Drug Class Review
on
Constipation Drugs

Final Report

September 2007

The Agency for Healthcare Research and Quality has not yet seen or approved this report

A literature scan of this topic is done periodically

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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Note: A scan of the medical literature relating to the topic is done annually (see http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description). Upon review of the last scan, the Drug Effectiveness Review Project governance group elected not to proceed with another full update of this report. Some portions of the report may not be up to date.

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INTRODUCTION

Background

Chronic constipation is a disorder characterized by unsatisfactory defecation that results from infrequent stools, difficult stool passage, or both over a time period of at least 12 weeks.[1] The diagnosis is primarily symptom-based, relying on the patient's self report of symptoms; however, the description of constipation symptoms varies significantly among patients. Common symptoms may include infrequent bowel movement, hard stool, too small stool, difficulties with stool expulsion (need for excessive straining), feeling of incomplete evacuation or simply a patient description of "a feeling of being constipated" without any of these constipation-related symptoms. While physicians traditionally defined constipation as fewer than three bowel movements per week,[2] more specific diagnostic criteria have been developed to better specify the nature and duration of symptoms (Table 1).[1]

Table 1. Symptom-based criteria for chronic functional constipation[1]

Rome II Criteria	ACG CC Task Force

At least 12 weeks, need not be consecutive, in past 12 months of ≥ 2 of:
• Straining in >25% of defecations
• Sensation of incomplete evacuation in >25% of defecations
• Sensation of anorectal obstruction/blockade in >25% of defecations
• Manuel maneuvers to facilitate >25% of defecations
• Fewer than three defecations per week
• Loose stools should not be present and there are insufficient criteria for IBS
	Symptoms for at least 3 of the last 12 months consisting of:
	• Infrequent stools: less than 3 per week, **or**
	• Difficult stool passage, which may include:
	  • Straining
	  • Sense of difficulty passing stool
	  • Incomplete evacuation
	  • Hard/lumpy stools
	  • Prolonged time to stool
	  • Need for manual maneuvers to pass stool
	• Can be a combination of both

ACG: American College of Gastroenterology; CC: chronic constipation; IBS: Irritable Bowel Syndrome

Chronic constipation appears to be very common in the general population although its prevalence varies depending on the diagnostic criteria used. Estimates suggest that 2% to 28% of the US population suffers from chronic constipation,[3, 4] with most estimates in the range of 12% to 19%.[2] Chronic constipation disproportionately affects women compared with men (2.2:1), and the prevalence increases with age.[2] Although symptoms may be benign, chronic constipation can significantly reduce quality of life, and, if left untreated, can result in fecal impaction, incontinence, and, very rarely, bowel perforation.[5] Approximately 2.5 million US physician visits are attributed to constipation each year;[3] assuming an average cost of approximately $3,000 per patient (in 2007 dollars),[6] the cost of diagnosing and treating constipation is roughly $7.5 billion annually.

Irritable Bowel Syndrome (IBS) is the most common and best studied functional gastrointestinal (GI) disorder. Epidemiological studies show that 8% to 23% of adults in the Western world have IBS of varying severity.[7, 8]

IBS symptoms are heterogeneous in their expression. The typifying clinical presentation is abdominal pain or discomfort associated with altered bowel habits (e.g., diarrhea, constipation, or a combination of both at times) and with a change in the consistency or frequency of stools. Other associated symptoms may include bloating, urgency, and/or a feeling of incomplete evacuation. Although symptoms tend to occur in clusters, individual symptoms may also occur sequentially and they may vary in type, location, and severity over time. IBS is classified as diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), or mixed—a combination of both (IBS-M), depending on the most prevalent bowel pattern. This sub-classification is determined by stool frequency, form, and passage. However, because the predominant symptom often changes over time, it is not uncommon for a patient to alternate between these IBS subgroups or between different functional bowel disorders such as IBS-C or IBS-D and functional constipation or functional diarrhea.[7, 8]

There are no biological markers or specific tests for the diagnosis of IBS. The diagnosis is therefore based on identifying a cluster of clinical symptoms that are consistent with the disorder and excluding other conditions by looking for clinical alert signs and performing limited diagnostic testing.

Since the pathophysiological mechanisms underlying the disorder are not known, the current approach to management is based primarily on the patients' predominant symptoms and overall wellbeing rather than on a specific underlying etiological mechanism. The specific treatment is determined by whether pain, diarrhea, or constipation is predominant and the targeted symptom is treated using the same medications as in other conditions. For example, symptom/s of constipation associated with IBS (i.e., IBS-C) are treated in the same way as in functional constipation and symptom/s of diarrhea associated with IBS (i.e., IBS-D) are treated in the same way as in functional diarrhea. Since the treatment of constipation symptoms is similar in the two conditions, we reviewed and included clinical trials related to constipation symptoms in these two conditions (IBS-C and chronic constipation).

Functional constipation is considered one of a group of five functional bowel disorders defined by the Rome III classification system (developed by multinational working teams known as the Rome Committees).[8] As a functional disorder, constipation can stand on its own as a distinct diagnosis of functional constipation or be part of another functional bowel disorder of IBS. IBS is the most common

functional gastrointestinal disorder. It is defined as a combination of chronic or recurrent gastrointestinal symptoms, not explained by structural or biochemical abnormalities. The diagnosis is based on identifying typifying symptoms, using of symptom-based diagnostic criteria, and limited diagnostic tests to exclude other conditions.

In order to meet the criteria patients must have abdominal pain or discomfort associated with alterations in stool frequency, form, and passage. IBS is sub-classified as diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), or mixed (combination of both), depending on the most prevalent bowel pattern. However, because the predominant symptom often changes over time, it is not uncommon for a patient to alternate between these IBS subgroups.[9] This report focuses on functional constipation and does not cover other IBS associated symptoms such as abdominal pain/discomfort, diarrhea, and bloating.

Etiology

There are many causes for constipation. The disorder may be secondary to systemic diseases (e.g., hypothyroidism, hyperparathyroidism, diabetes mellitus), gastrointestinal diseases (e.g., mechanical obstruction due to colon or rectal cancer), neurological disorders (e.g., autonomic neuropathy, Parkinson's disease, multiple sclerosis). Another common etiology is the use of prescription or over the counter (OTC) medications that slow down the intestinal transit (Table 2).

Chronic primary or idiopathic constipation is primarily a diagnosis of exclusion which is made when the other possible etiologies have been ruled out. Once primary idiopathic constipation has been diagnosed and "red flags" suggesting other serious diseases such as colon or rectal cancer have been eliminated, empiric treatment may be started with an appropriate follow-up to assess the response.

Table 2. Medications associated with constipation[10]

Prescription	Over the counter (OTC)
Opiates	Antacids, especially calcium containing
Anticholinergics	Calcium supplements
Tricyclic antidepressants	Iron supplements
Calcium channel blockers	Antidiarrheal agents
Antiparkinsonian drugs	NSAIDS
Sympathomimetics	
Antipsychotics	
Diuretics	
Antihistamines	

Approach to Management

I. Initial recommendations

In clinical practice patients with milder symptoms are usually offered behavioral, diet and lifestyle modifications as the first step of treatment. Despite the lack of controlled clinical trials to support these recommendations patients are often encouraged to increase their fluid intake, get involved with moderate increase in exercise, and use the bathroom daily in response to feeling of urge for a bowel movement or at a specific time, particularly after meals. Patients with more severe symptoms or those who do not respond to this initial treatment are usually offered an empiric medication treatment with fiber supplements and "simple laxatives."

II. Evaluation of chronic primary constipation

The initial evaluation is based on careful history and physical evaluation. Important historical features include bowel frequency, stool consistency, need for straining, and feeling of incomplete evacuation. Presence of abdominal pain/discomfort can suggest a diagnosis of other functional disorders (e.g., IBS-C). Identifying alarm symptoms (e.g., weight loss, reduced appetite, weakness) are important since they can suggest other underlying conditions which usually require further evaluation (e.g., abdominal imaging, colonoscopy). Patients' medications should be reviewed carefully and initial limited laboratory tests should be performed to exclude medications (e.g., calcium channel blockers, anticholinergics) or diseases (e.g., hypothyroidism) to which constipation is secondary.[11]

The majority of patients with constipation are seen by primary care physicians. Those who are more difficult-to-manage or fail to respond to the initial medical therapy are referred to GI specialists or tertiary care centers. In these settings, patients with primary constipation can be further evaluated for the underlying pathophysiological mechanism(s) of their constipation. Using functional tests of the colon and anorectum, primary constipation can be divided into three separate subgroups:

1. Slow transit constipation
2. Normal transit constipation
3. Obstructed defecation

Slow transit Constipation refers to a decrease in colonic transit particularly in its proximal parts (i.e., the ascending and transverse colon). *Normal transit constipation* refers to patients who meet the criteria for chronic functional constipation but testing of their colonic transit is between normal limits. These patients often have misperceptions of normal bowel movements and some may have psychosocial disorders. *Obstructed defecation* refers to organic/mechanical obstruction at the level of the rectosigmoid colon or

pelvic floor, or functional obstruction due to failure of the anorectal and pelvic floor muscles to relax during defecation. Combinations of theses three subtypes are possible.

In clinical practice only a small minority of patients with primary constipation undergo formal physiologic testing to identify the underlying pathophysiology and subgroup to which they belong. Patients who are refractory to behavioral (diet and lifestyle) measures and fail initial treatments are often referred for further physiological testing.[11] Subgrouping of functional constipation based on the underlying pathophysiological mechanism(s) may help direct treatment. For example, while education and psychological support may be sufficient in patients with normal transit constipation, patients with slow transit constipation usually require promotility and stimulant laxatives, and patients with obstructed defecation often need other interventions such as biofeedback and/or surgical repair.

III. Pharmacologic treatments for chronic constipation

Pharmacologic treatments for chronic constipation (Table 3) include several groups of medications with different mechanism/mode of action.

Bulk-forming agents are organic polymers that absorb water. These agents increase stool mass and water content thereby making it bulkier, softer and easier to pass. Examples include bran, psyllium and methylcellulose. These agents are often used as the first line treatment of constipation.

Stool softeners, like docusate sodium and docusate calcium, are surface-active agents that facilitate water interacting with the stool in order to soften the stool, make it more slippery, and easier to pass. These agents are often used as OTC medications for constipation.

Osmotic laxatives are poorly absorbed ions or molecules that create an osmotic gradient within the intestinal lumen, drawing water into the lumen and making stools soft and loose. Examples of this group of agents include poorly absorbed electrolytes such as milk of magnesia, magnesium citrate, and sodium phosphate; poorly absorbed disaccharides such as lactulose and sorbitol; and polyethylene glycol 3350 (PEG). These agents are usually used for short-term treatment of constipation or for intermittent use in chronic constipation. The PEG solution is also used for intestinal purges in preparation for diagnostic procedures (e.g., colonoscopy) or surgery.

Stimulant laxatives increase peristalsis in the large bowel and fluid and electrolyte secretion in the distal small bowel and colon. These agents include anthraquinones (senna, cascara, danthron), diphenylmethanes (bisacodyl and phenolphthalein) and castor oil. They are available in different OTC forms and are usually used for intermittent and short term treatment of constipation.

Secretory agents – this group is currently represented by Lubiprostone, a new agent that was recently approved by the US Food and Drug Administration (FDA) for the treatment of chronic idiopathic constipation in adults. It works by activating chloride channels on the small intestinal mucosa and thereby leading to chloride rich intestinal fluid secretion that increases luminal water content and stool hydration.

Prokinetic agents – These agents act by increasing intestinal motility and thereby accelerating intestinal transit. Tegaserod maleate is a 5-HT4 pre-synaptic receptor agonist that enhances the peristaltic reflex, increases colonic motility, decreases visceral hypersensitivity, and facilitates secretion into the colonic lumen. Note that marketing of tegaserod in the US and Canada was suspended in March of 2007 (more than halfway through this review) because of concern regarding serious cardiovascular events.[12] Detailed information regarding these cardiovascular adverse events and the US Food and Drug Administration (FDA) decision regarding the suspension of tegaserod is provided in Key Question 3 (General Risk of Harms) below.

With the exception of lubiprostone and lactulose (and previously, tegaserod maleate), drugs for chronic constipation are available without a prescription (i.e., OTC). They are given once to three times daily and typically work within 12 hours to 1 week. Table 4 summarizes the most common products available in the US and Canada.

Table 3. Medications associated with constipation

Class	Generic Name	Brand Name	Manufacturer	Indication	Rx/OTC
5-HT4 serotonin receptor agonist	Tegaserod maleate*	Zelnorm	Novartis	Chronic idiopathic constipation in men and women <65 Short term treatment of IBS in women	Rx
Bulking agents	Psyllium (ispaghula)	Metamucil	Proctor and Gamble	Occasional constipation Restoration of regularity	OTC
		Fiberall	Heritage Consumer		
		Genfiber	Goldline Consumer		
		Natural Psyllium Fiber	Plus Pharma		
		Hydrocil	Numark		
		Konsyl	Konsyl Pharm		
		Reguloid	Rugby		
		Natural Fiber Laxative	Apothecary		
		Syllact	Wallace		
		Serutan	Manley and James		
Chloride channel activator	Lubiprostone	Amitiza	Sucampo	Chronic idiopathic constipation in adults	Rx
Osmotic laxatives	Polyethylene glycol 3350	Glycolax	Schwarz	Occasional constipation	OTC
		MiraLax	Braintree		
		Generic	Multiple		
	Lactulose	Chronulac	Sanofi Aventis	Chronic constipation Portal systemic enecephalopathy	Rx
		Generic	Multiple		
Stool softeners	Docusate sodium	Docusate sodium	Multiple	Occasional constipation	OTC
		Ex-lax	Novartis		
		Dioctyn	Dixon-Shane		
		Colace	Purdue		
		D-S-S	Magno-Humphries		
		Dulcolax	Boehringer		
		Silace	Silarx		
		Stool softener	Rugby		
		Regulan SS	Republic		
		Genasoft	Goldline		
		Sof-lax	Fleet		
		Diocto	multiple		
		Docu	Hi-Tech Pharm		
		D.O.S.	Goldline		
	Docusate calcium	Docusate calcium	multiple	Occasional constipation	OTC
		Stool softener	Apothecary		
		Sulfolax	Major		
		Surfak Liquigels	Pharmacia and Upjohn		
		DC Softgels	Goldline		

*Marketing suspended March, 2007 because of increased risk of serious cardiovascular events

Table 4. Drugs for constipation: product information and directions for administration

Generic Name	Dosage Form	Strength	Frequency	Onset of Action	Usual Daily Dose	Directions
Docusate calcium	Capsules	240 mg/ capsule	Once daily	12-72 hours	240 mg	Take with water
Docusate sodium	Tablets	100mg/tab.	One to three times a day	12-72 hours	Adults: Up to 300 mg	Take with a glass of water
	Capsules	50mg/capsule			Children: Up to 100 mg	Syrup/liquid may be mixed with milk or juice
		100mg/capsule				
	Soft gels	50mg/gel				
		100mg/gel				
		250mg/gel				
	Syrup	20mg/5ml				
		50mg/15ml				
		60mg/15ml				
		100mg/30ml				
	Liquid	10mg/ml				
		150mg/ml				
Lactulose	Solution	10g/15ml	Once daily (twice daily if needed)	24-48 hours	Adults: 20-30 g	Dissolve in 120ml water
	Crystals	10g/packet 20g/packet			Children: 5g	
Lubiprostone	Soft gelatin capsules	24mcg/capsule	Twice daily	Within 24 hours	48 mcg	Take with food
Polyethylene glycol 3350	Powder packets	17g/packet	Once daily	48-96 hours	17 g	Dissolve in 8oz water
	Powder	17g/capful			17 g	
Psyllium	Capsules	0.52g/capsule	Three times a day	12-72 hours	Adults: 10.2-18 g	Take capsules with 8oz water
	Powder	3.4g/tsp			Children: ½ adult dose	Dissolve powder in 8oz water
		6g/tsp				Mix granules with 8oz water or sprinkle on cereal or food
	Granules	4.03g/tsp				
		2.5g/tsp				
	Wafers	3.4g/wafer				
Tegaserod*	Tablets	6mg/tablet	Twice daily	Within the first week	12 mg	Take 30 min. before meals
		2mg/tablet				

* Marketing suspended March, 2007 because of increased risk of serious cardiovascular events

Scope and Key Questions

In this report, we review the general and comparative effectiveness, safety, and tolerability of drugs for chronic constipation. Our review covers the use of the following in adults and children with chronic constipation and IBS-C: docusate calcium, docusate sodium, lactulose, lubiprostone, polyethylene glycol

3350, psyllium, and tegaserod. Our review does not include drugs for intermittent or short-term constipation, such as stimulant laxatives.

