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# Efficacy and Safety of Over-the-Counter Therapies for Chronic Constipation: An Updated Systematic Review

Satish S.C. Rao, MD, PhD[1] and Darren M. Brenner, MD[2]

INTRODUCTION: **Constipation is commonly treated with over-the-counter (OTC) products whose efficacy and safety remain unclear. We performed a systematic review of OTC therapies for chronic constipation and provide evidence-based recommendations.**

METHODS: **We searched PubMed and Embase for randomized controlled trials of ≥4-week duration that evaluated OTC preparations between 2004 and 2020. Studies were scored using the US Preventive Services Task Force criteria (0–5 scale) including randomization, blinding, and withdrawals. The strengths of evidence were adjudicated within each therapeutic category, and recommendations were graded (A, B, C, D, and I) based on the level of evidence (level I, good; II, fair; or III, poor).**

RESULTS: **Of 1,297 studies identified, 41 met the inclusion criteria. There was good evidence (grade A recommendation) for the use of the osmotic laxative polyethylene glycol (PEG) and the stimulant senna; moderate evidence (grade B) for psyllium, SupraFiber, magnesium salts, stimulants (bisacodyl and sodium picosulfate), fruit-based laxatives (kiwi, mango, prunes, and ficus), and yogurt with galacto-oligosaccharide/prunes/linseed oil; and insufficient evidence (grade I) for polydextrose, inulin, and fructo-oligosaccharide. Diarrhea, nausea, bloating, and abdominal pain were common adverse events, but no serious adverse events were reported.**

DISCUSSION: **The spectrum of OTC products has increased and quality of evidence has improved, but methodological issues including variability in study design, primary outcome measures, trial duration, and small sample sizes remain. We found good evidence to recommend polyethylene glycol or senna as first-line laxatives and moderate evidence supporting fiber supplements, fruits, stimulant laxatives, and magnesium-based products. For others, further validation with more rigorously designed studies is warranted.**

**SUPPLEMENTARY MATERIAL** accompanies this paper at http://links.lww.com/AJG/B929

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## INTRODUCTION

Constipation is a common condition with individual studies reporting prevalence rates ranging from 2% to 39% (1–5). This wide variability seems to be related to both differences in populations studied and the criteria used to define constipation (6–8). One systematic review found that when ROME criteria were applied, prevalence ranged from 6.8% (ROME III) to 15.0% (ROME II), whereas rates of self-reported constipation were generally higher (3). Constipation is more common in women than in men, and its incidence increases with advancing age (2). Constipation has significant clinical, economic, and quality of life (QoL) impacts (4,9) and correlates with significantly higher rates of psychological distress (10). The QoL impact is similar to that of numerous other chronic conditions, including sciatica, dermatitis, and chronic allergies (9).

Approximately 40% of patients with constipation in the United States self-treat with laxatives (11), and in 2019, more than $1.5 billion dollars were spent on over-the-counter (OTC) agents (12). A claims-based analysis estimated the cost of gastrointestinal (GI) symptom management in patients with chronic constipation to be $1,500 per patient per year, inflation adjusted to 2020 dollars (5,13). There are many OTC preparations available to manage constipation, each with a different mechanism(s) of action. However, there is considerable variability in both the quality and quantity of evidence supporting their use. One of the authors (S.R.) previously reviewed the efficacy and safety data for OTC therapies in the management of adult patients with chronic constipation (date range 1966–2004), identifying that many of the treatment options lacked robust supporting evidence (14). Since then, numerous additional products have become available, and new trials have been conducted.

Our objective here was to perform an updated evidence-based systematic review of OTC treatment options for chronic

[1]Division of Gastroenterology/Hepatology, Medical College of Georgia, Augusta University, Augusta, Georgia, USA; [2]Division of Gastroenterology Northwestern University—Feinberg School of Medicine, Chicago, Illinois, USA. **Correspondence:** Darren M. Brenner, MD. E-mail: Darren-brenner@northwestern.edu.
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constipation. We systematically reviewed new data published over the past 15 years and aimed to update the classification of products and provide new treatment recommendations based on levels and strength of evidence.

## METHODS

### Literature search

PubMed and Embase were searched from 2004 through July 2020 using the following search terms: (constipation OR opioid-induced constipation) AND (laxatives, stimulant OR laxatives, osmotic OR laxatives, irritant OR laxatives, bulk OR fecal softeners OR stool softener OR sorbitol OR magnesium OR milk of magnesia OR magnesium sulfate OR magnesium sulphate OR bisacodyl OR calcium polycarbophil OR polyethylene glycol OR PEG OR senna OR ispaghula OR bran OR celandin OR docusate OR aloevera OR aloe vera OR poloxalkol OR mineral oil OR glycerin OR glycerine OR psyllium OR methylcellulose OR herbal remedies OR traditional medicine OR Chinese herbal OR plantain OR doxinate OR prune OR kiwi OR fiber OR iberogast OR STW 5 OR sodium picosulfate OR macrogol OR sennosides OR inulin). Limits on the search were English language, randomized clinical trial, adults, and human.

### Selection criteria

Abstracts of articles were screened, potentially relevant studies published in full were reviewed, and the following selection criteria were applied for inclusion: (i) randomized controlled trial (placebo or active comparator), (ii) parallel or cross over design, (iii) established definition of constipation (preferably ROME criteria), (iv) minimum duration of 4 weeks of active treatment, and (v) well-defined clinical endpoints. Studies evaluating colonic cleansing before colonoscopy or surgery, acute constipation indications (typically 1–2 days or weeks in duration), and patients with irritable bowel syndrome and/or evacuation disorders were excluded. Certain studies in patients with chronic comorbidities (i.e., chronic kidney disease [CKD]) were included.

### Data extraction and analysis

Articles that met inclusion criteria were independently reviewed by both authors, and relevant data were extracted. This included therapeutic and control agent(s), study design, number of patients, mean age or age range, sex, study duration, outcome measures, efficacy, and safety outcomes.

### Qualitative assessment of study methodology

Next, each study was independently scored by both authors for quality of evidence using the US Preventive Services Task Force criteria (15). Any discrepancies between authors were reconciled by mutual discussion and a second review of all relevant articles. Final scores were adjudicated by consensus. Individual study quality was determined using a 0- to 5-point scale summating individual scores for randomization, blinding, and completeness of follow-up:

1. Randomization was scored as 1 (simply described as randomized) or 2 (appropriate randomization technique and concealed allocation explicitly described)
2. Blinding was scored as 0 (not blind), 1 (described as double blind but no details provided), or 2 (both subjects and investigators were explicitly said to be blinded, and an identical placebo was used)
3. Withdrawals were scored as 0 (no statement) or 1 (number of withdrawals and reason was stated)

### Levels of evidence classification of products and grading of recommendations

Current US Preventive Services Task Force (15) criteria were used to score the strength of evidence and grade recommendations. Once again, each investigator provided independent recommendations, and any differences were resolved by consensus. The level of evidence was graded as good (level I), fair (level II), or poor (level III). The recommendation was graded as A (good evidence in support), B (moderate evidence in support), C (poor evidence in support), D (moderate evidence against), or I (insufficient evidence). These criteria represent a slight modification of the grading criteria used in the previous systematic review (14). Detailed descriptions of the grading criteria and differences in the grading criteria between the previous review and the current review are summarized in Supplemental Table 1 (see Supplementary Digital Content 1, http://links.lww.com/AJG/B929).

After applying the selection criteria, we identified 41 studies that are included in this analysis. OTC products were grouped into the following 8 categories: osmotic laxatives, fiber laxatives, stimulant laxatives, magnesium-based laxatives, fruit-based laxative, foods with prebiotics, surfactants, and miscellaneous agents.

## RESULTS

### Studies

A total of 1,297 studies were identified from the Embase/PubMed literature searches. Of these, 110 were identified as randomized clinical trials evaluating treatments for constipation. Studies outside the selection criteria were excluded. In addition, we decided to limit the results to more readily available agents. Thus, some categories that were included in the search strategy (i.e., Chinese herbals, traditional medications, and probiotics) were not included in the results. Overall, a total of 40 studies were included in the analysis (Figure 1). In addition, a late-breaking study (16) published after our literature search was added, bringing the total number of qualifying studies to 41.

There was considerable variability in the quality of studies, the patient populations who were enrolled, and outcomes evaluated. A comparison of our current recommendations and those previously reported is summarized in Table 1. Study details and results for each product included in this review are summarized in Tables 2–7 and discussed in detail below. Studies that included products from more than one treatment category were included in both tables. Treatment categories are organized according to the quality of evidence, and those with the strongest evidence are discussed first.

### Osmotic agents

Osmotic agents draw fluid into the intestine, soften stool, and increase luminal water retention, and the ensuing luminal distention secondarily increases colonic peristalsis and causes laxation (17,18). PEG is an osmotic agent that is approved by the US Food and Drug Administration (US FDA) for the treatment of occasional constipation (19). It is poorly absorbed (<0.28%), and nearly 100% of PEG is excreted in the feces (20). No other osmotic agents meeting current inclusion criteria were identified (magnesium-based laxatives are discussed separately).

