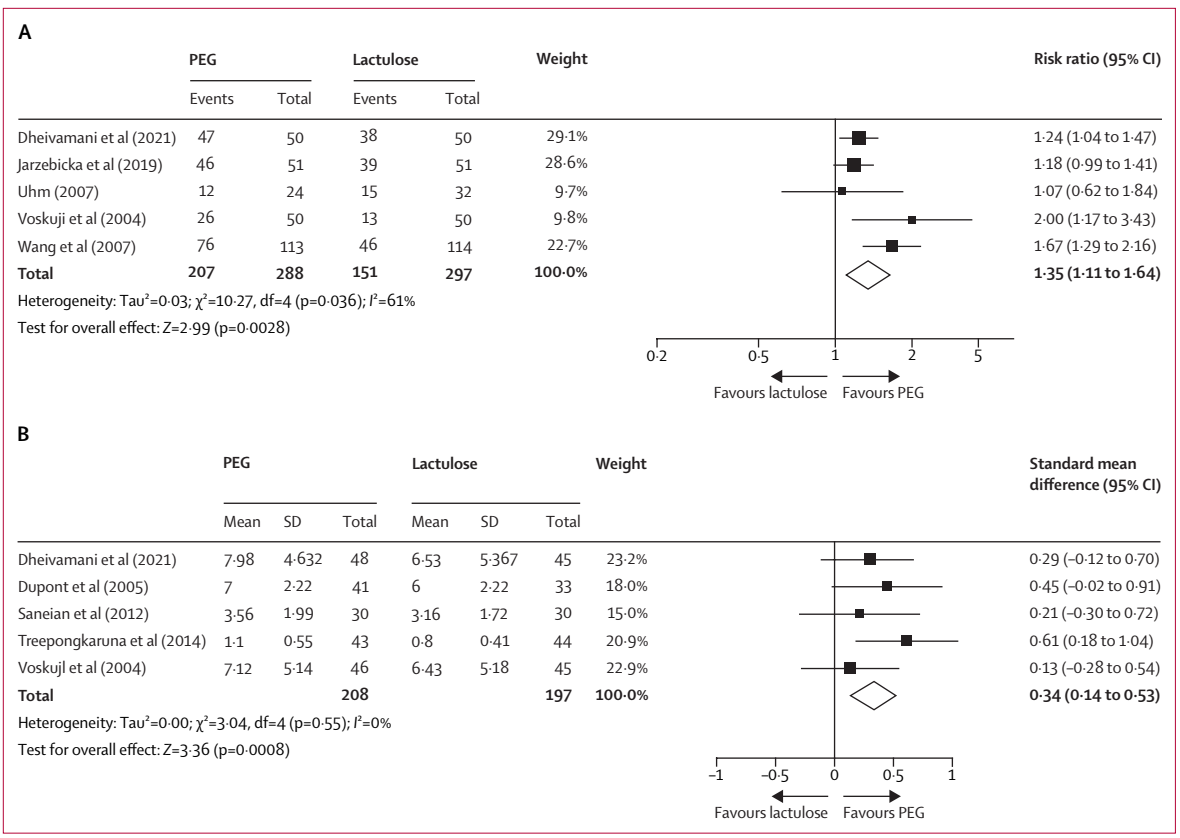

Figure 3: **Forest plots of efficacy outcomes for PEG versus lactulose**
(A) Results for treatment success. (B) Results for defecation frequency (standardised mean difference). PEG=polyethylene glycol.

group, RR 1·35 [95% CI 1·11–1·64], number needed to treat=5, moderate effect size magnitude; figure 3A; appendix p 59). Six studies reported on defecation frequency. The initial analysis had very low certainty of evidence due to substantial statistical heterogeneity (I^2 96%; appendix p 63). The study by Jarzebicka and colleagues reported a substantially greater effect than all other studies and attempts to contact the authors were unsuccessful and therefore this could not be explained clinically or methodologically. Consequently, we did a sensitivity analysis excluding this study (appendix pp 60–63). This analysis showed a trivial effect in favour of polyethylene glycol compared with lactulose in improving defecation frequency with moderate GRADE certainty (n=405 children, SMD 0·34 [95% CI 0·14–0·53], trivial effect size magnitude; figure 3B; appendix p 60). Six studies reported patient withdrawals due to adverse events. Cumulatively, 18 (7%) of 272 children withdrew due to adverse events in the polyethylene glycol group compared with 20 (7%) of 272 in the lactulose group, but this was of very low certainty. Apart from one study, which reported two withdrawals in the polyethylene glycol group due to vomiting and diarrhoea and fever and vomiting, other withdrawals did not provide detailed reasons.