In March 2007 the FDA issued a public health advisory to inform patients and health care professionals that the sponsor of tegaserod (Zelnorm®) agreed to stop selling the medication because a recent analysis of data from 29 RCTs including 11,614 patients treated with tegaserod found an increased risk of heart attack, stroke, and unstable angina in patients taking the medication.[12] The FDA reported that in clinical studies 0.1% (n = 13) of patients treated with tegaserod experienced serious and life-threatening cardiovascular adverse events, compared with 0.01% (n = 1) of patients on placebo. Of the 13 patients taking tegaserod having these events, four had a heart attack (1 died), six had unstable angina, and three had a stroke. The average age of subjects in these studies was 43 years and 88% were women.

The FDA has agreed to allow access to the medication through a special program when the benefits outweigh the risks of series adverse events or for patients with no other treatment options. The FDA also indicated that it will consider limited re-introduction of the medication at a later date.

The RTI-UNC Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the general effectiveness of drugs used to treat chronic constipation and chronic constipation associated with Irritable Bowel Syndrome? Given general effectiveness, what is the comparative effectiveness of drugs used to treat chronic constipation and chronic constipation associated with Irritable Bowel Syndrome?

2. Does treatment duration influence the effectiveness of drugs used to treat chronic constipation and chronic constipation associated with Irritable Bowel Syndrome? When should treatments be switched in patients not responding to a given drug?

3. What is the comparative tolerability and safety of drugs used to treat chronic constipation and chronic constipation associated with Irritable Bowel Syndrome?

4. Are there subgroups of patients based on demographics (age, racial or ethnic groups, and gender), other medications, or co-morbidities, including Irritable Bowel Syndrome, for which one symptomatic treatment is more effective or associated with fewer adverse events?

METHODS

Literature Search

To identify articles relevant to each key question we searched MEDLINE, Embase, The Cochrane Library, and the International Pharmaceutical Abstracts; we used either Medical Subject Headings (MeSH or MH) as search terms when available or key words when appropriate. We combined terms for selected indications (chronic constipation, irritable bowel disorder), drug interactions, and adverse events with a list of seven specific constipation drugs (docusate calcium, docusate sodium, lactulose, lubiprostone, polyethylene glycol, psyllium, tegaserod) and their trade names. We limited the electronic searches to "human" and "English language"; we searched sources from 1985 to 2007 (April) to delimit literature relevant to the scope of our topic.

We used the National Library of Medicine publication type tags to identify reviews, randomized controlled trials (RCTs), and meta-analyses; we also manually searched reference lists of pertinent review articles and letters to the editor. All citations were imported into an electronic database (EndNote, version X). Additionally, we hand-searched the Center for Drug Evaluation and Research (CDER) database to identify unpublished research submitted to the FDA.

Further, the Center for Evidence-based Policy at the Oregon Health and Science University (OHSU) contacted pharmaceutical manufacturers and invited them to submit dossiers, including citations, using a protocol available at www.ohsu.edu/drugeffectiveness. We received dossiers from two pharmaceutical companies (Novartis and Takeda Pharmaceuticals).

Our searches found 434 citations, unduplicated across databases; we found an additional 89 articles from manually reviewing the reference lists of pertinent review articles and an additional 12 articles in the pharmaceutical dossiers. The total number of citations included in the database was 535. For further details on the search strategy, see Appendix A.

Study Selection

Two people independently reviewed each abstract; if both reviewers agreed that the study did not meet eligibility criteria, it was excluded. We obtained the full text of all remaining articles. Records were considered for exclusion if they did not meet pre-established eligibility criteria with respect to study design, patient population, interventions, outcomes, and comparisons to medications outside our scope of interest.

All controlled, prospective studies were eligible for inclusion, regardless of sample size or study duration. For adverse events we also included case series and retrospective studies. Eligibility criteria and outcomes of interest are presented in Table 5.

Table 5. Eligibility criteria

Outcome	Outcome Measures	Study Eligibility Criteria
KQ1A: General Efficacy/ Effectiveness	• **General subjective measures** e.g., overall relief of GI symptoms, symptom composite score • **Specific GI symptom/s** e.g., straining, bloating, abdominal discomfort/pain, ease of defecation, complete spontaneous bowel movement • **Physiologic measure/s** e.g., increase in frequency of bowel movements, stool consistency • **General wellbeing and/or QOL**	Study Design: Any prospective, controlled study Minimum study duration: None Minimum sample size: None Study Population: All in- and outpatients with chronic constipation, IBS-C, adults and children
KQ1B: Comparative Efficacy/ Effectiveness	Like in KQ1A	Same as KQ1A
KQ2A: Treatment Duration	• **Time to effectiveness** • **Switching in patients not responding to a drug** • **Influence of treatment duration on the effectiveness of drugs**	Same as KQ1A
KQ3: Safety and Tolerability	• **Overall adverse events** • **Withdrawals because of adverse events** • **Specific Adverse Events:** E.g. electrolyte abnormalities, diarrhea, bloating, nausea, flatulence, dehydration, hypovolemia • **Serious Adverse Events:** E.g. hepatotoxicity	Study Design: All study designs except case reports Minimum study duration: None Minimum sample size: None Study Population: All in and outpatients with chronic constipation, IBS-C, adults and children
KQ4: Subgroups	Same outcomes as in KQ1-3	Same as in KQ 1A

GI: gastrointestinal; IBS-C: Irritable Bowel Syndrome constipation predominant; KQ: key question; QOL: quality of life;

Data Abstraction

We designed and used a structured data abstraction form to ensure consistency in appraisal for each study. Trained reviewers abstracted data from each study and assigned an initial quality rating. A senior reviewer read each abstracted article and evaluated the completeness of the data abstraction. We

abstracted the following data from included trials: study design, eligibility criteria, intervention (drugs, dose, duration), additional medications allowed, methods of outcome assessment, population characteristics, sample size, loss to follow-up, withdrawals attributed to adverse events, results, and adverse events reported. We recorded intention-to-treat results if available.

Quality Assessment

We assessed the internal validity (quality) of trials based on predefined criteria (Appendix B) developed by the US Preventive Services Task Force (ratings: good-fair-poor)[13] and the National Health Service Centre for Reviews and Dissemination.[14] External validity (generalizability) was assessed[15] and reported but did not influence quality ratings. We did not rate the quality of descriptive studies (case series).

Two independent reviewers assigned quality ratings; they resolved any disagreements by discussion and consensus or by consulting a third, independent party. Elements of internal validity assessment for RCTs included, among others, randomization and allocation concealment, similarity of compared groups at baseline, use of intention-to-treat analysis, and overall and differential loss to follow-up.

To assess the quality of observational studies, we used criteria outlined by Deeks et al.[16] Items assessed included selection of cases or cohorts and controls, adjustment for confounders, methods of outcomes assessment, length of follow-up and statistical analysis.

Loss to follow-up was defined as the number of persons randomized who did not reach the endpoint of the study,[17] independent of the reason and the use of intention-to-treat analysis. Appendix C describes our procedure for assessing quality in greater detail.

Trials that had a fatal flaw in one or more categories were rated poor quality; trials that met all criteria were rated good quality. Because of the lack of studies for this drug class we included poor quality studies in the synthesis of the evidence. For studies rated as poor, we provide the main reason for the poor rating in the in-text tables. Greater details about methodological shortcomings can be found in the evidence tables.

Data Synthesis

Throughout this report we synthesized the literature qualitatively. Because of the small number of studies and heterogeneous outcomes, no quantitative analyses were possible.

Rating the Strength of a Body of Evidence

We rated the strength of the available evidence in a three-part hierarchy based on an approach devised by the GRADE working group.[18] Developed to grade the quality of evidence and the strength of recommendations, this approach incorporates four key elements: study design, study quality, consistency of results, and directness. Directness refers to the availability of data on outcomes or populations of interest. GRADE also considers the presence of imprecise or sparse data, high probability of publication bias, evidence of a dose gradient, and magnitude of the effect.

As shown in Table 6, we used three grades: high, moderate, and low (combining the GRADE category of very low with low).[19] Grades reflect the strength of the body of evidence to answer key questions on the general and comparative efficacy and harms of drugs to treat chronic constipation or IBS-C; the critical element is the extent to which new evidence might alter the confidence we would have in our findings. Due to the lack of evidence and heterogeneous outcomes, we were unable to rate the strength of the evidence for individual outcomes; instead, we provided summary ratings on the general and the comparative efficacy and harms.

Table 6. Definitions of the grades of the overall strength of evidence

Grade	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate.

Source: Adapted from the GRADE working group.[18]

This approach does not incorporate other factors that might be relevant to assess reliably the comparative efficacy, effectiveness, and harms such as funding sources and comparable dosing. We have assessed these additional factors and highlighted issues that could potentially bias our assessments (e.g., all studies funded by the same manufacturer).

RESULTS

We identified 535 citations from searches and reviews of reference lists. We included a total of 262 articles on an abstract level and retrieved those as full text articles for background information or to be reviewed for inclusion into the evidence report. Studies published as abstracts only are listed in Appendix B. In total we included 33 studies: seven head-to-head RCTs, 16 placebo controlled trials, one observational extension of an RCT, one meta-analysis, six observational studies, and two pooled data analyses. We retrieved 75 articles for background information.

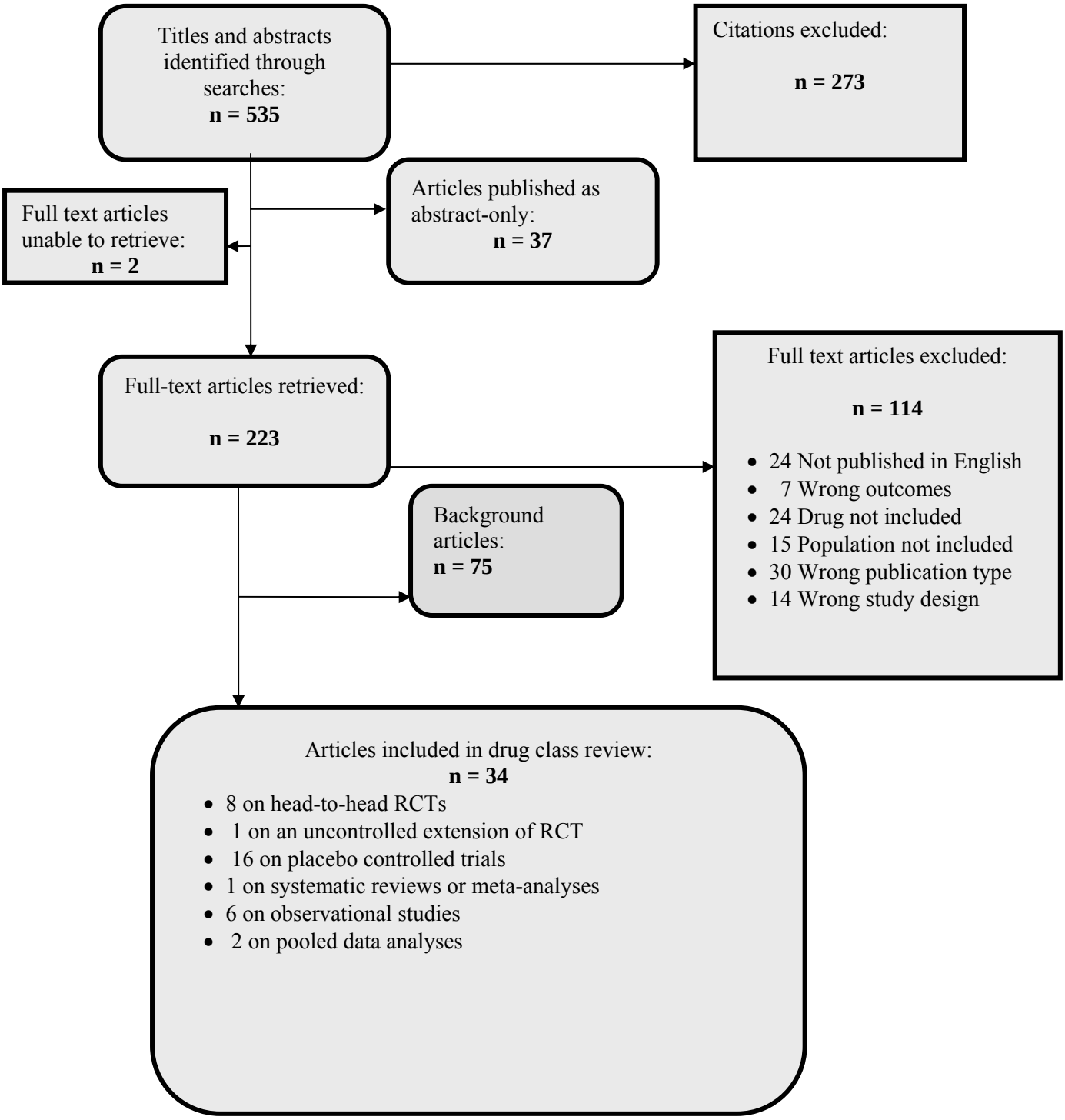
Reasons for exclusions were based on eligibility criteria (Figure 1, QUORUM Tree).

Of the 33 included studies, 67% were financially supported by pharmaceutical companies, 6% were funded by governmental agencies or independent funds, and 3% received both, pharmaceutical and government funding. We could not determine a funding source for 24% of the included studies.

Because Irritable Bowel Syndrome (IBS) is considered a disease of its own, we distinguish between chronic constipation and chronic constipation associated with IBS throughout the report. Furthermore we present evidence on pediatric populations separate from findings in adult populations.

