Polyethylene Glycol

Primary literature

Gremse D, Hixon J, Crutchfield A. Comparison of Polyethylene Glycol 3350 and Lactulose for Treatment of Chronic Constipation in Children. Clinical Pediatrics 2002;41:225.

Study Objective: Compare the use of PEG 3350 and lactulose for the treatment of constipation in children

Methods:

Design: cross-over study

Allocation: randomized but no allocation concealment

Blinding: unblinded

Setting: Division of Pediatric Gastroenterology and Nutrition, University of South Alabama, USA

Patients: (n =37) There were 44 participants originally 7 participants withdrew and were not included in the data analysis. Participants were between the age of 2 and 16 and suffering from constipation. Out of the 37 participants who completed the study 29 were Caucasian and 8 were black. A greater number were male (62%) than female (38%). Patients were excluded if they had an organic disease of the large or small bowel, a known allergy to PEG or lactulose, previous GI surgery, renal or heart failure, bowel obstruction, ileus, pregnancy, lactation, galactosaemia, or had diabetes mellitus.

Intervention: Patients received either PEG 3350 ($10g/m^2$/day) or lactulose (1.3g/kg/day) orally for two weeks, followed by the other agent for two weeks

Outcomes: Frequency of stool per week, score for form of stool using own qualitative scale (not the Bristol Stool Score), total and segmental colonic transits time, global assessment by patient and ease of passage

Patient Follow-up: 2 weeks with each intervention (Total 4 weeks)

Main Results: The PEG group (n=37), had a mean stool frequency of 14.8 per week (S.D. 1.4) compared with the lactulose group (n=37) who had a mean stool frequency of 13.5 per week (S.D. 1.5). Stool form was reported using a score (not Bristol stool score) and represented by a mean of total scores. The PEG group (n=37) had a mean stool score of 25.9 (S.D. 3.0) compared to the lactulose group (n=37) who had a mean stool score of 27.9 per week (S.D. 1.5); indicating firm to soft stool consistency during treatment. PEG reduced total colonic transit time to a greater extent than lactulose (47.6$\pm$ 2.7 vs 55.3 $\pm$ 2.4 hours P =0.038). The ease of passage for PEG was reported as 28.5 $\pm$ 4.2 compared to 26.2 for lactulose; indicating some effort to easy stool passage. Total colonic transit time of PEG was 47.6 $\pm$ 2.7h compared to 55.3 $\pm$ 2.4h (P=0.038). Based on global assessment by parent or guardian PEG was 84% (31/37) effective compared to lactulose which was 46% (17/37) effective during a 2-week period (P=0.002). PEG was preferred over lactulose by 73% (27/37).

Conclusions: Stool frequency, form and ease of passage where reported to be similar for both PEG and lactulose. PEG significantly decreased the total colonic transit time compared to lactulose, and was deemed more effective through a global assessment and preferred for treatment of CC over lactulose.

Comments:

Internal validity: In terms of internal validity, though the study appeared to be well-designed several factors may affect the studies reproducibility. Firstly, there is no clear definition of chronic constipation, the study was unblinded, the generation of the allocation sequence was not clearly stated and the initial sample size required to reach adequate power was also not stated. The small sample size on its own may not allow the study to be able detect a difference between PEG and lactulose. Furthermore, an intention to treat analysis was not performed. The design itself of the trial has its benefits and limitations. The cross-over design allows for each participant to be their own control and generally require a fewer number of participants to reach statistically efficient results. On the other hand, the order of treatment may have an impact on treatment outcomes and the initial treatment effect could carry-over into the second intervention (a wash-out period can reduce this confounding factor). Both group had appropriate outcome measures, including stool frequency, form of stool, ease of passage, transit time which were appropriately compared. The global assessment is highly subjective means of determining efficacy and preference.

External validity: In terms of the studies external validity, the study has issues with heterogeneity due to the use of its own qualitative scale of stool form. The use of a non-standardized scale renders results more subjective and reduces its ability to be compared to other trials with the same purpose. The study population of this study was children between the age of 2 and 16, thus should not be extrapolated to adult or elderly populations. Furthermore, only single doses of laxatives were tested when in practice in paediatric constipation laxative doses are titrated to improve more frequent, soft stools. The titration of the osmotic laxative would likely lead to better treatment outcomes. The global assessment of efficacy and preference can help with the applicability of PEG versus lactulose in a real setting.

