Lactulose

Ramkumar D, Rao SC. Efficacy and safety of traditional medical therapies for chronic constipation: systematic review. Am J Gastroenterol 2005;100:936-971.

Study objectives:
To undertake a systematic review of the efficacy and safety of traditional medical therapies for chronic constipation and make evidence-based recommendations.

Scope: In terms of the studies examining lactulose, 11 studies were identified in which 3 were direct comparisons of lactulose vs placebo. The remaining studies were comparisons of lactulose with other agents including PEG, psyllium, sorbitol or senna and their combinations. All patients in the trials were adults with chronic constipation. The outcomes measured included the stool frequency, stool consistency, stool weight, volume, symptoms, dose, and global improvement. All but one study also conducted safety analysis to examine the side-effects and safety of lactulose. The duration of the studies ranged from 10 days to 12 weeks and often included run-in and wash-out periods.

Methods: A search of the English literature for drug trials evaluating treatment of constipation was conducted using MEDLINE and PUBMED databases from 1966 to 2003. Studies were included if they were (i) randomized (open-labeled or placebo-controlled, parallel design or crossover design) comparing the agent in question with placebo, or comparing two separate agents for efficacy and safety in patients with chronic constipation, (ii) conducted using adult subjects; and (iii) published in full manuscript form. Studies were assigned a quality score based on published methodology. Standard forms were used to abstract data regarding study design, duration, outcome measures, and adverse events. By using the cumulative evidence of published data for each agent, recommendations were made regarding their use.
In terms of lactulose, the systematic review included three studies that compared lactulose with placebo and eight studies that compared lactulose to other agents including PEG, psyllium, sorbitol and senna. All studies were randomized and included placebo-controlled, double-blind, open-labeled, parallel design and crossover design studies.

Main results: Lactulose appears to be an effective (statistically and clinically significant improvement in stool frequency, consistency, weight and volume) and safe agent for use in idiopathic constipation, with the most common side-effects of bloating, flatulence, and loose stools. Compared to PEG solutions, lactulose was less efficacious and had more side effects. An open-labeled, randomized, parallel study which compared lactulose, psyllium, and placebo suggested that the two treatment agents were equally effective in the treatment of constipation. A single trial that compared the efficacy and safety of lactulose and sortibol suggested that the two agents were similarly effective, but lactulose had a greater propensity to cause nausea.

Conclusions: Currently, there is moderate evidence (Level II, Grade B) to support the use of lactulose in chronic constipation.

Comments/critical appraisal: In examining the internal validity, it is observed that this is a well-organized systematic review with various strengths. The review provided an accurate and thorough outline of this study selection including the inclusion and exclusion criteria of the studies and its patient selection. Study selection was limited to those that were randomized which further strengthened the quality of this review. Another strength was the standardized form and quality scoring system used to provide a score of each

study's methodology. This scoring system accounted for randomization, blinding, and statement on withdrawls, thus providing a thorough information for the reader to assess the quality of the trial. Finally, in terms of the individual studies examined, the systematic review provided information on the study design and intervention used. Therefore, this is a well-designed systematic review that provided thorough information on the study design, patient selection, intervention and assessment of study methodology. Nevertheless, the major limitation in the internal validity of this review is its limitation in the number and quality of the individual studies examined.

The external validity of this systematic review is limited by the lack of information on the patients included in the individual studies. Firstly, only studies conducted in adult patients were included in the study selection of the systematic review. Thus, we cannot generalize the results to other population groups such as children and the elderly. Secondly, in terms of the individual studies for lactulose, there is lack of information on patient description such as their presenting symptoms, concurrent medication use, comorbid conditions, lifestyle, diet, etc. We cannot be sure that the various confounders were taken into account. Therefore, due to such lack of patient information, it is hard to assess the generalizability of the results in the general population.

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

Study objectives:
To identify and review all relevant data in order to determine whether lactulose or polyethylene glycol (PEG) is more effective at treating chronic constipation and fecal impaction.

Scope: Ten randomised controlled trials were included in the systematic review. The ten trials enrolled a total of 858 participants and were conducted between 1997 and 2007. The participant were those diagnosed with chronic constipation (Rome III criteria) or fecal impaction, and ranging from 3 months to 70 years. The intervention studied was: treatment with lactulose versus PEG in adults and children with chronic constipation and/or fecal impaction. Different treatment protocols were used. The primary outcome measure was change in frequency of defecation. The secondary outcome measures were use of additional products (ie alternative laxative agents, enemas), percentage in global improvement of symptoms and relief of abdominal pain.

Methods: MEDLINE, EMBASE and CINAHL databases, and the Cochrane Central Register of Controlled Trials were searched for all randomised controlled trials comparing the use of lactulose and PEG in the management of fecal impaction and chronic constipation. Studies were included if they were randomised controlled trials which compared lactulose with PEG in the management of chronic constipation. Through this search, the systematic review included ten randomised controlled trials which were conducted in six different countries.