Because tegaserod is not available anymore for the general treatment of chronic constipation and chronic constipation associated with IBS, we are not discussing tegaserod studies in detail. Nevertheless, we are presenting the available evidence and report the major findings.

Figure 1. Results of literature search*



*Number of included articles differs from number of included studies due to the fact that some studies have multiple publications.

KEY QUESTION 1. What is the general efficacy and effectiveness of drugs used to treat chronic constipation and chronic constipation associated with Irritable Bowel Syndrome? Given general efficacy and effectiveness, what is the comparative effectiveness of drugs used to treat chronic constipation and chronic constipation associated with Irritable Bowel Syndrome?

We included 19 RCTs; four RCTs were head-to-head trials. No study was characterized as an effectiveness trial according to the standard criteria used for our DERP literature syntheses.[15] Most of the included efficacy studies were conducted in narrowly defined populations and/or were limited to less than 2 months of follow-up.

I. Chronic constipation in adults

A. Summary of findings

General efficacy

The evidence on the general efficacy for most drugs is sparse, fraught with methodological issues, or entirely missing. No controlled evidence is available for docusate calcium, docusate sodium and lactulose for the treatment of chronic constipation in adults.

Three trials provide moderate strength evidence on the general efficacy of PEG 3350 for the treatment of chronic constipation. None of these studies, however, had a follow-up of more than 2 weeks. Inferences about the long-term efficacy of PEG 3350, therefore, cannot be drawn.

The available evidence on the general efficacy of psyllium is limited to two studies of mixed methodological quality. Although both studies indicated a beneficial treatment effect for psyllium, bias cannot be ruled out, and no firm conclusions about efficacy can be drawn.

Studies assessing the efficacy of lubiprostone have been published as abstracts only. The available information, therefore, is insufficient to critically appraise the underlying methods and draw firm conclusions.

Tegaserod was taken off the market in March 2007 because of an increased risk of cardiovascular events. Multiple studies provide evidence on the general efficacy of tegaserod for the treatment of chronic constipation.

Comparative efficacy

No head-to head evidence is available for most comparisons of constipation drugs. Available evidence is limited to three head-to-head trials on comparisons of docusate sodium versus psyllium, lactulose versus PEG 3350, and PEG 3350 versus psyllium. Two out of three studies had severe methodological limitations and were rated as poor.

A poor quality RCT indicated no difference in efficacy between docusate sodium and psyllium. Another poor quality RCT reported a greater improvement of symptoms for patients on PEG 3350 than on lactulose after 4 weeks of treatment. Findings of both studies must be interpreted cautiously because bias cannot be ruled out.

The comparison of PEG 3350 with psyllium is limited to one fair open-label RCT. This study indicated a statistically significantly greater rate of improvements in patients on PEG 3350 than on psyllium. No controlled evidence is available for docusate calcium, docusate sodium and lactulose.

B. Detailed assessment

General efficacy and effectiveness

Table 7 summarizes the trials assessing the general efficacy of constipation drugs in adults; Table 10 summarizes the evidence profile of the general efficacy of constipation drugs.

Docusate calcium

We did not find any studies on the general efficacy and effectiveness of docusate calcium that met our eligibility criteria.

Docusate sodium

We did not find any studies on the general efficacy and effectiveness of docusate sodium that met our eligibility criteria.

Lactulose

We did not find any studies on the general efficacy and effectiveness of lactulose that met our eligibility criteria.

Lubiprostone

We did not find any evidence on the efficacy of lubiprostone published as full text articles. The literature search, however, detected 12 published abstracts.[20-30] Most trials were of relatively short durations (3 to 4 weeks). In general, lubiprostone had a statistically significant treatment benefit compared with placebo. Consistently higher percentages of patients on lubiprostone than on placebo had spontaneous bowel movements within 24 hours. Only one open-label study over 24 weeks suggested a durable response of lubiprostone.[22] Because these abstracts did not provide enough information to critically appraise methods of individual studies, we do not report findings in detail.

Polyethylene Glycol

Three RCTs determined the general efficacy of PEG 3350.[31-33] The largest trial, a fair double-blinded RCT, enrolled 151 patients with chronic constipation who had fewer than three stools during a 7 day run-in period.[31] Treatment success was defined as a frequency of more than three stools during a 7 day period. After 2 weeks of treatment, significantly more patients on PEG 3350 (17g/d) achieved treatment success than patients on placebo (65.8% vs. 47.8%; $P < 0.001$). The mean number of bowel movements was 4.5 for patients on PEG 3350 compared with 2.7 for patients on placebo ($P < 0.001$) The other two studies were cross-over RCTs and reported similar results after 5 days and 2 weeks of treatment, respectively.[32, 33]

An uncontrolled before-after study[34] did not meet our formal eligibility criteria for efficacy; however, because it was the only study with a post-treatment follow-up, we are briefly summarizing its findings. This study enrolled 50 patients with chronic constipation and treated them with PEG 3350 for 14 days. At the end of the active treatment period, 83.3% of patients had more than three bowel movements per week and no longer met Rome II criteria for functional constipation. During the post treatment follow-up (mean 38.4 days), however, no lasting relief of symptoms could be detected. Overall, 61.7% of patients needed new treatment for constipation during this time period.

Psyllium

Two studies provide consistent evidence on the efficacy and effectiveness of psyllium for the treatment of chronic constipation.[35, 36] Both studies, however, have methodological limitations. The larger study (n = 201) was a poor, single-blinded RCT.[35] This study was rated poor primarily because of the lack of an intention-to-treat (ITT) analysis. Furthermore, it remained unclear whether the study population consisted of patients with chronic constipation or a mixed population of acute and chronic constipation. This trial was conducted by 17 general practitioners in the United Kingdom (UK) and funded by a manufacturer of a psyllium product. After 2 weeks of treatment, most parameters of bowel function (stool consistency,

frequency of stools, ease of defecation, abdominal pain/discomfort, straining) employed in this study were statistically significantly more improved in patients on psyllium (10.8g/d) than on placebo. For example, more patients on psyllium than on placebo reported improvement of straining (data not reported, $P = 0.003$). The second study was of fair methodological quality; however, only 22 patients were enrolled in this RCT.[36] Therefore chance findings (random error) cannot be ruled out. Results are consistent with findings from the open-label RCT. After 8 weeks of treatment, patients on psyllium (10g/d) had a statistically significantly higher stool frequency than patients on placebo (3.8 vs. 2.9; $P < 0.05$). Nevertheless, given the methodological limitations of both studies, results must be interpreted cautiously.

Tegaserod

Tegaserod, a 5-HT4 serotonin receptor agonist, has been FDA used for the treatment of chronic constipation in men and women under the age of 65. Five RCTs provide good evidence on the general efficacy of tegaserod for the treatment of chronic constipation.[37-41] These studies are listed in Table 8.

Table 7. Summary of trials assessing the general efficacy of drugs for the treatment of chronic constipation in adults

Author, year	Study design	N; Study duration	Comparisons	Population, % female, setting	Results	Quality rating
PEG 3350						
Andorsky et al., 1990[32]	RCT, cross-over	37; 5 days	Placebo	Patients with chronic constipation, 76% female, setting NR	Statistically significantly higher mean stool frequency/week with PEG (7.75 vs. 4.88; $P < 0.01$)	Fair
Cleveland et al., 2001[33]	RCT, cross-over	23, 2 weeks	Placebo	Patients with chronic constipation, 96% female, from GI-practices and primary care practice	Statistically significantly higher mean stool frequency/week with PEG (7.0 vs. 3.6; $P = 0.001$)	Poor (high attrition, no ITT analysis)
DiPalma et al., 2000[31]	RCT	151; 2 weeks	PEG 3350 (17g/d) vs. placebo	Patients with chronic constipation, 87% female, from GI-practices	Statistically significantly more with treatment success with PEG (66% vs. 48%; $P < 0.005$)	Fair
PSYLLIUM						
Ashraf et al., 1995[36]	RCT	22, 8 weeks	Psyllium (10g/d) vs. placebo	Patients with chronic constipation,	Statistically significant increase in stool	Fair

				64% female, tertiary care	frequency (3.8 vs. 2.9; $P <$ 0.05)	
Fenn et al., 1986[35]	RCT, single-blinded	201; 2 weeks	Psyllium (10.8g/d) vs. placebo	British primary care population, 75% female	Statistically significant reduction in abdominal pain ($P = 0.035$) and straining ($P =$ 0.003) for psyllium	Poor (no ITT analysis)

GI: gastrointestinal; ITT: intent-to-treat; NR: not reported; PEG: polyethylene glycol; RCT: randomized controlled trial

Table 8. Summary of trials assessing the general efficacy of tegaserod for the treatment of chronic constipation in adults

Author, year	Study design	N; Study duration	Comparisons	Population, % female, setting	Results	Quality rating
Johanson et al. 2004[37]	RCT	1348; 12 weeks	Tegaserod (2 mg and 6 mg BID) vs. placebo	Patients with chronic constipation, 90% female	CSBM response weeks 1-4 tegaserod groups 6 mg 43.2% 2mg 41.4% vs. placebo 25% ($P <$ 0.0001)	N/A*
Kamm et al. 2005[38]	RCT	1264; 12 weeks	Tegaserod (2 mg and 6 mg BID) vs. placebo	Patients with chronic constipation, 86% female	CSBM response weeks 1-4 were significantly greater ($P < 0.05$) in the tegaserod groups 56% vs. placebo 35%	N/A*
Lin et al. 2007[39]	RCT	607; 4 weeks	Tegaserod 6 mg BID vs. placebo	Patients in China with chronic constipation, 78% female	Increase $\geq$ CSBM/wk over wk 1-4 (47.7% vs. 35.0%, tegaserod vs. placebo, respectively, $P =$ 0.0018)	N/A*
Sullivan et al. 2006[41]	RCT	15 4 weeks	Tegaserod 6 mg BID vs. placebo	Patients with constipation and Parkinson's disease, 33% female	Overall SGA of satisfaction tegaserod 8.3 vs. placebo 8.7 $P =$ 0.1	N/A*

BID: twice a day; CSBM: complete spontaneous bowel movement; N/A: not applicable; RCT: randomized controlled trial; SGA: subject's global assessment

*Because tegaserod has been taken off the market in the US, we did not rate the internal validity of individual studies

Comparative efficacy and effectiveness

Table 9 summarizes the trials assessing the comparative efficacy of constipation drugs in adults; Table 11 summarizes the evidence profile for the comparative efficacy.

Docusate sodium vs. psyllium

A double-blinded RCT randomized 187 patients with chronic constipation to docusate sodium (200 mg/d) or psyllium (10.2 g/d).[42] This study received a poor quality rating because of a high rate of post-randomization exclusions (9%) and the lack of an ITT analysis. After 2 weeks of treatment no significant differences between treatment groups in subjective outcomes (straining, pain with bowel movement, evacuation completeness, constipation) were apparent. Patients on psyllium had more bowel movements (3.51 vs. 2.87/week) and a higher stool water content (73.89% vs. 71.58%) than patients on docusate sodium. These differences reached statistical significance. However, statistical testing was exclusively based on one-sided tests and absolute differences might not be clinically relevant.

Lactulose vs. PEG 3350

One open-label, head-to-head RCT randomized 115 patients to lactulose (10 – 30 g/d) or PEG 3350 (13 – 39 g/d) for the treatment of chronic constipation.[43] Thirty-eight percent of participants were geriatric patients. This study, however, was rated as poor because no ITT analysis was conducted. More than 13% of patients dropped out prior to the study endpoint. A completers only analysis indicated that after 4 weeks patients on lactulose had fewer weekly stools (1.3 vs. 0.9; $P = 0.005$) and more straining (score for straining: 0.5 vs. 1.2; $P = 0.0001$) than patients on PEG 3350. The overall visual analogue scale (VAS) for improvement was lower in patients on lactulose than on PEG 3350 (5.2 vs. 7.4; $P = 0.0001$). Although these differences achieved statistical significance, the clinical relevance remains unclear.

PEG 3350 vs. psyllium

The only available evidence comparing PEG 3350 (25g/d) with psyllium (7g/d) was an open-label RCT enrolling 126 Chinese patients with chronic constipation.[44, 45] This study was funded by a producer of a PEG 3350 formulation. Both treatment groups increased in mean weekly defecation rates. Statistically significantly more patients on PEG 3350 than on psyllium, however, experienced improvement after 2 weeks of treatment with respect to a composite outcome including defecation frequency, stool form, and difficulty of defecation (92% vs. 73%, $P = 0.005$).

Table 9. Summary of trials assessing the comparative efficacy of constipation drugs in adults

Author, year	Study design	N; Study duration	Comparisons	Population, % female, setting	Results	Quality rating
DOCUSATE SODIUM VS. PSYLLIUM						
McRorie et al., 1998[42]	RCT	170; 2 weeks	Docusate sodium (200mg/d) vs. psyllium (10.2 g/d)	US patients with chronic constipation, 92% female, setting NR	No difference in subjective outcome measures	Poor (no ITT analysis, high post-randomization exclusions)
LACTULOSE VS. PEG 3350						
Attar et al., 1999[43]	RCT, open-label	115, 4 weeks	Lactulose (10-39g/d) vs. PEG 3350 (13-39g/d)	French and Scottish patients with chronic constipation, 82% female, general and geriatric hospitals	Less improvement for lactulose than for PEG 3350 (VAS 5.2 vs. 7.4; $P < 0.001$)	Poor (no ITT analysis)
PEG 3350 VS. PSYLLIUM						
Wang et al., 2005[45]	RCT, open-label	126, 2 weeks	PEG 3350 (25g/d) vs. psyllium (7g/d)	Chinese patients with chronic constipation, 60% female, setting NR	Greater rate of improvements with PEG 3350 than with psyllium (92% vs. 73%; $P = 0.005$)	Fair

ITT: intent-to-treat; NR: not reported; PEG: polyethylene glycol; RCT: randomized controlled trial; VAS: visual analogue scale

Table 10. Evidence Profile of the general efficacy of constipation drugs for the treatment of chronic constipation in adults

Evidence Profile: General efficacy of constipation drugs							
No. of Studies/ Patients	**Design**	**Quality**	**Consistency**	**Directness**	**Magnitude of Effect**	**Other modifying factors***	**Overall Grade of the Evidence**
Outcome: Efficacy of docusate calcium							
No evidence							
Outcome: Efficacy of docusate sodium							
No evidence							
Outcome: Efficacy of lactulose							
No evidence							
Outcome: Efficacy of lubiprostone							
13 abstracts	RCTs	N/A (published as abstracts only)	No inconsistencies	Yes	N/A	No	N/A (published as abstracts only)
Outcome: Efficacy of PEG 3350							
3 RCTs/ 210 patients	RCTs	Serious methodological problems in 1 study	No inconsistencies	Yes	Higher mean stool frequency per week for PEG 3350: 7.0 vs. 4.88	No	Moderate
Outcome: Efficacy of psyllium							
1 RCT / 201 patients	RCT, single-blinded	Serious methodological problems	N/A	Yes	NR	No	Low
Outcome: Efficacy of tegaserod							
5 RCTs/ 3234 patients	RCTs	No serious methodological problems	No inconsistencies	Yes	Rates of CSBM 12-21 percentage points higher for tegaserod than placebo	No	N/A

*Imprecise or sparse data; a strong or very strong association; high risk of reporting bias; dose response gradient; effect of plausible residual confounding
CSBM: complete spontaneous bowel movements; N/A: not applicable; NR: not reported; PEG: polyethylene glycol; RCT: randomized controlled trial

Table 11. Evidence profile of the comparative efficacy of constipation drugs for the treatment of chronic constipation in adults

Evidence Profile: Comparative efficacy of constipation drugs in adults							
No. of Studies/ Patients	**Design**	**Quality**	**Consistency**	**Directness**	**Magnitude of Effect**	**Other modifying factors***	**Overall Grade of the Evidence**
Outcome: Docusate sodium vs. psyllium							
1 RCT, 170 patients	RCT	Serious methodological problems	N/A	Yes	No difference	None	Low
Outcome: Lactulose vs. PEG 3350							
1 RCT, 115 patients	RCT	Serious methodological problems	N/A	Yes	Less improvement for lactulose than for PEG 3350 (VAS 5.2 vs. 7.4; $P < 0.001$)	None	Low
Outcome: PEG 3350 vs. psyllium							
1 RCT, 126 patients	RCT, open-label	Some methodological problems	N/A	Yes	Greater rate of improvements with PEG 3350 than with psyllium (92% vs. 73%; $P = 0.005$)	None	Low
Outcome: All other comparisons							
No evidence							

*Imprecise or sparse data; a strong or very strong association; high risk of reporting bias; dose response gradient; effect of plausible residual confounding
IBS: Irritable Bowel Syndrome; N/A: not applicable; PEG: polyethylene glycol; RCT: randomized controlled trial; VAS: visual analogue scale

II. Chronic constipation in children

A. Summary of findings

General efficacy

We found no studies on general efficacy for the treatment of chronic constipation in children.