Though the study does present with some limitations, it provides more insight into PEG's place in therapy. When considering the impact of this study on the algorithm, the results of the study suggest that PEG is superior in efficacy than lactulose in reducing colonic transit time and global assessment and preferred by children's caregivers or parents (due to ease of administration). However PEG and lactulose were found to be similar in terms of stool frequency, form and ease of passage and tolerability.

DiPalma JA, Cleveland MV, McGowan J, Herrera JL. A Randomized, Multicenter, Placebo-Controlled Trial of Polyethylene Glycol Laxative for Chronic Treatment of Chronic Constipation. The American Journal of Gastroenterology. 2007;102 (7):1436-1441.

Study Objective: Compare the safety and efficacy of PEG 3350 laxative versus placebo over a 6-month period

Methods:

Design: Randomized controlled clinical trial

Allocation: allocation concealed

Blinding: double-blind

Setting: Multicenter (50 centers) in United States

Patients: (n=304) Patients were eligible if they met modified ROME criteria for CC characterized by the following: on average for past 3 months, and not on laxatives, they had less than 3 satisfactory stools per week and ≥1 of following ROME symptom criteria in >25% of defecations: 1) straining; 2) lumpy or hard stools; and/or 3) sensation of incomplete evacuation. In addition, participants had to have had <3 satisfactory defecations in a 14-day observational qualification period to confirm baseline constipation. A subgroup (n=75) of elderly patients were included in the total participants group. Participants must also be in good health based on a laboratory and physical assessment. Participants were excluded if they had an allergy or sensitivity to the study medication, had prior GI surgery, known or suspected GI obstruction, ileus, heart failure, renal failure, ascites, or other known chronic liver, bowel or cardiopulmonary disorders. Pregnancy or lactation are also exclusion criteria Patients with loose stools, or who were currently taking or had used PEG were also excluded from the study. Patients who required starting medications that could cause constipation were allowed to continue the study and included in the intention-to-treat analysis (ITT). In the study 85% of participants were female, patients ranged from 20 to 92 years of age, 84% were Caucasian, 13% were African American, and 6.3% were Hispanic/Latino.

Intervention: The group assigned PEG 3350 received 17g/day and the placebo group received placebo, each for 6 months. Patients were allowed the use of bisacodyl 10mg as a rescue medication if they suffered severe discomfort but were prohibited from using fibre. The placebo and treatment groups were similar in characteristics.

Outcomes: The primary outcome was treatment success which is defined as a relief of modified ROME criteria for constipation for ≥50% of the duration of treatment. Secondary efficacy outcome measures included: frequency of bowel movements (BM) per week, satisfactory bowel movements per week, complete spontaneous BM, a global assessment, and number of rescue tablets per week.

Patient Follow-up: 6 months

Main Results: Successful treatment (relief from modified ROME criteria for ≥50% of duration of treatment) was 52% for PEG and 11% for the placebo group ($P<0.001$); a 41% difference in favour of PEG. Similar efficacy was seen in a subgroup of elderly participants (n=75) with a 46% difference in favour of PEG. Treatment response with PEG was rapid in the first month, with a maximum response in the second month and was also statistically significant compared to placebo throughout all 6 months of the study. In the PEG group 61% of treatment weeks were successful and in placebo group 22% of treatment weeks were successful ($P<0.001$). Analysis of secondary efficacy outcomes and individual ROME criteria (Number of successful weeks with improvement of straining, hard stool, and incomplete bowel movement) favour PEG and are all statistically significant ($P<0.001$), with

the exception of the number of rescue tablets required per week P<0.138. There were no significant difference in laboratory findings or side effects, with the exception of GI category where the PEG group had a greater frequency of diarrhea, flatulence and nausea (PEG 39.7% vs 25% Placebo; P = 0.015). Similarities in results were obtained with analysis of data based on age, gender or race.