 

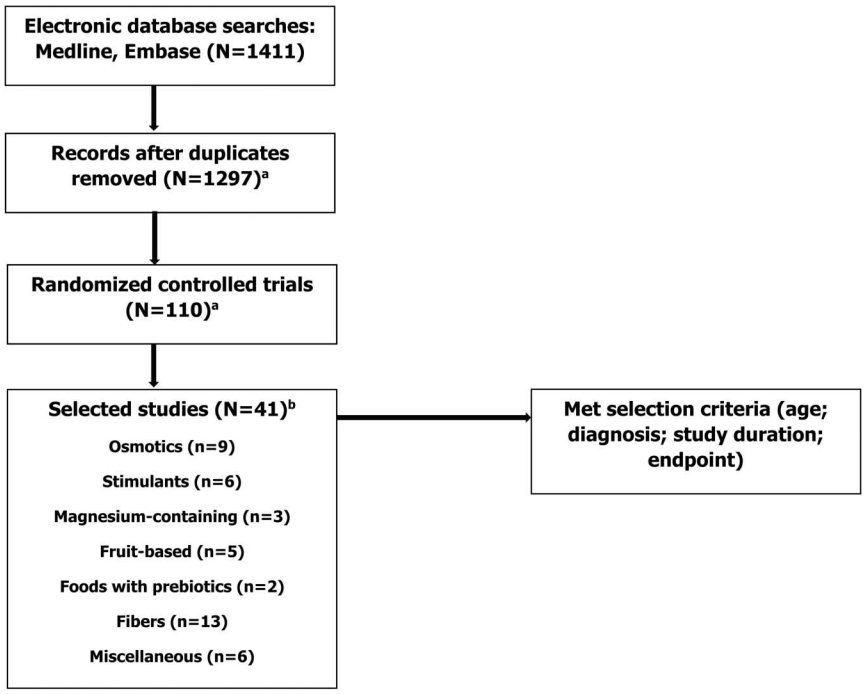


**Figure 1.** Flow diagram of study. [a]One study added after literature search. [b]Three studies were included in 2 categories.

Nine PEG studies satisfied the selection criteria in this updated analysis (Table 2), with methodological scores of 5 (n = 3), 4 (n = 1), 3 (n = 3), and 2 (n = 2). Three were placebo controlled (21–23), one compared PEG with PEG plus electrolytes (24), and 6 compared PEG with another active product. Two studies compared PEG with lactulose (25,26), whereas single studies compared PEG with tegaserod (27), prucalopride (28,29), and naloxegol (30). The 3 placebo-controlled trials were well designed, included large numbers of patients, and had appropriate clinically relevant endpoints. In these studies, PEG formulations demonstrated significantly greater responses versus placebo on primary (mainly ROME-based response criteria) and secondary endpoints following both short- (4 weeks) and long-term administration (6 months) (21–23). PEG preparations also demonstrated significantly greater efficacy across various endpoints compared with tegaserod (27), prucalopride (28,29), and lactulose (25) in patients with ROME-defined constipation. In patients with opioid-induced constipation, patient preferences for PEG were equivalent to naloxegol (30). In a comparative trial, iso-osmotic and hypo-osmotic formulations of PEG demonstrated similar efficacy and safety, indicating that the addition of electrolytes to PEG formulations may not yield significant clinical advantages in the context of constipation (24).

Consistent with their lack of significant systemic absorption and low rates of metabolism, PEG formulations were well tolerated with low incidences of adverse events. Most events were GI and mild to moderate in intensity and included abdominal distension, diarrhea, loose stools, flatulence, and nausea (21,22,24).

Overall, the data support PEG as an effective treatment with minimal side effects. Response rates were superior to psyllium and prescription agents and similar to naloxegol for the treatment of chronic and opioid-induced constipation, respectively. These data confirm and support PEG as a first-line agent for the treatment of chronic constipation.

**PEG: Level I Evidence, Grade A Recommendation**

### Stimulant agents

Stimulant laxatives can be subdivided into 2 categories: diphenylmethane derivatives (e.g., bisacodyl and sodium picosulfate) and plant-based anthraquinones (e.g., senna, aloe, and cascara). All act locally at the nerve plexus of smooth muscle in the intestine to stimulate colonic motility.

Four trials using diphenylmethane derivatives (Table 3) were identified in the current analysis. Two (1 bisacodyl, 1 sodium picosulfate) were placebo controlled. Both were large, rigorously designed studies (methodological scores = 5), and active treatment with both agents was associated with significant increases in mean complete spontaneous bowel movements (CSBMs)/week (the primary endpoint in both trials) compared with placebo (31,32). In a comparative trial, bisacodyl and sodium picosulfate demonstrated similar efficacy (i.e., number of bowel movements [BMs]/stool consistency) and safety (33). Bisacodyl proved inferior to the cholinesterase inhibitor pyridostigmine in the final study based on BM frequency and a visual analog scale assessing pain on a 0- to 10-point scale (34).

Two studies also evaluated the anthraquinone senna (methodological score = 5; Table 3). In the first, senna was superior to placebo and had similar efficacy to a Chinese herbal preparation used for constipation (MaZiRenWan) as assessed by complete response rates (i.e., increase of ≥1 CSBM/week) (35). Senna was also superior to placebo for secondary endpoints, including frequency of CSBMs and spontaneous BM (SBMs), severity of constipation, and sensation of straining. In a recently published study from Asia, senna (at a starting dose of 1 g/d, which could subsequently be reduced) was superior to placebo in improving

**Table 1. Comparative, evidence-based recommendations for OTC products in the management of constipation from 1996 to 2004 (14) and 2004–2020 (current review)**

| | Ramkumar/Rao 1966–2004 (14) | | Current review 2004–2020 | |
|---|---|---|---|---|
| OTC products for constipation | Level of evidence | Recommendation grade | Level of evidence | Recommendation grade |
| Osmotic laxatives | | | | |
| PEG | I | A | I | A |
| Stimulants | | | | |
| Senna | III | C | I | A |
| Bisacodyl | III | C | I | B |
| Sodium picosulfate | III | C | I | B |
| Magnesium | | | | |
| Magnesium hydroxide | III | C | NA | NA |
| Magnesium-rich water | NA | NA | I | B |
| Magnesium oxide | NA | NA | I | B |
| Fruit-based laxatives and foods with prebiotics | | | | |
| Kiwi | NA | NA | I | B |
| Mango | NA | NA | II | B |
| Ficus | NA | NA | II | B |
| Prunes | NA | NA | II | B |
| Rye bread with yogurt | NA | NA | III | C |
| Yogurt with galacto-oligosaccharide + prunes + linseed oil | NA | NA | II | B |
| Fiber-containing products | | | | |
| Soluble fiber | | | | |
| Psyllium | II | B | II | B |
| Polydextrose | NA | NA | I | Insufficient |
| Inulin | NA | NA | I | Insufficient |
| Insoluble fiber | | | | |
| Bran, methylcellulose | III | C | NA | NA |
| Mixed fiber | | | | |
| SupraFiber | NA | NA | II | B |
| Miscellaneous[a] | | | | |
| Polydextrose | NA | NA | II | B |
| Flaxseed oil | NA | NA | II | C |
| Fructo-oligosaccharide | NA | NA | III | Insufficient |
| Surfactants | | | | |
| Docusate | III | C | NA | NA |

NA, not assessed; OTC, over-the-counter; PEG, polyethylene glycol.
[a]Assessed in patients with chronic kidney disease.

overall symptoms (primary endpoint), stool frequency, and QoL; however, the doses of senna consumed were significantly greater than those used in clinical practice in the United States (16).

Most adverse events were GI in nature owing to the irritant properties of stimulants. Increased rates of diarrhea (32%–53% vs 2%–5%) and abdominal pain (6%–25% vs 2%–3%) in comparison to placebo may limit the tolerability of bisacodyl (31) and sodium picosulfate (32). Senna was well tolerated in 1 study (35), but in the more recent study, 83.3% of subjects requested dose reduction of senna because of abdominal pain and diarrhea but completed the 4-week trial (16).

Overall, these data indicate that senna, bisacodyl, and sodium picosulfate are effective for the treatment of chronic constipation, although they are associated with increased potential for dose reduction or intolerance.

 

**Table 2. Osmotic laxatives in the treatment of constipation**

| Reference | Methodologic score[a] | Intervention | Study design | Patients N | Patients Mean age, yrs | Patients F/M | Patients Diagnosis | Duration | Outcomes Outcome parameters | Outcomes Main efficacy results | Outcomes Safety |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PEG | | | | | | | | | | | |
| PEG vs placebo | | | | | | | | | | | |
| DiPalma et al. (21) | 5 (2,2,1) | PEG 3350 17 g vs PBO QD (2:1) | r, db, mc, pc, pg | 304 | 53–54 | 258/46 | Constipation—modified ROME criteria | 6 mo | Response[b] (primary); % of pts with ≥50% of treatment wks scored as "successful" on modified ROME; % of wks meeting ROME; super efficacy; individual ROME symptoms | PEG associated with significantly higher response vs PBO: 52% vs 11%, $P < 0.001$ (primary endpoint); PEG > PBO for 11 of 12 primary and secondary endpoints ($P < 0.001$) | No safety differences except for GI complaints: PEG 40%, PBO 25%, $P = 0.015$ |
| DiPalma et al. (22) | 5 (2,2,1) | PEG 3350 17 g vs PBO QD (1:1) | r, db, mc, pc, pg | 100 | 58 | 74/26 | Constipation—ROME II | 4 wks | Treatment success[c] (primary), no. of BMs, CBMs, satisfactory BMs | Treatment success significantly higher with PEG vs PBO: 78% vs 39% ($P < 0.001$); PEG > PBO at 4 wks for BMs (8.1 vs 5.4; $P = 0.001$), CBMs (6.2 vs 3.7; $P = 0.005$), satisfactory BMs (5.9 vs 3.6; $P = 0.008$) | No statistically significant differences in AEs, including GI complaints (32% vs 20%; $P = 0.254$) |
| Zangaglia et al. (23) | 4 (1,2,1) | PEG 4000 + E 7.3 g vs PBO BID (1:1) | r, db, mc, pg | 57 | 71 | 23/34 | Constipation—ROME II and Parkinson disease | 8 wks | Response[d] SF, SC, straining | Response greater for PEG 4000 + E at wk 4 (78% vs 25%; $P = 0.0003$) and wk 8 (80% vs 30%; $P = 0.0012$). SF increased significantly more than PBO at wk 4 (5.7 vs 3.4) and wk 8 (6.6 vs 3.7; $P < 0.002$ for both) | Higher rate of withdrawals with PEG 4000 + E vs PBO (31% vs 18%) |
| PEG vs tegaserod | | | | | | | | | | | |
| DiPalma et al. (27) | 3 (2,0,1) | PEG 3350 17 g QD vs tegaserod 6 mg BID (1:1) | r, ol, mc, pg | 239 | 46 | 213/24 | Constipation—modified ROME criteria | 4 wks | Response[b] (primary); no. of wks meeting primary definition; no. of wks meeting ROME definition; no. of wks with complete response[e]; individual ROME symptoms; BM frequency, satisfactory BMs, CSBMs | PEG associated with significantly higher response vs tegaserod: 50% vs 31%, $P = 0.003$ (primary endpoint); PEG > tegaserod for many secondary endpoints including meeting: Primary definition ($P = 0.003$), ROME definition ($P = 0.006$), complete response ($P = 0.028$) | No differences in AEs except for more headache in tegaserod group (6% vs 0%) |