Comparative efficacy

No head-to-head evidence is available for most comparisons of constipation drugs. The evidence on the comparative efficacy of constipation drugs is limited to one head-to-head trial of PEG 3350 and lactulose. Findings indicated significant improvement in both treatment groups in primary outcomes (defecation and encopresis frequency/week). This study, however, had severe methodological limitations and was rated as poor.

No controlled evidence is available for docusate calcium, docusate sodium, lubiprostone, psyllium, or tegaserod.

B. Detailed assessment

General efficacy and effectiveness

We did not find any studies on the general efficacy and effectiveness of any included drugs that met our eligibility criteria. Table 13 summarizes the evidence profile for the general efficacy of constipation drugs in children.

Comparative efficacy and effectiveness

Table 12 summarizes the trials assessing the comparative efficacy of constipation drugs in children; Table 14 summarizes the evidence profile for the comparative efficacy of constipation drugs in children.

PEG 3350 vs. lactulose

A double-blinded RCT randomized 100 pediatric patients with constipation to PEG 3350 with electrolytes or lactulose. Patients under 6 years of age received PEG 3350 (2.95 g/sachet) or lactulose (6 g/sachet) while children 6 years or older started with 2 sachets/day.[46] This study was rated as poor quality because of a lack of ITT analysis and a high rate of post-randomization exclusions (9%). After 8 weeks of treatment, both groups showed a significant increase in mean defecation frequency per week (PEG 3350: 3 pre vs. 7 post treatment; lactulose: 3 pre vs. 6 post treatment) and a significant decrease in mean

encopresis frequency per week (PEG 3350: 10 pre vs. 3 post; lactulose: 8 pre vs. 3 post treatment). There was no significant difference between treatment groups with respect to either of these parameters at 1, 2, 4, and 8 weeks of the study. Authors defined overall treatment success as three or more bowel movements per week and one or fewer encopresis episodes every 2 weeks. According to this parameter, a significantly higher number of patients in the PEG group were successfully treated compared with the lactulose group (56% vs. 29%, $P = 0.02$).

Table 12. Summary of trials assessing the comparative efficacy of constipation drugs in children

Author, year	Study design	N; Study duration	Comparisons	Population, % female, setting	Results	Quality rating
PEG 3350 vs. LACTULOSE						
Voskuijl et al., 2004[46]	RCT	100; 8 weeks	PEG 3350 (2.95g or 5.9g) vs. lactulose (6g or 12g)	Children age 6 to 15 years with chronic constipation, 45% female, multi-center, referral population	Higher "success" rates as defined by authors for PEG than lactulose (56% vs. 29%; $P = 0.02$)	Poor (no ITT analysis, high rate of post-randomization exclusions)

ITT: intent-to-treat; PEG: polyethylene glycol; RCT: randomized controlled trial

Table 13. Evidence profile of the general efficacy of constipation drugs for the treatment of chronic constipation in children

Evidence Profile: General efficacy of constipation drugs							
No. of Studies/ Patients	**Design**	**Quality**	**Consistency**	**Directness**	**Magnitude of Effect**	**Other modifying factors***	**Overall Grade of the Evidence**
Outcome: All comparisons							
No evidence							

*Imprecise or sparse data; a strong or very strong association; high risk of reporting bias; dose response gradient; effect of plausible residual confounding

Table 14. Evidence profile of the comparative efficacy of constipation drugs for the treatment of chronic constipation in children

Evidence Profile: Comparative efficacy of constipation drugs in children							
No. of Studies/ Patients	**Design**	**Quality**	**Consistency**	**Directness**	**Magnitude of Effect**	**Other modifying factors***	**Overall Grade of the Evidence**
Outcome: PEG 3350 vs. Lactulose							
1 RCT, 100 patients	RCT	Serious methodological problems	N/A	Yes	No difference	None	Low
Outcome: All other comparisons							
No evidence							

*Imprecise or sparse data; a strong or very strong association; high risk of reporting bias; dose response gradient; effect of plausible residual confounding; N/A: not applicable; PEG: polyethylene glycol; RCT: randomized controlled trial

III. Constipation associated with IBS in adults

A. Summary of findings

No controlled evidence is available for docusate calcium, docusate sodium, lactulose, PEG 3350, and psyllium for the treatment of Irritable Bowel Syndrome with predominant constipation (IBS-C) in adults.

Five RCTs support the general efficacy of tegaserod for the treatment of IBS-C in women.

Only one study, published as an abstract only, examined the efficacy of lubiprostone in patients with IBS-C.

B. Detailed assessment

General efficacy and effectiveness

No controlled evidence is available on the efficacy of docusate calcium, docusate sodium, lactulose, PEG 3350, and psyllium for the treatment of IBS-C in adults. Available trials were all conducted in mixed populations of IBS-C and IBS-D and, therefore, did not meet our eligibility criteria.

Five RCTs support the general efficacy of tegaserod for the treatment of IBS-C.[47-51] These studies are presented in Table 15. However, as mentioned above, tegaserod is currently not available in the US or Canada because of safety concerns.

Only one study, published as an abstract only, examined the efficacy of lubiprostone in patients with IBS-C.[52] Because the reported information was insufficient to critically appraise the methods of this study, we did not formally include it. Results, however, suggest that lubiprostone is an efficacious treatment for IBS-C. Table 16 summarizes the evidence profile for the general efficacy for the treatment of IBS-C with constipation drugs.

Table 15. Summary of trials assessing the efficacy of tegaserod for the treatment of IBS-C in adults

Author, year	Study design	N; Study duration	Comparisons	Population, % female	Results	Quality rating
Nyhlin et al. 2004[47]	RCT	647 12 weeks	Tegaserod 6 mg BID vs. placebo	Patients with IBS-C, 86% female	Over weeks 1 to 12, the odds ratio of satisfactory relief was 1.78, in favor of tegaserod (95% CI (1.35, 2.34), $P <$ 0.0001).	N/A*
Kellow et al. 2003[48]	RCT	520 12 weeks	Tegaserod 6 mg BID vs. placebo	Patients with IBS-C from the Asia-Pacific region, 88% female	Overall satisfactory relief was greater in tegaserod the weeks 1-12 (62% v 44%, respectively; $P <$ 0.0001)	N/A*
Muller-Lissner et al. 2001[49]	RCT	881 12 weeks	Tegaserod (2 mg and 6 mg BID) vs. placebo	Patients with IBS-C, 83% female	Responder rates for the SGA of relief were 46.5%, 46.3% and 34.5% for the 2 mg BID, 6 mg BID and placebo groups, respectively.	N/A*
Novick et al. 2002[50]	RCT	1519 12 weeks	Tegaserod 6 mg BID vs. placebo	Female patients with IBS-C, 100% female	Improvements in the SGA tegaserod 43.5% vs. placebo 38.8% ($P < 0.05$)	N/A*
Tack et al. 2005[51]	RCT	2660 1 month	Tegaserod 6 mg BID vs. placebo	Female patients with IBS-C, 100% female	Tegaserod 33.7% vs. placebo 24.2% for overall relief of IBS symptoms	N/A*

BID: twice a day; CI: confidence interval; IBS: Irritable Bowel Syndrome; RCT: randomized controlled trial; SGA: subject's global assessment

*Because tegaserod has been taken off the market in the US, we did not rate the internal validity of individual studies

Comparative efficacy and effectiveness

We did not find any evidence on the comparative efficacy and effectiveness of included drugs for the treatment of IBS-C in adults. Table 17 summarizes the evidence profile for the comparative efficacy for the treatment of IBS-C with constipation drugs.

Table 16. Evidence profile of the general efficacy of constipation drugs for the treatment of IBS-C in adults

Evidence Profile: General efficacy of constipation drugs							
No. of Studies/ Patients	**Design**	**Quality**	**Consistency**	**Directness**	**Magnitude of Effect**	**Other modifying factors***	**Overall Grade of the Evidence**
Outcome: Efficacy of docusate calcium							
No evidence							
Outcome: Efficacy of docusate sodium							
No evidence							
Outcome: Efficacy of lactulose							
No evidence							
Outcome: Efficacy of lubiprostone							
1 abstract	RCT	N/A (published as abstracts only)	N/A	Yes	N/A	N/A	N/A (published as abstracts only)
Outcome: Efficacy of PEG 3350							
No evidence							
Outcome: Efficacy of psyllium							
No evidence							
Outcome: Efficacy of tegaserod							
5 RCTs /6227	RCTs	No serious methodological problems	No inconsistencies	Yes	Relief rates were 10-18 percentage points higher for tegaserod than placebo	No	N/A

*Imprecise or sparse data; a strong or very strong association; high risk of reporting bias; dose response gradient; effect of plausible residual confounding; N/A: not applicable; PEG: polyethylene glycol; RCT: randomized controlled trial

Table 17. Evidence profile of the comparative efficacy of constipation drugs for the treatment of IBS-C in adults

Evidence Profile: Comparative efficacy of constipation drugs							
No. of Studies/ Patients	**Design**	**Quality**	**Consistency**	**Directness**	**Magnitude of Effect**	**Other modifying factors***	**Overall Grade of the Evidence**
Outcome: All comparisons							
No evidence							

*Imprecise or sparse data; a strong or very strong association; high risk of reporting bias; dose response gradient; effect of plausible residual confounding

IV. Constipation associated with IBS in children

A. Summary of findings

No controlled evidence is available for docusate calcium, docusate sodium, lactulose, PEG 3350, and psyllium for the treatment of IBS-C in children.

One RCT supports the general efficacy of tegaserod for the treatment of IBS-C in adolescents, particularly in reduction in pain.[53]

B. Detailed assessment

General efficacy and effectiveness

No controlled evidence is available on the efficacy of docusate calcium, docusate sodium, lactulose, PEG 3350, and psyllium for the treatment of IBS-C in children. Table 19 summarizes the evidence profile for the general efficacy for the treatment of IBS-C with constipation drugs.

One RCT randomized 48 postpubertal adolescents with constipation predominant IBS to laxative only or laxative plus tegaserod (6mg/bid).[53] Both groups showed an increase in mean frequency of bowel movements per week (5.04 vs. 6.57; $P < 0.05$). A significantly higher percentage of patients in the tegaserod group experienced "good" pain reduction (defined as a reduction in pain of at least 3 points on the pain rating scale compared to pre-treatment levels) than in the laxative only group (66.7% vs. 18.5%; $P < 0.05$). Fewer tegaserod-treated patients experienced post-treatment worsening of pain than laxative only patients (9.5% vs. 22.2%; $P < 0.05$). However, as mentioned above, tegaserod is currently not available in the US or Canada because of safety concerns.

Table 18. Summary of trials assessing the efficacy of tegaserod for the treatment of IBS-C in children

Author, year	Study design	N; Study duration	Comparisons	Population, % female	Results	Quality rating
Khoshoo et al. 2006[53]	RCT	48; 4 weeks	Laxative only or combination therapy with laxative and tegaserod 6 mg BID	Postpubertal adolescents with constipation predominant IBS, 60% female	Increase in the frequency of bowel movements was similar in both (Data = NR) Good reduction in pain tegaserod 66.7% vs. placebo 18.5% ($P < 0.05$).	N/A*

BID: twice a day; IBS: Irritable Bowel Syndrome; N/A: not applicable: NR: not reported; RCT: randomized controlled trial

*Because tegaserod has been taken off the market in the US, we did not rate the internal validity of individual studies

Comparative efficacy and effectiveness

We did not find any evidence on the comparative efficacy and effectiveness of included drugs for the treatment of IBS-C in children. Table 20 summarizes the evidence profile for the comparative efficacy for the treatment of IBS-C with constipation drugs

Table 19. Evidence profile of the general efficacy of constipation drugs for the treatment of IBS-C in children

Evidence Profile: General efficacy of constipation drugs							
No. of Studies/ Patients	**Design**	**Quality**	**Consistency**	**Directness**	**Magnitude of Effect**	**Other modifying factors***	**Overall Grade of the Evidence**
Outcome: Efficacy of docusate calcium							
No evidence							
Outcome: Efficacy of docusate sodium							
No evidence							
Outcome: Efficacy of lactulose							
No evidence							
Outcome: Efficacy of lubiprostone							
No evidence							
Outcome: Efficacy of PEG 3350							
No evidence							
Outcome: Efficacy of psyllium							
No evidence							
Outcome: Efficacy of tegaserod							
1 RCT, 48 patients	RCT	No serious methodological problems	N/A	Yes	More tegaserod patients had "good" reduction in pain level: 66.7% vs. 18.5%	None	N/A

*Imprecise or sparse data; a strong or very strong association; high risk of reporting bias; dose response gradient; effect of plausible residual confounding

Table 20. Evidence profile of the comparative efficacy of constipation drugs for the treatment of IBS-C in children

Evidence Profile: Comparative efficacy of constipation drugs							
No. of Studies/ Patients	**Design**	**Quality**	**Consistency**	**Directness**	**Magnitude of Effect**	**Other modifying factors***	**Overall Grade of the Evidence**
Outcome: All comparisons							
No evidence							

*Imprecise or sparse data; a strong or very strong association; high risk of reporting bias; dose response gradient; effect of plausible residual confounding; N/A: not applicable; PEG: polyethylene glycol; RCT: randomized controlled trial

KEY QUESTION 2. Does treatment duration influence the effectiveness of drugs used to treat chronic constipation and chronic constipation associated with Irritable Bowel Syndrome? When should treatments be switched in patients not responding to a given drug?

