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Efficacy and Safety of Traditional Medical Therapies for Chronic Constipation: Systematic Review

Davendra Ramkumar, M.D., and Satish S.C. Rao, M.D., Ph.D.
Division of Gastroenterology, University of Iowa Carver College of Medicine, Iowa City, Iowa

OBJECTIVES: Constipation is common, and its treatment is unsatisfactory. Although many agents have been tried, there are limited data to support their use. Our aim was to undertake a systematic review of the efficacy and safety of traditional medical therapies for chronic constipation and to make evidence-based recommendations.

METHODS: We searched the English literature for drug trials evaluating treatment of constipation by using MEDLINE and PUBMED databases from 1966 to 2003. Only studies that were randomized, conducted on adult subjects, and published as full manuscripts were included. 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 following the United States Preventive Services Task Force guidelines.

RESULTS: Good evidence (Grade A) was found to support the use of polyethylene glycol (PEG) and tegaserod. Moderate evidence (Grade B) was found to support the use of psyllium, and lactulose. There was a paucity of quality data regarding many commonly used agents including milk of magnesia, senna, bisacodyl, and stool softeners.

CONCLUSIONS: There is good evidence to support the use of PEG, tegaserod, lactulose, and psyllium. Surprisingly, there is a paucity of trials for many commonly used agents. These aspects should be considered when designing trials comparing new agents with traditional therapies because their use may not be well validated.

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INTRODUCTION

Constipation is a common problem, with an estimated prevalence of 2–20% (1–4). It is one of the more common presenting complaints to both general practitioners and gastroenterologists, and carries a significant economic impact (4, 5). Constipation appears to be more prevalent in the elderly, women, nonwhites, and persons in lower socio-economic and education classes (4).

Although a common problem, the treatment of constipation has been far from satisfactory. A recent metaanalysis suggested that there was little credible evidence to support many of the drugs that are commonly used in the treatment of this disorder (6). However, this analysis lumped all agents into a single "laxative group," which may have obscured any benefits of individual medications.

It is generally recommended that lifestyle measures such as adequate hydration, nonstrenuous exercise, increased natural fiber intake, and dedicated time to have a bowel movement be attempted first before medical therapy is tried. It should be noted that none of these measures has been validated in a proper controlled trial.

With regard to medical therapy, the following categories of drugs have been used to treat constipation:

a. Bulk or hydrophilic laxatives—psyllium (isphagula), methylcellulose, bran, celandine, plantain derivatives, and aloe vera
b. Surfactant or softening or wetting agents—docusate, poloxalkol
c. Osmotic laxatives—lactulose, sorbitol, milk of magnesia (MOM) (magnesium hydroxide), polyethylene glycol (PEG) solutions
d. Peristaltic stimulants or sometimes referred to as irritant laxatives—senna, bisacodyl, danthron, cascara, erythromycin, misoprostol
e. Others (prokinetic, prosecretors)—colchicine, tegaserod.

The purpose of this systematic review is to assess the available evidence in the English literature, particularly randomized, controlled trials addressing the efficacy and safety of various medical therapies in adult patients with chronic constipation.

Literature Search

MEDLINE and PUBMED databases for the period from 1966 to 2004 were used to search the literature. Constipation was combined with the following terms: osmotic laxatives, irritant laxatives, stimulant laxatives, bulk laxatives, fecal softeners, lactulose, sorbitol, MOM, magnesium sulfate, PEG, senna, bisacodyl, danthron, cascara, psyllium, methylcellulose, calcium polycarbophil, isphagula, bran, celandin, plantain, alovera, aloe vera, docusate, poloxalkol, mineral oil, glycerine, misoprostol, erythromycin, loxiglumide, tegaserod, herbal remedies, traditional medicine, Chinese herbal, plantain, and colchicine. Exploded terms were reviewed, and where appropriate, the search was expanded to include them.

Abstracts of the English language articles were all screened. Potentially relevant studies were then reviewed, and selection criteria applied. The bibliographies of the studies found by this method and in reviews were manually searched.

Selection Criteria

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.

Data Extraction and Analysis

The articles were reviewed and the relevant data were abstracted to standard forms. Data extracted included (i) the therapy studied; (ii) the control agent; (iii) study design; (iv) number of patients; (v) mean age or age range; (vi) analysis by sex if available; (vii) duration of the study or crossover periods and, where necessary, wash-out intervals; (viii) outcome measures including stool frequency and consistency, straining, use of rescue medications; (ix) results in the form of percentage improvement or other suitable variable measuring the degree of change in the outcome measure in individual patients as well as between patients treated with different measures; and (x) an assessment of adverse reactions and other aspects of the safety of the treatment measure. Meta-analysis was not performed.

Qualitative Assessment of Study Methodology

The identified studies were carefully assessed using criteria previously established (7, 8), for methodology that minimizes bias and enhances validity of trials about therapy. The following were evaluated (i) how randomization was performed and described; (ii) use of concealed allocation; (iii) blinding; and (iv) completeness of follow-up. A scoring system was then used to rate the strength of the studies. A score of 1 or 2 was given for randomization (2 for appropriate randomization technique and concealed allocation explicitly stated or described, 1 for study simply described as "randomized"). Scores of 0–2 were given for blinding (2 when both subjects and investigators were explicitly said to be blinded to the treatment by use of identical placebo or other technique, 1 when the study is described as "double-blind,", and 0 when the study was not double-blind). A score of 0 or 1 was given for frequency of withdrawals (1 when the number of withdrawals and reason for withdrawals were stated and 0 when no statement was made pertaining to withdrawals). Thus, the quality score ranged from 1 to 5 with 5 being the highest possible score. The studies were all reviewed by both authors, and scored independently. When there were discrepancies, the papers were reviewed again, and the final scores were decided by consensus.

Levels of Evidence and Grading of Recommendations

The strength of evidence and grading of recommendations was as utilized by the U.S. Preventive Services Task Force (9).

LEVELS OF EVIDENCE.

(i) Good evidence (Level I)—consistent results from well-designed, well-conducted studies.
(ii) Fair evidence (Level II)—results show benefit, but strength is limited by the number, quality, or consistency of the individual studies.
(iii) Poor evidence (Level III)—insufficient because of limited number or power of studies, flaws in their design or conduct.

CLASSIFICATION OF RECOMMENDATIONS.

(i) Grade A—good evidence in support of the use of a modality in the treatment of constipation.
(ii) Grade B—moderate evidence in support of the use of a modality in the treatment of constipation.
(iii) Grade C—poor evidence to support a recommendation for or against the use of the modality.
(iv) Grade D—moderate evidence against the use of the modality.
(v) Grade E—good evidence to support a recommendation against the use of a modality.

RESULTS

Effectiveness and Safety of PEG Solution in the Treatment of Constipation

PEG is a nonabsorbable, nonmetabolized osmotic agent that is most often used in lavage solutions for gut cleansing for colonoscopy and surgery. Its use as a laxative has garnered much interest recently.

Eight studies were found that satisfied the selection criteria (10–17). These are summarized in Table 1. Five of these studies evaluated the efficacy of PEG solutions *versus* placebo, while one compared PEG solution to lactulose in patients with chronic constipation. Another evaluated the efficacy and tolerance of PEG solutions, lactulose, and placebo in relieving

Table 1. Summary of the Trials Evaluating the Efficacy and Safety of PEG in the Treatment of Constipation

References	Score	Intervention	Study Design	Patient			Duration	Outcomes		
				N	Mean Age (year)	F/M		Outcome Measure	Results	Safety Analysis
10	5	PEG (8–16 ozs) or placebo	Double-blind, placebo-controlled, crossover	32	62	28/9	Two 5-day periods with 2-day washout	SF, SC, SE, and UOL	SF (PEG 7.75 ± 4.55 *vs* placebo 4.88 ± 2.62, $p < 0.01$) SC (PEG 2.56 ± 1.17 *vs* placebo 1.91 ± 0.94, $p < 0.05$)	Side effects of PEG (cramping, gas, nausea, unpleasant taste, and loose stools) were minimal and tolerable*
11	5	PEG (26 g/day) or lactulose (20 g/day)	Multicenter, randomized, comparative	99 of 115 completed	30 to ≤65 >43 to 65	94/21	4 + 8 wk open	SF and straining, use of additional laxatives, liquid stools, flatus, bloating rumbling, abdominal pain	PEG group had more daily stools (1.3 *vs* 0.9, $p = 0.005$) and less straining ($p = 0.0001$) Low dose PEG was more effective than lactulose and better tolerated (on visual analog scale $p = 0.001$) Open-labeled phase with PEG following the study—no loss of efficacy Less use of additional laxatives in the PEG group ($p = 0.04$)	No significant adverse events in either group. Significantly more flatulence, with a tendency to more bloating, abdominal pain, and rumbling with lactulose
12	3	PEG (17 g/day) or placebo	Randomized double crossover trial of placebo *vs* 17 g of PEG daily	23	47.7	22/1	7-day placebo control period then 14 days	SF, SC, EOD, cramping, rectal irritation, and flatus. Adverse events	PEG increased mean daily SF to 1 per day by the last 7 days of the 14-day treatment period *vs* placebo, which provided about 1 bowel movement every 2 days during the last week of therapy ($p = 0.0001$) There was statistically significant improvement in subjective scores for SC, EOD, cramping, and rectal irritation, but not for passage of flatus	No significant adverse events. No clinically significant changes in blood chemistry, complete blood count (CBC), or urinalysis