**Table 2.** (*continued*)

| Reference | Methodologic score[a] | Intervention | Study design | Patients N | Mean age, yrs | F/M | Diagnosis | Duration | Outcomes: Outcome parameters | Main efficacy results | Safety |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PEG vs PEG + E | | | | | | | | | | | |
| Seinela et al. (24) | 3 (1,1,1) | PEG 4000 12 g vs PEG 4000 + E 12 g QD, BID, or QOD (1:1) | r, db, mc, pg | 62 | 85–86 | 41/21 | Constipation, elderly, institutionalized | 4 wks | SF (primary), SC, straining | Mean weekly SF similar between PEG 4000 and PEG 4000 + E at wk 2 (9.5 vs 8.7) and wk 4 (8.5 vs 8.4 [primary endpoint]); % of patients with soft/normal SC was not significantly different at wk 2 (59% vs 38%) and wk 4 (70% vs 52%); No difference in straining | Overall rate of AE low and not significantly different; most common events in PEG 4000 and PEG 4000 + E: flatulence (24% vs 40%), abdominal pain (21% vs 17%), bloating (14% vs 10%), and nausea (3% vs 10%) |
| PEG vs prucalopride | | | | | | | | | | | |
| Cinca et al. (28,29) | 5 (2,2,1) | PEG 3350 + E 13 g BID vs prucalopride 1–2 mg QD (1:1) | r, db, pg | 240 | 40–41 | 240/0 | CC—ROME III criteria | 4 wks | ≥3 CSBMs in last treatment wk (primary), mean weekly CSBMs, CTT | ≥3 CSBMs in last treatment wk higher for PEG 3350 + E than for prucalopride (66.7% vs 56.5%; rate difference 10.1% with 97.5% lower CI limit, −2.7% above preset margin of −20%); Mean weekly CSBMs significantly higher with PEG 3350 + E during each wk (13.1 vs 9.0; $P < 0.001$) | Most frequent AEs occurred less often with PEG 3350 + E: headache (37% vs 55%); dysmenorrhea (13% vs 16%); nausea (6% vs 13%); pharyngitis (6% vs 11%) |
| PEG vs naloxegol | | | | | | | | | | | |
| Brenner et al. (30) | 2 (1,0,1) | PEG 3350 17 g QD vs naloxegol 25 mg QD (1:1) | r, mc, co, ol | 270 | 56 | 176/94 | OIC—ROME-IV | 6 wks | Secondary endpoints: Change in BFI and PGIC | Similar change from baseline in BFI and PGIC for both treatment groups | PEG vs naloxegol: GI AEs 10.8% vs 16.2%; nervous system AEs 0% vs 4.4% |

**Table 2. (*continued*)**

| Reference | Methodologic score[a] | Intervention | Study design | Patients | | | | Duration | Outcomes | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | N | Mean age, yrs | F/M | Diagnosis | | Outcome parameters | Main efficacy results | Safety |
| PEG vs lactulose | | | | | | | | | | | |
| Chassagne et al. (25) | 3 (2,0,1) | PEG 4000 10 g QD to TID vs lactulose 10 g QD to TID (1:1) | r, mc, sb, pg | 245 | 82 | 186/59 | CC—ROME I | 6 mo | SF, SC, fecaloma, fecal incontinence, sensation of rectal emptying, difficulty passing stool, and meteorism rescue medication | SF significantly higher with PEG 400 vs lactulose from month 2 onward (7.0–7.3/wk vs 5.5–6.2/wk); PEG associated with significantly improved SC ($P < 0.05$) and less rescue treatment ($P = 0.004$); Other endpoints generally similar between treatments | No difference in overall pattern of AEs between groups; PEG 4,000 vs lactulose: Total AEs 57% vs 50%; diarrhea 9% vs 9%; abdominal pain 8% vs 4% |
| Piche and Dapoigny (26) | 3 (2, 0, 1) | PEG 3350 13.125 g vs lactulose 3.5 g + paraffin 4.29 g QD (1:1) | r, mc, sb, pg | 363 | 53 | 263/100 | CC—ROME III | 4 wks | PAC-SYM (primary); PAC-QOL SBMs, SC | PAC-SYM significantly decreased from baseline in both groups (2.1–0.9 for both) with noninferiority between groups. Similar improvements in SBMs, SC, and PAC-QOL | AEs were similar in PEG (14.2%) and lactulose/paraffin group (11.2%); primarily mild-to-moderate GI AEs |

AE, adverse event; BFI, Bowel Function Index; BID, twice daily; BM, bowel movement; CBM, complete bowel movement; CC, chronic constipation; CI, confidence interval; co, cross-over; CSBM, complete spontaneous bowel movement; CTT, colonic transit time; db, double blind; E, electrolytes; GI, gastrointestinal; F/M, female/male; mc, multicenter; OIC, opioid-induced constipation; ol, open label; PBO, placebo; pc, placebo controlled; PAC-QOL, Patient Assessment of Constipation-Quality of Life; PAC-SYM, Patient Assessment of Constipation Symptom; PEG, polyethylene glycol; pg, parallel group; PGIC, Patient Global Impression of Change; pts, patients; QD, once daily; QOD, every other day; r, randomized; sb, single blind; SBM, spontaneous bowel movement; SC, stool consistency; SF, stool frequency; TID = 3 times daily.

[a]Total methodologic score with individual scores for randomization, blinding, and statement on withdrawals shown in parentheses.

[b]Weekly treatment success (response), defined as meeting all 3 elements: (i) no rescue laxative; (ii) satisfactory stool ≥3 time/wk; (iii) ≤1 of remaining ROME-based symptom criteria (straining in >25% of defecations; lumpy/hard stool in >25% of defecations; sensation of incomplete evacuations in >25% of defecations).

[c]Success defined as ≤1 of ROME-based symptom criteria (straining in >25% of defecations; lumpy/hard stool in >25% of defecations; sensation of incomplete evacuations in >25% of defecations; sensation of anorectal obstruction/pageage in >25% of defecations; <3 bowel movements per wk).

[d]Response defined as complete relief or a marked improvement of the predominant symptom and ≥1 associated symptom or sign (e.g., SF, SC, straining, rescue therapy).

[e]No ROME symptom criteria met.

**Senna: Level I Evidence, Grade A Recommendation**
**Bisacodyl: Level I Evidence, Grade B Recommendation**
**Sodium Picosulfate: Level I Evidence, Grade B Recommendation**

### Magnesium-containing agents

Magnesium-based compounds are laxatives that act by retaining water in the intestinal lumen, resulting in bulking and softening of stool (36). Magnesium salts have historically been classified as osmotic, saline, or mixed osmotic-saline laxatives with categorization dependent on the magnesium compound used. Although magnesium citrate is a stronger formulation with more characteristically osmotic properties, other agents including magnesium hydroxide, magnesium gluconate, and magnesium oxide or magnesium enriched water act as more gentle saline laxatives. Given the breadth of new studies evaluating different magnesium-based formulations, these results have been categorized and addressed separately from the other osmotic agents. This review identified 4 new relevant studies using magnesium-based regimens, 3 evaluating magnesium-rich water vs placebo (Table 4) with methodological scores of 5 (n = 2) and 4 (n = 1) and one evaluating magnesium oxide versus placebo or senna (16). The amount of elemental magnesium consumed in the 3 magnesium water studies varied from 105 mg/d (1,000 mL/d of water containing 105 mg/L Mg) (37), 60 or 119 mg/d (500 or 1,000 mL/d of water containing 119 mg/L Mg) (38) to 500 mg/d (500 mL/d of water containing 1,000 mg/L of Mg) (39). None of the trials demonstrated a statistically significant difference versus placebo for their primary endpoints (based on stool frequency per week or ROME II–based response), although various secondary endpoints, including stool frequency at alternative time points and stool consistency, were significantly improved (37–39). Magnesium-containing mineral water preparations were well tolerated with low rates of adverse events (diarrhea and abdominal distention). In the magnesium oxide study, subjects were administered a total of 1.5 g in 3 divided doses and reported significant overall improvements in constipation, SBMs, CSBMs, and QoL when compared with placebo but no differences compared with senna (16). Although not explicitly stated, abdominal pain and diarrhea were adverse events, necessitating a dose reduction in 53.3% of subjects. None of the studies reported hypermagnesemia as a potential adverse event.