Conclusions: PEG 3350 laxative is safe and effective for use in patients with CC for 6 months.

Comments:
Internal validity: In terms of internal validity, the study was well-designed, blinded, and randomized. Patients were also selected through a clearly defined CC criteria and their baseline constipation was assessed. The study had clear inclusion criteria and accounted for baseline health of participants through an initial health assessment, which reduces effect of confounders. The sample size was large in comparison to other smaller not-well designed studies encountered through research on CC. An ITT analysis was performed making study results more reproducible and less biased. All patients were accounted for, and drop-outs were explained. Since Patients were provided and allowed the use of bisacodyl 10mg as a rescue medication, this could act as a confounder in the study results.

External validity: In terms of external validity the RCT was very clearly designed in terms of inclusion and exclusion criteria. Furthermore, data was further analyzed in terms of age, race and gender which allows the results of the study to be more generalizable to specific sub-groups analysed, including the elderly.

The study was well-designed and has a limited amount of weaknesses. In considering the application to the algorithm and place in therapy, the study holds value as it provides credible efficacy and safety evidence for the long-term (6 months) use of PEG in the management of CC in adults and the elderly.

Tertiary Literature or Secondary Literature

Lee-Robichaud H, Thomas K, Morgan J, Nelson RL. Lactulose versus polyethylene glycol for chronic constipation. Cochrane Database Syst Rev. 2010;(7):CD007570.

Study Objective: The authors in this Cochrane review, sought to identify and review all pertinent data to determine whether lactulose or polyethylene glycol is more effective in the treatment of chronic constipation (CC) and fecal impaction. As both are safe and effective in chronic constipation they sought to determine, which of the two is the best treatment option in CC.

Design: Meta-analysis (Cochrane Review)

Scope of included studies:

Patients: Participants with CC (Rome III criteria) or faecal impaction, including adults and children treated with PEG or lactulose. The review included a total of 868 participants in 10 randomised controlled trials (RCTs) ranging from 3 months to 70 years of age.

Interventions: Treatment with PEG compared to lactulose (+/- placebo) in adults and children with CC or fecal impaction. Note that different treatment protocols where used in the RCT considered.

Outcomes: Primary outcomes were change in frequency of defecation (measured on a weekly basis), these were assessed using weighted mean difference with 95% confidence intervals (CI).

Secondary outcomes included use of additional products (e.g.: alternative laxatives, enemas), percentage in global improvement of symptoms and relief of abdominal pain. The secondary outcomes were assessed through odds ratio (OR) with 95% CI and OR greater than 1.0 favoured the intervention group such that PEG was deemed superior compared to lactulose.

Methods:

How studies identified: Search of Medline, Embase and CINAHL databases, and the Cochrane Central Register of Controlled Trials) were searched to 2008 for RCTs comparing the use of lactulose and polyethylene glycol to manage faecal impaction and chronic constipation. Authors also reviewed bibliographic references of studies retrieved, as well as relevant conference proceedings, and corresponded with experts and pharmaceutical companies.

Number of trials included: 10 RCTs (n= 868) met the selection criteria and were included in the review.

Types of trials included: Randomized controlled trials comparing lactulose with polyethylene glycol with lactulose in the management of chronic constipation.

Any relevant information: Data on study methods, participants, interventions, and outcomes were analysed using Cochrane MetaView. Studies with inadequate concealment allocation were excluded.

Main Results: Initially all 10 RCTs with a total of 868 enrolled participants, ranging from 3 months to 70 years of age were considered. The trials were conducted between 1997 and 2007, and in six different countries. When looked at individually, all trials results showed a higher frequency of stool per week when compared to lactulose. Compared with patients received lactulose, patients receiving PEG were found to have a greater stool frequency per week (weighted mean difference 0.65, 95% CI: 0.15-1.15; 0.28 [0.11-0.45]) excluding studies to improve heterogeneity). Two of the ten trials used the Bristol Stool Scale and reported a softer stool (higher Bristol Stool score) with PEG versus lactulose (weighted mean difference 0.89, 95% CI [0.43-1.35]). Four of the ten trials reported relief of abdominal pain, but only three were suitable for meta-analysis. One of which found PEG and lactulose to have a similar effect on relief [odds ratio 0.86, 95% CI [0.25-2.90]) two of which found PEG to be superior at providing relief (odds ratio 7.50 , 95% CI [0.92-61.05] and odds ratio 2.32 , 95% CI [2.32-4.14]). When pooled together the data suggests PEG is superior at providing relief compared to lactulose (odds ratio 2.09, 95% CI; [1.26-3.44]). Three of the ten studies reported on the need to use additional products, all of which found patients