(continued)

Table 1. Continued

References	Score	Intervention	Study Design	Patient			Duration	Outcomes		
				N	Mean Age (year)	F/M		Outcome Measure	Results	Safety Analysis
13	5	PEG (17 g/day) or placebo	Multicenter, double-blind, placebo-controlled parallel group trial	48 of 55 completed 25 PEG, 23 placebo	48 ± 15	37/11	4 wk placebo run in, then 8 wk (two 4-wk periods)	SF, SC, straining, use of laxatives, and transit times	PEG increased SF at 4 wk and at the 8 wk (PEG: 4.8 ± 2.3 *vs* placebo: 2.8 ± 1.6; $p < 0.002$) PEG decreased straining at defecation ($p < 0.01$) PEG improved SC ($p < 0.02$) Oroanal, left colon, and rectal transit times were significantly shortened by PEG treatment PEG decreased use of laxatives ($p < 0.03$)	There was no difference between controls and PEG-treated patients in abdominal symptoms and side effects
14	5	PEG (17 g/day) or placebo	Double-blind, placebo-controlled, parallel group study	70 of 78	Mean 43 (18–73)	58/12	4 wk run in with PEG followed by randomization to PEG or placebo for 20 wk in responders	SF and modality of evacuation, UOL, and relevant symptoms	PEG group had significantly higher SF (week 12: 7.4 *vs* 4.3 BM/wk, and week 24: 7.4 *vs* 5.4 BM/wk) At end, 77% of the PEG group and 20% of the placebo group were not constipated ($p < 0.01$) PEG reported less hard/pellety stools at defecation Less UOL in PEG group and reduced mean number of PEG sachets used PEG group had less dropouts for therapy failure (16 *vs* 3; $p < 0.005$).	No significant differences in adverse events between the two groups for symptoms (including nausea, vomiting, and discomfort), laboratory values, heart rate, and blood pressure

15	4	PEG (17 g/day) or placebo	Randomized, placebo-controlled, blinded, multicenter parallel trial	151	45.2	131 F 20 M	2 wk	SF, SC, EOD, cramps, and flatus. Investigator and patient subjective assessment of perception of treatment effectiveness	SF improved with PEG week 2 4.5 BM/wk compared to placebo 2.7 BM/wk ($p < 0.001$) Patient evaluations of SC showed significant improvement in the active treatment group ($p < 0.001$) Patient evaluations of EOD showed significant improvement in the active treatment group ($p < 0.001$) Investigator ($p < 0.005$) and patient ($p < 0.001$) subjective assessment of perception of treatment effectiveness were better with PEG	No significant changes in adverse symptoms, CBC, blood chemistries, and urinalysis were noted between the two groups
16	3	PEG (8 ozs/day), placebo, lactulose (30 ml/day)	Randomized, triple crossover after control run-in	57—all on opiates	18–50	Not stated	One week run in control (no treatment) followed by 3 treatment phases of 2 wk each	SF, SC, UOL, EOD, and SE	PEG solution and lactulose produced more "nonhard" stools than the placebo ($p < 0.01$) and control ($p < 0.003$). PEG produced the loosest stool ($p < 0.0001$) compared with the control There were no significant differences in stool consistency in either experimental group, but both were better than having nothing or just the placebo UOL increased only in group treated in the run-in control period	No change in electrolytes noted between the groups. Lactulose had more adverse effects* (presumably abdominal pain, bloating, and nausea, based on the description of the method)

Table 1. Continued

References	Score	Intervention	Study Design	Patient			Duration	Outcomes		
				N	Mean Age (year)	F/M		Outcome Measure	Results	Safety Analysis
17	4	Hypo-osmotic PEG 4000 (Forlax) 10 or 20 g and iso-osmotic PEG 3350 (Transipeg) 5.9 or 11.8 g	Prospective, randomized, double-blind, parallel-group	263 of 266	52 ± 18.5	85% were F	Randomized to 1 of 4 treatment groups: High or low dose PEG 4000, or high or low dose PEG 3350 for 4 wk	SF secondary efficacy parameters included SC, date of occurrence of first motion, St, rectal evacuation, abdominal pain, and distension	SF was significantly increased compared with baseline in all treatment groups ($p = 0.0001$) with no difference between groups SC significantly improved compared with baseline in all treatment groups ($p = 0.0001$). The percentage of patients with normal SC was significantly higher for standard-dose PEG 3350 *vs* both maximum-dose treatments ($p < 0.01$). ≥67.3% had their first stool within 1 day of starting treatment Rectal evacuation, straining, bloating, and pain were also significantly improved compared with baseline in all treatment groups ($p = 0.0001$)	All medications were well tolerated. The higher dose groups had more reports of diarrhea. Distension, flatulence, and abdominal pain occurred evenly in all four groups*.

SF, stool frequency; SC, stool consistency; St, straining; UOL, use of additional laxatives; EOD, ease of defecation; SE, side effects; , not otherwise specified.

Table 2. Methodologic Quality of Trials with PEG

Reference	Randomization	Blinding	Statement on Withdrawals	Total Score
10	2	2	1	5
11	2	2	1	5
12	1	2	0	3
14	2	2	1	5
13	2	2	1	5
15	1	2	1	4
16	1	2	0	3
17	1	2	1	4

A score of 1 or 2 was given for randomization (2 for appropriate randomization technique and concealed allocation explicitly stated or described, 1 for study simply described as "randomized"). Scores of 0–2 were given for blinding (2 when both subjects and investigators were blinded to the treatment by use of identical placebo or other technique, 1 when the study is described as "double-blind," and 0 when the study was not double-blind). Score of 0 or 1 was given for frequency of withdrawals (1 when the number of withdrawals and reason for withdrawals were stated and 0 when no statement was made pertaining to withdrawals).

opiate-induced constipation (16). The last study compared two doses of two commercially available PEG formulations, an iso-osmotic preparation, and a hypo-osmotic solution (17). Constipation was variously defined, with only two studies utilizing the Rome criteria to identify suitable patients (13, 14). Six of the studies evaluated the short-term efficacy and safety of PEG solution. The longest duration in this category was 8 wk. One trial looked at the same parameters over a 6-month period (14) and therefore provides longer-term data. The qualitative assessment of these studies and the extracted data are presented in Table 2.

PEG is an effective form of treatment with few side effects and it is modestly more effective than lactulose. Decision analysis modeling suggests that PEG, despite its higher cost, is ultimately more cost-effective than lactulose, at least from the perspective of the National Health Service of the United Kingdom. (18).

PEG: Level I Evidence, Grade A Recommendation.

Efficacy and Safety of Lactulose in the Treatment of Constipation

Lactulose is a nonabsorbable synthetic disaccharide which functions as an osmotic laxative and which appears to have been accorded the role of the standard against which newer agents are compared for efficacy and safety. Three studies compared lactulose with placebo (19–21). The others were all comparisons with other agents in which the efficacy of lactulose was determined by the improvement from baseline in the parameters that assess constipation (11, 16, 22–27). The characteristics and results are summarized in Table 3. The qualitative assessments of these studies are summarized in Table 4.

Lactulose appears to be an effective and safe agent for use in idiopathic constipation, with the most common side effects (bloating, flatulence, and loose stools) being an extension of its mechanism of action. Compared to PEG solutions, lactulose was less efficacious and had more side effects (11, 16). 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 (26). A single trial that compared the efficacy and safety of lactulose and sorbitol suggested that the two agents were similarly effective, but lactulose had a greater propensity to cause nausea (23).

Lactulose: Level II Evidence, Grade B Recommendation.

Sorbitol: Level III Evidence, Grade C Recommendation.

Efficacy and Safety of MOM in the Treatment of Constipation

There is one trial in the English literature evaluating the efficacy of MOM in the treatment of constipation (28). MOM was compared to a bulk laxative and was found to cause more frequent bowel movements than bulk laxative, and additional laxative was not needed as often as with bulk laxative. Stool consistency was more normal during the magnesium hydroxide treatment. In two patients, serum magnesium was over 1.25 mmol/L after the magnesium hydroxide treatment but there were no clinical signs of hypermagnesemia. This is more likely to be a problem in patients with renal insufficiency. Hypermagnesemia, paradoxically, causes paralytic ileus that in turn leads to obstipation. This study suggests that MOM is effective, but there is a risk of hypermagnesemia with frequent use.

There are no trials that have evaluated the utility of magnesium sulfate (Epsom salts) in the treatment of constipation after 1966.

MOM: Grade III Evidence, Grade C Recommendation.