**Magnesium-containing Agents: Level I Evidence, Grade B Recommendation**

### Fruit-based laxatives

Fruits contain varying proportions of soluble and insoluble dietary fiber (including nonfermentable, slowly fermentable, and rapidly fermentable fibers), sugars (e.g., fructose and sucrose), and sorbitol (40). Fruit-based laxatives increase intestinal water retention and colonic volume, resulting in increased stool frequency and softer stools (41). In this updated review, 5 studies were identified (Table 5). These trials evaluated preparations of kiwi (n = 2), mango (n = 1), ficus (n = 1), and prune (n = 1). The methodological scores of these studies were 5 (n = 3), 3 (n = 1), and 2 (n = 1).

In a small study (N = 9), a kiwi fruit–based supplement had no significant effect on stool frequency or stool consistency versus placebo (42), although a second larger study (N = 87) found that a kiwi-derived powder was associated with significant improvements in the frequency of CSBMs, SBMs, and stool consistency compared with placebo-treated patients (43). Prunes were associated with significantly greater improvements in mean CSBMs per week (primary outcome) and stool consistency compared with psyllium in 40 patients with chronic constipation (44). A mango-based supplement was associated with significantly improved evacuation categorization (based on stool consistency and shape) compared with psyllium in a pilot study in 36 patients with chronic constipation (45). A *ficus carica* paste significantly improved colonic transit time (primary endpoint), stool consistency, and abdominal discomfort but had no effect on stool frequency, defecation time, abdominal pain, effort for evacuation, and sensation of incomplete evacuation (46).

Fruit-based laxatives were very well tolerated with few (mild GI-related events) or no adverse events reported. Based on the small numbers of patients enrolled in these trials, the data suggest that fruit-based laxatives are a well-tolerated and promising option for the treatment of constipation. Additional well-designed trials are required to confirm their efficacy.

**Kiwi-based Laxatives: Level I Evidence, Grade B Recommendation**
**Mango-based Laxatives: Level II Evidence, Grade B Recommendation**
**Ficus-based Laxatives: Level II Evidence, Grade B Recommendation**
**Prune-based Laxatives: Level II Evidence, Grade B Recommendation**

### Foods with prebiotics

Prebiotics are nondigestible fibers (oligosaccharides such as oligofructose, galacto-oligosaccharides, inulin, and lactulose) that are fermented by and support the growth of beneficial intestinal bacteria (e.g., bifidobacteria and lactobacillus) (47). It is hypothesized that intestinal microbiota increase colonic peristalsis via a number of potential mechanisms and that prebiotics augment this process by supporting a healthy microbiome (48).

Two studies are included in the current analysis. One study (methodologic score = 5) found that a yogurt containing galacto-oligosaccharides, prunes, and linseed oil was associated with significantly greater stool frequency, easier defecation, and softer stools compared with a control yogurt in elderly patients with mild constipation (Table 5) (49). Another study (methodological score = 2) evaluated rye bread, with or without *Lactobacillus* GG–containing yogurt versus yogurt alone and control (low-fiber toast) in patients with self-reported constipation (50). The rye bread–containing groups experienced shortened intestinal transit time, increased stool frequency, softened stool, and easier defecation compared with low-fiber toast but were associated with increased GI side effects (flatulence and bloating) (50).

**Yogurt with Galacto-Oligosaccharides + Prune + Linseed Oil: Level II Evidence, Grade B Recommendation**
**Rye Bread with Yogurt: Level III Evidence, Grade C Recommendation**

### Fiber-containing agents

Fiber laxatives work by increasing the weight and water-absorbent properties of stool, thereby increasing stool bulk and

 

**Table 3. Stimulant laxatives in the treatment of constipation**

| Reference | Methodologic score[a] | Intervention | Study design | Patients | | | | Duration | Outcomes | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | N | Mean age, yrs | F/M | Diagnosis | | Outcome parameters | Main efficacy results | Safety |
| Stimulant laxatives | | | | | | | | | | | |
| Bisacodyl vs placebo | | | | | | | | | | | |
| Kamm et al. (31) | 5 (2,2,1) | Bisacodyl 10 mg vs PBO QD (2:1) | r, db, mc, pc, pg | 368 | 55 | 275/93 | CC, Rome III | 4 wks | CSBMs (primary), SBMs, constipation-related symptoms | Mean no. of CSBMs/wk were significantly higher with bisacodyl vs PBO (5.2 vs 1.9; $P <$ 0.0001); SBMs significantly greater with bisacodyl vs PBO (10.0 vs 5.1; $P <$ 0.0001). | Diarrhea (53% vs 2%) and abdominal pain (25% vs 3%) more common with bisacodyl |
| Bisacodyl vs Na picosulfate | | | | | | | | | | | |
| Kienzle-Horn et al. (33) | 2 (1,0,1) | Bisacodyl 5–10 mg QD vs Na picosulfate 5–10 mg QD (1:1) | r, ol, mc, pg | 144 | 62–64 | 104/40 | CC (<3 BMs/wk × 6 mo) | 4 wks | SF, SC (co-primary) | No significant difference between bisacodyl and Na picosulfate for SF per day (1.06 vs 1.11) and SC score (2.43 vs 2.51 at 28 d); Both treatments produced significant improvements in SF and SC vs baseline | No significant difference in no. or severity of AEs; Most common AE in bisacodyl and Na picosulfate groups: Flatulence (7% vs 10%), headache (9% vs 7%), abdominal pain (7% vs 7%) |
| Na picosulfate vs placebo | | | | | | | | | | | |
| Mueller-Lissner et al. (32) | 5 (2,2,1) | Na picosulfate 10 mg QD vs PBO QD (2:1) | r, db, mc, pg | 367 | 50–52 | 285/82 | CC, Rome III | 4 wks | CSBMs (primary), SBMs, constipation-related symptoms | Mean no. of CSBMs per wk significantly higher with Na picosulfate vs PBO (3.4 vs 1.7; $P <$ 0.001). Change in CSBMs, per wk (66% vs 32%); % with ≥3 CSBMs per wk (51% vs | Diarrhea (32% vs 5%) and abdominal pain (6% vs 2%) greater with Na picosulfate vs PBO |

**Table 3.** (*continued*)

| Reference | Methodologic score[a] | Intervention | Study design | Patients | | | | Duration | Outcomes | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | N | Mean age, yrs | F/M | Diagnosis | | Outcome parameters | Main efficacy results | Safety |
| | | | | | | | | | | 18%), and % with ≥1 CSBMs/day (10% vs 0%) all significantly greater with Na picosulfate ($P < 0.001$ for all) | |
| Bisacodyl vs pyridostigmine | | | | | | | | | | | |
| Soufi-Afshar et al. (34) | 3 (1,1,1) | Bisacodyl 5 mg TID vs pyridostigmine 60 mg TID (1:1) | r, db | 68 | 50 | 40/28 | CC—Rome III | 4 wks | BMs, VAS | Significantly greater increase in BMs/wk with pyridostigmine vs bisacodyl (4.3 vs 3.0; $P = 0.005$); Significantly greater decrease in VAS scores ($P = 0.002$), Bristol score ($P = 0.005$), time to defecation ($P = 0.002$) with pyridostigmine | Not reported |
| Herbal stimulant laxatives | | | | | | | | | | | |
| Senna vs MaZiRenWan vs placebo | | | | | | | | | | | |
| Zhong et al. (35) | 5 (2,2,1) | Senna 15 mg QD vs MaZiRenWan 7.5 g BID vs PBO (1:1:1) | r, db, mc, pc | 291 | 45 | 263/28 | FC—ROME III | 8 wks + 8 wks follow-up | Complete response (increase of ≥1 CSBMs/wk [primary]); colonic transit; symptoms; QoL (SF-36) | Senna and MaZiRenWan both associated with significantly greater complete response vs PBO (58%, 68%, 33%; $P <$ 0.005 for both); Senna significantly superior to PBO for severity of constipation, straining, and bloating | All treatments well tolerated with no serious AEs; no significant differences between groups for renal and liver function |

**Table 3.** (*continued*)

| Reference | Methodologic score[a] | Intervention | Study design | Patients | | | | Duration | Outcomes | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | N | Mean age, yrs | F/M | Diagnosis | | Outcome parameters | Main efficacy results | Safety |
| Morishita et al. (16) | 5 (2,2,1) | Senna 1 g/d vs Mg oxide 1.5 g/d vs PBO (1:1:1) | r, db, pc, pg | 90 | 42 | 84/6 | CC, ROME IV | 4 wks | Response (primary; defined as score of 1 or 2 on 5-point scale), SBM, CSBM, BSFS, and QoL | Response rates with both senna (69.2%) and Mg oxide (68.3%) were both significantly higher ($P <$ 0.0001) vs placebo (11.7%); By wk 4, increases in weekly average SBMs, CSBMs, BSFS scores, and QoL scores were significantly higher with senna and Mg oxide vs placebo | No severe symptoms were noted, although dose reductions occurred in 83.3%, 53.3%, and 50% of senna, Mg oxide, and PBO groups ($P$ = 0.02 senna vs PBO). No patients dropped out of the study |

AE, adverse event; BID, twice daily; BM, bowel movement; BSFS, Bristol Stool Form Scale; CC, chronic constipation; CSBM, complete spontaneous bowel movement; db, double blind; FC, functional constipation; F/M, female/male; mc, multicenter; ol, open label; PBO, placebo; pc, placebo controlled; pg, parallel group; QD, once daily; QoL, quality of life; r, randomized; SBM, spontaneous bowel movement; SC, stool consistency; SF, stool frequency; SF-36, Short Form-36 health survey; TID, 3 times daily; VAS, visual analog scale.
[a]Total score with individual scores for randomization, blinding, and statement on withdrawals in parentheses.

softening stool consistency. Fiber products can be classified based on solubility (soluble vs insoluble), viscosity (viscous vs nonviscous), and fermentability (fermentable vs nonfermentable) (40). Soluble fiber (e.g., psyllium, gums, and pectins) blends with water, forming a gel-like substance, whereas insoluble fiber (e.g., cellulose, lignin, and oligosaccharides) remains unchanged as it passes through the GI tract. Fermentable fibers such as gums, inulin, oligosaccharides, and wheat dextrin can be digested by gut bacteria.