We did not find any evidence to answer this key question conclusively. Most studies lasted between 2 and 8 weeks, none was longer than 12 weeks. Effect sizes of treatments were similar between short-term studies and trials lasting 3 months. None of the studies addressed the question of when to switch therapies in non-responders.

KEY QUESTION 3. What is the comparative tolerability and safety of drugs used to treat chronic constipation and chronic constipation associated with Irritable Bowel Syndrome?

We included 22 RCTs, one systematic review, one open-label extension of an RCT, six observational studies and two pooled data analyses. Five RCTs were head-to-head trials.

Most studies that examined the comparative efficacy of our drugs of interest also examined their harms. Methods of adverse events assessment, however, differed greatly. Few studies used objective scales. Most studies combined patient-reported adverse events with a clinical examination and laboratory values. Often determining whether assessment methods were unbiased and adequate was difficult due to limited reporting in the articles. Rarely were adverse events pre-specified and defined. Short study durations and small sample sizes additionally limited the validity of adverse events assessment with respect to rare but serious adverse events. Most importantly, the quality of most of the included studies was poor. Thus, results must be interpreted cautiously.

I. Chronic constipation and constipation associated with IBS in adults

A. Summary of findings

General tolerability and safety

The evidence is generally poor quality and sparse. We found no studies on the general tolerability and safety of docusate calcium, docusate sodium, or lactulose that met our eligibility criteria.
Studies assessing the tolerability and safety of lubiprostone have been published as abstracts only. Therefore, the available information is insufficient to critically appraise the underlying methods and draw firm conclusions. The abstracts consistently reported a higher incidence of nausea in lubiprostone treated

subjects than in those treated with placebo. The most common adverse events reported were nausea, headache, diarrhea, and bloating. Discontinuations due to adverse events ranged from 3% to almost 20%.

Three placebo-controlled RCTs and one open-label observational study examined the tolerability and safety of PEG 3350. The largest and only fair quality RCT (N = 151) found no significant differences in adverse events. Patients treated with PEG 3350 had lower rates of severe cramping and severe gas than patients on placebo. The other three studies were poor quality and were consistent in reporting only minor adverse events (nausea, gas, cramps, and diarrhea). All four studies were funded by the makers of PEG formulations.

We found only two poor quality RCTs meeting our inclusion criteria that examined the general tolerability and safety of psyllium. Both enrolled subjects with chronic constipation and were funded by the makers of psyllium preparations. The studies consistently reported that psyllium was well tolerated. None of the studies reported statistically significant differences in adverse events between psyllium and placebo and none reported any serious adverse events. Given the poor quality of these studies, results must be interpreted cautiously.

Sixteen studies reported data on the general tolerability and safety of tegaserod for the treatment of chronic constipation and IBS-C in adults. Most report a greater incidence of diarrhea with tegaserod than placebo.

Comparative tolerability and safety

No head-to head evidence is available for most comparisons of the included medications. The evidence is limited to 4 head-to-head trials on comparisons of PEG 3350 versus lactulose, lactulose versus psyllium (2 trials), and PEG 3350 versus psyllium. All of these studies had severe methodological limitations and were rated as poor quality for assessment of adverse events and the results should be interpreted cautiously.

An open-label, single blind RCT comparing PEG 3350 with lactulose for the treatment of chronic constipation found some evidence that those treated with PEG had lower rates of flatus and abdominal pain but higher rates of diarrhea. There were no other significant differences for tolerability or safety.

Two poor quality open-label RCTs reported inconsistent results comparing the tolerability and safety of lactulose and psyllium. One reported numerically lower rates of diarrhea and abdominal pain with

psyllium; the other reported no differences in abdominal pain or straining and better tolerance with lactulose due to palatability.

The evidence comparing PEG 3350 with psyllium was limited to one open-label RCT of Chinese patients with chronic constipation. There were no significant differences in adverse events between the groups.

B. Detailed assessment

General risk of harms

Table 21 summarizes the trials assessing the general harms of constipation drugs; Table 24 summarizes the evidence profile for the general tolerability and safety of individual drugs.

Docusate calcium

We did not find any studies on the general harms of docusate calcium that met our eligibility criteria.

Docusate sodium

We did not find any studies on the general harms of docusate sodium that met our eligibility criteria.

Lactulose

We did not find any studies on the general harms of lactulose that met our eligibility criteria.

Lubiprostone

We did not find any evidence on the safety of lubiprostone published as full text articles. The literature search detected 12 published abstracts addressing safety/harms for patients with chronic constipation or IBS-C.[21, 23-29, 52, 54-56] Most studies were conducted in patients with chronic constipation; only one abstract enrolled patients with IBS-C.[52] Most trials were of relatively short durations (3 to 4 weeks), but two were long-term studies of 24 and 48 weeks.[21, 25] The incidence of nausea was consistently higher in lubiprostone than in placebo in controlled studies. The most common adverse events reported were nausea, headache, diarrhea, and bloating. Discontinuations due to adverse events ranged from 3% to almost 20%. These abstracts did not provide enough information to critically appraise the methods of individual studies. Thus, we cannot report findings in detail.

The FDA CDER medical review of lubiprostone[57] assessed safety data for 1,113 subjects from phase 2 and 3 clinical trials. The most common adverse events reported were headache and gastrointestinal events (nausea, diarrhea, abdominal distention or pain). Gastrointestinal events were the most common

events leading to medication withdrawal. There was no evidence that lubiprostone causes adverse events on heart rate, cardiac conduction, cardiac repolarization, or bone mineral density.

Polyethylene Glycol 3350 (PEG 3350)

Three RCTs[31-33] and one open-label observational study[34] examined the general harms of PEG 3350. The largest trial, a fair double-blinded placebo-controlled RCT, enrolled 151 patients with chronic constipation and found no significant differences between PEG and placebo for laboratory measurements or adverse events.[31] The PEG 3350 patients had lower rates of severe cramping and severe gas. The other two RCTs were cross-over studies[32, 33] that were poor quality. They reported minor adverse events for subjects taking PEG including nausea, gas, cramps, and diarrhea. All four studies were funded by the makers of PEG formulations.

The fair double-blinded placebo-controlled RCT[31] enrolled 151 adult subjects with a history of constipation and randomized them to PEG 3350 without electrolytes or placebo. Patients were required to have less than two bowel movements during a 7 day qualification period. The groups were similar at baseline for age (mean 46.7 for PEG group and 45.8 for placebo) and gender. They also had similar rates of severe cramping and severe gas during the 7 day pretreatment qualification period. Over the 2 week treatment period, patients treated with PEG had lower rates of severe cramping (12.0% vs. 22.6%; $P = 0.001$) and severe gas (24% vs. 40.2%; $P = 0.001$) than those treated with placebo. There were no statistically or clinically significant differences between groups for laboratory measurements (complete blood count [CBC], blood chemistry, and urinalysis after 14 days of treatment) or other adverse events between the groups (data not reported).

The first cross-over RCT[32] compared PEG 3350 with electrolytes (8 ounces or 16 ounces) with placebo in 37 adults with chronic constipation. Nausea was reported in 8.3% of subjects in the 8 ounce PEG group and 0% in the other groups. Gas/cramps were reported in 16.7% of the 8 ounce PEG group, 75% of the 16 ounce PEG group, and 0% of the placebo group (*P*-value not reported). The study was rated as poor quality for adverse events.

The other cross-over RCT[33] randomized 23 patients in a private practice to 2 weeks of treatment with PEG 3350 without electrolytes followed by 2 weeks of placebo or vice versa. Subjects were 18 or older, had a history of constipation, and 3 or fewer BMs during a 7 day placebo run-in. The mean age of subjects was 47.7 years and over 95% were female. Thirteen percent of subjects reported diarrhea while taking PEG (not reported for placebo). There were no significant differences in nausea or heartburn. The

authors report that there were no clinically significant differences in blood chemistry, CBC, or urinalysis between the active treatment and placebo patients (numbers not reported). While taking PEG, subjects reported lower scores (0-4 scales rated by patients) for cramping (0.6 vs. 0.9; $P < 0.001$) and rectal irritation (0.4 vs. 0.6; $P = 0.001$) compared to placebo. There was no difference in flatus (1.9 vs. 2.0; $P = 0.25$). The study was rated as poor quality mainly due to high attrition, as 56% of the study population requested termination (44% during placebo and 11% during PEG treatment).

The open-label observational study[34] was an uncontrolled before-after study that included a post-treatment follow-up. The study enrolled 50 adults with chronic constipation from a university gastroenterology practice using local advertising. All subjects were treated with PEG 3350 without electrolytes 17 g/d for 14 days. The mean age of patients was 52.1 years, 94% were female, and 60% were Caucasian. The mean duration of constipation was about 22 months. After 14 days, the following adverse events were reported: nausea (2%), constipation (2%), chest congestion (2%), high blood pressure (2%), and headache (4%). The study was rated poor quality for numerous reasons including the lack of a comparison group and no blinding.

The FDA CDER medical review of PEG and the resulting drug labeling note that nausea, abdominal bloating, cramping, and flatulence may occur. In addition, they state that high doses may produce diarrhea and excessive stool frequency, particularly in elderly nursing home patients.

Psyllium

We did not find any good or fair quality evidence on the general harms of psyllium. Two poor quality RCTs examined the general harms of psyllium.[35, 36, 58] Both studies enrolled subjects with constipation and were funded by the makers of psyllium preparations. Psyllium was well tolerated in both trials. Neither of the studies reported significant increases in adverse events between psyllium and placebo and neither reported any serious adverse events. Given the poor quality of these studies, results should be interpreted cautiously.

The first RCT[36, 58] compared 11 subjects treated with psyllium (Metamucil®) to 11 treated with placebo for 8 weeks. They enrolled adults aged 19-85 with chronic constipation. After a 4 week run-in, 22 subjects were confirmed by stool diaries to demonstrate constipation and were randomized. The psyllium group had more females (72.7% vs. 54.5%) and a longer mean duration of constipation (33.7 vs. 19.6 months). Psyllium was well tolerated as no patients withdrew from the study due to adverse events. All 22 subjects completed the study. There were no statistically significant differences in the adverse events

reported, but there was a trend toward more abdominal pain in the psyllium group (abdominal pain: 18% psyllium vs. 0% placebo; *P*-values not reported). These results should be interpreted with caution due to the poor quality of the study for evaluating adverse events. Adverse events were not prespecified or defined, ascertainment techniques were not adequately described, and there was no statistical control for potential confounders.

The second RCT[35] randomized 201 adults with functional constipation to psyllium (Regulan, ispaghula 3.6 grams three times daily) or placebo for 2 weeks. It was a multi-site study in the UK involving 17 general practitioners. The groups were similar at baseline and had median durations of constipation of 2 (psyllium) and 3 years (placebo). Five subjects in each treatment group named side effects as reason for withdrawal from study. There were no serious adverse events reported.

Tegaserod

Fifteen studies, including 9 RCTs,[37-39, 47-51, 59] 1 systematic review,[60] 2 pooled analyses,[40, 61] 2 open-label prospective cohort studies,[62, 63] and 1 uncontrolled extension of an RCT[64] report data on the general safety and harms of tegaserod for the treatment of chronic constipation and IBS-C in adults. These are summarized in Table 22. Most report a greater incidence of diarrhea with tegaserod than placebo. The cardiovascular events reported in these studies for patients treated with tegaserod are included in Table 22.

Table 21. Summary of trials assessing the general harms of constipation drugs

Author, year	Study design	N; Study duration	Comparisons	Population, % female, setting	Results	Quality rating
PEG 3350						
DiPalma et al., 2000[31]	RCT	151; 2 weeks	Placebo	Adults with constipation, 87% female, US multicenter	PEG group had lower rates of severe cramping (12.0% vs. 22.6%; $P = 0.001$) and severe gas (24% vs. 40.2%; $P = 0.001$). No differences for laboratory measurements or other AEs (data NR).	Fair
Andorsky and Goldner, 1990[32]	RCT, cross-over	37; 5 days	Placebo	Adults with chronic constipation, 76% female, setting outpatient	Nausea in 8.3% vs. 0% vs. 0% (PEG 8 oz group vs. PEG 16 oz vs. placebo; *P* NR). Gas/cramps in 16.7%, 75%, and 0% (*P* NR).	Poor (for AEs, fair for efficacy)
Cleveland et al., 2001[33]	RCT, cross-over	23; 4 weeks	Placebo	Adults with constipation, 96% female, USA private practice	No difference laboratory measurements between groups (data NR). On 0 to 4 scale, less cramping (0.6 vs. 0.9; $P < 0.001$) and rectal irritation (0.4 vs. 0.6; $P = 0.001$) while taking PEG than while taking placebo, but no difference in flatus (1.9 vs. 2.0; $P = 0.25$).	Poor (High attrition, no ITT analysis)
*Tran et al., 2005[34]	Open-label observational study	50; 14 days	None	Adults with chronic constipation, 84% female, a university gastroenterology practice	Nausea (2%), constipation (2%), chest congestion (2%), high blood pressure (2%), and headache (4%)	Poor (No comparison group, no blinding)
PSYLLIUM						
Ashraf et al., 1995 and 1996[36, 58]	RCT	22; 8 weeks (after 4 week run-in)	Placebo	Adults with chronic constipation responding to advertisements in local newspapers, 64% female, general medicine, GI, and geriatric clinics	Well tolerated as all subjects completed treatment; no statistically significant differences in adverse events between psyllium and placebo	Poor for adverse events (Fair for efficacy)
Fenn et al., 1986[35]	RCT, blinding status NR	201; 2 weeks	Placebo	Adults with functional constipation, 75% female, setting NR	Psyllium resulted in greater frequency of improvement in abdominal pain ($P < 0.035$) and greater reduction in moderate or severe straining ($P = 0.003$).	Poor (No ITT analysis)

AE: adverse events; GI: gastrointestinal; IBS: Irritable Bowel Syndrome; NR: not reported; NS: not significant; PEG: polyethylene glycol; RCT: randomized controlled trial

* Did not meet eligibility criteria for efficacy; included for adverse events only

Table 22. Summary of trials assessing the general safety and harms of tegaserod for the treatment of chronic constipation and IBS-C in adults