Efficacy and Safety of Stimulant Laxatives in the Treatment of Constipation

For the period reviewed, no placebo-controlled trials were found. The studies reviewed all compared a laxative containing only an irritant/stimulant agent, or agents containing an irritant/stimulant as one of its active ingredients with other agents (22, 24, 25, 27, 29–34). Tables 5 and 6 summarize the study characteristics and methodologic assessment. Three studies that compared a preparation containing psyllium and senna with lactulose suggested that the fiber/stimulant combination was more efficacious and may even be more cost-effective (22, 24, 25). Another study compared lactulose with irritant laxatives containing senna, anthraquinone derivatives, or bisacodyl (31). Lactulose was found to be more effective than each of these three irritant laxatives. A comparison between bisacodyl and bisoxatin acetate, both irritant laxatives, showed similar efficacy (32). The latter agent is no longer marketed. Preparations with and without senna were evaluated (30); laxation appears to be similar, with the combination appearing to cause more side effects compared with just

Table 3. Summary of the Trials Evaluating the Efficacy and Safety of Lactulose in the Treatment of Constipation

References	Score	Intervention	Study Design	Patient			Duration	Outcomes		
				N	Mean Age (year)	F/M		Outcome Measure	Results	Safety Analysis
19	3	Lactulose (60 ml/day) or placebo	Constipated subjects double-blind parallel	24 10 took lactulose 14 took placebo	28.2	22/2	1 wk baseline—all took placebo (single-blind), the second week was a double-blind treatment period	SF, stool weight, volume, SC, and water content	SF—lactulose syrup produced clinically and statistically significant increases (4.5 *vs* 1.6 stools per week, $p < 0.05$) SC—lactulose produced stools of softer consistency compared to baseline values, as well as to a sucrose-treated control group in both normal and constipated subjects Lactulose produced stools of greater weight, volume, and water content	Adverse effects were all extensions (flatulence) of the pharmacologic effects of the drug and were in general well tolerated
21	4	Lactulose (15–30 ml/day) or placebo dose escalation allowed	Multicenter, randomized, double-blind, placebo-controlled, parallel study	103	>60	Not stat-ed	2-wk run-in. 3-wk treatment, then 2-wk lead out	SF, UOL, possible SE	The success rate for lactulose was 86 *vs* 60% placebo ($p < 0.02$). Truly constipated patients were determined based on their laxative requirement posttreatment. The success rate of lactulose was increased to 80% in these patients and placebo 33% ($p < 0.01$)	None mentioned

20	4	Lactulose (30 ml of 50% solution) or placebo (glucose)	Randomized, double-blind, placebo-controlled	47 of 55—nursing home patients 19 lactulose, 23 glucose	84.7	39 F 6 M	2-wk run-in, 12-wk treatment, then 1-wk observation	SF, symptoms of constipation, episodes of stool impaction, UOL	SF—laculose was superior to glucose with mean BM per day of 0.7 *vs* 0.5 ($p < 0.02$) and in the percentage of days in which at least one bowel movement occurred ($p < 0.05$) Reduction in the severity of each of cramping, griping, flatulence, tenesmus, bloating was greater with lactulose. For relief of all five symptoms, lactulose was more effective than glucose ($p < 0.04$) The reduction in the number of fecal impactions (6 in the lactulose patients *vs* 66 in the controls) was highly significant ($p < 0.015$) The lactulose patients needed fewer enemas than did the controls	No adverse clinical of laboratory effects
11	5	PEG (26 g/day) or lactulose (20 g/day)	Multicenter, randomized, comparative	115–91 completed	30 to ≤65 >43 to 65	94/21	Two 5-day periods with 2-day washout	SF and St	PEG group had more daily stools and less straining Low dose PEG was more effective than lactulose and better tolerated Open-labeled phase with PEG following the study—no loss of efficacy	No significant adverse events in either group. More flatulence with lactulose

(continued)

Table 3. Continued

References	Score	Intervention	Study Design	Patient			Duration	Outcomes		
				N	Mean Age (year)	F/M		Outcome Measure	Results	Safety Analysis
16	3	PEG (8 ozs/day), placebo, lactulose (30 ml/day)	Randomized, triple crossover after control run-in	57—all on opiates	18–50	Not stated	1-wk run in control (no treatment) followed by three treatment phases of 2 wk each	SF, SC, and EOD	PEG solution and lactulose produced more "nonhard" stools than the placebo ($p < 0.01$) and control ($p < 0.003$). PEG produced the loosest stool ($p < 0.0001$) compared with the control There were no significant differences in SC in either experimental group, but both were better than having nothing or just the placebo	Lactulose had more adverse effects
22	2	Lactulose 30 cc or a preparation containing ispaghula (psyllium) and senna (Agiolax)	Open, randomized, and controlled crossover	30 long-stay geriatric patients	81.8	25/5	1-wk run in followed two 5-wk treatment periods separated by 1 wk	SF, SC, UOL (bisacodyl), and SE	The Agiolax produced 4.5 BM/wk (in both periods) compared with 2.2 and 1.9 per wk in periods one and two, respectively, for lactulose The frequency of loose stools was greater with Agiolax than with lactulose ($p < 0.05$)	No significant adverse effects noted
24	5	Lactulose (30–60 ml/day) and combination of psyllium and senna pod (Agiolax 10–20 ml/day)	Multicenter, double-blind crossover	77 of 85 long-stay geriatric patients	82.9	57/28	Senna-fibre combination or lactulose with matching placebo for two 14-day periods, with 3–5 days before and between treatments	SF, SC, EOD; deviation from recommended dose; daily dose and cost per stool; adverse effects	SF was greater with the senna-fibre combination (0.8 per day than lactulose (0.6 per day, $p \leq 0.001$) Scores for SC and EOD were significantly higher for the senna-fibre combination than for lactulose	No difference in adverse effects

										The recommended dose was exceeded more frequently with lactulose than the senna-fibre combination ($\chi^2 = 8.38$, $p \leq 0.01$) The cost per stool was approximately four times higher for lactulose than for the senna-fiber combination	
26	2	Lactulose (30 ml/day) or isphagula (psyllium) 7 g/day	Open, randomized, parallel group study	112	50.6	Not stated	4 wk	SF, SC, St, global improvement, medication acceptability	Both treatments resulted in statistically significant ($p < 0.0001$) increases in stool frequency over baseline but not between the treatment groups (baseline 2 per week *vs* 6.5 per week for lactulose and 7.5 per wk for ispaghula) Both treatments caused improved SC ($p = 0.027$), but there were no differences between the groups There was no significant difference in St There was no significant clinical difference in global improvement More patients found ispaghula unpalatable at 28 days (15.7 *vs* 4.2%) $p = 0.063$	No serious adverse effects

(continued)

Table 3. Continued

References	Score	Intervention	Study Design	Patient			Duration	Outcomes		
				N	Mean Age (year)	F/M		Outcome Measure	Results	Safety Analysis
25	3	Lactulose 15 ml or Agiolax 10 ml (mixture of ispaghula and senna)	Randomized, double-blind, crossover	77 long-stay geriatric patients	82.9	57/20	Two 14-day treatment periods with 3–5 d laxative free period before and between treatments	SF, SC, EOD, adverse effects	Agiolax resulted in statistically significant increases in SF (0.8 per day *vs* 0.6 per day $p < 0.001$) Agiolax resulted in statistically significant improvement in SC ($p < 0.005$) Agiolax resulted in statistically significant improvement in EOD ($p = 0.02$)	No differences in adverse effects between the treatment groups
23	5	Sorbitol and lactulose—up to 60 ml/day of either	Randomized, double-blind, crossover trial	30	65–86	All men	Lactulose and 70% sorbitol were each given for 4 wk preceded by a 2-wk washout period	SF, preference of laxative, adverse effects	The average number of bowel movements per week was 6.71 with sorbitol and 7.02 with lactulose, and the average number of days per week with bowel movements was 5.23 with sorbitol and 5.31 with lactulose 11 patients stated a preference for sorbitol, 12 for lactulose, and 7 had no preference	There were no significant differences between sorbitol and lactulose in any outcome measured except nausea, which was increased with lactulose ($p \leq 0.05$).

									On a visual analog scale measuring severity of constipation (0–100 mm), the average score for sorbitol was 35.6 *vs* 37.1 mm for lactulose The sorbitol and lactulose treatment periods were also similar in percent of bowel movements recorded as "normal"	
27	1	Lactulose (20 ml/day) or Dorbanex 10 ml/day—mixture of poloxalkol and an anthraquinone—or control (enemas if no BM in 5 days)	Randomized, open trial with control group	37 long-stay geriatric patients	82	Not stated	Randomly assigned to one of the treatment groups for 27 days	80% transit time (TT—time for 80% of ingested markers to be defecated)	All patients had 80% TT prior to treatment. 10/14, 12/15, and 6/6 has 80% TT after 6 d ays following 27 days of treatment with lactulose, Dorbanex, and control, respectively	No serious adverse effects. 19 lactulose, 23 glucose

Table 4. Methodologic Scores for the Studies Evaluating Lactulose

Reference	Randomization	Blinding	Statement on Withdrawals	Total Score
11	2	2	1	5
19	1	2	0	3
22	1	0	1	2
23	2	2	1	5
24	2	2	1	5
20	1	2	1	4
21	2	2	0	4
26	1	0	1	2
25	1	2	0	3
27	1	0	0	1
16	1	2	0	3

A score of 1 or 2 was given for randomization (2 for appropriate randomization technique and concealed allocation explicitly stated or described, 1 for study simply described as "randomized"). Scores of 0–2 were given for blinding (2 when both subjects and investigators were blinded to the treatment by use of identical placebo or other technique, 1 when the study is described as "double-blind," and 0 when the study was not double-blind). Score o f 0 or 1 was given for frequency of withdrawals (1 when the number of withdrawals and reason for withdrawals were stated, and 0 when no statement was made pertaining to withdrawals).

psyllium. Sodium picosulfate, a stimulant laxative similar to bisacodyl, has been compared to senna. The agents appear to be similar in their beneficial effects on stool frequency, although sodium picosulfate seems to cause more side effects. An agent comprised of the combination of a surfactant (poloxalkol) and an anthraquinone performed well compared with placebo in postpartum constipation (33), and similar to lactulose in another study (27). This combined agent was similar in efficacy to the stimulant sodium picosulfate (34).