Five RCTs compared polyethylene glycol with magnesium hydroxide (n=317 children, aged 6 months to 18 years). Two studies provided a definition of treatment success (appendix pp 30–35). Owing to risk of bias, inconsistency (I^2 95%), and very serious imprecision, there was very low certainty of evidence (appendix pp 64–66). Four studies reported on defecation frequency. Meta-analysis and GRADE assessment resulted in very low certainty of evidence due to risk of bias, inconsistency, and imprecision, and therefore no conclusion could be drawn. Withdrawals due to adverse events were reported in three studies. Cumulatively, 6 (6%) of 103 children withdrew due to adverse events in the polyethylene glycol group compared with 18 (17%) of 108 in the magnesium hydroxide group. Due to risk of bias, there was moderate certainty of evidence that polyethylene glycol leads to less withdrawals due to adverse events than magnesium hydroxide (n=211 children, 6 [6%] of 103 in the polyethylene glycol group *vs* 18 [17%] of 108 in the magnesium hydroxide group, RR 0·38 [95% CI 0·16–0·92], large effect size magnitude; figure 4; appendix p 64).

Only one RCT compared lactulose to placebo (n=100 children, aged 2–6 years). Treatment success was

not reported and measure of spread for defecation frequency was not adequately reported, which precluded the use of the data in the meta-analysis. Withdrawals due to adverse events were reported. 4 (8%) of 50 children withdrew in the lactulose group and 5 (10%) of 50 in the placebo group, and all withdrawals did not have detailed reasons. Due to very serious imprecision, there was low certainty evidence that there is no difference in withdrawals due to adverse events for lactulose compared with placebo (n=100 children, RR 0·80 [95% CI 0·23–2·81]; appendix p 98).

Three RCTs compared linaclotide to placebo (n=536 children, aged 2–17 years). Two of the three studies provided a definition of treatment success (appendix pp 30–35). Owing to very serious imprecision, there was low certainty evidence that there is no difference between linaclotide and placebo for treatment success (27 [15%] of 177 patients in linaclotide group *vs* 21 [12%] of 172 in the placebo group, RR 1·21 [95% CI 0·69–2·13]; figure 5A; appendix p 138). All three studies reported on defecation frequency. Owing to serious

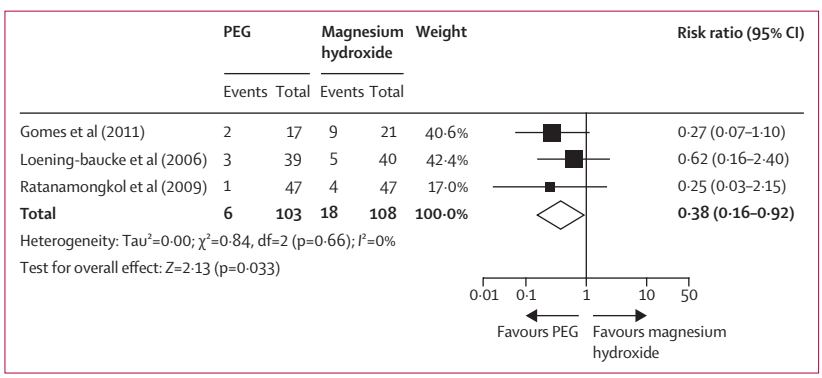

Figure 4: **Forest plot of withdrawals due to adverse events for PEG versus magnesium hydroxide**
PEG=polyethylene glycol.