Main results: Five trials reported stool frequency per week – all five trials showed that PEG resulted in a higher stool frequency per week when compared with lactulose. Two trials reported form of stool on the Bristol Stool Scale, and both studies reported a higher Bristol Stool Score when using PEG compared with lactulose (softer stool). Three trials reported

relief of abdominal pain. Two favoured PEG in this outcome: one found lactulose and PEG to be comparable in this outcome.

Conclusions: The findings of this systematic review indicate that PEG is better than lactulose in outcomes of stool frequency per week, form of stool, relief of abdominal pain and the need for additional products. On subgroup analysis, this is seen in both adults and children, except for relief of abdominal pain. PEG should be used in preference to lactulose in treatment of chronic constipation.

Comments/critical appraisal: There are several factors that threaten the internal validity of this systematic review. Firstly, the ten studies included in this systematic review had considerable difference between them with respect to the study design, treatment protocol, study duration, methodology and reporting of outcomes. This heterogeneity negatively affects the uniformity and reproducibility of the results of the systematic review. Secondly, the trials lacked a standardized definition for chronic constipation. Thirdly, the strength of the secondary outcome results must be questioned as it was pooled together from results of 3 out of the 10 trials due to the variability in outcome reporting. Fourthly, several studies utilized a cross-over study design. Considering the follow-up duration and the wash-out periods between the two intervention, there may still be some cross-over/residual effects of the initial treatment while the second treatment is being studied. There is a lack of information or analysis to rule out this carry-over effect. Finally, there may be potential for bias in the review process as some included trials were drug company sponsored studies.

As a result of the high degree of heterogeneity in the included trials, the external validity of this review is also threatened. Although the study participants included children and adults, due to the heterogeneity, the results may not be generalizable to all age groups. Furthermore, there is lack of information on the patient descriptions such as their presenting symptoms, concurrent medication use, comorbid conditions, lifestyle, diet, etc. Thus, we cannot account for confounders. Overall, the generalizability of the results of this systematic review is relatively limited.

Passmore AP, Wilson-Davies K, Stoker C, Scott ME. Chronic constipation in long stay elderly patients: a comparison of lactulose and a senna-fibre combination. British Medical Journal 1993:307(6907):769-771.

Study objectives: To compare the efficacy and cost effectiveness of a senna-fibre combination and lactulose in treating constipation in long stay elderly patients.

Methods:

Design: Randomised, double blind, cross over study
Allocation: Patients were allocated to receive active senna-fibre continuation daily with lactulose placebo twice daily, or active lactulose twice daily with senna-fibre placebo daily for two 12 day periods, according to a computer generated randomisation.
Blinding: Randomised, double blind
Follow-up period: Not available
Setting: Four hospitals in Northern Ireland, one hospital in England, and two nursing homes in England
Participants: 77 elderly patients with a history of chronic constipation (fewer than 3 bowel movements a week) or a need for regular laxatives in long term hospital or

nursing home. Exclusion criteria were important bowel pathology, diabetes mellitus, severe renal impairment, antidarrheal therapy, and faecal incontinence.
Intervention: A senns-fibre combination (10ml daily) or lactulose (15ml twice daly) with matching placebo for two 14 days periods, with 3-5 days before and between treatments.
Outcomes: Stool frequency, stool consistency and ease of evacuation; deviation from recommended dose; daily doses and cost per stool; adverse effects.
Patient follow-up: Initially 85 patients were included. Data suitable for analysis were available in 77 patients, with the following exclusions: 3 patients were withdrawn after the first treatment period; 3 patients had unacceptable compliance; 1 patient had deteriorating health; and 1 patient had incomplete data.

Main results: Mean daily bowel frequency was greater with the senna-fibre combination (0.8; CI 0.7-0.9) than lactulose (0.6; CI 0.5-0.7; $p<0.001$). Scores for stool consistency and ease of evacuation were significantly higher for the senna-fibre combination than for lactulose. The recommended dose was exceeded more frequently with lactulose than senna-fibre combination. The dose and cost per stool was greater with lactulose than senna-fibre combination.

Conclusions: Both the senna-fibre combination and lactulose were effective, well tolerated treatments for chronic constipation in long-stay elderly patients. Under the study conditions, the senna-fibre combination was more effective than lactulose and was a less expensive regimen.

Comments/critical appraisal: The internal validity of this study is strengthened by its use of good randomization, allocation and blinding protocols. In addition, the inclusion and exclusion criteria used to select subjects led to a subject group that accurately reflected the study objective. However, there were some limitations to the internal validity of the study. Firstly, it is unclear what the formulation of the senna-fibre combination was. Secondly, the study failed to account for cross-over effects that may have occurred. For example, the effects of the first intervention (ie the senna-fibre combination) may have occurred while the second intervention was given (ie when the patient was crossed-over to the lactulose intervention).