While few studies suggest that combining stimulant laxatives with fiber or surfactant agents may provide some relief of symptoms in patients with constipation, there are no placebo-controlled trials.

Stimulant Laxatives: Level III Evidence, Grade C Recommendation.

Efficacy and Safety of Bulk Laxatives in the Treatment of Constipation

A study which compared increased dietary fiber with regular diet in posthysterectomy patients suggested that increased dietary fiber is beneficial in improving stool frequency, stool consistency, time to defecate, and other symptoms of difficult defecation (35). The individual agents that can be used to supplement the diet with fiber are discussed below. The characteristics of the trials evaluating bulking agents and qualitative assessment of the methodology are summarized in Tables 7 and 8.

Efficacy and Safety of Methylcellulose in the Treatment of Constipation

There are no placebo-controlled trials. One study (36) comparing three doses of methylcellulose against psyllium satisfied the screening criteria and is summarized in Table 5. The lack of an appropriate control group and its low methodologic score argues against accepting the results.

Methylcellulose: Level III Evidence, Grade C Recommendation.

Efficacy and Safety of Bran in the Treatment of Constipation

The studies evaluating the efficacy of bran and increased dietary fiber on constipation all suggest benefits (37–41). In a trial of the addition of wheat bran and corn bran supplements compared with no fiber supplementation, there was improvement in stool frequency and consistency, with no appreciable side effects (37). When bran was compared to just a regular diet in elderly patients, there was a decrease in laxative requirements, but, paradoxically, these patients seemed to require more assistance with actual defecation as evidenced by increased use of enemas and suppositories (41). A smaller study compared wheat bran with regular diet in elderly patients (42). There was significant improvement in stool frequency and consistency (42). No significant difference was found in laxative or suppository requirements. Another study also showed the beneficial effects on stool frequency, and also suggested that oroanal transit times improved, but only in patients with slow colonic transit and not in those with slow rectal transit times (38). Comparison of corn bran and wheat bran showed that both products were beneficial from the standpoint of improvement in stool frequency and intestinal transit times, but corn bran was rated by patients as being better at relieving the symptoms of constipation (39). A comparison of bran with senna suggested that there was no significant difference on frequency and consistency of stools, but bran decreased the incidence of "large" stools (40).

Level III Evidence, Grade C Recommendation.

Efficacy and Safety of Psyllium in the Treatment of Constipation

Psyllium (ispagula), a derivative of the husk of *Plantago ovata*, has been evaluated in several trials (30, 36, 43–47). Compared with placebo, psyllium seems to clearly improve stool frequency (43, 44). One study suggested that total gut transit time improved (44), while another suggested that there was no change in colon transit (43). Similarly, the effect on stool consistency in these placebo-controlled trials was controversial with one study suggesting no change (44) and another suggesting significant improvement (43). A third larger trial with a single-blind design comparing psyllium with placebo showed statistically significant improvement in both stool frequency and consistency with both the investigator, and patient noting significant improvement in the constipation (48). In an open trial, psyllium was noted to be superior to three different stimulant/irritant laxatives, lactulose, and magnesium sulfate in the treatment of constipation as well as being more palatable and acceptable to patients (46). A comparison of a preparation of psyllium with senna, and psyllium alone showed the combination to be more effective than

Table 5. Summary of the Trials Evaluating the Efficacy and Safety of Irritant and Stimulant Laxatives in the Treatment of Constipation

			Patient				Outcomes			
References	Score	Intervention	Study Design	N	Mean Age	Women	Duration	Outcome Measure	Results	Safety Analysis
31	2	Lactulose 15 ml b.i.d. or "irritant" laxatives (of patients choice) containing senna, anthraquinone derivatives or bisacodyl	Open, randomized, crossover	194 of 227	Not stated	Not stated	Two treatment periods of 1 wk separated by 1-wk washout	Stool consistency, side effects	By day 7, 58% of the lactulose-treated group were passing a normal stool whereas only 42% ($p < 0.001$) of the patients receiving an "rritant" laxative Lactulose preparation had a persistent carry-over effect than the irritant laxatives	No difference was noted in the recording of side effects during treatment and nontreatment periods
32	2	Bisacodyl 10 mg/day or bisoxatin acetate 60 mg/day	Randomized, double-blind, comparative	51 of 61	21–69	All male prisoners	Two consecutive 4-wk periods	Onset of first BM, stool frequency, consistency, patient satisfaction, adverse reactions	There were no differences between bisoxantin and bisacodyl in the mean time to first BM (7 *vs* 5 h) No difference in stool frequency (1.7 per day *vs* 2.1 per day) No difference in stool consistency There were less satisfaction with bisacodyl (73% *vs* 82%)	Bisacodyl appeared to cause more abdominal pain
22	2	Lactulose 30 cc or a preparation containing ispaghula (bulking agent) and senna (Agiolax)	Open, randomized, and controlled crossover	30 long-stay geriatric patients	81.8	25 F 5 M	1-wk run in followed two 5-wk treatment periods separated by 1 wk	Stool frequency, consistency, use of additional laxative (bisacodyl) and side effects	The Agiolax produced 4.5 stools a week (in both periods) compared with 2.2 and 1.9 per week in periods one and two, respectively, for lactulose The frequency of loose stools was greater with Agiolax than with lactulose ($p < 0.05$)	No significant adverse effects noted

(continued)

Table 5. Continued

References	Score	Intervention	Patient				Outcomes			
			Study Design	N	Mean Age	Women	Duration	Outcome Measure	Results	Safety Analysis
30	2	Psyllium (P) and psyllium with senna (PS)	Open, randomized, single-blind controlled	40 of 42	26.1	35 F 5 M	1 wk placebo and 1 wk treatment	SF, SC symptoms with BMs	Both laxatives increased SF [P 3.6 BM/wk *vs* PS 6.8 BM/wk ($p <$ 0.001)] Both P and PS increased wet and dry stool weights with the added effect of the senna clearly evident. Only the psyllium with senna increased stool moisture Both laxatives improved SC (similar) Both laxatives provided a high degree of subjective relief	P group 3/22 cramping and gas PS group7/22 had cramps, uncomfortable diarrhea, bloating gas, and nausea
24	5	Lactulose (L) 30 ml/day and combination of fibre—ispaghula (psyllium) and senna pod (PS)—Manevac 10–20 ml/day	Multicenter, double-blind, crossover	77 of 85 long-stay geriatric patients	82.9	57 F	Senna-fibre combination or lactulose with matching placebo for two 14-day periods, with 3–5 days before and between treatments	SF, SC, EOD; deviation from recommended dose; daily dose, and cost per stool; adverse effects	SF was greater with the senna-fibre combination (0.8 per day than lactulose (0.6 per day, $p \leq$ 0.001) Scores for SC and EOD were significantly higher for the senna-fibre combination than for lactulose The recommended dose was exceeded more frequently with lactulose than the senna-fibre combination ($\chi^2 =$ 8.38, $p \leq 0.01$) The cost per stool was approximately four times higher for lactulose than for the senna-fiber combination	No difference in adverse effects

25	3	Lactulose 15 ml or Agiolax 10 ml (mixture of Ispaghula (psyllium) and senna)	Randomized, double-blind, crossover	77 long-stay geriatric patients	82.9	57 F 20 M	Two 14-day treatment periods with 3–5 days laxative free period before and in between treatments	SF, SC, EOD, adverse effects	Agiolax resulted in statistically significant increase in SF (0.8 per day *vs* 0.6 per day, $p < 0.001$) Agiolax resulted in statistically significant improvement in SC ($p < 0.005$) Agiolax resulted in statistically significant increases in ($p = 0.02$) EOD	No differences in adverse effects between the treatment groups
29	2	Sodium picosulfate SP 10 mg/day or standardized senna (S) 2 tabs/day	Open, randomized parallel	50 long-stay geriatric patients	78.5	36 F 14 M	2 wk	Stool frequency, timing, consistency, and side effects	The number of BMs per week were similar for S (4.41) and SP (4.97) SP caused more loose or unformed stools than senna	There were few minor side effects all related to the action of the drugs on the bowel
33	3	Dorbanex (mixture of poloxalkol and dihydro-anthroquinolone) (PD) or placebo	Randomized, double-blind, placebo-controlled	200 postpar-tum patients with con-stipation	Child-bearing age range (cannot infer from data)	All women	6 days	Stool output, requirement for enemas and suppositories,	By the second day of treatment 50% in the treatment group had a BM compared with less than one-eighth in the placebo group ($p < 0.001$). Decreased requirement for enemas and suppositories (statistically significant)	No adverse effects observed

(continued)