using PEG reported using less additional products compared patients using lactulose (odds ratio 4.00, 95% CI [2.01-7.95]).

Conclusions: PEG is more effective than lactulose for the treatment of chronic constipation, since it has better outcomes in terms of weekly frequency of stools and forms of stool. PEG is preferred treatment compared to lactulose in the management of chronic constipation.

Comments

Internal validity: Ten RCTs meet the inclusion criteria defined by the meta-analysis, which in themselves are quality studies and 3 RCT met greater than 4 of the 6 inclusion criteria. The use of different treatment protocols in the RCTs included in the meta-analysis will affect the reproducibility and uniformity of the results in the meta-analysis. There were also differences between the trial with respect to non-standardized definitions of CC, differences in study design (e.g.: treatment protocols) and the reporting of outcomes. Use of a standard definition of CC such as the Rome II criteria as well as standardized validated scales such as the Bristol Stool Score in all trials would have increased the internal reproducibility and objectivity of the study results. It is important to note that the greater efficacy in improving frequency of stools is based on 5 RCTs (n=407). Secondary outcomes were pooled together from only a few trials (1, 2 or 3) and were variability in reporting can be found between trials. The meta-analysis was limited in its ability to combine results between trials.

The meta-analysis was found to have a high level of heterogeneity due to different investigators conducting trials of varying duration of time, and variation in the outcome of stool frequency and secondary outcomes reporting. Heterogeneity among the studies threatens the review's internal validity, as this can negatively impact the meta-analysis's reproducibility. The RCTs quality was assessed and studies greatly increasing heterogeneity were excluded.

There may also be some conflicts of interest introducing bias in some of the trials included in the review. Some trials included were sponsored by drug company which in some instances supplied the PEG or lactulose used. In some cases it was unclear whether the company supplied or produced the drugs used.

External validity: Taking into account all the study outcomes from the RCTs included in the review, there was significant heterogeneity among the studies. The high level of heterogeneity among the studies threatens the review's external validity, though the review did assess each RCT for quality. The meta-analysis results for this reason may not be as generalizable to the full-range of the population included in meta-analysis (3months to 70 years). It would be helpful to have further information on subgroups, (e.g.: the pediatric or elderly) to have a better idea if the data collected can be applied in more specific subgroups. Though difficult with meta-analyses more heterogeneity and defined subgroups would provide greater strength to evidence.

In considering the application of this meta-analysis to the self-care algorithm, the review is limited due to weaknesses in the internal and external validity. However, the meta-analysis provides a good review of RCTs, in a setting where few well-designed RCTs compare lactulose and PEG. The meta-analysis aids in establishing a place in therapy for PEG compared to lactulose, though caution must be used in generalizing the results to

subpopulations such as in the elderly. PEG should be considered as a potentially superior, more efficacious and safe option compared to lactulose.

P Paré, R Bridges, MC Champion, et al. Recommendations on chronic constipation (including constipation associated with irritable bowel syndrome) treatment. Can J Gastroenterol 2007;21(Suppl B):3B-22B.

Design: Expert Opinion/Guideline, Review Article

Study objectives: The authors, a panel of 10 gastroenterologists, sought out to develop guidelines for the management of primary chronic constipation (CC) or constipation associated with irritable bowel syndrome (C-IBS). The authors want to provide treatment recommendations in order to guide health care professionals, including Canadians to optimize the clinical approach for the management and treatment of CC and C-IBS. The authors would like to better allow health care professionals to provide appropriate treatment strategies that best for each of their patients. The recommendations as well as the algorithm were developed using evidence-based approaches and expert opinions. The scope of the guidelines include: epidemiology, quality of life and threshold of treatment, definitions and diagnostic criteria, changes in lifestyle, pharmacological treatment, biofeedback and behavioural approaches and surgery. Pharmacologic treatment recommendations include a number of laxative and non-laxative options; bulk-forming agents, stool softeners, osmotic agents, prokinetics, stimulant laxatives, suppositories, enemas, other drugs and probiotics. Recommendations on the management of CC and C-IBS consist of non-pharmacologic options, pharmacologic options and suggestions for follow-up and referral.