***Soluble and mixed fibers.*** Psyllium (also known as ispaghula) is a soluble fiber derivative of the husk of *Plantago ovata*. We identified 9 new studies that evaluated psyllium (Table 6), with methodological scores of 5 (n = 2), 3 (n = 4), 2 (n = 2), and 1 (n = 1). The doses of psyllium varied substantially in these studies, ranging from 3.5 g/d to 11 g twice daily. Three studies included a placebo arm, and 7 studies included an active comparator (lactitol, flaxseed oil, sodium bicarbonate suppository, lactulose, prunes, mango, and mixed fiber [n = 1 each]). Whereas some studies used an active comparator, in 2 placebo-controlled studies, no differences between psyllium and placebo in global constipation symptom scores were identified, but more patients receiving psyllium had a greater than 2-point symptom improvement from baseline (5-point Likert scale) (51–53). Psyllium was also associated with improved stool consistency at various time points. In the third placebo-controlled trial, which also included lactitol and psyllium + lactitol as comparators, there were no significant differences between any of the 4 groups in terms of stool frequency (primary endpoint), stool consistency, QoL, or patient-assessed symptoms in subjects with self-reported constipation (<3 BMs/week) (54). In other comparative trials, lactulose (55), mango (45), and prunes (44) significantly outperformed psyllium in stool frequency and consistency.

Two placebo-controlled trials evaluated inulin (56,57), receiving methodological scores of 5 and 4, respectively. In the first study, inulin was associated with increased stool frequency but showed no differences in stool consistency or straining compared with placebo (56). In the second study, no differences in stool frequency or consistency were detected between the inulin and placebo cohorts. Inulin was associated with increased numbers of patients achieving >1 BM/day and fewer defecation difficulties (not defined) compared with baseline (57).

Two placebo-controlled trials (methodological scores = 5) evaluated the potential for polydextrose to improve GI transit time. In both studies, polydextrose proved no more effective than placebo (58,59). One study did identify an increase in SBM frequency (59), but this response was not corroborated by the second (58).

One study (methodological score = 5) compared mixed fiber (plum-derived soluble/insoluble fiber) with psyllium over 4 weeks. Within-group comparisons from baseline identified increased mean numbers of CSBMs per week (primary endpoint), improved stool consistency, and reduced straining but no significant differences between the groups. Mixed fiber was associated with a significantly greater improvement in flatulence compared with psyllium (60).

**Table 4. Magnesium-based laxatives in the treatment of constipation**

| Reference | Methodologic score[a] | Intervention | Study design | Patients | | | | Duration | Outcomes | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | N | Mean age, yrs | F/M | Diagnosis | | Outcome parameters | Main efficacy results | Safety |
| Mg-rich mineral water vs placebo | | | | | | | | | | | |
| Bothe et al. (39) | 4 (1,2,1) | $MgSO_4$-rich mineral water (500 mg Mg/d) vs PBO | r, db, pc, pg | 75 of 106 | 46 | 63/12 | CC, ROME III | 6 wks | CSBMs (primary), BMs, SBMs, CBMs, and SC | Trend toward more CSBMs/wk for MW vs PBO at 6 wks (2.16 vs 1.16; $P = 0.054$); SBMs/BMs/wk significantly higher with MW vs PBO at wk 6 (6.62 vs 4.47 $P = 0.01$); SC improved more for MW vs PBO ($P < 0.001$) | No difference in AEs between treatment groups |
| Dupont et al. (38) | 5 (2,2,1) | MgSO4-rich MW (low dose [60 mg Mg/d] or high dose [120 mg Mg/d]) vs control water | r, db, mc, pc | 244 | 41–44 | 244/0 | CC, ROME III | 4 wks | Response during wk 1 (primary)[b], response at wks 2, 4; SC, individual and total Rome III diagnostic criteria; abdominal pain, CGIC, PGIC, QoL, rescue medication | Response at wk 1 (33% [low-dose], 34% [high-dose], vs 25% [PBO]) not significantly different ($P = 0.099$); Response at wk 2 and 4 for MW high-dose group vs PBO (38% vs 21%; $P = 0.013$ and 39% vs 24%; $P = 0.028$); SC significantly higher in MW high-dose vs PBO | Similar rates of AEs with MW (n = 15) and PBO (n = 13) |
| Naumann et al. (37) | 5 (2,2,1) | Ca/Mg SO4-rich MW QID (105 mg Mg/d) vs PBO QID | r, db, pc | 100 | 45 | 85/15 | CC, ROME III | 6 wks | Change in SF at 6 wks (primary); SF at 3 wks; change in SF per wk; SC, GIQLI, SF-12 | Change in SF at wk 6 not significantly different with MW vs PBO (1.74 vs 1.22; $P = 0.163$); Change in SF at wk 3 significantly greater for MW vs PBO (2.02 vs 0.88; $P = 0.005$); Significantly greater SF per wk (4.8 vs 3.8; $P = 0.036$) and stool consistency (3.1 vs 2.7; $P = 0.044$) for MW vs PBO at wk 3 | 10 minor to moderate AEs reported (not specified) |

**Table 4. (*continued*)**

| Reference | Methodologic score[a] | Intervention | Study design | Patients | | | | Outcomes | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | N | Mean age, yrs | F/M | Diagnosis | Duration | Outcome parameters | Main efficacy results | Safety |
| Morishita et al. (16) | 5 (2,2,1) | Senna 1g/d vs Mg oxide 1.5g/d vs PBO (1:1:1) | r, db, pc, pg | 90 | 42 | 84/6 | CC, ROME IV | 4 wks | Response (primary; defined as score of 1 or 2 on 5-point scale), SBM, CSBM, BSFS, and QoL | Response rates with both senna (69.2%) and Mg oxide (68.3%) were both significantly higher ($P <$ 0.0001) vs placebo (11.7%); By wk 4, increases in weekly average SBMs, CSBMs, BSFS scores, and QoL scores were significantly higher with senna and Mg oxide vs placebo | No severe symptoms were noted, although dose reductions occurred in 83.3%, 53.3%, and 50% of senna, Mg oxide, and PBO groups ($P = 0.02$ senna vs PBO). No patients dropped out of the study |

AE, adverse event; BM, bowel movement; BSFS, Bristol Stool Form Scale; CBM, complete bowel movement; CC, chronic constipation; CGIC, Clinician's Global Impression of Change; CSBM, complete spontaneous bowel movement; db, double blind; F/M, female/male; GIQLI, Gastrointestinal Quality of Life Index; mc, multicenter; MW, mineral water; PBO, placebo; pc, placebo controlled; pg, parallel group; PGIC, Patient's Global Impression of Change; QID, 4 times daily; QoL, quality of life; r, randomized; SBM, spontaneous bowel movement; SC, stool consistency; SF, stool frequency; SF-12, Short Form Health Survey-12.
[a]Total score with individual scores for randomization, blinding, and statement on withdrawals in parentheses.
[b]Response defined as ≥4 stools per wk or an increase of ≥2 stools per wk vs baseline and <25% lumpy/hard stools.

Soluble fibers (psyllium, inulin, and polydextrose) seem safe and well tolerated. Abdominal distension/pain and flatulence were the most common adverse events and were mild to moderate in nature.

Overall, considering the differences in products tested, dosages used, and variability in study design, the current data suggest that both soluble fiber, psyllium, and mixed fiber (SupraFiber) have modest efficacy for treating constipation. The data are most robust for psyllium. However, it is worth noting that the highest graded placebo-controlled psyllium study (54) revealed no significant benefit over placebo and head-to-head trials revealed that psyllium is less effective than comparator agents (e.g., PEG, lactulose, and fruits).

**Psyllium: Level II Evidence, Grade B Recommendation**
**Polydextrose: Level I Evidence, Grade I (Insufficient) Recommendation**
**Inulin: Level I Evidence, Grade I (Insufficient) Recommendation**
**Mixed Fiber: Level II Evidence, Grade B Recommendation**

### Miscellaneous agents

Table 7 summarizes studies evaluating miscellaneous patient groups and therapeutic agents. Three high-quality studies evaluated constipated patients with CKD (methodological scores of 5 [n = 2] or 4 [n = 1]) (61–63). Polydextrose (61) and fructo-oligosaccharide (63) both demonstrated significant increases in stool frequency versus placebo. In another study, flaxseed oil, olive oil, and mineral oil (control) all significantly reduced the frequency of symptom scores (ROME criteria) from baseline (62).

In other studies evaluating miscellaneous synbiotics or prebiotics, a combination synbiotic of psyllium, inulin, and probiotics significantly increased stool frequency versus baseline at weeks 1 and 2 (but not weeks 3 or 4) and had no effect on stool consistency (64). A prebiotic combination of inulin, lactitol, and aloevera had no significant benefit for any outcome parameter (19).