Table 5. Continued

References	Score	Intervention	Patient				Outcomes			
			Study Design	N	Mean Age	Women	Duration	Outcome Measure	Results	Safety Analysis
27	2	Lactulose 20 ml b.i.d. or Dorbanex (mixture of poloxalkol and dihydro-anthroquinolone) (PD)—10 ml/day, or enema if no BM in 5 days (control group)	Open, randomized, controlled	35 of 37 long-stay elderly patients	81	30 F 7 M	27 days	Improvement in transit times by Hinton method	There were statistically significant improvements in the transit times in the lactulose and PD groups both within the group compared with baseline, and when compared with the control group	No significant adverse effects noted
34	2	Sodium picosulfate (SP—10 mg/day) or Dorbanex (mixture of poloxalkol and dihydro-anthroquinolone (PD—10 ml/day)	Open, randomized, crossover	38 of 40 long-stay patients	75.6	31 F 7 M	2-wk run in followed by two 2-wk treatment periods with a 3-day washout in between	Stool frequency, size, side effects	The average number of BM per day increased from 0.56 in the pretrial period, to 0.96 for SP and 0.86 for PD Both SP and PD resulted in normalization in stool size in the majority of patients	High incidence of incontinence in the group that received SP as their first treatment. Other effects were minimal

Table 6. Methodologic Scores of the Studies Evaluating the Stimulant and Irritative Laxatives

Reference	Randomization	Blinding	Statement on Withdrawals	Total Score
22	1	0	1	2
24	2	2	1	5
25	1	2	0	3
30	1	0	1	2
31	1	0	1	2
32	1	2	1	4
29	1	0	1	2
27	1	0	1	2
33	1	2	0	3
34	1	0	1	2

A score of 1 or 2 were given for randomization (2 for appropriate randomization technique and concealed allocation explicitly stated or described, 1 for study simply described as "randomized"). Scores of 0–2 were given for blinding (2 when both subjects and investigators were blinded to the treatment by use of identical placebo or other technique, 1 when the study is described as "double-blind," and 0 when the study was not double-blind). Score o f 0 or 1 was given for frequency of withdrawals (1 when the number of withdrawals and reason for withdrawals were stated, and 0 when no statement was made pertaining to withdrawals).

psyllium alone. However, the combination appeared to cause more side effects. A study evaluating the efficacy of psyllium compared with docusate revealed that psyllium was superior in its effect on stool frequency, stool water content, total stool output, and the combination of several objective measures of constipation (45). The combination of psyllium, celandin, and aloe vera was superior to placebo in the treatment of constipation (47). Three studies that compared a combination of psyllium and senna with lactulose are discussed in the section on lactulose and stimulant/irritant laxatives (22, 24, 25). The comparison of two preparations of psyllium and senna, one with a higher dose of senna, revealed that the preparation with the higher senna dose increased stool frequency more than the other (49). In elderly, bed-ridden, nursing home patients, psyllium and calcium polycarbophil have been noted to be similar in their effect in improvement in stool frequency, stool consistency, and ease of defecation (50). Psyllium and methylcellulose were similarly effective in constipated subjects in another study (36).

Level II Evidence, Grade B Recommendation.

The Efficacy and Safety of Calcium Polycarbophil in the Treatment of Constipation

Apart from the study mentioned in the discussion of psyllium, no other trials were found in the English literature evaluating this drug. Additional clinical trials are required to further evaluate the utility of this agent.

Level III Evidence, Grade C Recommendation.

Efficacy and Safety of Cisapride in the Treatment of Constipation

Three randomized studies are presented (51–53). These are summarized in Tables 9 and 10. Two of these studies included placebo (51, 53); in the third (52) study, comparative results of efficacy were inferred from periods when study patients were not receiving any therapy. The results demonstrating the efficacy of cisapride in the treatment of idiopathic constipation were seen in a pilot study as well (54). Open trials have evaluated the efficacy of cisapride in the constipation of Parkinson's disease (55, 56); over the long-term, the efficacy may wane (56). The drug may also be useful for treating constipation patients with spinal cord injury (57) and systemic sclerosis (58), although this remains to be validated in a controlled manner.

Though it appears that cisapride may be a useful agent in the treatment of idiopathic constipation, it is no longer marketed in the United States.

Cisapride: No Recommendation.

Efficacy and Safety of Colchicine in the Treatment of Constipation

No randomized studies in otherwise healthy patients with idiopathic constipation have been reported, apart from a single study that is in abstract only. One randomized trial performed on developmentally disabled patients is presented (59). This is summarized in Tables 11 and 12. In an open-labeled trial in seven patients with chronic constipation, the mean number of spontaneous bowel movements significantly increased ($p < 0.05$) from 1.7 ± 0.5 noted during routine therapy of constipation with laxatives and enemas to 6.4 ± 0.7 per week; mean colonic transit time significantly ($p < 0.05$) decreased from 58.1 ± 2.5 to 47.1 ± 5.0 h; and symptoms of abdominal pain, nausea, and bloating significantly ($p < 0.05$) improved during therapy with colchicine (60). This pilot study was followed by a double-blind, placebo-controlled, randomized, crossover study in 16 chronically constipated subjects. As alluded to above, this has been published in abstract form only to date (61). Colchicine 0.6 mg t.i.d. was the dose and schedule utilized in a 4-wk treatment interval. Colchicine resulted in reduced transit time and increased number of bowel movements per week (9.9 *vs* 3.8) compared with placebo. A significant placebo effect was noted. No significant side effects were observed. Observations in patients with Parkinson's disease (62) and persistent constipation after total abdominal colectomy with ileorectostomy for colonic inertia (63) suggest that colchicine may be useful in these settings as well.

The utility of colchicine in the treatment of chronic idiopathic constipation remains to be confirmed.

Colchicine: Level III Evidence, Grade C Recommendation.

Effectiveness and Safety of Misoprostol in the Treatment of Constipation

Only one suitable randomized trial was found (64). The number of patients was small (n = 8). The qualitative assessment of this study and the extracted data are presented in Tables 13 and 14.

Table 7. Summary of the Trials Evaluating the Efficacy and Safety of the Bulk Laxatives

References	Score	Intervention	Study Design	Patient			Duration	Outcomes		
				N	Mean Age (year)	F/M		Outcome Measure	Results	Safety Analysis
37	1	10 g fiber from corn-based biscuits (gp A), wheat bran (gp B), or no intervention (gp C)	Randomized open in patients in the third trimester of pregnancy	40	28		2-wk baseline followed by 2-wk treatment	SF, SC, presence of pain, straining, and blood	Mean daily dietary fibre intake in all groups, in the first 2 wk 20.4 g was similar to that in the general population. In the final 2-wk changes in fiber intakes were Gp A, mean increase 7.2 g/day ($p < 0.001$); Gp B, mean increase 9.1 g/day ($p < 0.001$); Gp C mean decrease 3.50 g/day ($p < 0.005$). Stool frequency improved in Gps A and B with no changes in Gp C. Stool frequency and consistency improved in Gps A and B, with no changes in Gp C.	There was a tendency for the fiber supplemented groups to experience less pain and straining, but this did not achieve statistical significance
38	4	Bran 6.6 g t.i.d. or placebo	Randomized, double-blind, placebo-controlled, crossover	24 of 29	37 (20–65)	26/3	3 week baseline, then two consecutive 4-wk treatment periods	Segmental transit times, SF, stool weight, and other symptoms	SF for placebo was 1.2 ± 1.3 per wk *vs* 3.5 ± 1.8 for bran ($p < 0.01$) There was no difference in stool weight During bran treatment oroanal transit time normalized only in patients with slow colonic transit and not in those with slow rectal transit	No significant adverse effects

									The occurrence and severity of the most frequent accompanying symptoms of chronic constipation did not differ with placebo and bran treatments	
39	1	10 g b.i.d. of corn bran or wheat bran	Open, randomized, controlled	10	26.3	10/0	1-wk adjustment, 2-wk control, and 2-wk treatment period	Fecal weight, fecal moisture content, SF, intestinal transit time, and symptoms	The administration of both bran products was associated with an increase in fecal weight (157%, $p < 0.05$), and whereas Bran increased SF (2.3 ± 0.3 to 3.5 ± 0.5 BM/wk; 55%, $p < 0.05$) Bran decreased intestinal transit time (50%) Percentage fecal moisture increased only with wheat bran (67.4–72.1%) Corn bran was significantly better than wheat bran in relieving symptoms of constipation ($p < 0.05$)	None reported
49	2	Agiolax and Lunelax	Open, randomized, controlled, crossover	19 of 20	83	16/4	1-wk run-in followed by two consecutive treatment periods	SF, SE, taste of the preparation, use of enemas	The SF tended to be higher with Lunelax (which contains a higher dose of senna) than with Agiolax There were no difference in the "ease of swallowing" There were no difference in "ease of administration" and There were no differences in "taste"	No side effects seen

(continued)

Table 7. Continued

References	Score	Intervention	Study Design	Patient			Duration	Outcomes		
				N	Mean Age (year)	F/M		Outcome Measure	Results	Safety Analysis
40	1	10 g unrefined bran, 10 g of bran as bran biscuits or 10 ml of senokot	Open, randomized	23 psycho-geriatric patients	50.3	15/8	Each received the three agents in three consecutive periods of 3 wk, the sequence randomly determined	SF, SC, size of bowel movements, use of enemas	There was no significant difference SF. There was no significant difference in use of enemas. There was no significant difference in the consistency of the motions. There was little difference in the proportion of "large" stools in the three treatment periods, but a significantly higher proportion of smaller stools were reported with bran.	None mentioned
48	3	Ispaghula (psyllium) 3.6 g t.i.d. or placebo	Multicenter, randomized, placebo-controlled, single-blind, parallel	201	49	151/50	14 days	SF, SC, abdominal discomfort, # of sachets taken	SF—showed statistically significant increases from 2.3 per week baseline, to 7 per week with ispaghula and 4.5 per week for placebo. SC—the number of hard-or pellet-like stools were also significantly lower, and loose or watery stools increased in the ispaghula group Statistically significant decreases in abdominal discomfort, and straining in the isphagula group Both investigators and patients noted statistically significant improvement in the constipation	No significant adverse effects