Scope of included studies:

Patients: Adults with CC or C-IBS

Interventions: Non-pharmacological treatment including lifestyles changes such as additional fluid intake, fibre intake, and exercise. Pharmacologic treatment recommendations include a number of laxative and non-laxative options including bulk-forming agents, stool softeners, osmotic agents, prokinetics, stimulant laxatives, suppositories, enemas, other drugs and probiotics.

Outcomes: Outcomes measured were varied depending on the study and intervention in question.

Duration: The durations of the trials were variable depending on the study and intervention in question.

Methods:

How studies identified: Clinically relevant issues were identified through literature searches by members of the consensus group. Eleven topics or treatment categories were identified and assigned to each consensus group member to research and make recommendations. Recommendations were evidence- based when supporting evidence was retrieved through MEDLINE, PubMed or EMBASE search or Cochrane review search on each topic. A

number of search terms were used and full articles were restricted to English full publications in adult populations from 1996 to April 2006. Evidence from strictly abstracts was not used.

How recommendations were graded: A number of recommendations were made for each category based on the evidence retrieved and analysed by the consensus group and graded accordingly. The grade of evidence was also voted upon based on the quality of evidence of the studies (See Table 1). Statements were voted on using a five-point Likert Scale: A: Accept completely, B: Accept with some reservation, C: Accept with major reservation, D: Reject with reservation, and E: Reject completely. Furthermore, recommendation were only accepted if 80% of the consensus group voted "A: Accept completely" or "B: accept with some reservation". Final recommendations or statements were presented with their supporting evidence, and graded based on the strength and quality of evidence (Table 1) which finally agreed upon through an anonymous vote. The Chair and GP did not vote on the recommendations.

Table 1: Classification of recommendations (Adapted from[2])

Nature of evidence	Study Design	Study Executive	Consistency	Directness of Evidence
A	Meta-analysis of RCTs (for interventions) RCTs (for interventions)	No important flaws	Consistent (at two levels: Design, outcomes and statistical)	Direct (Relevant patient benefit and harm measured) or strong indirect (Surrogate endpoint strongly related to desirable endpoints or direct evidence available for related patient group)
B	Meta-analysis of RCTs or RCTs (for interventions) Nonrandomized studies (for diagnosis or prognosis)	Important flaw <OR>	Inconsistent <OR>	Weak Indirect (Relationship between study outcomes and patient benefits) <OR>
	Nonrandomized controlled studies (for interventions)	No important flaws	Consistent	Direct or strong indirect
C	Nonrandomized controlled studies (for interventions)	Important flaw <OR>	Inconsistent <OR>	Weak Indirect <OR>
D	Other evidence (not expert opinion)			
E	Expert opinion			

Algorithms were then created based on the recommendations that achieved a voting consensus. All members of the consensus group and a general practitioner asked to partake in the approved the recommendations, treatment algorithms and supporting article.

Main Results: Not applicable to a guideline.

Conclusions: The pharmacologic treatment recommendations explored a number of laxative and non-laxative options including: bulk-forming agents, stool softeners, osmotic

agents, prokinetics, stimulant laxatives, suppositories, enemas, other drugs and probiotics. Chronic constipation affects individuals' quality of life and CC sufferers can benefit from lifestyle, pharmacological and behavioural interventions. The use of certain laxatives can be beneficial in increasing stool frequency and stool consistency. There is evidence for appropriateness of psyllium (bulk-forming), PEG (osmotic), lactulose (osmotic) or short-term use of stimulant laxatives such as sennosides or glycerine suppositories in the treatment and/or management of CC. Among laxative agents, daily use of PEG is effective at treating CC by normalizing bowel frequency and consistency (Level A) for long-term (found to be effective up to 6 months). PEG also facilitates discontinuation of other laxatives (Level B). Osmotic laxatives, including PEG or lactulose are recommended in CC if a gradual increase in fibre does not result in improvement of constipation.