Author, year	Study design	N; Study duration	Comparisons	Population, % female, setting	Results	Quality rating
CHRONIC CONSTIPATION						
Johanson et al., 2004[37]	RCT	1348; 12 weeks	Tegaserod (2 mg and 6 mg BID) vs. placebo	Adults with chronic constipation, 90% female	No significant differences in AEs or discontinuation due to AEs; Diarrhea (4.5% vs. 7.3% vs. 3.8%); Most frequent AEs were headache (9.2% vs. 9.8% vs. 12.8%) and nasopharyngitis (7.6% vs. 8.4% vs. 10.8%)	N/A*
Kamm et al., 2005[38]	RCT	1264; 12 weeks	Tegaserod (2 mg and 6 mg BID) vs. placebo	Adults with chronic constipation, 86% female	No significant differences in AEs or discontinuation due to AEs between groups; Diarrhea was more common in 6mg than placebo ($P = 0.007$) but not in 2mg ($P = 0.1516$ vs. placebo); most common AEs were headache and abdominal pain; both were more common among placebo.	N/A*
Lin et al., 2007[39]	RCT	607; 4 weeks	Tegaserod 6 mg BID vs. placebo	China; adults with chronic constipation, 78% female	Diarrhea was the most common AE and was more common with tegaserod (3.6% vs. 1.7%). Frequency and severity of AEs and withdrawal due to AEs was otherwise comparable.	N/A*
Quigley et al., 2006[40]	2 RCTs – pooled for safety analysis	2612; 12 weeks	Tegaserod (2 mg and 6 mg BID) vs. placebo	Adults with chronic constipation, 88% female	AE incidence was similar for all groups (56.3% vs. 57.1% vs. 59.6% for 2mg, 6mg, and placebo); most common AE was headache which was more common with placebo (10.1% vs. 11% vs. 13.2%); only diarrhea was	N/A*

					significantly different between groups (6.6% for 6mg vs. 3.0% for placebo; $P = 0.0005$)	
Fried et al., 2007[59]	RCT	322; 12 weeks	Tegaserod (6mg BID) vs. placebo	Adults with chronic constipation, 0% female	Similar frequency of total AEs (37.3% vs. 32.3%); GI disturbances were more common with tegaserod (17.1% vs. 8.5%); diarrhea (8.2% vs. 0.6%); Among 4 non-fatal serious AEs in the tegaserod group (vs. 2 with placebo), all were cardiac disorders (2 CAD, 1angina, 1 atrial fibrillation)	N/A*
Muller-Lissner et al., 2006[64]	Uncontrolled extension of a 12 week RCT	842 entered, 451 completed; 13 months	Tegaserod (2mg BID or 6mg BID)	Adults with chronic constipation, 87% female	No notable differences in AEs compared to short-term treatment; only half of patients completed the extension study; discontinuation reasons: 19.3% lack of efficacy, 11% withdrawal of consent; 6.3% AEs; headache and abdominal pain were the most common AEs; diarrhea in 2.0-8.5%	N/A*
IRRITABLE BOWEL SYNDROME						
Evans et al., 2004[60]	Systematic review	4040; 8 to 12 weeks	Tegaserod (2 mg and 6 mg BID) vs. placebo	12 years or older with IBS-C, primarily female (overall % NR)	Diarrhea was significantly higher in the tegaserod 6mg BID than placebo (RR 2.75; 95% CI 1.90, 3.97); NNH 20; trend toward higher frequency of headache (RR 1.18; 95% CI 0.97-1.44) abdominal pain (RR 1.11; 95% CI 0.86, 1.43) and nausea (RR 1.20; 95% CI 0.88, 1.63) with tegaserod (6mg BID) than placebo.	N/A*

Fried et al., 2005[62]	Open-label PCS	843; 8 weeks	Tegaserod 6mg BID	Adults with IBS-C, 72% female	AEs in 38%; diarrhea in 13% during first week and 7% thereafter; headache 12%; about 25% left the study early, mainly due to AEs; 0.9% serious AEs, 1 was cardiovascular (chest pain); no deaths	N/A*
Kellow et al., 2003[48]	RCT	520 12 weeks	Tegaserod 6 mg BID vs. placebo	Adults with constipation predominant IBS-C, 88% female, Asia-Pacific region	Diarrhea (10% vs. 3.1%) and abdominal pain (5.8% vs. 3.1%) were more frequent with tegaserod; other AE frequencies were similar; headache was most common AE (12% tegaserod vs. 11.1% placebo); discontinuation due to diarrhea in 2.3% of tegaserod; serious AEs (1.5% vs. 3.4%); more SAEs in the placebo group; no deaths	N/A*
Morganroth et al., 2002[61]	3 RCTs – pooled for safety analysis	2516; 12 weeks	Tegaserod (2 mg and 6 mg BID) vs. placebo	Adults with IBS-C, 84% female	No difference in new or worsening EKG abnormalities (tegaserod groups 11% vs. placebo 10%), QTc interval changing from normal to prolonged (0.4% vs. 0.6%), or frequency of cardiac arrhythmias (1.5% vs. 1.5%); no VT or SVT; diarrhea 11.7% vs. 5.4%	N/A*
Muller-Lissner et al., 2001[49]	RCT	881 12 weeks	Tegaserod (2 mg and 6 mg BID) vs. placebo	Adults with 3-month history of IBS-C, 83% female	AEs were similar in all groups; only diarrhea was more frequent with tegaserod than placebo (7.1%, 9.6%, 2.5%); headache (27.3%-30.6%) and abdominal pain (16.5%-17.1%) were the most common AEs	N/A*

Novick et al., 2002[50]	RCT	1519; 12 weeks	Tegaserod 6 mg BID vs. placebo	Adult females with IBS-C, 100% female	Overall AEs (58.3% vs. 55.7%); headache (9.0 vs. 5.7%), nausea (6.8% vs. 4.7%), and diarrhea (6.4% vs. 2.9%) were more frequent in the tegaserod group	N/A*
Nyhlin et al., 2004[47]	RCT	647; 12 weeks	Tegaserod 6 mg BID vs. placebo	Adults with constipation predominant IBS-C, 86% female	More overall AEs with tegaserod (55% vs. 50%); headache was the most frequently reported AE overall (8.0% vs. 4.7%); diarrhea more frequent with tegaserod (9.2% vs. 1.3%) and led to discontinuation in 2.8% of tegaserod group; 1 death in the tegaserod group due to acute myocardial infarction	N/A*
Tack et al., 2005[51]	RCT	2660; 1 month	Tegaserod 6 mg BID vs. placebo	Adult females with IBS-C, 100% female	Only diarrhea was reported significantly more frequently with tegaserod (3.8% vs. 0.6%; $P < 0.0001$); headache was the most common AE reported (5.5% vs. 5.0%; *P* NS); discontinuations due to AEs were similar; no deaths	N/A*
Tougas et al., 2002[63]	Open-label PCS	579 (53% completed trial); 12 months	Tegaserod 2 or 6 mg BID, flexible dose titration	Adults with constipation predominant IBS-C, 90% female	Diarrhea 10.1%; headache 8.3%; abdominal pain 7.4%; flatulence 5.5%; SAEs in 4.4% including chest pain in 2 patients; 11.2% of all subjects discontinued due to AEs	N/A*

AE: adverse events; BID: twice a day; CAD: coronary artery disease; EKG: electrocardiogram; GI: gastrointestinal; IBS-C: Irritable Bowel Syndrome; NNH: number needed to harm; NR: not reported; NS: not significant; QTC: Q; PCS: prospective cohort study; PEG: polyethylene glycol; RCT: randomized controlled trial; RR: risk ratio; SAEs: serious adverse events; SVT: supraventricular tachycardia; VT: ventricular tachycardia
*Because tegaserod has been taken off the market in the US, we did not rate the internal validity of individual studies

Comparative risk of harms

Table 23 summarizes trials assessing the comparative harms of constipation drugs; Table 25 summarizes the evidence profiles for the comparative tolerability and safety.

Lactulose vs. PEG 3350

We found just one poor quality open-label, head-to-head RCT that randomized 115 patients to lactulose (10 – 30 g/d) or PEG 3350 (with electrolytes, 13–39 g/d) for the treatment of chronic constipation.[43] The study was rated poor primarily because there was no ITT analysis; results should be interpreted cautiously. There were no significant differences in median daily scores for symptoms reflective of tolerance including: liquid stools, abdominal pain, flatulence, bloating and rumbling. However, the number of days with scores greater than 1 (0 to 3 scale) was lower in the PEG group for flatus (3.8 vs. 9.2; $P = 0.01$) and abdominal pain (3.9 vs. 6.8; $P = 0.08$). For the 4 week duration of the study, the mean number of liquid stools was higher in the PEG group (2.4 vs. 0.6; $P = 0.001$). There were 16 premature withdrawals from the study. Three were due to adverse events (2 PEG, diarrhea/vomiting/fever and abdominal pain vs. 1 lactulose, depression). For laboratory assessments, the only statistically significant change was a slight decrease in sodium in the lactulose group from 140 to 139 ($P = 0.02$). A mild hypokalemia (values not reported) was reported in two patients, one in each group, that were concurrently being treated with diuretics. A total of 61 of the 65 subjects treated with PEG completed an additional 2 months of follow up. There were no significant changes in adverse symptoms or laboratory results during this period. Four adverse events led to drug withdrawal during the additional 2 months: acute diarrhea with fever (1), abdominal pain (2), and vomiting (1).

Lactulose vs. psyllium

We found only 2 poor quality open-label RCTs from the UK comparing the harms or tolerability of lactulose and psyllium.[65, 66] One RCT funded by the makers of psyllium[65] reported numerically lower rates of diarrhea and abdominal pain with psyllium. The other RCT[66] reported no differences in abdominal pain or straining and better tolerance with lactulose due to palatability. The results of these studies should be interpreted with caution due to the poor quality.

The first open-label RCT[65] randomized 394 subjects to 4 weeks of treatment with psyllium (ispaghula husk, n = 224), lactulose (n = 91), or other laxatives (n = 79). This study included adult patients presenting to general physicians with simple constipation, defined as a change in bowel habits resulting in straining or passage of hard stools. The majority (63%) were female. The duration of constipation ranged from 7 days or less in 37 patients to more than 90 days in 36 patients. The reported incidences of diarrhea (1.5% of days vs. 2.2% of days vs. 4.4% of days; *P*-values not reported) and abdominal pain or

griping during weeks 3 to 4 (15.1% vs. 22.0% vs. 29.5%; *P*-values not reported) were numerically lower in the psyllium group than the lactulose group or the other laxative group. The study was rated poor quality for numerous reasons including no ITT analysis, no blinding, and adverse events were not pre-specified or defined.

The second open-label RCT[66] randomized 124 adult patients with chronic constipation to treatment with psyllium (ispaghula 3.5g twice daily) or lactulose (15 ml twice daily up to 60 ml as needed) for 4 weeks. Subjects entered the study via 21 general practitioners. There were no significant differences between the groups for abdominal pain or straining (*P*-value not reported). For tolerability, there was a statistically significant difference favoring the palatability of lactulose at 7 days (18.5% said psyllium was unpalatable vs. 5.7% for lactulose; $P = 0.04$). The trend continued at 28 days, but the difference was no longer statistically significant (15.6% vs. 4.2%; $P = 0.063$). The study was rated poor quality primarily for attrition of almost 26%.

PEG 3350 vs. psyllium

The only available evidence comparing PEG 3350 plus electrolytes (25 g/d) with psyllium (7 g/d) was an open-label RCT enrolling 126 Chinese patients with chronic constipation.[44, 45] This study was funded by makers of a PEG 3350 formulation. There were no significant differences in adverse events between the groups. The most common adverse events in the PEG 3350 group were dizziness (5%) and fatigue (3.3%); the most common in the psyllium group was dry mouth (5%).

Table 23. Summary of trials assessing the comparative harms of constipation drugs

Author, year	Study design	N; Study duration	Comparisons	Population, % female, setting	Results	Quality rating
LACTULOSE VS. PEG 3350						
Attar et al., 1999[43]	RCT, single-blind, open-label	115, 4 weeks	Lactulose vs. PEG 3350	French and Scottish patients with chronic constipation, 82% female, general and geriatric hospitals	No significant differences in median daily scores for diarrhea, abdominal pain, flatulence, or bloating. Fewer days with flatulence in the PEG group (3.8 vs. 9.2; *P* = 0.01) and a trend toward fewer with abdominal pain (3.9 vs. 6.8; *P* = 0.08). Mean number of liquid stools was higher in the PEG group (2.4 vs. 0.6; *P* = 0.001)	Poor (No ITT analysis)
LACTULOSE VS. PSYLLIUM						
Dettmar, 1998[65]	RCT, open-label	394, 4 weeks	Psyllium vs. lactulose vs. other laxatives	Adults with constipation, 63% female, Multi-site, outpatient, UK	Diarrhea (1.5% of days vs. 2.2% of days vs. 4.4% of days; *P* NR) and abdominal pain or griping during weeks 3 to 4 (15.1% vs. 22.0% vs. 29.5%; *P* NR) were numerically lower in the psyllium group.	Poor (No ITT analysis, no blinding, AEs not prespecified or defined)
Rouse et al., 1991[66]	RCT, open-label	124, 4 weeks	Psyllium vs. lactulose	Adults with chronic constipation, % female NR, multi-site, outpatient UK	No significant differences for abdominal pain or for straining (*P* NR). Palatability: At 7 days 18.5% said psyllium was unpalatable vs. 5.7% for lactulose (*P* = 0.04); at 28 days 15.6% vs. 4.2% (*P* = 0.063)	Poor (High attrition)
PEG 3350 VS. PSYLLIUM						
Wang et al., 2005[45]	RCT, open-label	126, 2 weeks	PEG 3350 vs. psyllium	Chinese patients with chronic constipation, 60% female, multicenter, outpatient	No significant differences in adverse events	Poor for AEs (Fair for efficacy)

AE: adverse events; ITT: intent-to-treat; NR: not reported; PEG: polyethylene glycol; RCT: randomized controlled trial; UK: United Kingdom

Table 24. Evidence profile of the general tolerability and harms of constipation drugs in adults

Evidence Profile: General tolerability and harms of constipation drugs in adults							
No. of Studies/ Patients	**Design**	**Quality**	**Consistency**	**Directness**	**Magnitude of Effect**	**Other modifying factors**	**Overall Grade of the Evidence**
Outcome: Tolerability and harms of docusate calcium							
No evidence							
Outcome: Tolerability and harms of docusate sodium							
No evidence							
Outcome: Tolerability and harms of lactulose							
No evidence							
Outcome: Tolerability and harms of lubiprostone							
12 abstracts	RCTs	N/A (published as abstracts only)	No inconsistencies	Yes for chronic constipation Yes for IBS-C	N/A	No	N/A (published as abstracts only)
Outcome: Tolerability and harms of PEG 3350							
4 studies/ 261 patients	3 RCTs	3 poor quality and 1 fair quality	Minor inconsistencies in the AEs reported	Yes for chronic constipation No for IBS-C	NR	Yes	Low
Outcome: Tolerability and harms of psyllium							
2 RCTs / 223 patients	RCTs	Serious methodological problems, both poor quality	No inconsistencies	Yes for chronic constipation No for IBS-C	NR	No	Low
Outcome: Tolerability and harms of tegaserod							
15 studies/ 21,207 patients (and FDA report on analysis of 29 RCTs)	9 RCTs	No serious methodological problems	No inconsistencies	Yes for chronic constipation Yes for IBS-C	Increased risk of cardiovascular AEs (0.1% vs. 0.01%) Greater incidence of diarrhea (3.6-10.1% vs. 0.6-3.1%) and GI disturbances (5.8-17.1% vs. 3.1-8.5%)	No	N/A

AE: adverse events; IBS-C: Irritable Bowel Syndrome; N/A: not applicable; NR: not reported
*Imprecise or sparse data; a strong or very strong association; high risk of reporting bias; dose response gradient; effect of plausible residual confounding

Table 25. Evidence profile of the comparative tolerability and harms of constipation drugs in adults

Evidence Profile: Comparative tolerability and harms of constipation drugs in adults							
No. of Studies/ Patients	**Design**	**Quality**	**Consistency**	**Directness**	**Magnitude of Effect**	**Other modifying factors***	**Overall Grade of the Evidence**
PEG 3350 vs. lactulose							
1 RCT/ 115 patients	RCT, open-label, single blind	Poor, Serious methodological problems	N/A	Yes for chronic constipation No for IBS-C	Days with flatulence (3.8 vs. 9.2; *P* = 0.01); days with abdominal pain (3.9 vs. 6.8; *P* = 0.08); Mean number of liquid stools (2.4 vs. 0.6; *P* = 0.001)	None	Low
Lactulose vs. psyllium							
2 RCTs/ 518	RCTs, open-label	Poor, Some methodological problems	Some inconsistencies	Yes for chronic constipation No for IBS-C	No significant differences	None	Low
PEG 3350 vs. psyllium							
1 RCT / 126 patients	RCT, open-label	Poor, Some methodological problems	N/A	Yes for chronic constipation No for IBS-C	No significant differences	None	Low
Outcome: All other comparisons							
No evidence							

*Imprecise or sparse data; a strong or very strong association; high risk of reporting bias; dose response gradient; effect of plausible residual confounding; IBS-C: Irritable Bowel Syndrome; N/A: not applicable; PEG: polyethylene glycol; RCT: randomized controlled trial

II. Chronic constipation in children

A. Summary of findings

General tolerability and safety in children

The evidence is very poor quality and sparse. We found no studies on the general tolerability and safety of docusate calcium, docusate sodium, lactulose, lubiprostone, and psyllium that met our expanded eligibility criteria. All of the studies we found were rated poor quality for the assessment of adverse events and results should be interpreted with caution.