The main limitation to the external validity of this study is that the study was only performed in an elderly population living in long-term hospitals or nursing homes. Considering the vast co-morbid conditions these patients may have, as well as the possibility of different pathologies associated with chronic constipation in patients of different ages, it is difficult to generalize the findings of this study to younger patients.

Quah HM, Ooi BS, Seow-Choen, Sng KK, Ho KS. Prospective randomized crossover trial comparing fibre with lactulose in the treatment of idiopathic chronic constipation. Tech Coloproctol 2006,10:111-114.

Study objectives: To compare the clinical efficacy and tolerability of fibre versus lactulose in outpatients with chronic constipation.

Methods:

Design: Prospective randomized crossover trial

Allocation: Patients were assigned to treatment groups according to a randomization code obtained by telephoning the department's research office. Randomization was performed by a computer-generated code using the blocked randomization method.

Blinding: As the formulation of fibre and lactulose were very different, it was not possible to blind the patients to their treatment assignments.

Follow-up period: Not addressed

Setting: Outpatient clinic of the department of colorectal surgery of Singapore General Hospital

Participants: Eligibility criteria included functional constipation as defined by Rome II criteria. Moreover, patients had to be older than 18 years and to have normal thyroid function. Patients who were more than 40 years of age, and had constipation secondary to colonic pathology were excluded by means of colonoscopy or barium enema in the previous year. Patients taking concomitant medications that could modify bowel habit were excluded, but patients previously exposed to Fybogel or lactulose were not excluded. Patients with severe liver, renal or cardiac disease, uncontrolled diabetes mellitus or faecal incontinence as well as pregnant women were excluded.

Intervention: Fibre (one 3.5g sachet of Fybogel diluted in approximately 125ml of water) versus lactulose (10ml twice daily)

Outcomes: Main outcome measures were stool frequency, consistency, ease of evacuation, and adverse effects. Patients' recorded improvement score (0-10 on a visual analogue scale where 0 indicates no effect at all and 10 indicates an excellent result) and final preference for the type of treatment were also documented.

Patient follow-up: 50 patients were recruited and 39 patients completed the trial.

Main results: Compared to fibre, lactulose resulted in significantly higher mean bowel frequency (7.3, 95% CI 5.7 to 8.9 vs. 5.5, 95% CI 4.4 to 6.5; p=0.001) and stool consistency score (3.4, 95% CI 3.1 to 3.7 vs. 2.9, 95% CI 2.5 to 3.3; p=0.018). Scores for ease of evacuation were similar. The frequencies of adverse effects were not significantly different, but greater in the lactulose group. Mean patients' recorded improvement score was significantly higher after taking lactulose than fibre (6.2, 95% CI 5.5 to 7.0 vs. 4.8, 95% CI 4.0 to 5.9; p=0.017). Of the 39 patients who completed the trial, 24 (61.5%) preferred lactulose and 14 (35.9%) preferred fibre.

Conclusions: Lactulose had better efficacy than fibre for chronic constipation in ambulant patients, although both treatments were equally well tolerated in terms of adverse effects.

Comments/critical appraisal: In assessing this study, there are both strengths and limitations to its internal validity. In terms of its strength, the study provided a clear outline of how patients were selected and how the randomization process was performed. In addition, it provided a standard definition of "chronic constipation," and its patient selection

criteria was appropriate to assess the outcomes of this study while minimizing confounding factors. However, there were also several limitations in its internal validity. Firstly, the study was not a RCT but rather a prospective crossover design. As such, it is difficult to deduce a clear cause-and-effect relationship with this study. Secondly, the study was not blinded and patients were aware which treatment they were receiving. Considering that much of the outcomes were measured through subjective patient reported measurements, the lack of blinding is a significant limitation. This also leads to the third limitation in that many of the outcomes were measured using patient reported daily stool chart where they recorded the number of stools, stool consistency and ease of evacuation. Furthermore, patients subjectively recorded their overall improvement score using a visual analogue scale. Therefore, much of the measurements in this study were subjective measurements. The fourth limitation is the potential for confounders in patient's compliance to therapy, which was not examined, and the lack of consistent/standard dose. Patients were allowed to increase their dose as needed which further conflicts the results. Lastly, there is no control of patient's dietary fibre intake which would also have confounded the results.

The external validity of the study is limited to the fact that the study was only conducted in a Chinese population. Diets of western and eastern populations are quite different. As such, the dietary fiber intake is also quite different. Considering that we are examining the efficacy of fibre vs lactulose, the heterogeneity is dietary fiber can conflict the results. In addition, the subjects in the trial were permitted to change the doses of their intervention as needed. However, this final doses actually used by the patients is not stated. As such, when trying to apply this study's results to the general population, we cannot be sure of the doses to use. Finally, it must be noted that this study was originally published in Chinese. Reviewers of this study have noted that in the process of translation to English, some important points and results were misinterpreted or left out.