Comments:

Internal validity: A strength of this review is that the authors included a search strategy explaining how they found and chose to select and discuss studies as well as the process used to classify and define statements for recommendations. Having this search strategy and explanation of the process of defining and grading the recommendation makes this guideline more reproducible, credible and less subject to various forms of bias. However, the guideline does not specifically state the kind of studies that were selected (e.g.: RCTs, observational) thus it is difficult to assess the quality of studies. This is however accounted for by the fact that the recommendations were graded based on a clear classification system that lays out the type and quality of evidence based on the study design. The grading of the recommendation can thus be weighed appropriately based on the level of evidence the consensus group has retrieved. There is no data regarding the participants in the studies included such as gender, age, race, co-morbidities, concomitant medications, heterogeneity and other confounders, other than the fact that articles were retrieved in a target adult population. Thus this may affect the internal validity in terms of reproducibility and heterogeneity. Furthermore, any conflicts of interest among the consensus group members were identified.

External validity: The fact that there is no data regarding the participants in the studies included such as gender, age, race, co-morbidities, concomitant medications, heterogeneity and other confounders, affects the guideline's external validity as well. This review cannot be extended to the treatment of CC in children or in elderly as the search criteria was filtered for an adult population. A strength of the recommendation is that the consensus group clearly provided recommendations for CC and C-IBS and these are easily distinguishable.

In considering the application of the recommendations and algorithm, this guideline provides a general overview of the non-pharmacological and pharmacological management of CC and C-IBS in an adult population. The review does not give a clear picture of the individuals looked at in the trials, other than they are adults with CC or C-IBS. Caution should be used in applying the recommendations to children and elderly. However, the authors research, and grading of available evidence is clearly outlined and provides tertiary level evidence in the evidence based management of CC and C-IBS. The guideline is very helpful in indentifying a place in therapy for PEG in CC as osmotic agents are first-line therapy following increasing fibre and fluid intake.

of Gastroenterology. 2005; 100(S1)S1-S4.

In conjunction with

Brandt LJ, Prather CM, Quigley EMM, Schiller LR, Schoenfeld P, Talley NJ. Systematic Review on the Management of Chronic Constipation in North America. American Journal of Gastroenterology. 2005; 100(S1)S5-S22.

Design: Expert Opinion/Guideline, Review Article

Study objectives: The task force members, sought out to develop guidelines on the diagnosis, treatment and epidemiology of CC. The authors want to provide treatment recommendations in order to guide and educate physicians on how to optimize the clinical approach for the management and treatment of CC. The evidence-based recommendations were developed using evidence-based approaches and expert opinions. The scope of the guidelines include: symptom-based criteria for CC and threshold to treat CC, epidemiology, diagnostic approach, and pharmacological treatment. Pharmacological treatment recommendations include a number of laxative and non-laxative options: bulking agents, stool softeners, osmotic agents, stimulant laxatives, tegaserod, herbal supplements, lubricants and combination laxatives Recommendations on the management of CC consist of recognition of symptoms, diagnostic criteria, non-pharmacologic options, pharmacologic options and suggestions for follow-up and referral.

Scope of included studies:

Patients: North American adults with CC

Interventions: Treatments for CC available in the United States (US)

Outcomes: Outcomes measured were varied depending on the study and intervention in question.

Duration: The durations of the trials were variable depending on the study and intervention in question.

Methods:

How studies identified: Systematic reviews of selected categories were performed. A comprehensive literature search with pre-specified study selection criteria as well as a standardized and transparent data extraction method was used in the identification and selection of studies. In the identification of therapeutic trials, separate PUBMED and MEDLINE searches in English from 1966 to 2003 were performed using a combination of specified search terms. Bolographic references were scanned and searches exploring new search terms were expanded. Studies for CC therapeutics were eligible for selection if they were: RCTs; in an adult population with CC; comparing CC therapy +/- placebo or control therapy; evaluated the relief of CC symptoms; published in English and available in full; and the therapy was available in the US.