**Polydextrose: Level II Evidence, Grade B Recommendation (patients with CKD)**
**Flaxseed Oil: Level II Evidence, Grade C Recommendation (patients with CKD)**
**Fructo-Oligosaccharide: Level III Evidence, Grade I (Insufficient) Recommendation (patients with CKD)**

### Surfactants

Docusate is an anionic surfactant that is purported to lower the surface tension at the oil–water interface of stools, allowing water and lipids to penetrate, thereby hydrating and softening stool. Although docusate is one of the most commonly used OTC agents for the treatment of constipation, inconsistent clinical data have led to questions regarding its efficacy. There have been no additional studies since 2004 that met the inclusion criteria for this new analysis. We conclude that despite docusate's frequent use in constipated patients, there is little clinical evidence to support its use.

**Surfactants: Level III Evidence, Grade I (Insufficient) Recommendation**

## DISCUSSION

We have systematically reviewed new evidence supporting the use of OTC laxatives because the previous review was published in 2005. In the previous review, PEG had level I evidence and a

**Table 5. Fruit-based laxatives and foods with prebiotics in the treatment of constipation**

| Reference | Methodologic score[a] | Intervention | Study design | Patients N | Patients Mean age, yrs | Patients F/M | Patients Diagnosis | Duration | Outcomes Outcome parameters | Outcomes Main efficacy results | Outcomes Safety |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Fruit-based laxatives | | | | | | | | | | | |
| Kiwi vs placebo | | | | | | | | | | | |
| Ansell et al. (42) | 5 (2,2,1) | Kiwi powder (Actazine-L® [600 mg/d], Actazine-H® [2,400 mg/d], Gold® [2,400 mg/d]) vs PBO | r, db, pc, co | 9 | 44 | 8/1 | Constipation—ROME III | 4 wks × 4 | SF, Bristol scale, symptoms | No significant differences between interventions for BMs, Bristol stool scale | Well tolerated with no significant AE reported |
| Udani et al. (43) | 5 (2,2,1) | Kivia powder 5.5 g QD vs PBO 5.5 g QD (1:1) | r, db, pc, pg | 87 | 38–41 | 55/32 | Occasional constipation (ROME) | 4 wks | SF (primary), SC, urgency, bloating discomfort, satisfaction, flatulence, burping | Kivia associated with significant improvements in SBMs and CSBMs at weeks 1, 2, 3, and 4; SC significantly improved with Kivia; Significant improvements for Kivia vs PBO for flatulence, burping, urgency; no difference for bloating or satisfaction | AE: Kivia (n = 7); PBO (n = 1); included flatulence, and bloating |
| Mango vs psyllium | | | | | | | | | | | |
| Venancio et al. (45) | 2 (1,0,1) | Mango 300 g/d vs psyllium 5.8 g/d (1:1) | r | 36 | 24–29 | 25/11 | CC—ROME III | 4 wks | Evacuation (primary; difference from ideal [Bristol score = 4]; Agachan score) | Mango significantly improved evacuation category vs psyllium ($P$ = 0.0269); No significant difference for Agachan score; Individual Agachan improved from baseline; Evacuation improved from baseline for mango | No AEs occurred |

**Table 5.** (*continued*)

| Reference | Methodologic score[a] | Intervention | Study design | Patients | | | | Duration | Outcomes | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | N | Mean age, yrs | F/M | Diagnosis | | Outcome parameters | Main efficacy results | Safety |
| Ficus vs placebo | | | | | | | | | | | |
| Baek et al. (46) | 5 (2,2,1) | *Ficus carica* paste 100 mg TID vs PBO TID (1:1) | r, db, pc | 80 | 24 | 71/9 | FC—ROME III | 8 wks | CTT (primary); constipation-related symptoms; SC | CTT significantly improved with *F. carica* vs PBO ($P = 0.045$); *F. carica* associated with significant effects on SC ($P = 0.024$) and abdominal discomfort ($P = 0.012$) vs PBO but not other symptoms | Safety assessments reported within normal range; no AE-related withdrawals |
| Prunes vs psyllium | | | | | | | | | | | |
| Attaluri et al. (44) | 3 (2,0,1) | Prunes 50 g BID vs psyllium 11 g BID (1:1) | r, sb, co | 40 | 38 | NR | CC—ROME III | 3 wks × 2 | CSBMs (primary), global constipation symptom score, SC, straining | Mean CSBMs/week significantly higher with prune vs psyllium (3.5 vs 2.8; $P = 0.006$); Stool consistency score higher with prune (3.2 vs 2.8; $P = 0.02$); Mean straining scores were similar between treatment groups | Palatability, satiety, postprandial fullness, and bloating were similar |

**Table 5.** (*continued*)

| Reference | Methodologic score[a] | Intervention | Study design | Patients N | Patients Mean age, yrs | Patients F/M | Patients Diagnosis | Duration | Outcomes Outcome parameters | Outcomes Main efficacy results | Outcomes Safety |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Foods with prebiotics | | | | | | | | | | | |
| Yogurt containing GOS, prunes, and linseed oil vs control yogurt | | | | | | | | | | | |
| Sairanen et al. (49) | 5 (2,2,1) | Active yogurt 130 g BID vs control yogurt 130 g BID | r, db, co | 43 | 76 | 32/11 | >60 yrs, mild constipation | 3 wks × 2 | SF, SC, symptoms, difficulty with defecation | SF significantly higher with active yogurt (8.0 vs 7.1/wk; $P = 0.011$); Defecation easier with active yogurt ($P = 0.010$); Overall GI symptoms did not differ between groups but abdominal pain significantly lower with active yogurt ($P = 0.031$); active yogurt rated more effective ($P = 0.005$) | AE not reported |
| Rye bread vs yogurt vs rye bread + yogurt vs control | | | | | | | | | | | |
| Hongisto et al. (50) | 2 (1,0,1) | Rye bread (39 g fiber/day) vs yogurt vs rye bread + yogurt vs control (low-fiber toast [4.5 g/fiber/day]; 1:1:1:1) | r, 2 × 2 | 59 | 41 | 59/0 | Self-reported constipation | 1 week baseline; 3 wks intervention; 3 wks follow-up | TITT, SF, SC, difficulty of defecation | Rye bread groups associated with higher SF ($P = 0.001$), easier defecation ($P < 0.001$), softer stool ($P < 0.001$) vs low fiber toast; Rye bread associated with significantly shorter TITT vs control ($P = 0.007$) | GI symptoms increase with rye bread (flatulence, bloating) vs low-fiber toast ($P < 0.001$); yogurt lowered GI symptoms ($P = 0.05$) |

AE, adverse event; BID, twice daily; BM, bowel movement; CC, chronic constipation; co, crossover; CSBM, complete spontaneous bowel movement; CTT, colonic transit time; db, double blind; FC, functional constipation; F/M, female/male; GI, gastrointestinal; GOS, galacto-oligosaccharides; NR, not reported; PBO, placebo; pc, placebo controlled; pg, parallel group; QD, once daily; r, randomized; sb, single blind; SBM, spontaneous bowel movement; SC, stool consistency; SF, stool frequency; TID, 3 times daily; TITT, total intestinal transit time.

[a]Total score with individual scores for randomization, blinding, and statement on withdrawals in parentheses.

**Table 6. Fiber laxatives in the treatment of constipation**

| Reference | Methodologic score[a] | Intervention | Study design | Patients | | | | Duration | Outcomes | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | N | Mean age, yrs | F/M | Diagnosis | | Outcome parameters | Main efficacy results | Safety |
| Soluble and mixed fibers | | | | | | | | | | | |
| Psyllium vs placebo | | | | | | | | | | | |
| Cheng et al. (54) | 5 (2,2,1) | Psyllium 3.5 g vs lactitol 10 g vs psyllium + lactitol vs PBO QD (1:1:1:1) | r, db, pc | 172 | 40 | 92/80 | Constipation—ROME III | 4 wks | SF (primary), SC, QoL | No significant increase in SF from baseline for any treatment; No significant difference between any of the 4 treatment groups for all endpoints | AEs reported in 5%, most commonly mild/moderate GI events |
| Soltanian et al. (51) | 3 (2,0,1) | Psyllium 10 g BID vs flaxseed oil 10 g BID vs PBO BID (1:1:1) | r, sb, pc | 77 | 56–58 | 64/13 | Constipation—ROME III and T2DM | 12 wks | Symptom score, SF, SC | Flaxseed, but not psyllium associated with improved symptom score vs baseline ($P < 0.001$); Psyllium and flaxseed associated with improved SC vs PBO | Well tolerated with no serious AEs |
| Soltanian et al. (52) | 3 (2,0,1) | Psyllium 10 g BID vs PBO BID (1:1) | r, sb, pc, pg | 51 | 56–58 | 42/9 | Constipation—ROME III and T2DM | 12 wks | Symptom score, SF, SC, feeling of complete evacuation, straining | Psyllium but not PBO associated with significant improvement vs baseline in symptom score but no significant difference between groups ($P = 0.095$); Psyllium associated with significant improvement in SC vs PBO at wk 8 ($P = 0.001$) but not weeks 4 and 12 | No AEs observed |