42	2	Wheat bran 1.5–4.5 g qd or regular diet	Open, randomized, parallel	12 of 14 long-stay geriatric patients	80	14/0	6 wk, then placebo group were treated with bran as well	SF, stool size, SC, EOD, UOL	SF—the number of spontaneously passed BMs in the bran group was statistically significant compared to the placebo group All patients in the bran group, and the patients in the placebo group following commencement of bran supplementation showed improvement in the quantity and consistency of stools passed	One patient reported difficulty swallowing bran
41	1	Bran (0.5–1.5 g) or regular diet	Open, randomized, controlled	37 of 50	>60 yr—extended care hospital	—	13 wk	Requirement for laxative use	There was an overall decrease in laxative use in the bran group. However, there was also an increase in the use of enemas and suppositories	No significant adverse effects
35	3	High fiber (22.9 g daily) diet or regular diet	Open, randomized, controlled	35 of 49 patients undergoing radical hysterectomy 17 control (C) 18 treatment (T)	35	49/0	7 months	SF, SC, EOD gas, cramping	SF—T group had a significant increase in the frequency of BM ($p = 0.0096$); this was not seen in the C group. The T group took less time to defecate ($p < 0.001$) but had more BMs accompanied by gas ($p < 0.001$). The C group had significantly more BM with cramps ($p < 0.001$), straining ($p < 0.001$), and retention ($p < 0.001$) SC—the C group had significantly more BMs, which were hard ($p < 0.001$)	No significant adverse effects

(continued)

Table 7. Continued

References	Score	Intervention	Study Design	Patient			Duration	Outcomes		
				N	Mean Age (year)	F/M		Outcome Measure	Results	Safety Analysis
46	2	Ispaghula (IS) (psyllium) 3.5 g, or another laxative (lactulose, bisacodyl, docusate, senna, and magnesium sulfate)	Open, multicenter, randomized, controlled	381 of 394 224 (56.9%) ispaghula 170 (43.1%) other laxative	30–59	250/139	4 wk	SF/SC of soiling, acceptability, palatability, treatment-related upsets	IS was assessed by the GPs to be superior to the other treatments in improving bowel function and in overall effectiveness. IS was more palatable and acceptable to patients. IS produced a higher percentage of normal, well-formed stools and fewer hard stools than other laxatives. Incidences of soiling, diarrhea, and abdominal pain were lower in the IS group.	No significant adverse effects
43	3	Psyllium 24 g/day or placebo	Single-blind, randomized, placebo-controlled fiber intervention with crossover	10	>60	5/5	4 wk in each arm	SF, SC, and weights daily	Fiber decreased total gut transit time from 53.9 h (placebo condition) to 30.0 h ($p < .05$). Stool weights and consistency were not significantly improved by fiber. There was a trend toward an increase in SF (1.3 *vs* 0.8BM/day) in the fiber group	No significant adverse effects
44	4	Psyllium (10 g/day) and placebo	Double-blind, placebo-controlled	22	51	14/8	8 wk with 4-wk run-in on placebo and 4 wk washout	SF, SC, EOD and weekly stool weight. Colon transit and ARM	SF increased significantly after 8 wk of psyllium treatment (3.8 *vs* 2.9 BM/wk, $p < 0.05$) Subjects reported improvement in SC (stool consistency score: 3.2 ± 0.2 *vs* 3.8 ± 0.2, $p < 0.05$) on psyllium EOD improved on psyllium (pain score: 2.0 ± 0.4 *vs* 2.6 ± 0.5, $p < 0.05$) Colon transit and ARM unchanged	No significant adverse effects

30	2	Psyllium (P) 7.2 g/day and psyllium with senna (PS) (6.5 + 1.5 g/day)	Open, randomized, single-blind controlled	40 of 42	26.1	35 F 5 M	1-wk placebo and 1-wk treatment	SF, SC, symptoms with BMs	Both laxatives increased SF [P 3.6 *vs* PS 6.8 BM/wk ($p < 0.001$)] Both laxatives improved SC (similar) Both P and PS increased wet and dry stool weights with the added effect of the senna clearly evident. Only the psyllium with senna increased stool moisture Both laxatives provided a high degree of subjective relief	P group 3/22 cramping and gas PS group 7/22 had cramps, uncomfortable diarrhea, bloating gas, and nausea
45	5	Psyllium 5.1 g b.i.d. and docusate 100 mg b.i.d.	Multicenter, randomized, double-blind, parallel design	170 of 187	37.2	156/14	1-wk washout followed by 1-wk baseline (placebo) followed by 2-wk treatment	Stool water content (SWC), stool water weight (SWW), total stool output, SF	Compared to baseline, psyllium increased SWC *vs* docusate (psyllium 2.33% *vs* docusate 0.01%, $p = 0.007$ and) Psyllium also increased SWW (84.0 g/BM) *vs* docusate (71.4 g/BM); $p = 0.04$ Total stool output higher with psyllium (359.9 g/wk) *vs* docusate (271.9 g/wk); $p = 0.005$ Psyllium had a higher O'Brien rank-type score combining objective measures of constipation (psyllium 475.1; docusate 403.9; $p = 0.002$) SF was significantly greater for psyllium (3.5 BM/wk) *vs* docusate (2.9 BM/wk) in treatment week 2 ($p = 0.02$)	None stated

(continued)

Table 7. Continued

References	Score	Intervention	Study Design	Patient			Duration	Outcomes		
				N	Mean Age (year)	F/M		Outcome Measure	Results	Safety Analysis
47	3	Psyllium, celandin, and aloevera combination (CAP) 1–3 capsules per day or placebo	Double-blind randomized, placebo-controlled	32 of 35	51.5	22/10	28 days to-2 wk pretrial baseline	SF, SC, and other symptoms	In the (CAP) group, bowel movements became more frequent (4.6 *vs* 7.9 BM/wk). ($p < 0.002$) SC—stools softer in CAP group compared with placebo. ($p < 0.002$) Less laxative dependence in CAP group ($p < 0.01$) Abdominal pain was not reduced in either group	No side effects detected*
50	1	Calcium polycarbophil (C) 2 tabs/day or psyllium (P) two teaspoons/day	Open, randomized controlled, crossover	32 bed-ridden nursing home residents	77 ± 10.4	26/6	Two consecutive 3-wk treatment periods	SF, SC, EOD	There were no statistically significant changes in SF (for C 7.2 ± 2.4 *vs* for P 7.22 ± 2.2) No difference in EOD No difference in SC More patients seemed to favor C	None mentioned
36	2	1, 2, or 4 g of methylcellulose (M) or 3.4 gm of psyllium (P)	Two phase	50 healthy subjects,59 chronically constipated	27 (18–70) 28 (18–70)	56/3	1-wk run-in (taking placebo), then 10-day treatment period with one of the regimens described	SF, stool weight, stool water and solids. Adverse events	Healthy subjects: methylcellulose in daily doses of 4 g demonstrated a statistically significant increase in fecal frequency, fecal water, and fecal solids Chronically constipated individuals—all doses of M and P statistically significant increases in SF Chronically constipated individuals—all doses of M and P statistically significant increased water content, and fecal solids There was no increase in individual stool weight from any of the laxative doses	No difference in the incidence of abdominal cramps, flatulence, or abdominal pain between the treatment and placebo periods

*Because this study is double-blind and placebo-controlled, the total score here is highly based on the criteria set out; the study description reveals very little information, and as such the overall quality is not as good as the score suggests.

Table 8. Methodologic Scores of the Studies Evaluating the Bulk Laxatives

Reference	Randomization	Blinding	Statement on Withdrawals	Total Score
38	1	2	1	4
37	1	0	0	1
39	1	0	0	1
49	1	0	1	2
40	1	0	0	1
48	1	1	1	3
42	1	0	1	2
41	1	0	0	1
35	2	0	1	3
46	1	0	1	2
30	1	0	1	2
44	1	2	1	4
45	2	2	1	5
43	1	1	1	3
47	1	2	1	4
50	1	0	0	1
36	1	1	0	2

A score of 1 or 2 was given for randomization (2 for appropriate randomization technique and concealed allocation explicitly stated or described, 1 for study simply described as "randomized"). Scores of 0–2 were given for blinding (2 when both subjects and investigators were blinded to the treatment by use of identical placebo or other technique, 1 when the study is described as "double-blind," and 0 when the study was not double-blind). Score o f 0 or 1 was given for frequency of withdrawals (1 when the number of withdrawals and reason for withdrawals were stated, and 0 when no statement was made pertaining to withdrawals).

Misoprostol: Level III Evidence, Grade C Recommendation.

Efficacy and Safety of Stool Softeners in the Treatment of Constipation

Docusate sodium and docusate calcium are the major drugs in this category. Poloxalkol is another stool softener; no studies were found in which this agent was used by itself in a treatment arm. The studies reviewed are summarized in Tables 15 and 16. Three studies where it is combined with a stimulant/irritant laxative are summarized in the section dealing with this latter class of drugs. Four studies are presented that evaluate the utility of docusate in the treatment of constipation (45, 65–67). One of these compares it with psyllium (45). Psyllium appears to be superior to docusate sodium in the doses utilized. The other studies either compare docusate sodium and docusate calcium or these drugs *versus* placebo. One study suggests that docusate calcium may be more effective than docusate sodium (65). The efficacy of docusate in the treatment of constipation is modest at best, with one study, albeit small, suggesting no significant benefit compared with placebo (66). There are studies that have evaluated docusate prior to 1966, and these have been included in previous reviews (68).