We found three poor quality studies that reported safety or tolerability information for PEG 3350 without a comparison group. All three had serious methodological problems. The most common adverse events reported were diarrhea in 10-13%, bloating/flatulence in 6-18%, and pain/cramping in 2-5%. They found no significant laboratory abnormalities and reported that PEG 3350 was well tolerated by children.

We found one RCT that reported on the tolerability and harms of tegaserod for the treatment of postpubertal adolescents with constipation predominant IBS. The study reported that no adverse events were observed in any patient and there were no dropouts.

Comparative tolerability and safety in children

The evidence was limited to one poor quality RCT comparing PEG 3350 with lactulose in children. It did not report any serious adverse events. This study reported more abdominal pain, pain at defecation, and straining at defecation in those treated with lactulose and worse palatability with PEG. The results should be interpreted cautiously due to the poor quality of the study.

B. Detailed assessment

General risk of harms

Table 26 summarizes the trials assessing the general harms of constipation drugs in children; Table 29 summarizes the evidence profile for the general tolerability and safety of individual drugs.

Docusate calcium, Docusate sodium, Lactulose, Lubiprostone, and Psyllium

We did not find any studies on the general harms of these medications in children that met our eligibility criteria.

Polyethylene glycol

We found no studies reporting the general safety of PEG that included a placebo comparison group. Three poor quality studies reported safety or tolerability information without a comparison group.[67-69] Two studies[67, 69] were funded by the makers of PEG without electrolytes. The other study[68] did not report a source of funding or any conflicts of interest, but was by the same group of authors as the prospective cohort study. The most common adverse events reported were diarrhea in 10-13%, bloating/flatulence in 6-18%, and pain/cramping in 2-5%. They found no significant laboratory abnormalities. PEG 3350 was well tolerated by children. Results of these studies should be interpreted with caution due to the poor quality.

One prospective cohort study[67] included 83 children over the age of 2 treated with PEG without electrolytes (mean required dose 0.75 g/kg/d) at pediatric clinics at a referral center for a mean of 8.7 months (range 3 to 30 months). The mean age of subjects was 7.4 (range 2.0-16.9). Previous therapies for constipation had been attempted in 82% of subjects prior to enrollment. For safety and adverse events, the study reported diarrhea in 10%, abdominal pain in 2%, bloating or flatulence in 6%, elevated alanine aminotransferase (ALT) in 11%, and elevated aspartate transaminase (AST) in 4%. No abnormalities in electrolytes were found. Of the 9 patients with abnormal ALTs during treatment, 8 had repeat values 8 weeks later. Seven of the 8 were still on PEG therapy. Seven of the 8 had normal repeat values; one subject had a level 1.2 x normal (28 U/L). The 3 elevated ASTs were <1.5 times normal and all had normal repeat values 8 weeks later while still receiving PEG. The duration and dose of PEG was not different between those with elevated liver function tests (LFTs) and those with normal labs. No major adverse events were reported in the study. For tolerability, PEG was liked by 93% of children. All children (n = 68, 82%) who had used other therapies in the past preferred PEG to other laxatives.

One retrospective chart review[68] examined the safety of PEG without electrolytes in 75 infants and toddlers with functional constipation under the age of 2 over a 3.5 year period examined. Although they were not required to have *chronic* constipation, the mean duration of constipation was 10 months (range 0.5 to 23 months). Diarrhea was reported in 7% of 71 subjects followed for up to 4 months and in an additional 2% of 47 subjects followed for over 6 months. Parents did not report increased flatus, abdominal distention, vomiting, or new onset abdominal pain in any subjects. None stopped PEG due to adverse events. Lab tests (CBC, electrolytes, and LFTs) were occasionally done in some subjects and all those checked were normal. The study was rated poor quality for several reasons including: no comparison group, adverse events were not defined, adverse events were not clearly pre-specified, and high attrition.

One dose response study[69] was a prospective, double-blind, parallel trial that randomized children aged 3 to 18 years with chronic constipation to 4 doses of PEG 3350 without electrolytes (Miralax®, 0.25 g/kg/d, 0.50 g/kg/d, 1 g/kg/d, or 1.5 g/kg/d). All groups were treated for 3 days and evaluated 5 days after beginning treatment. They enrolled forty-one subjects referred to a pediatric gastroenterology clinic for evaluation of chronic constipation with evidence of fecal impaction. For all subjects, the following adverse events were reported: diarrhea (13%), nausea (5%), vomiting (5%), bloating/flatulence (18%), and pain/cramping (5%). Diarrhea was more prevalent in the high dose groups than the low dose groups (25% vs. 10%; $P < 0.02$). No patients had clinically significant abnormal laboratory values after the use of PEG 3350. For tolerability, 95% of children took the medication on the first attempt. In addition, all children said that they would repeat a 3-day regimen of PEG 3350 to help treat a future fecal impaction. The results of the study should be interpreted with caution due to poor quality (no control group).

Tegaserod

As described in the tegaserod section for general harms in adults (see above), the FDA issued a public health advisory to inform patients and health care professionals that the sponsor of tegaserod agreed to stop selling the medication because of cardiovascular adverse events.[12] We found one RCT that reported on the safety and harms of tegaserod for the treatment of postpubertal adolescents with constipation predominant IBS.[53] The study reported that no adverse events were observed in any patient, including diarrhea, dehydration, vomiting, rectal bleeding, weight loss, or headache. In addition there were no dropouts. This study is summarized in Table 27.

Table 26. Summary of trials assessing the general safety and harms of constipation drugs in children

Author, year	Study design	N; Study duration	Comparisons	Population, % female, setting	Results	Quality rating
PEG 3350						
Pashankar et al., 2003[67]	Prospective cohort	83, 3-30 months (mean 8.7 months)	PEG 3350 without electrolytes (0.8g/kg per day, titrated to results by parents); no comparison group	Children > 2 years old with chronic constipation, 42% female, outpatient pediatric	No major AEs. Diarrhea 10%; abdominal pain 2%; bloating or flatulence 6%; elevated ALT 11%; elevated AST 4%. Tolerability: PEG was liked by 93%; All children (82%) who had used other therapies in past preferred PEG to other laxatives.	Poor
Loening-Baucke et al., 2004[68]	Retrospective chart review	75, subjects treated over 3.5 years (Jan 2000 to Aug 2003)	PEG 3350 without electrolytes; no comparison group	Children < 2 years old; at least 2 weeks of constipation (mean 10 months), 52% female	Diarrhea 7%; no reported increased flatus, abdominal distention, vomiting, or new onset abdominal pain. None stopped PEG due to adverse events. Blood counts, electrolytes, and LFTs were done in some and were normal.	Poor (No comparison group, AEs not pre-specified and defined, high attrition)
Youssef et al., 2002[69]	Dose response study (prospective, double-blind, randomized, parallel)	40, 5 days	PEG 3350 without electrolytes (4 doses compared); no non-PEG comparison group	Children ages 3 to 18 years, referred to a pediatric gastroenterology clinic, 73% female	Diarrhea (13%), nausea (5%), vomiting (5%), bloating/flatulence (18%), pain/cramping (5%). Diarrhea was more prevalent in the high dose groups than the low dose groups (25% vs. 10%; $P < 0.02$). No patients had clinically significant abnormal laboratory values. Tolerability: 95% took the medication on the first attempt; all would repeat the regimen for a future fecal impaction.	Poor (No control group)

AE: adverse events; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LFT: loss to follow-up; PEG: polyethylene glycol

Table 27. Summary of trials assessing the general safety and harms of tegaserod for the treatment of chronic constipation and IBS-C in children

Author, year	Study design	N; Study duration	Comparisons	Population, % female, setting	Results	Quality rating
IBS-C						
Khoshoo et al. 2006[53]	RCT	48; 4 weeks	Laxative only (PEG 3350) or combination therapy with laxative and tegaserod 6 mg BID	Postpubertal adolescents with constipation predominant IBS, 60% female	No AEs were observed in any patient including diarrhea, dehydration, vomiting, rectal bleeding, weight loss, or headache; no dropouts	N/A*

AE: adverse events; BID: twice a day; IBS: Irritable Bowel Syndrome; PEG: polyethylene glycol; RCT: randomized controlled trial
*Because tegaserod has been taken off the market in the US, we did not rate the internal validity of individual studies

Comparative risk of harms

Table 28 summarizes the trial assessing the comparative harms of constipation drugs; Table 30 summarizes the evidence profile for the comparative tolerability and harms.

PEG 3350 vs. lactulose

We found one poor quality RCT[46] meeting our inclusion criteria that compared PEG 3350 with lactulose in children. This study did not report any serious adverse events; it reported more abdominal pain, pain at defecation, and straining at defecation in those treated with lactulose and worse palatability with PEG.[46] The results should be interpreted cautiously due to the poor quality of this study.

The RCT[46] was a multicenter head-to-head trial from the Netherlands that randomized 100 patients to PEG 3350 with electrolytes (Transipeg) (2.95-11.8 g/d) or lactulose (6-24 g/d) for 8 weeks of treatment. The trial enrolled children from the ages of 6 months to 15 years (mean 6.5 years) with constipation. Stimulant laxatives were prescribed during the treatment phase if the treatment they were randomized to was unsuccessful. The authors report that 20% of both groups required stimulant laxatives during the study. Adverse events were assessed on a 3 point scale by patients. There were more patients with a weekly score > 1 for abdominal pain, pain at defecation, and straining at defecation in the lactulose group (values not reported, $P < 0.05$), and more patients had a weekly score > 1 for bad palatability in the PEG group (values not reported, $P < 0.05$). There were nine premature withdrawals between the two groups, with 4 in the PEG group (2 lost to follow-up, 1 unknown reason, and 1 bad palatability) and 5 in the lactulose group (2 lost to follow-up, 2 helicobacter positive, and 1 unknown). There were no serious adverse events reported. However, the authors did not define serious adverse events or how these were assessed. For tolerability, more patients reported "bad palatability" in the PEG group (%s not reported, *P*

< 0.05). The study was rated poor for several reasons including: lack of an ITT analysis and adverse events were not pre-specified and defined.

Table 28. Summary of trials assessing the comparative harms of constipation drugs

Author, year	Study design	N; Study duration	Comparisons	Population, % female, setting	Results	Quality rating
PEG 3350 vs. LACTULOSE						
Voskuijl et al., 2004[46]	RCT	100; 8 weeks	PEG 3350 (Transipeg, PEG-ELS) vs. lactulose	Children age 6 months to 15 years, 45% female, multicenter, referral population (referred to pediatric gastroentero logists); Netherlands	No serious AEs. More patients with abdominal pain, pain at defecation, and straining at defecation with lactulose (%s NR, shown in graph; $P < 0.05$). More "bad palatability" in the PEG group (%s NR, shown in graph; $P < 0.05$).	Poor (AEs not prespecified and defined)

AE: adverse events; ITT: intent-to-treat; NR: not reported; PEG: polyethylene glycol; PEG-ELS: PEG with electrolytes; RCT: randomized controlled trial

Table 29. Evidence Profile of the general tolerability and harms of constipation drugs in children

Evidence Profile: General safety of constipation drugs in children							
No. of Studies/ Patients	**Design**	**Quality**	**Consistency**	**Directness**	**Magnitude of Effect**	**Other modifying factors***	**Overall Grade of the Evidence**
Outcome: Tolerability and harms of docusate calcium							
No evidence							
Outcome: Tolerability and harms of docusate sodium							
No evidence							
Outcome: Tolerability and harms of lactulose							
No evidence							
Outcome: Tolerability and harms of lubiprostone							
No evidence							
Outcome: Tolerability and harms of PEG 3350							
3 RCTs/ 199 patients	RCTs	Poor, Serious methodological problems	No inconsistencies	Yes for chronic constipation No for IBS	NR	No	Low
Outcome: Tolerability and harms of psyllium							
No evidence							
Outcome: Tolerability and harms of tegaserod							
1 RCT/ 48 patients	RCT	Poor for AEs, Serious methodologic problems	N/A	No for chronic constipation Yes for IBS in postpubertal adolescents	No AEs were observed in any patient and there were no dropouts	No	N/A

IBS: Irritable Bowel Syndrome; NR: not reported; PEG: polyethylene; RCT: randomized controlled trial
*Imprecise or sparse data; a strong or very strong association; high risk of reporting bias; dose response gradient; effect of plausible residual confounding;

Table 30. Evidence profile of the comparative tolerability and harms of constipation drugs in children

Evidence Profile: Comparative safety of constipation drugs in children							
No. of Studies/ Patients	**Design**	**Quality**	**Consistency**	**Directness**	**Magnitude of Effect**	**Other modifying factors***	**Overall Grade of the Evidence**
PEG 3350 vs. Lactulose							
1 RCT / 137 patients	RCT	Poor, Serious methodological problems	N/A	Yes for chronic constipation No for IBS	NR	None	Low

*Imprecise or sparse data; a strong or very strong association; high risk of reporting bias; dose response gradient; effect of plausible residual confounding; IBS: Irritable Bowel Syndrome; NR: not reported; PEG: polyethylene glycol; RCT: randomized controlled trial

KEY QUESTION 4. Are there subgroups of patients based on demographics (age, racial or ethnic groups, and gender), other medications, or co-morbidities, including Irritable Bowel Syndrome, for which one symptomatic treatment is more effective or associated with fewer adverse events?