**Table 6.** (*continued*)

| Reference | Methodologic score[a] | Intervention | Study design | Patients N | Patients Mean age, yrs | Patients F/M | Patients Diagnosis | Duration | Outcomes Outcome parameters | Outcomes Main efficacy results | Outcomes Safety |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Psyllium vs Na bicarbonate suppository vs psyllium + Na bicarbonate suppository | | | | | | | | | | | |
| Bouchoucha et al. (53) | 1 (1,0,0) | Psyllium 3.6 g TID vs Na bicarbonate suppository QD vs psyllium 3.6 g TID + Na bicarbonate suppository QD | r, nb, co | 20 | 51 | 16/4 | Constipation (self-assessed; n = 20) and healthy controls (n = 20) | 2 wks × 3 | CTT, symptom self-assessment and physician assessment; SF, % of hard stools, incomplete evacuation | CTT decreased in all 3 treatment groups vs baseline but significantly more with suppository alone vs psyllium or suppository + psyllium (pts + controls); Psyllium alone had no effect on clinical parameters vs baseline | Not reported |
| Psyllium vs prunes | | | | | | | | | | | |
| Attaluri et al. (44) | 3 (2,0,1) | Psyllium 11 g BID vs prunes 50 g BID (1:1) | r, sb, co | 40 | 38 | NR | CC—ROME III | 3 wks × 2 | CSBMs (primary), global constipation symptom score, SC, straining | Mean CSBMs/wk significantly higher with prune vs psyllium (3.5 vs 2.8; $P = 0.006$); Stool consistency score higher with prune (3.2 vs 2.8; $P = 0.02$); mean straining scores were similar; No of CSBMs/week in the psyllium group vs baseline (mean ± SE) 1.6 ± 0.2 vs 2.8 ± 0.2 $P = 0.001$ | Palatability, satiety, postprandial fullness, and bloating were similar |

**Table 6.** (*continued*)

| Reference | Methodologic score[a] | Intervention | Study design | Patients | | | | Duration | Outcomes | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | N | Mean age, yrs | F/M | Diagnosis | | Outcome parameters | Main efficacy results | Safety |
| Psyllium vs mango | | | | | | | | | | | |
| Venancio et al. (45) | 2 (1,0,1) | Psyllium 5 g/d vs mango 300 g/d (1:1) | r | 36 | 24–29 | 25/11 | CC—ROME III | 4 wks | Evacuation (primary; difference from ideal [Bristol score = 4]; Agachan score | Mango ($P = 0.003$), but not psyllium, significantly improved evacuation category from baseline; Mango significantly improved evacuation category vs fiber ($P = 0.0269$); No significant difference between groups for Agachan score | No AEs occurred |
| Psyllium vs lactulose | | | | | | | | | | | |
| Quah et al. (55) | 3 (2,0,1) | Psyllium 3.5 g BID vs lactulose 10–30 mL BID (1:1) | r, co | 50 | 50 | 34/16 | CC—ROME II | 4 wks × 2 | SF, SC, EOE | SF (7.3 vs 5.5; $P = 0.001$) and SC score (3.4 vs 2.9; $P = 0.018$) significantly greater with lactulose vs psyllium; No significant difference between treatments for EOE score | No significant difference in AEs between groups |
| Inulin vs placebo | | | | | | | | | | | |
| Micka et al. (4) | 5 (2,2,1) | Inulin 12 g/d vs maltodextrin 12 g/d (PBO) | r, db, pc, co | 44 | | 33/11 | CC (2–3 BMs/wk × 6 mo) | 4 wks × 2 | SF, SC, symptoms | Significantly greater SF with inulin vs PBO (4.0 vs 3.0/wk; $P = 0.038$); No significant difference between treatments for SC or straining | Significantly more flatulence with inulin vs PBO ($P < 0.001$) |

**Table 6.** (*continued*)

| Reference | Methodologic score[a] | Intervention | Study design | Patients N | Patients Mean age, yrs | Patients F/M | Patients Diagnosis | Duration | Outcomes Outcome parameters | Outcomes Main efficacy results | Outcomes Safety |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Marteau et al. (57) | 4 (1,2,1) | Inulin 15 g/d vs maltodextrin 15 g/d (PBO) | r, db, pc, pg | 50 | 57 | 44/6 | Constipation—ROME | 4 wks | Microflora (primary); symptoms, BMs | No difference in SF or SC vs PBO; Significant increase in no. of pts with >1 BM/day and improvement in defecation difficulties vs baseline in inulin group but not PBO group ($P < 0.01$) | Flatulence significantly more frequent in inulin group vs PBO ($P < 0.01$) |
| Polydextrose vs placebo | | | | | | | | | | | |
| Duncan et al. (58) | 5 (2,2,1) | Polydextrose (8 or 12 g/d) vs PBO (1:1:1) | r, db, pc, pg | 119 | 29–47 | 111/8 | CC (CCCS 8–20 and criteria for constipation) | 4 wks | Whole GI transit time (primary); SBMs; symptoms | No significant difference between groups in whole GI transit time; No difference in SBMs between treatment groups; Significant improvement with polydextrose in some symptoms (global score 8 g/d vs PBO; $P = 0.018$; abdominal subdomain score 8 g/d vs PBO; $P = 0.039$) | No difference between treatment groups |
| Ibarra et al. (59) | 5 (2,2,1) | Polydextrose (4, 8, 12 g/d) vs PBO (1:1:1:1) | r, db, pc, pg | 192 | 43 | 133/59 | CC—ROME III | 2 wks PBO run-in + 2 wks | CTT (primary); symptoms; BMs | No significant difference between groups for CTT and most symptoms; Significant increase in BM frequency with 12 g polydextrose vs PBO ($P = 0.017$) | Mild to moderate GI symptoms with polydextrose |

**Table 6. (*continued*)**

| Reference | Methodologic score[a] | Intervention | Study design | Patients | | | Diagnosis | Duration | Outcomes | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | N | Mean age, yrs | F/M | | | Outcome parameters | Main efficacy results | Safety |
| Mixed fiber | | | | | | | | | | | |
| Mixed fiber vs psyllium | | | | | | | | | | | |
| Erdogan et al. (60) | 5 (2,2,1) | Mixed fiber (SupraFiber) 5 g BID vs psyllium 5 g BID vs PBO (1:1) | r, db | 72 | 43 | 66/6 | CC—ROME III | 4 wks | CSBMs (primary), SC, symptoms | Both treatments increased CSBMs vs baseline with no difference between groups; Both treatments improved SC with no difference between groups | Flatulence was improved more in mixed fiber group ($P = 0.01$) |

AE, adverse event; BID, twice daily; BM, bowel movement; CC, chronic constipation; CCCS, Cleveland Clinic Constipation Score; co, crossover; CSBM, complete spontaneous bowel movement; CTT, colonic transit time; db, double blind; EOE, ease of evacuation; F/M, female/male; GI, gastrointestinal; nb, nonblind; NR, not reported; PBO, placebo; pc, placebo controlled; pg, parallel group; pts, patients; QD, once daily; QoL, quality of life; r, randomized; sb, single blind; SBM, spontaneous bowel movement; SC, stool consistency; SE, standard error; SF, stool frequency; T2DM, type-2 diabetes mellitus; TID, 3 times daily.
[a]Total score with individual scores for randomization, blinding, and statement on withdrawals in parentheses.

grade-A recommendation, psyllium had level II evidence with a grade-B recommendation, and stimulant laxatives, magnesium hydroxide (milk of magnesia), and docusate all had level III evidence with grade C recommendations. Fruit-based laxatives and foods with prebiotics were not assessed (14). In general, the spectrum of OTC products that have been tested has increased and the quality of evidence has improved. Today, there are a greater number of placebo-controlled trials of higher quality, but there remains considerable variability in trial design. Definitions of constipation have become more standardized, with most studies in this analysis using ROME-based criteria (30/41 [73%]). The remainder did not use these criteria, which limited their quality. The biggest hinderance to evaluating these studies is a lack of consistent outcome measures between trials. Stool frequency (CSBMs, SBMs, or BMs) and stool consistency were the most common outcomes used, but the manner in which these were defined, measured, and the intervals of measurement varied.

The current FDA responder criteria for chronic idiopathic constipation trials are based on a CSBM weekly response (i.e., $\geq$3 CSBMs/week plus an increase of $\geq$1 CSBM/week from baseline). These were not used in any of the studies. Other measures of outcome included response rates (varying definitions), ease of defecation, straining, symptoms, transit times, and patient-reported outcomes (PROs) such as the Patient Global Impression of Change, the Patient Assessment of Constipation Symptoms, and the Patient Assessment of Constipation-Quality of Life. It should be noted that PRO measures have become increasingly important clinical tools, and the US FDA developed a draft guidance statement on their use for GI conditions (65). Another limitation was that there were only single studies available for many of the treatment categories. Consequently, the lack of confirmatory studies resulted in both a lower level of evidence category and a lower grade of recommendation. Most studies were of very short duration (typically 4 weeks) except for PEG studies, which ranged up to 6 months. Given that constipation is often a chronic problem, it behooves all investigators to consider longer-term (3- to 12-month) studies to provide confidence regarding durability of response. If the indication of an OTC product is for occasional and/or short-term use, then a 4- to 6-week study design may be appropriate, with stricter appraisal of changes in daily stool habits, ideally using validated paper form stool diary (66) or a recently validated electronic constipation stool APP diary (67).

Overall, PEG was the OTC laxative with the most robust clinical evidence (i.e., 3 placebo-controlled trials with quality scores of 5, 5, and 4), and it and senna are the only OTC agents with level I evidence and grade A recommendations. For PEG, this recommendation remains unchanged with newer studies providing further evidence supporting its use as a first-line treatment for chronic idiopathic constipation. PEG is highly effective with similar or superior efficacy to other OTC and prescription therapies and is well tolerated with long-term administration. In comparison studies, adverse events associated with PEG were similar in pattern and frequency to those of lactulose (25,26) and tegaserod (increased rates of headaches with tegaserod) (27) and lower in frequency compared with prucalopride (68% vs 85%) (28,29) and naloxegol (17% vs 24%) (30).

