Treatments for intractable constipation in childhood: A Cochrane systematic review

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Background: Constipation is one of the most common reasons for referrals to paediatricians, the vast majority of those being for chronic constipation without a physical aetiology, known as functional constipation. A universal case definition of intractable constipation remains elusive, but it is broadly defined as constipation that does not respond to conventional medical therapy. Regardless of the case definition used to define intractable constipation, the impact of constipation on the child and their caregivers is universally recognised, as it can negatively impact health-related quality of life indicators, with additional implications for providing healthcare systems. Our objective was to evaluate the efficacy and safety of treatments used for intractable constipation in children.

Methods: We searched Pubmed, MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, ClincalTrials.gov, and the World Health Organization International Clinical Trial Registry Platform (ICTRP) froth their inception to July 2021. We included randomised controlled trials (RCTs) that assess therapeutic interventions for intractable constipation in children and adolescents.

Our primary outcomes were 1)Non-fulfilment of the Rome IV criteria for functional constipation, measured at the end of the study period 2)The frequency of defecation, measured at the end of the study period 3)Treatment success (as defined by the original studies) 4) Adverse events (as defined by the original studies).

Results

We identified 10 studies for inclusion all of which compared different interventions and used differing definitions for intractable constipation.

The compared interventions were: Botulinum toxin injection vs stool softeners; Lubiprostone vs Placebo; conventional therapy (with oral laxatives, educational and behavioural modifications) vs conventional therapy plus rectal enemas; Erythromycin vs Placebo; Biofeedback therapy vs no intervention; Botulinum toxin combined with electromotive drug administration vs botulinum toxin; Botulinum toxin vs myectomy of the internal anal sphincter; Physician dietary advice plus personalized dietary advice vs physician dietary advice; Prucalopride vs Placebo; Transcutaneous electrical stimulation vs sham stimulation.

The evidence suggests that Lubiprostone results in little to no difference and prucalopride probably results in little to no difference in treatment success when compared with placebo. These results may be used to inform clinicians and guideline developers.

It is uncertain whether any of the other interventions are safe or effective, either because they did not report on our outcomes of interest or when they did, the certainty of outcomes was downgraded due to very serious imprecision and risk of bias.

Discussion

Although many of the therapeutic interventions included are being used in managing children with intractable constipation in practice at present, paediatric gastroenterologists, patients, and their families must understand the lack of clear evidence for any of these management strategies.

Further well-designed, appropriately powered, randomized controlled trials are essential to generate more robust evidence-based clinical interventions for the management of intractable constipation. Before such studies, work is needed to clarify a consensus definition for intractable constipation to ensure populations being considered in future reviews are homogenous. It is apparent that without this, such reviews could be including highly diverse populations of children with very different journeys.

The evidence base would be strengthened if researchers considered the possibility of bias in their reporting and also reported data by the primary and secondary outcomes defined by the Rome foundation paediatric subcommittee on clinical trials. This approach would undoubtedly provide uniformity of data in different studies.

All of the studies included in this review had a very small sample size. It is imperative to perform a power calculation in order to have a sample that provides an adequate number of subjects and controls to give adequate power to the study to detect the effectiveness of an intervention. Such precise calculations are critical for putting an end to the proliferation of underpowered studies and increasing the precision of findings.

Finally, other therapeutic modalities, both surgical and medical, are being used to treat children with intractable constipation. Researchers are encouraged to conduct trials using these interventions, thereby expanding the therapeutic armoury for children with intractable constipation.