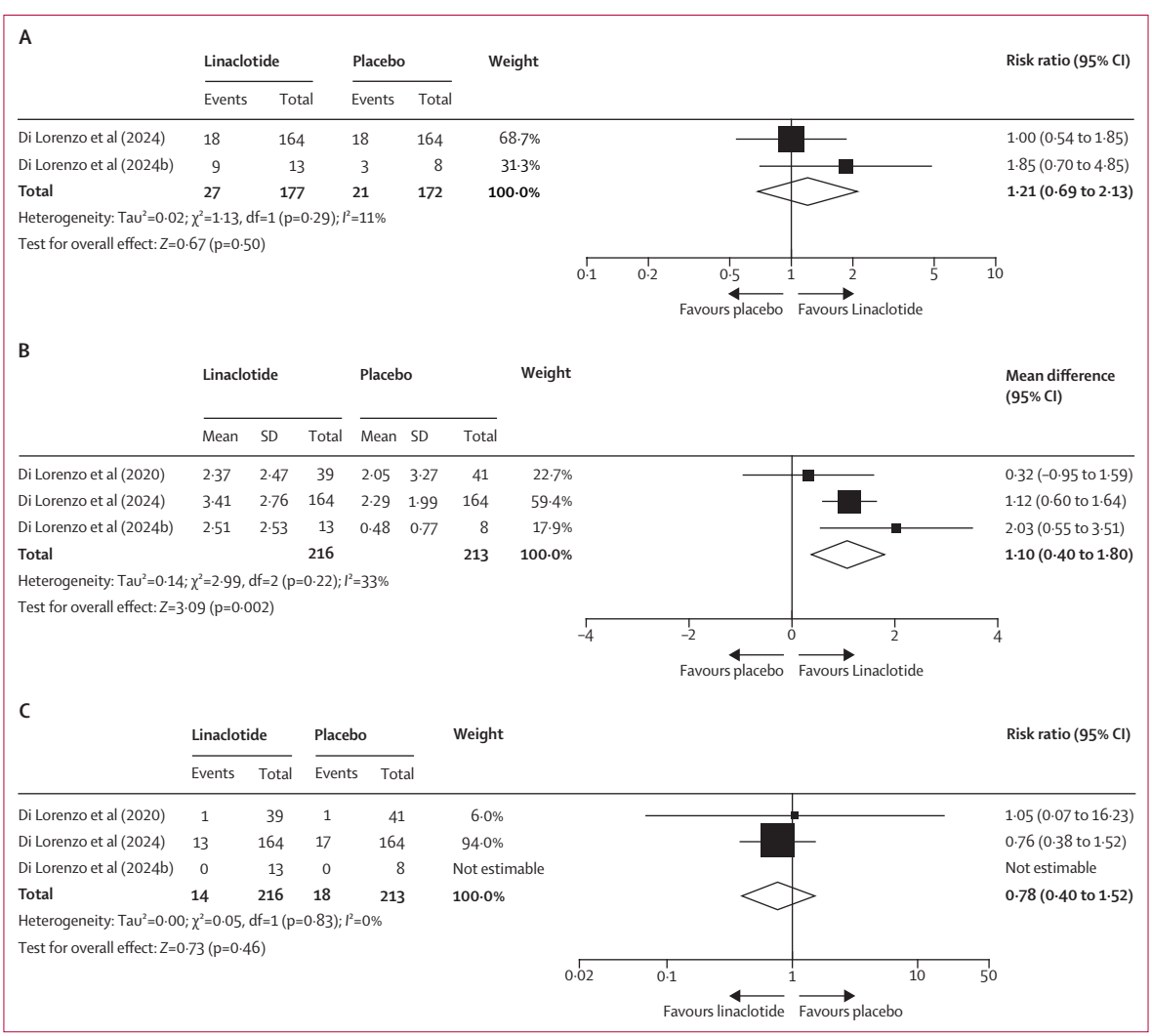

Figure 5: **Forest plots of efficacy and safety outcomes for linaclotide versus placebo**
(A) Results for treatment success. (B) Results for defecation frequency per week. (C) Results for withdrawals due to adverse events.

imprecision, there was moderate certainty of evidence that linaclotide leads to higher defecation frequency than placebo (n=429 children, MD 1·10 [95% CI 0·40–1·80], small effect size; figure 5B; appendix p 138). Withdrawals due to adverse events were reported in all studies. 14 (6%) of 216 participants were reported to withdraw due to adverse events in the linaclotide group and 18 (8%) of 213 in the placebo group. Reasons for withdrawals due to adverse events in the linaclotide group included faecaloma (n=1); diarrhoea, nausea, and dehydration (n=1); unspecified adverse event (n=1); and non-compliance to the study drug (n=3). Remaining withdrawals did not provide detailed reasons (n=8). Due to very serious imprecision, there was low certainty evidence that there is no difference between linaclotide and placebo for withdrawals due to adverse events (n=429 children, 14 [6%] of 216 in the linaclotide group *vs* 18 [8%] of 213 in the placebo group, RR 0·78 [95% CI 0·40–1·52]; figure 5C; appendix p 138).