Docusate: Level III Evidence, Grade C Recommendation.

Efficacy and Safety of Other Agents on the Treatment of Constipation

A recent randomized, double-blind placebo-controlled trial evaluated the efficacy of tegaserod in the management of chronic constipation (69). This drug is a selective agonist of the serotonin subtype 4 (5-HT_4). It has been shown to enhance gastrointestinal motility in animals and healthy volunteers, and it has also been shown to be effective for symptom relief in patients with constipation predominant irritable bowel syndrome. This was a large well-designed trial with a quality score of 5. The doses used were tegaserod 2 mg b.i.d., tegaserod 6 mg b.i.d., or placebo. A total of 1,116 patients completed the treatment phase of the trial. The mean age was 47 yr and 90% of the subjects were women. Treatment duration was 12 wk. Responders were patients treated for $\geq$7 days with an increase of $\geq$1 complete spontaneous BM per week *versus* baseline during weeks 1–4 (primary variable) and weeks 1–12 (secondary variable). Other secondary variables included SF, stool form, abdominal bloating/distention, straining, and abdominal pain/discomfort, and global assessment of constipation and bowel habits. Responder rates for complete spontaneous bowel movement during weeks 1–4 were significantly greater ($p < 0.0001$) in the tegaserod 2 mg twice daily (41.4%) and 6 mg twice daily groups (43.2%) *versus* placebo (25.1%). This effect was maintained over 12 wk. Statistically significant improvements over placebo were observed across the majority of secondary variables for both tegaserod doses. No rebound effect was observed after treatment withdrawal. As such, there appears to be clear, statistically significant benefit of the two doses used *versus* placebo, with no clear benefit of the higher dose compared with the lower dose. Overall, tegaserod was well tolerated; headache and nasopharyngitis, the most frequent adverse events, were more common in the placebo group than in either tegaserod group.

Tegaserod: Level I Evidence, Grade A Recommendation.

A pilot study was undertaken to evaluate the efficacy of oral *erythromycin* in the treatment of idiopathic constipation (70). Eleven male patients were treated for 1 month with erythromycin (1 g/day for 2 wk then 500 mg/day for 2 wk) in an open, nonrandomized trial. Colon transit time improved as did stool frequency (2.3–6.7 per week). Two of the patients complained of borborygmi, otherwise there were no significant side effects. These results suggest that erythromycin warrants trial in a controlled manner to see if this dramatic improvement could be reproduced.

Loxiglumide, a cholecystokinin antagonist, was evaluated for its efficacy in a prospective, randomized, double-blind controlled trial (71) in 21 nursing home patients with a mean age of 83 yr. There were 13 male and 8 female patients. They were randomized to receive loxiglumide 800 mg t.i.d. or identical placebo.

Table 9. Summary of the Studies Evaluating the Efficacy and Safety of Cisapride in the Treatment of Constipation

			Patient				Outcomes			
References	Score	Intervention	Study Design	N	Mean Age	F/M	Duration	Outcome Measure	Results	Safety Analysis
51	5	Cisapride 20 mg b.i.d. or placebo	Randomized, double-blind, placebo-controlled	126 (64 cisapride, 62 placebo)	50.5	75/51	4-wk baseline phase, 8-wk treatment phase and 4-wk run out (placebo) phase	SF, SC, EOD, UOL, and overall state with respect to constipation (visual analog scale)	Cisapride and placebo increased spontaneous SF from 1.1 to 3.0 BM/wk ($p \leq 0.001$) and from 1.2 to 1.5 BM/wk ($p > 0.05$), respectively Laxative consumption was decreased from 3.6 to 1.8 doses per week by cisapride ($p \leq 0.001$) and from 3.3 to 2.8 by placebo ($p < 0.05$). Both drugs improved constipation as assessed by the patient by means of a visual analog scale, but cisapride did so to a larger extent than placebo	No data
52	5	Different doses of cisapride or no treatment	Randomized, double-blind. Two groups: A and B	119			Gp A—12 wk of cisapride 20 mg/day, then 12 wk of freedom to take up to 20 mg/day in 5 mg increments. Gp B—20 mg/day for 6 wk, then 10 mg/day for 6 wk, then no treatment for 12 wk	SF and UOL	SF was increased in both groups during active treatment and was not reduced when the dose was decreased from 20 to 10 mg twice daily in group B but was maintained in group A Laxative intake fell by 50% in both groups, but this effect was maintained during follow-up in group A only Group A patients took nearly the maximum dosage of cisapride tablets allowed during follow-up (3.3 tablets per day ± 0.2 SEM)	No data

53	4	One of two cisapride doses (5 or 10 mg) or placebo	Randomized, double-blind, parallel group design	46 of 48	Median of 50 yr	34 F 12 M	Three phases—3-wk baseline, followed by 12-wk double-blind period, and 4-wk follow-up	SF, SC, EOD, UOL, SE	Both cisapride 5 and 10 mg increased stool frequency by about 70% from baseline after 8–12 wk ($p <$ 0.002), but placebo also increased SF by 43% ($p < 0.07$). The difference between the treatment groups did not meet statistical significance Cisapride decreased SC and resulted in greater EOD compared with placebo, both in a statistically significant manner ($p < 0.002$ and $p < 0.002$, respectively) Cisapride therapy decreased laxative consumption, while the placebo group did not Relapse after withdrawal of therapy occurred slowly. No significant difference was found between the two different doses of cisapride	Patients in the cisapride reported abdominal cramps (4), dyspepsia, gastric problems, epigastric pain, flatulence diarrhea, and dizziness (1 each)

Table 10. Methodologic Scores of the Trials Evaluating Cisapride

Reference	Randomization	Blinding	Statement on Withdrawals	Total Score
51	2	2	1	5
52	2	2	1	5
53	1	2	1	4

A score of 1 or 2 was given for randomization (2 for appropriate randomization technique and concealed allocation explicitly stated or described, 1 for study simply described as "randomized"). Scores of 0–2 were given for blinding (2 when both subjects and investigators were blinded to the treatment by use of identical placebo or other technique, 1 when the study is described as "double-blind," and 0 when the study was not double-blind). Score o f 0 or 1 was given for frequency of withdrawals (1 when the number of withdrawals and reason for withdrawals were stated, and 0 when no statement was made pertaining to withdrawals).

It was noted that stool frequency improved from 3.9 per week in the placebo group to 4.8 per week in the treatment group ($p < 0.006$). Colon transit time was also significantly improved. No serious side effects or exocrine pancreatic insufficiency was encountered. These results suggest a larger trial involving more patients is indicated to further define the role of this agent in the treatment of constipation, and such a trial is ongoing.

No studies were found in the English literature that supported the use of herbal remedies in the treatment of constipation, although there may be studies in the Chinese and Japanese literature.

DISCUSSION

The tables summarize individual studies where subjects were randomized to receive either the active drug or placebo. A surprising observation was that apart from PEG and Tegaserod, there was paucity of placebo-controlled studies of high quality. Without placebo-controlled trials, it is impossible to judge an agent's efficacy. Also, in general, sample sizes were small. Consequently, two drugs, PEG and tegaserod, were accorded a Grade A recommendation and two drugs, lactulose and psyllium were given a Grade B recommendation. One of our key observations was that the definition of constipation was quite varied among the various studies. While many of the studies defined constipation as the presence of less than 2 or 3 stools per week, and a few confirmed this in an observation period prior to randomization, very few utilized criteria developed in consensus meetings, such as the Rome criteria. This prevented effective comparisons of trials that were otherwise similar. Similar difficulties were encountered when assessing outcome measures for different trials. Stool frequency and measures of stool consistency were the most common parameters that were assessed. Other measures that were reported included ease of defecation use of additional laxatives, stool weight, stool water content, and transit times. These problems notwithstanding, based on the results, the following recommendations can be made regarding the currently available agents for the treatment of chronic constipation.

Table 11. Summary of the Study Evaluating the Efficacy and Safety of Colchicine in the Treatment of Constipation

References	Score	Intervention	Study Design	Patient			Duration	Outcomes		
				N	Mean Age (year)	F/M		Outcome Measure	Results	Safety Analysis
59	5	Colchicine (1.2 or 1.8 mg/day) or placebo in developmentally disabled patients	Double-blind, crossover	11 of 12 completed	24–60	7/5	4-wk baseline, followed by two 8-wk treatment periods with a 3-wk wash-out in between	SF, and need for additional laxatives	8 of 11 patients experienced an improved bowel pattern while on colchicine compared with placebo, as defined by an increase in SF or a decrease in total number of rectal laxatives used. 7 of 8 patients who had an increase in SF required a decrease in rectal laxative use.	No significant clinical or lab complications were recognized

Table 12. Methodologic Score of the Study Evaluating Colchicine in the Treatment of Constipation

Reference	Randomization	Blinding	Statement on on Withdrawals	Total Score
59	2	2	1	5

A score of 1 or 2 was given for randomization (2 for appropriate randomization technique and concealed allocation explicitly stated or described, 1 for study simply described as "randomized"). Scores of 0–2 were given for blinding (2 when both subjects and investigators were blinded to the treatment by use of identical placebo or other technique, 1 when the study is described as "double-blind," and 0 when the study was not double-blind). Score o f 0 or 1 was given for frequency of withdrawals (1 when the number of withdrawals and reason for withdrawals were stated, and 0 when no statement was made pertaining to withdrawals).