Psyllium and SupraFiber both have level II evidence and grade B recommendations. Despite the addition of 9 new studies, psyllium seems to have only modest efficacy and in head-to-head trials seems inferior to some other agents (e.g., PEG, lactulose, and prunes). Thus, its level of evidence and grade recommendation remains unchanged. Other fiber laxatives (polydextrose,

**Table 7. Miscellaneous agents in the treatment of constipation**

| Reference | Methodologic score[a] | Intervention | Study design | Patients N | Patients Mean age, yrs | Patients F/M | Patients Diagnosis | Duration | Outcomes Outcome parameters | Outcomes Main efficacy results | Outcomes Safety |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Constipation in chronic kidney disease | | | | | | | | | | | |
| Shimada et al. (61) | 5 (2,2,1) | Polydextrose 10 g QD vs PBO (1:1) | r, tb, pc | 50 | 51–79 | 16/34 | Hemodialysis; ≥1 laxative tablet for >3 mo | 8 wks | SF (primary), SC, abdominal pain, bloating | Polydextrose associated with significant increase in SF/wk vs PBO (8.5 vs 5.0; $P < 0.05$); No significant difference in abdominal distension | Clinical biochemistry values did not change |
| Ramos et al. (62) | 5 (2,2,1) | Flaxseed oil 2 mL/d vs olive oil 2 mL/d vs mineral oil 2 mL/d (control; 1:1:1) | r, db | 50 | 51 | 21/29 | Hemodialysis pts with constipation—ROME III | 4 wks | Frequency of symptoms (ROME III score); SC, SF | All groups significantly reduced symptom scores from baseline; SF and SC only improved from baseline with flaxseed oil (no *P* values reported) | All well tolerated; 5 pts discontinued due to oil taste (n = 2), persistent constipation (n = 2), diarrhea (n = 1) |
| Meksawan et al. (63) | 4 (1,2,1) | Fructo-oligosaccharide 20 g/d vs PBO (1:1) | r, db, pc, co | 13 | 71 | 5/8 | CC—ROME II and ESRD/CAPD (≥50 yrs) | 30 d | BMs, colonic transit | BM/wk significantly increased vs PBO 10.5 vs 6.2 ($P < 0.005$); Significant increase in colonic transit with fructo-oligosaccharide ($P = 0.0028$) | Mild flatulence and abdominal discomfort with fructo-oligosaccharide |
| Miscellaneous probiotic/synbiotic | | | | | | | | | | | |
| Psyllium, inulin, and probiotics vs placebo | | | | | | | | | | | |
| Cudmore et al. (64) | 5 (2,2,1) | Lepicol® (psyllium, inulin, probiotics) 5 g BID vs PBO 5 g BID (1:1) | r, db, pc, pg | 69 | 42–45 | 64/5 | CC—ROME III | 4 wks | Increase in BMs of 1.5/wk; SC | Significant improvement in BM/wk vs PBO in weeks 1 and 2 but not weeks 3 and 4; No difference in SC between groups | No difference between groups |

**Table 7.** (*continued*)

| Reference | Methodologic score[a] | Intervention | Study design | Patients N | Patients Mean age, yrs | Patients F/M | Patients Diagnosis | Duration | Outcomes Outcome parameters | Outcomes Main efficacy results | Outcomes Safety |
|---|---|---|---|---|---|---|---|---|---|---|---|
| UG1601 (inulin, lactitol, aloevera) vs placebo | | | | | | | | | | | |
| Chu et al. (19) | 5 (2,2,1) | UG1601 (inulin, lactitol, aloevera) 13 g QD vs PBO 13 g QD (1:1) | r, db, pc, pg | 40 | 24–25 | 30/10 | Constipation (ROME) | 4 wks | SF score, symptoms (SC, incomplete evacuation time for evacuation, flatulence) | No significant difference for any parameter | Not reported |
| Oligofructose vs placebo | | | | | | | | | | | |
| Buddington et al. (36) | 4 (1,2,1) | Oligofructose 15 g/d vs maltodextrin 5–15 g/d (PBO; 1:1) | r, db, pg | 97 | 33–34 | 76/23 | Constipation (1–3 BMs/wk) and low fiber intake | 16 wks | SF (primary); SC | SF significantly higher with oligofructose ($P = 0.023$) with benefit especially in pts with lowest fiber intake; No difference in SC | Not reported |

BID, twice daily; BM, bowel movement; CAPD, continuous ambulatory peritoneal dialysis; CC, chronic constipation; co, crossover; db, double blind; ERSD, end-stage renal disease; F/M, female/male; PBO, placebo; pc, placebo controlled; pg, parallel group; pts, patients; QD, once daily; r, randomized; SC, stool consistency; SF, stool frequency; tb, triple blind.
[a]Total score with individual scores for randomization, blinding, and statement on withdrawals in parentheses.

inulin, and insoluble fibers) have insufficient evidence to recommend for or against their use in the treatment of constipation.

Magnesium-containing agents seem to be effective. Four high-quality placebo-controlled trials demonstrated the efficacy of both magnesium-containing mineral water and, more recently, magnesium oxide, resulting in level I evidence and a grade B recommendation. However, there was a lack of standardization of magnesium content in the evaluated preparations. The starting dose of magnesium oxide was 1.5 g daily, but 53.3% of subjects required a dose reduction during the 4-week trial. Allowance for dose reduction resulted in a lack of any withdrawals. No further studies evaluating magnesium hydroxide (milk of magnesia) were identified. More recent studies using stimulant laxatives (bisacodyl, sodium picosulfate, and senna) have yielded improved levels of evidence and grade recommendations. Although all 3 had level III evidence with grade C recommendations in the previous systematic review, the current review identified level I evidence with grade B recommendations for both bisacodyl and sodium picosulfate and level I evidence and a grade A recommendation for senna. However, diphenylmethane derivatives are associated with a significantly greater incidence of GI adverse events (diarrhea and abdominal pain) which may limit their clinical utility. Senna was tested in 2 randomized placebo-controlled studies with both yielding improvements in constipation. The most recent study with senna used a starting dose of 1 g/d, and although it was significantly more efficacious than placebo and comparable with magnesium oxide, dose reductions were required in 83.3% of subjects. Thus, whether a smaller dose of this product is as effective and better tolerated, especially for the occasional constipation, merits further study. Of the fruit-based laxatives evaluated, kiwi was the only one with Level I evidence (i.e., 2 randomized controlled trials), whereas mango, prunes, and ficus all had level II evidence (1 trial each). These products were efficacious (grade B recommendation), but because of the few studies with limited numbers of patients, they were afforded lower Grade recommendations.

Despite docusate's wide use for constipation, there have been no new studies evaluating its efficacy. In the previous review, docusate had level III evidence and a grade C recommendation, based on trials that found docusate to be no more effective than placebo and significantly inferior to psyllium (14). Given the current literature or lack thereof, we are unable to provide a recommendation for docusate.

Overall, the OTC products analyzed in this review seemed to be safe and well tolerated, with no reports of serious adverse events, although some studies failed to report any adverse events. GI symptoms (abdominal pain, cramps, bloating, diarrhea, and nausea) were the most common adverse events reported with a variable incidence for each product, and headache was the chief non-GI adverse event reported.

The limitations of our systematic review include that only studies published in the English literature were assessed, and given that constipation is a common global problem, it is possible that there are some remedies that have been tested and published in other languages that have been excluded in this review. We did exclude studies of less than 4 weeks' duration because we believed that a product that is likely to benefit a chronic condition should demonstrate both efficacy and safety over at least a one-month period. Although there are several methods of categorizing the basis of evidence for drug efficacy and safety, we chose the USPSTF criteria to provide meaningful comparative data with our previous analysis (14).

In conclusion, PEG and senna are the only OTC laxatives with level I evidence and grade A recommendations for the treatment of constipation, although PEG is the only one supported by both short- and long-term studies. Other OTC laxatives with a grade B recommendation include psyllium, SupraFiber, magnesium-rich water, magnesium oxide, diphenylmethane stimulants (bisacodyl and sodium picosulfate), fruit-based laxatives (kiwi, mango, prunes, and ficus), and yogurt plus galacto-oligosaccharide, prunes, and linseed oil. There was insufficient evidence (grade I) for polydextrose, inulin, and fructo-oligosaccharide. For these and other alternative products, there is a clear need for more rigorous, high-quality studies using standardized endpoints. Docusate lacks well-controlled trials demonstrating its efficacy and has poor evidence to support its use in clinical practice.

## CONFLICTS OF INTEREST

**Guarantor of the article:** Darren M. Brenner, MD.
**Specific author contributions:** S.S.C.R. and D.M.B. conceived the project and developed the search criteria and parameters for the systematic review, reviewed the literature independently, and provided independent recommendations regarding the quality of studies, strength of evidence, and recommendation grading. Both authors equally contributed to the writing of the manuscript and provided extensive revisions.
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## Study Highlights

### WHAT IS KNOWN

- ✓ Chronic constipation is a common condition that significantly affects quality of life.
- ✓ Approximately 40% of individuals with constipation self-treat with over-the-counter (OTC) laxatives.
- ✓ Multiple classes of OTC therapies are available for treating chronic constipation.
- ✓ Polyethylene glycol was the only OTC therapy to receive a strong recommendation based on high levels of evidence in a previous systematic review published in 2005.

### WHAT IS NEW HERE

- ✓ The spectrum of OTC products that have been tested has increased and the quality of evidence has improved.
- ✓ There is now good evidence based on high-quality trials supporting the use of polyethylene glycol and senna for constipation.
- ✓ Moderate evidence supports the use of psyllium, fruits, magnesium-containing compounds, bisacodyl, and sodium picosulfate for the treatment of constipation.
- ✓ There is a clear need for more rigorous, high-quality studies using standardized endpoints.

 

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