From one RCT, there was low certainty evidence that there was no difference in defecation frequency for polyethylene glycol compared with picosulfate (n=33 children, 10 [63%] of 16 patient in the polyethylene glycol group *vs* 8 [47%] of 17 in the picosulfate group, RR 1·33 [95% CI 0·71–2·50]; appendix p 67).

From one RCT, there was low certainty of evidence that prucalopride is not more effective than placebo regarding treatment success (n=215 children; treatment success in 15 [14%] of 107 patients in the prucalopride group *vs* 9 [8%] of 108 in the placebo group, RR 1·68 [95% CI 0·77 to 3·68]) and moderate certainty of evidence of no effect regarding defecation frequency per week (MD 0·50 [95% CI –0·06 to 1·06]). There was low certainty evidence that prucalopride does not lead to more withdrawals due to adverse event (8 [7%] of 107 in the prucalopride group *vs* 5 [5%] of 108 in the placebo group, RR 1·61 [95% CI 0·55 to 4·78]; appendix pp 131–133).

Two RCTs investigated lubiprostone: one comparing lubiprostone to placebo (n=606 children) and the other to different laxatives (n=280 children; appendix pp 8–29). These RCTs yielded contradictory results of low to high certainty of evidence regarding the drug's efficacy for primary and secondary outcomes (appendix pp 134–137).

There was low certainty evidence that the addition of an enema as maintenance therapy to polyethylene glycol does not lead to more treatment success than polyethylene glycol alone (n=102 children, treatment success in 24 [47%] of 51 patients in the polyethylene glycol and enema group *vs* 18 [35%] of 51 in the polyethylene glycol alone group, RR 1·33 [95% CI 0·83–2·14]; appendix p 134).

Discussion

This systematic review and meta-analysis has investigated the efficacy and safety of all pharmacological therapies in children with functional constipation. When treatment success is considered, polyethylene glycol is the only therapy that was probably more effective than placebo (with a large effect size) and may be more effective than lactulose (with a moderate effect size). Polyethylene glycol is probably more effective than lactulose in improving defecation frequency, but the difference in effect size was trivial.

One trial comparing lactulose with placebo did not provide efficacy data to allow any analysis. Linaclotide probably leads to higher defecation frequency than placebo (with a small effect size) and there might be no difference in treatment success and defecation frequency for prucalopride compared with placebo.

Perhaps the more striking finding is that most other therapies provided evidence that did not show no effect but instead was of very low certainty, meaning no conclusions of any kind can be drawn. These inconclusive results are similar to functional abdominal pain disorders of childhood and are due to various pervasive reasons.[13]

First, there is poor reporting of foundational elements of trial design. Consequently, it is impossible to judge whether issues were related to reporting or the underlying quality of the trial. This incomplete reporting is not uncommon in the field, but what was more unusual was that despite multiple attempts to contact the primary study authors to rectify these issues and clarify the methods, few responses were received.[14,15]

Second, many studies were underpowered, contributing to large amounts of imprecision and low certainty of evidence. Again, underpowered studies are common in the field but was particularly problematic for these RCTs as many of them compared two active interventions, which is an approach that requires larger sample sizes than comparisons to placebo to detect significant differences.[16,17] Recruiting large sample sizes in paediatric studies is challenging due to smaller eligible populations, scarce funding, doctors overburdened with patient care, and parental reluctance to enrol their child in research. These challenges add to general challenges of achieving large sample sizes in medical research, such as institutional review boards, administrative tasks for the physician, and discomfort of the physician with randomising patients (especially when they believe their own treatment is most effective).

Third, there are pervasive issues with heterogeneity. The use of concomitant therapeutics or permitted interventions and the disease severity of the patient populations varied greatly from study to study . The issue of disease severity is not helped by the historical lack of clarity for definitions on key elements of constipation presentations.[18] In 2024 a proposed definition for therapy-resistant constipation was published and, in line with this definition, many of the studies included patients that could and perhaps should have been defined as therapy resistant.[19,20] Inconsistent reporting of severity characteristics probably contributed to unexplained heterogeneity in this meta-analysis. Finally, outcome measures also varied (both

across and within categories of outcomes) and many different specific measures, scales, and a range of dichotomous or continuous measures were used.