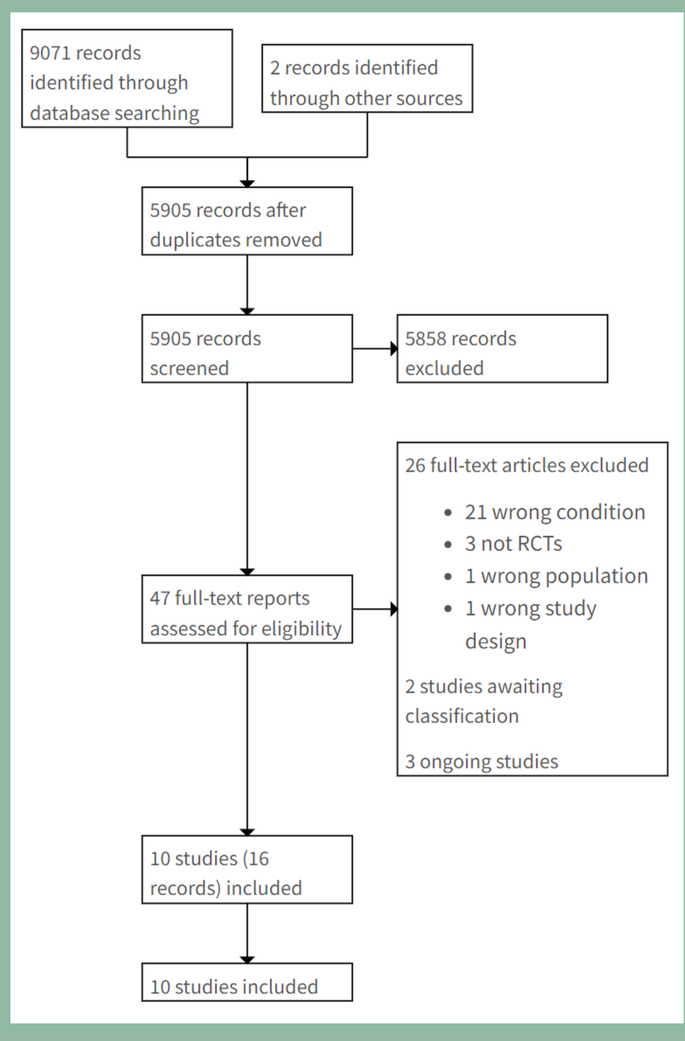

Figure 1: PRISMA flowchart

Lubiprostone against placebo

Patient or population: children with intractable constipation
Setting: Multicenter study in the US, Canada, and Europe
Intervention: Lubiprostone
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI) Risk with placebo	Risk with Lubiprostone	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
Non-fulfillment of the Rome IV criteria for functional constipation, measured at the end of the study period	-	-	-	-	-
Frequency of defecation	-	-	-	-	-
Treatment success defined by authors	Study population		RR 1.29 (0.87 to 1.92)	606 (1 study)	⨁⨁⨁⨁ high
	143 per 1000	185 per 1000 (124 to 275)			
Adverse events	-	-	-	-	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

RR: risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Figure 2: Summary of findings table for Lubiprostone vs placebo

Prucalopride against placebo

Patient or population: children with intractable constipation
Setting: Multicenter study in Europe
Intervention: Prucalopride
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI) Risk with placebo	Risk with Prucalopride	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
Non-fulfillment of the Rome IV criteria for functional constipation, measured at the end of the study period	-	-	-	-	-
Change in frequency of defecation	-	MD 0.50 lower (1.06 lower to 0.06 higher)	-	215 (1 study)	⨁⨁⨁⊖ moderate [a]
Treatment success defined by authors	Study population		RR 0.96 (0.53 to 1.72)	215 (1 study)	⨁⨁⨁⊖ moderate [a]
	176 per 1000	169per 1000 (93 to 303)			
Adverse events	Study population		RR 1.15 (0.94 to 1.39)	215 (1 study)	⨁⨁⨁⊖ moderate [a]
	611 per 1000	703 per 1000 (574 to 849)			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

MD: Mean Difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Figure 3: Summary of findings table for Prucalopride vs placebo

Declarations of interest

MG: Since August 2016, I received travel fees to attend international scientific and training meetings from Pharma companies. These grants included no honoraria, inducement, advisory role, or any other relationship, and were restricted to the travel and meeting-related costs of attending such meetings. The companies include: Biogaia (2017 to 2019), Ferring (2018), Allergan (2017), Synergy (bankrupt in 2018), and Tillots (2017 to 2019). None of these companies had any involvement in any works completed by me, and I have never had any payment for any other activities for them, as confirmed below. From these date onwards, I have made a personal undertaking to take no further funds from any pharmaceutical or formula company in any form, for travel or other related activities. This is to lift the limitations such funding has on my ability to act as a first and corresponding author on reviews, in line with the Cochrane policies on such matters, and is reported in line with these policies.
CGC has none to declare
SR has none to declare.
MAB is a consultant for Shire, Sucampo, Takeda, AstraZeneca, Norgine, Coloplast, Allergan, Danone, Novalac, Sensus, and FrieslandCampina.
VS has none to declare
AA has none to declare