Casparis AW, Braadbaart SGE, Bergh-Bohlken, Mimica M. Treatment of chronic constipation with lactulose syrup: results of a double-blind study. Gut 1978,9,84-86.

Study objectives: To study the effect of lactulose in patients with chronic constipation.

Methods:

Design: Double-blind randomized placebo controlled study

Allocation: Patients were allocated at random to two groups, to be treated with either lactulose syrup 50% or with placebo (glucose syrup).

Blinding: Double-blind

Follow-up period: Pre-treatment period of two weeks, treatment period of three weeks, and post-treatment period of two weeks.

Setting: Three different centres: Rotterdam, Eindhoven, and Zagreb

Participants: 103 elderly patients who were regularly taking laxatives for the treatment of chronic constipation.

Intervention: Lactulose syrup 50% or placebo (glucose syrup). After a pre-treatment period of two weeks, during which the frequency of defecation and the quantity and brand of laxatives were recorded daily, treatment with syrup was started after the first defecation in the third week. The initial dose of 15 ml daily was administered every day at 4 p.m. The daily dose was reduced by half (8 ml daily) after three consecutive days with defecation, but if no defecation occurred for more than 48 hours, the dose was doubled (i.e. from 15 to 30 ml or from 8 to 15 ml daily). If no defecation occurred on three consecutive days with the doubled dose, a laxative was administered according to the previous therapeutic regimen. If defecation occurred on three consecutive days with the doubled dose, the patient was treated again with the former dose but if the response on the doubled dose remained unsatisfactory, treatment with 30 ml syrup daily was continued until three weeks were completed. After three weeks' treatment the frequency of defecation was recorded for another two weeks, during which no treatment took place.

Outcomes: Effectiveness of the treatment of lactulose was measured by the need for additional laxative during the treatment period. The treatment was considered to be a success if the patient needed no laxatives at all or once in the 21 day of treatment period.

Patient follow-up: All patients were followed-up.

Main results: The success rate in the lactulose group (86%) was higher than in the placebo group (60%), the difference being statistically significant ($P < 0.02$).

Conclusions: Lactulose was significantly better than glucose (placebo) in promoting defecation in chronically constipated patients.

Comments/critical appraisal: Upon analyzing the internal validity of this study, it is noted that the trial is flawed by several limitations. Firstly, the study does not outline the blinding, randomization or allocation strategies used. As such, it is difficult to assess the quality of the study and its methodology. Secondly, although the study was a double-blind study, there could have been differences in the appearance and taste between the interventions that threatened the blinding. Thirdly, all patients were already using laxatives on a regular basis. Although the study did have a pre-treatment washout period to eliminate the effects of their previous laxative, the duration of two weeks may not have been a sufficient wash-out period for some laxatives. As a result, the result could be confounded by their baseline laxative use. Finally, the study failed to provide a description of its definition for chronic constipation. Furthermore, it was noted that 50% of patients did not need any laxatives in the post-treatment period, although all used laxatives prior to the study. Therefore, the study included some patients who were not truly constipated leading to heterogeneous study group and confounding results.

Further to the limitations in internal validity, the external validity of this trial is also limited. Firstly, the study was limited to the elderly population. As such, the generalizability to all age groups is questionable. Secondly, the study only examined the efficacy of lactulose versus placebo. Other factors such as the stool consistency, straining necessary for defecation and other factors that are also important in the management of constipation were not examined. Similarly, the study did not address any side-effects or safety issues

with the therapies. Lastly, this study is dated back to 1968, as such, the type and quality of treatment and study methodology used may not reflect what is performed in currently.

Canadian Pharmacist Association. Patient Self Care, 2010. Chapter 31: Constipation. Page 262-80.

Source description:

- Type: Textbook
- Published by Canadian Pharmacist Association
- Late updated in 2012

Summary: There are few trials that have compared the effectiveness of different types of laxatives and the data that are available show no statistically significant different between the treatments. Some initial data suggest that in the management of chronic constipation, osmotic laxatives may be considered as a second line agent after a 4-6 week trial of initial therapy that includes patient education, lifestyle and diet modification, fibre supplementation and bulk-forming laxatives. Lactulose should be avoided in patients who require a galactose-free diet. However, since it is not absorbed systematically, it can be used in diabetics.

Comments/critical appraisal: The information provided in this textbook on chronic constipation is very limited. Much of the information focuses on acute constipation and it is difficult to extrapolate such results to the case of chronic constipation. There is little evidence provided behind the recommendations and thus it is difficult to assess the appropriateness and quality.