Table 14. Methodologic Score of the Study Evaluating Misoprostol in the Treatment of Constipation

Reference	Randomization	Blinding	Statement on Withdrawals	Total Score
64	1	2	1	4

A score of 1 or 2 was given for randomization (2 for appropriate randomization technique and concealed allocation explicitly stated or described, 1 for study simply described as "randomized"). Scores of 0–2 were given for blinding (2 when both subjects and investigators were blinded to the treatment by use of identical placebo or other technique, 1 when the study is described as "double-blind," and 0 when the study was not double-blind). Score o f 0 or 1 was given for frequency of withdrawals (1 when the number of withdrawals and reason for withdrawals were stated, and 0 when no statement was made pertaining to withdrawals).

Osmotic Laxatives

(i) Lactulose (Kristalose)—three placebo-controlled trials (19–21) with quality scores of 3, 4, 4. Evidence fair, Grade B recommendation.

(ii) PEG (Miralax)—five placebo-controlled trials (10, 12–15) (9, 11, 12, 13, 14) with quality scores of 5, 3, 5, 5, 4; two lactulose-controlled trials (10, 15) with quality scores of 5, 3. Evidence good, Grade A recommendation. PEG superior to lactulose.

Bulking Agents

(i) Psyllium (Metamucil)—three placebo-controlled trials (43, 44, 48) with quality scores of 3, ˙, 3; two lactulose-controlled trial (26, 46) with quality scores of 2, 2. Evidence fair, Grade B recommendation.

(ii) Calcium polycarbophil (Perdiem fiber therapy)—one trial against psyllium (50) with quality score of 1. Evidence poor, Grade C recommendation.

(iii) Bran—one placebo-controlled trial (38) with quality score of 4; one trial against "no treatment" (37) with a quality score of 1; one trial of wheat bran *versus* corn bran *versus* baseline (39) with a quality score of 1. Evidence poor, Grade C recommendation.

(iv) Methylcellulose—one nonplacebo-controlled trial with a quality score of 2 (36). Evidence poor, Grade C recommendation.

Wetting Agents

A. Dioctyl sulfosuccinate—one trial of dioctyl calcium (not available in the United States) and dioctyl sodium (DSS, Colace) *versus* placebo (65) with a quality score of 3; two

Table 13. Summary of the Study Evaluating the Efficacy and Safety of Misoprostol in the Treatment of Constipation

				Patient				Outcomes		
References	Score	Intervention	Study Design	N	Mean Age (year)	F/M	Duration	Outcome Measure	Results	Safety Analysis
64	4	Misoprostol (1,200 μg/day) or placebo	Randomized, double-blind, crossover	8 of 9	18 and older. Not otherwise qualified	9/0	Two 1-wk treatment periods (placebo or misoprostol) separated by 1-wk washout	Colon transit time, SF, and stool weight	Colonic transit time was significantly and consistently decreased by misoprostol compared to placebo [66 $\pm$ 10.2 *vs* 109.4 $\pm$ 8.1 h ($p = 0.0005$)] Misoprostol significantly increased the total stool weight per week [976.5 $\pm$ 288.8 *vs* 434.6 $\pm$ 190.5 g ($p = 0.001$)] Misoprostol significantly increased the number of stools per week compared to placebo [6.5 $\pm$ 1.3 *vs* 2.5 $\pm$ 0.11 ($p = 0.01$)]	No differences in the incidences of abdominal pain

Table 15. Summary of the Studies Evaluating the Efficacy and Safety of Stool Softeners in the Treatment of Constipation

			Patient				Outcomes			
References	Score	Intervention	Study Design	N	Mean Age	F/M	Duration	Outcome Measure	Results	Safety Analysis
65	3	Dioctyl sodium sulfosuccinate (Colase) (DSS) 100 mg qd or 100 mg b.i.d. or dioctyl calcium sulfosuccinate (Surfak) DCS, 240 mg qd	Randomized, single-blind, controlled	46 of 47	82.1	40/6	2-wk run-in (placebo) followed by 3-wk treatment phase	SF, SC, disimpaction, adverse effects	SF—81% of the patients receiving DCS improved 1.75–2.83 BM/wk, ($p <$ 0.02). DSS caused no significant improvement over placebo in either the qd or b.i.d. dosing (1.5–1.95 BM/wk and 1.76–2.29 BM/wk, respectively) The mean number of natural bowel movements (without other laxatives or disimpaction) among the DCS group increased approximately 62% over the placebo period, more than twice the 30% increase seen with DSS administered either bid or qd	No significant adverse effects or changes in laboratory measurements were reported in any of the groups
45	5	Psyllium 5.1 g b.i.d. and docusate 100 mg b.i.d.	Multicenter, randomized, double-blind, parallel design	170 of 187	37.2	156/14	1-wk washout followed by 1-wk baseline (placebo) followed by 2-wk treatment	Stool water content, stool weight, total stool output, SF	Compared to baseline, psyllium increased SWC *vs* docusate (psyllium 2.33% *vs* docusate 0.01%, $p = 0.007$and) Psyllium also increased SWW (84.0 g/BM) *vs* docusate (71.4 g/BM); $p = 0.04$	None stated

									Total stool output higher with psyllium (359.9 g/wk) *vs* docusate (271.9 g/wk); $p = 0.005$) Psyllium had a higher O'Brien rank-type score combining objective measures of constipation (psyllium 475.1; docusate 403.9; $p = 0.002$)	
67	4	Dioctyl sodium sulfosuccinate (DSS) 100 mg t.i.d. or placebo	Randomized, double-blind, placebo-controlled, crossover	34 of 40 elderly	Geriatric—not otherwise specified	Not specified	Two consecutive 4-wk treatment periods	SF, overall improvement in constipation	DSS increased SF by a mean of 1 BM/wk compared with placebo ($p < 0.01$) The difference in the overall improvement in constipation was statistically significant ($p < 0.05$)	None stated
66	4	Dioctyl calcium sulfosuccinate (DCS) 240 mg b.i.d. or placebo	Randomized, double-blind, placebo-controlled, crossover	15 of 22	78 yr	4/11	2-wk run-in, two 3-wk treatment separated by a 2-wk washout	SF, SC, UOL	No significant differences in the stool frequency, volume, and need for additional laxatives between the docusate and placebo groups Patient perception of constipation and discomfort with defecation was also not significantly different between the groups	None stated

Table 16. Methodologic Scores of the Studies Evaluating Stool Softeners

Reference	Randomization	Blinding	Statement on Withdrawals	Total Score
65	1	1	1	3
45	2	2	1	5
67*	1	2	1	4
66	1	2	1	4

*Because this study is double-blind and placebo controlled, the total score here is high based of the criteria set out; the study description reveals very little information, and as such the overall quality is not as good as the score suggests.A score of 1 or 2 was given for randomization (2 for appropriate randomization technique and concealed allocation explicitly stated or described, 1 for study simply described as "randomized"). Scores of 0–2 were given for blinding (2 when both subjects and investigators were blinded to the treatment by use of identical placebo or other technique, 1 when the study is described as "double-blind," and 0 when the study was not double-blind). Score o f 0 or 1 was given for frequency of withdrawals (1 when the number of withdrawals and reason for withdrawals were stated, and 0 when no statement was made pertaining to withdrawals).

trials of DSS *versus* placebo (66, 67) with quality scores of 4, 4; one trial of DSS *versus* psyllium (45) with a quality score of 5. Evidence poor, Grade C recommendation. Psyllium superior.

Stimulant Laxatives

(i) Senna (Sennokot, Perdiem overnight therapy)—one trial *versus* sodium picosulfate (not available in the United States) (29) with a quality score of 2; one trial *versus* bran (40) with a quality score of 2. Evidence poor, Grade C recommendation.

(ii) Bisacodyl (Gentlax)—one trial *versus* bisoxatin (not Available in the United States) (32) with a quality score of 2. Evidence poor, Grade C recommendation.

(iii) "Irritant"—one trial *versus* lactulose (31) with a quality score of 2. Lactulose better.

Others

Tegaserod (Zelnorm) one very large trial with a quality score of 5. Evidence good. Category A recommendation.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

(i) Constipation is a common problem for which a wide range of medicines are used.

(ii) Many of the current recommendations for clinical practice are based on evidence from trials.

(iii) Although metaanalysis of drug treatment of constipation has been reported, there has been no systematic review of the quality or number of clinical trials or an in-depth evaluation of the safety and efficacy of these agents.

(iv) This review could serve to enlighten practitioners about the evidence pertaining to various agents that are traditionally used to treat constipation, and thus serve as a guide for selecting appropriate agents.

(v) In addition, this review highlights the fact that there is minimal or weak evidence to support the use of many commonly used drugs for the treatment of constipation.

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Reprint requests and correspondence: Satish S.C. Rao, M.D., Ph.D., Neurogastroenterology, University of Iowa Carver College of Medicine, Iowa City, IA 52242.

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