How recommendations were graded: Recommendations were made for each category identified based on the evidence retrieved and analysed by the task force. The recommendations were graded using a formalized system quantifying the strength of evidence and recommendations (Table 2). Level III to V evidence was not utilized to make recommendations on CC therapies. Grade A recommendations have the highest level of accuracy based on evidence.

Table 2: Levels of Evidence and Grading of Recommendations

Level I Evidence	RCTs with $p<0.05$, adequate sample sizes and appropriate methodology
Level II Evidence	RCT with $p>0.05$, or inadequate sample sizes and/or inappropriate methodology
Level III Evidence	Non-randomized trials with contemporaneous controls
Level IV Evidence	Non-randomized trials with historical controls
Level V Evidence	Case series
GRADE A recommendations	Recommendations supported by two or more level I trials without conflicting evidence from other level I trials
GRADE B recommendations	Recommendations based on evidence from: single level I trial; based on evidence from 2 or more level I trials with conflicting evidence from other level I trial; supported by evidence from two or more level II trials
GRADE C recommendations	Recommendation based on level III-V evidence

Main Results: Not applicable to a guideline.

Conclusions: The guidelines explored and analysed a number of pharmacological options including a number of laxative and non-laxative options: bulking agents, stool softeners, osmotic agents, stimulant laxatives, tegaserod, herbal supplements, lubricants and combination laxatives. Recommendations using an evidence-based approach were made for each therapeutic category identified. Chronic constipation affects individuals' quality of life and CC sufferers can benefit from lifestyle, pharmacological interventions. The use of certain laxatives can be beneficial in increasing stool frequency and stool consistency. There is only sufficient evidence for appropriateness and efficacy of psyllium (bulk-forming), PEG (osmotic) and lactulose (osmotic) in the treatment and/or management of CC. Among laxative agents, pyllium increases stool frequency in CC (Grade B recommendation). PEG and lactulose are each effective at improving stool frequency and consistency in CC (Grade A recommendation). The evidence is consistent with PEG improving stool frequency and consistency though FDA-reported side effects include diarrhea and excessive stool frequency (especially in elderly).
PEG and lactulose have the highest Grade A level evidence for the management and treatment of CC.

Comments

Internal validity: In terms of the internal validity, a strength of the review is that task members included a search strategy which explained how they found and chose to select and discuss studies as well as the process used to grade their recommendations. The recommendations were graded based on a clearly laid out formalized system quantifying the strength of evidence. The grading of the recommendation is thus weighed appropriately based on the level of evidence the consensus group has retrieved. Having a search strategy and explanation of the grading process for the recommendation makes this guideline more reproducible, credible and less subject to various forms of bias. In terms of therapy studies, only RCT were selected which allows for the recommendations to be based on high level evidence. The guideline does have some weakness, affecting its reproducibility. The systematic review does not clearly define the population or participants of the studies other than the fact that they selected RCT in North American adults with CC. Thus this may affect the internal validity in terms of reproducibility and heterogeneity. Furthermore, any conflicts of interest among the consensus group members were identified.

External validity: Only North American populations were examined and products available in the United States. Thus the recommendations from this review are not generalizable to population outside of North America, or the pediatric or elderly population. Furthermore there maybe be products that are not available in other countries which may limit the applicability of the recommendations to populations outside the US. It is acknowledged in the guidelines that side effects, contraindications and patient preference can affect how the recommendations are utilised and for this reason these have been described for each specific treatment. This allows for the recommendations to be more easily applied to specific individuals within the population.

In considering the application of the recommendations, this guideline provides a great overview of the non-pharmacological and pharmacological management of CC in an adult population. The review does not give a clear picture of the individuals looked at in the trials, other than they are North American adults with CC. Caution should be used in applying the recommendations to children and elderly. However, the authors research, and grading of available evidence is clearly outlined and provides tertiary level evidence in the evidence based management of CC. The guideline is very helpful in indentifying a place in therapy for PEG in CC as osmotic agents are the only agents with Grade A recommendations.