The methods used for this review follow the highest standards, and the application of GRADE analysis was particularly innovative. This GRADE analysis used predetermined thresholds for assessing the magnitude of effects and, as such, gives a more clinically relevant and objective measure of imprecision.[8,11] These strengths are key to consider in the context of the evidence base we synthesised, as this review suggests there is little evidential certainty, despite a substantial volume of evidence.

There are also limitations related to decisions we made on key methods within this review. The previously discussed issues with definitions of constipation were a challenge. The classification of a treatment targeting functional constipation, rather than therapy-resistant constipation or even disimpaction, often relied on how authors reported their interventions and how they defined functional constipation. This definition did not rely on any objective standard, as there is no consensus on a definition for disimpaction and only a recent proposal for an evidence-based definition for therapy-resistant constipation.[18,19,21] The varied classifications of functional constipation could have affected inclusion decisions and could have excluded key groups of therapies used in the field.[22] Additionally, the use of predetermined effect size thresholds to support judgments about imprecisions and interpretation of effect size is limited by the thresholds used. These thresholds were produced as part of an international guideline[11] but as there is no global consensus on these thresholds, some degree of subjectivity is inevitable. Furthermore, the topic of this review is very broad but there are key groups of therapies that are not included (non-pharmacological treatments such as dietary measures and psychosocial measures) and should be considered when planning a therapeutic strategy for constipation, particularly as they have shown efficacy in related conditions, such as functional abdominal pain disorders.[23,24] Finally, masking was a key issue for many of the interventions as it was not a viable option. In the quality assessment elements of GRADE, there is precedent for considering such weaknesses as less impactful, but this has a key influence on the certainty judgements in the review.[7]

There is much for future researchers to focus on. Given the clear certainty and magnitude data supporting polyethylene glycol, it should be considered the first-line standard of care in all future studies. In this context, researchers might wish to consider additional concomitant therapies rather than direct comparisons of efficacy, as this is more clinically relevant. One group of therapies that are commonly used in practice as adjunctive therapies, but not seen in the evidence in this review, are stimulant laxatives. Such laxatives would be useful to study as add-on therapies to polyethylene glycol. We would advise that polyethylene glycol is used as the standard comparator in all studies evaluating interventions intended as adjunct therapies in clinical practice. However, polyethylene glycol as a comparator is not appropriate for interventions that share a similar mechanism of action as polyethylene glycol (eg, magnesium hydroxide) or for novel agents for which efficacy and safety should first be established against placebo. We also recommend that the patient groups being targeted in future studies should be more clearly defined. The use of standard definitions for faecal impaction or treatment-resistant therapy will help, but clear reporting of previous therapeutic approaches and the health-care level of the research centres (ie, secondary *vs* tertiary care) will support transparent interpretation and homogenous analysis of studies in future reviews. Key for all researchers is to use core outcome sets, prospectively register the trial, and appropriately report methods to further support interpretation of the results.[25] All randomised trials should follow the CONSORT 2025 guidelines.[26]

In conclusion, polyethylene glycol should be considered the first-line treatment for standard care. Linaclotide might be effective for improving frequency of defecation. Other therapies had evidence that was very uncertain and so no conclusions can be drawn. Future studies should consider polyethylene glycol as the index therapy and the effect of add-on therapies, as well as clearly describing methods, patient characteristics, and previous therapeutics.

Contributors

MG conceptualised the study, supervised data extraction and data analysis, and wrote the manuscript. AdG conceptualised the study and participated in data extraction, data analysis, and writing of the manuscript. VS conceptualised the study, supervised data extraction and data analysis, and critically reviewed the manuscript. AA participated in data extraction and writing of the manuscript. AJT participated in data extraction and analysis. SL participated in data extraction and writing of the manuscript. DANA participated in data extraction. MAB and MMT conceptualised the study and supervised and critically reviewed the final manuscript. All authors had full access to all data. AG and MG verified the data in the study and MG is guarantor and had final responsibility for the decision to submit for publication. All authors agreed to submission.

Declaration of interests

MAB received consulting fees from Coloplast, Wellspect, Danone, Sensus, Cosun, FrieslandCampina, Cosun, Allergan, Abbott, and Mallinckrodt. All other authors declare no competing interests.

Data sharing

A prospectively published protocol for this manuscript is available online. Most data can be found in the appendix. Any additional information will be shared upon reasonable request to the corresponding author.

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