I. Summary of findings

We did not find any studies published as full text articles specifically designed to examine the general or comparative efficacy of docusate calcium, docusate sodium, lactulose, lubiprostone, PEG 3350, psyllium, or tegaserod for chronic constipation or constipation associated with IBS in subpopulations.

Only one study, published as an abstract only, examined differences in the general efficacy of lubiprostone for chronic constipation based on sex.

Two RCTs support the general efficacy of tegaserod for the treatment of IBS-C in women. However, there is insufficient evidence available to determine whether any difference in efficacy between men and women existed.

Only two published abstracts examined the general efficacy of lubiprostone in elderly patients.

Tables 31 and 32 summarize the evidence profiles for the treatment of chronic constipation and IBS-C with constipation drugs for subgroups.

II. Detailed assessment

Sex

Chronic constipation

We did not find any studies published as full text articles specifically designed to examine the general or comparative efficacy of docusate calcium, docusate sodium, lactulose, lubiprostone, PEG 3350, psyllium, or tegaserod for chronic constipation in men versus women. The available direct evidence is limited to one pooled data analysis comparing lubiprostone and placebo.[28]

This published abstract compared the efficacy of lubiprostone and placebo for treating chronic constipation in men versus women.[28] Data were combined from three clinical trials. Men and women both responded favorably to lubiprostone experiencing approximately twice as many spontaneous bowel movements (SBMs) per week as placebo patients. Response rates were similar in males and females

treated with lubiprostone (5.69-6.05 SBMs/week vs. 4.99-5.75 SBMs/week). No differences in harms were reported. This study was published as an abstract only; the information presented is insufficient to critically appraise the underlying methods of this study and draw firm conclusions.

Multiple studies enrolled primarily females as study participants.[31, 33 37, 38 42] For example, in two RCTs on tegaserod 90%[37] and 86%[38] of patients were female. In general, effect sizes of treatment responses in such populations did not appear to be substantially different from those in populations with higher proportions of male participants. However, no firm conclusions about any differences in efficacy and safety between men and women can be drawn based on such assessments.

Constipation associated with IBS

We did not find any studies published as full text articles specifically designed to examine the general efficacy of docusate calcium, docusate sodium, lactulose, lubiprostone, PEG 3350, psyllium, or tegaserod for IBS-C in men versus women.

Two RCTs assessed the efficacy of tegaserod for IBS-C in female patients.[50, 51] Both studies provide evidence that tegaserod provides a rapid and sustained improvement in IBS-C symptoms in female patients. Tegaserod has never had FDA approval for the treatment of IBS-C in males, and evidence on the general efficacy of tegaserod in men is sparse. Only three studies enrolled males and females with IBS-C (males comprised 12%-17% of patients). From these studies it remains unclear, however, whether any differences in efficacy between men and women existed.

We did not find any studies specifically designed to examine the comparative efficacy of docusate calcium, docusate sodium, lactulose, lubiprostone, PEG 3350, psyllium, or tegaserod for chronic constipation in men versus women.

Age

Chronic constipation

We did not find any studies published as full text articles specifically designed to examine the general efficacy of docusate calcium, docusate sodium, lactulose, lubiprostone, PEG 3350, psyllium, or tegaserod for chronic constipation in elderly populations. The available evidence is limited to two pooled data analyses comparing lubiprostone and placebo.[26, 27]

Two published abstracts examined the efficacy of lubiprostone in patients ≥ 65 years.[26, 27] In each study, data were pooled from three RCTs to provide an adequate pool of elderly subjects for analysis. Lubiprostone was well tolerated by elderly subjects in both studies. With regard to long-term efficacy, in the first pooled analysis, improvements in assessments of constipation severity, abdominal bloating, and abdominal discomfort, were all statistically significant at all post baseline time points from week 1 to week 48 in both elderly and non-elderly subgroups ($P < 0.0001$).[27] In the second study, mean changes from baseline in SBM rates were significantly improved among lubiprostone elderly subjects compared to their placebo counterpoarts during weeks 1,2, and 4 ($P \leq 0.0286$).[26] However, because these studies were published as abstracts only, the available information is insufficient to critically appraise the underlying methods and draw firm conclusions.

We did not find any studies specifically designed to examine the comparative efficacy of docusate calcium, docusate sodium, lactulose, lubiprostone, PEG 3350, psyllium, or tegaserod.

Constipation associated with IBS

We did not find any evidence on differences of efficacy and harms of constipation drugs based on age.

Race or Ethnicity

We did not find any evidence on differences of efficacy and harms of constipation drugs for the treatment of chronic constipation or constipation associated with IBS based on race or ethnicity.

Co-morbidities

We did not find any evidence on differences of efficacy and harms of constipation drugs for the treatment of chronic constipation or constipation associated with IBS based on co-morbidities.

Table 31. Evidence profile of the general efficacy and harms of constipation drugs for chronic constipation and IBS-C in subgroups

Evidence Profile: General efficacy and harms of constipation drugs for chronic constipation and IBS-C in subgroups							
No. of Studies/ Patients	**Design**	**Quality**	**Consistency**	**Directness**	**Magnitude of Effect**	**Other modifying factors***	**Overall Grade of the Evidence**
Outcome: Differences in SEX—lubiprostone							
1 abstract	Pooled data from 3 RCTs	N/A (published as an abstract only)	N/A	Yes	N/A	N/A	N/A (published as an abstract only)
Outcome: Differences in SEX—docusate calcium, docusate sodium, lactulose, psyllium, and tegaserod							
No evidence							
Outcome: Differences in AGE—lubiprostone							
2 abstracts	Pooled data from 3 RCTs	N/A (published as abstract only)	N/A	Yes	N/A	N/A	N/A (published as an abstract only)
Oucome: Differences in AGE: docusate calcium, docusate sodium, lactulose, PEG 3350, psyllium, and tegaserod							
No evidence							
Outcome: Differences in RACE OR ETHNICITY—docusate calcium, docusate sodium, lactulose, lubiprostone, PEG 3350, psyllium, and tegaserod							
No evidence							
Outcome: Differences in CO-MORBIDITIES—docusate calcium, docusate sodium, lactulose, lubiprostone, PEG 3350, psyllium, and tegaserod							
No evidence							

*Imprecise or sparse data; a strong or very strong association; high risk of reporting bias; dose response gradient; effect of plausible residual confounding

Table 32. Evidence profile of the comparative efficacy and harms of constipation drugs for chronic constipation and IBS-C in subgroups

Evidence Profile: Comparative efficacy and harms of constipation drugs for chronic constipation and IBS-C in subgroups							
No. of Studies/ Patients	**Design**	**Quality**	**Consistency**	**Directness**	**Magnitude of Effect**	**Other modifying factors***	**Overall Grade of the Evidence**
Outcome: Differences in SEX—all comparisons							
No evidence							
Outcome: Differences in AGE—all comparisons							
No evidence							
Outcome: Differences in RACE OR ETHNICITY—all comparisons							
No evidence							
Outcome: Differences in CO-MORBIDITIES—all comparisons							
No evidence							

*Imprecise or sparse data; a strong or very strong association; high risk of reporting bias; dose response gradient; effect of plausible residual confounding

SUMMARY AND DISCUSSION

Chronic constipation and constipation associated with IBS are some of the most frequent gastrointestinal complaints in adults and children. Multiple drugs are commonly used to treat these conditions. Many of these drugs are available over the counter and have been available for decades. Despite the high prevalence and the enormous socioeconomic burden associated with these conditions,[2, 70] results of our review highlight that for most treatments, objective evidence from well-conducted studies on efficacy and safety is largely missing.

For medications that are considered first-line treatments such as bulking agents or stool softeners, solid evidence is missing or of questionable methodological quality. Even for drugs that are considered first-line prescription medications such as osmotic laxatives, the evidence is sparse and fraught with severe methodological problems.

Although we revised our eligibility criteria while conducting this report to include any controlled prospective study, regardless of design, we could not find any studies on the efficacy and safety of docusate calcium, docusate sodium, and lactulose for the treatment of chronic constipation or IBS-C. A systematic review reported some low-quality evidence supporting the use of lactulose for occasional constipation.[71] However, these findings cannot be extrapolated to populations with chronic constipation or IBS-C.

Although multiple studies support the general efficacy of PEG 3350 for the treatment of chronic constipation in adults and children, most of them are short-term (i.e., less than 4 weeks) and many have considerable methodological problems. The general safety evidence from three RCTs (1 fair and 2 poor quality) suggests PEG 3350 is well tolerated with only minor adverse events (nausea, gas, cramps, and diarrhea). However, the strength of evidence is low.

Multiple studies support the efficacy of tegaserod for the treatment of chronic constipation in adults and children and IBS-C. However, tegaserod has been taken off the market because of safety concerns due to a recent analysis reporting an increased risk of cardiovascular events. Several previous studies on the general safety and tolerability of tegaserod consistently reported an increased incidence of diarrhea compared to placebo. At present it remains unclear whether tegaserod will be re-approved for selected indications in the future.

Multiple RCTs provide evidence on the efficacy and safety of lubiprostone for the treatment of chronic constipation. However, all these trials have been published as abstracts only. Therefore, no firm conclusions about the net benefits or harms of lubiprostone for the treatment of chronic constipation can be drawn. Overall, lubiprostone appeared to be efficacious. With regard to tolerability and safety, the incidence of nausea was consistently higher in patients on lubiprostone than on placebo.[23, 54, 55, 72] In phase III trials, 10% of patients on lubiprostone discontinued treatment because of adverse events, mainly gastrointestinal symptoms.[71]

Evidence comparing one agent with another is similarly sparse. For the treatment of chronic constipation in adults we found three head-to-head trials comparing the efficacy of docusate sodium with psyllium,[42] lactulose with PEG 3350,[43] and PEG 3350 with psyllium.[45] These studies are all less than 4 weeks of duration and all have considerable methodological limitations. Therefore, no firm conclusions can be drawn about the comparative efficacy of these drugs. In addition, it should be noted that only one study compared medications from the same groups (i.e., lactulose vs. PEG 3350). The other two studies compared medications from different groups i.e., the bulking agent psyllium with either docusate sodium (a stool softener) or PEG 3350 (an osmotic laxative). In clinical practice, these medications are often used together since they work in different ways to improve bowel movements. For comparative safety in adults we found four head-to-head trials comparing PEG 3350 with lactulose,[43] lactulose with psyllium (2 trials),[65, 66] and PEG 3350 with psyllium.[45] All four of these studies had severe methodological limitations and were rated as poor quality for assessment of adverse events and no firm conclusions can be drawn about the comparative safety of these drugs.

For pediatric populations, the evidence for general efficacy and safety is very poor quality and sparse. We found no studies on the general efficacy, tolerability, or safety of docusate calcium, docusate sodium, lactulose, lubiprostone, and psyllium that met our eligibility criteria. All of the studies we found were rated poor quality and results should be interpreted with caution.

For comparative evidence of general efficacy and safety in pediatric populations, we found just one head-to-head trial comparing PEG 3350 with lactulose.[46] However, this study was of poor quality due to methodological limitations. The results should be interpreted cautiously due to the poor quality of the evidence.

Likewise, no evidence is available to determine the ideal treatment duration of drugs used to treat chronic constipation or when treatments should be switched if patients do not respond. Similarly, we did not find any studies published as full text articles specifically designed to compare the effect of constipation drugs in particular subpopulations.

The lack of scientific evidence for drugs used to treat constipation has been pointed out in several systematic reviews.[71, 73-75] Some of these studies focused on interventions not included in this report; others examined the efficacy and safety in populations with occasional constipation. All of them stress the lack of high quality evidence to support the efficacy and safety of most interventions.

Nevertheless, the absence of evidence of an effect cannot be interpreted as evidence of no effect. Therefore, it is important that well conducted future studies reliably establish the efficacy of all commonly used medications used for treatment of constipation. Furthermore, the comparative efficacy and effectiveness of first-line over-the-counter treatments and first-line prescription treatments have to be compared. Moreover, it is important to examine whether new second-line treatments, such as lubiprostone, have an additional, clinically significant treatment benefit as well as better tolerability and safety compared with other available interventions. In addition, it is important that these studies will investigate the effects of these interventions on a variety of constipation related symptoms including straining, bloating, and abdominal discomfort as well as on the patients' overall well-being and quality of life. Finally, future research should more fully assess comprehensive safety and tolerability data, because much of the current literature does not adequately address these issues. This data will provide clinicians with helpful information needed for better selection of appropriate intervention for patients with chronic functional constipation.

Table 33. Summary of the evidence by key question

Indication	Strength of the Evidence	Conclusion
Key Question 1a: General Efficacy		
Chronic constipation in adults	Moderate	Consistent evidence of three studies with mixed methodological quality supports the efficacy of PEG 3350 for the treatment of chronic constipation.
	Low	Two studies of mixed quality support the efficacy of psyllium for the treatment of chronic constipation.
	N/A	Multiple well conducted studies provide evidence of the efficacy of tegaserod for the treatment of chronic constipation. However, because of safety concerns, tegaserod is currently not available in the US. Studies of lubiprostone have been published as abstracts only. No evidence is available on docusate calcium, docusate sodium, and lactulose.
Chronic constipation in children	No evidence	
IBS-C in adults	N/A	Multiple, well conducted studies provide evidence of the efficacy of tegaserod for the treatment of IBS-C in adults. However, because of safety concerns, tegaserod is currently not available in the US.
	N/A	Studies of lubiprostone have been published as abstracts only and available information is insufficient to critically appraise the methods and draw firm conclusions.
	N/A	No evidence is available on docusate calcium, docusate sodium, lactulose, PEG 3350, and psyllium for the treatment of IBS-C in adults.
IBS-C in children	N/A	One RCT provided evidence of the efficacy of tegaserod for the treatment of IBS-C in adolescents, particularly in reduction in pain. However, because of safety concerns, tegaserod is currently not available in the US.
	N/A	No evidence is available on docusate calcium, docusate sodium, lactulose, PEG 3350, and psyllium for the treatment of IBS-C in children.
Key Question 1b: Comparative Efficacy		
Chronic constipation in adults	Low	**Docusate sodium vs. psyllium:** One poor quality study indicated no difference in efficacy.

	Low Low	**Lactulose vs. PEG 3350:** One poor quality RCT reported fewer weekly stools and less overall improvement for lactulose than PEG 3350 **PEG 3350 vs. psyllium:** One fair, open-label RCT reported more improvement for PEG 3350 than psyllium
Chronic constipation in children	Low	**PEG 3350 vs. lactulose:** One poor quality RCT reported no significant difference between treatment groups in mean defecation frequency per week.
IBS-C in adults	No evidence	
IBS-C in children	No evidence	
Key Question 2: Treatment duration		
No evidence		
Key Question 3: General Safety		
Chronic constipation or IBS-C in adults	Low Low N/A N/A N/A	One fair and 2 poor quality studies reported that PEG 3350 was well tolerated with only minor gastrointestinal adverse events. Three poor quality studies consistently reported that psyllium was well tolerated with no difference in adverse events from placebo. Multiple well conducted studies provide consistent evidence of an increased incidence of diarrhea with tegaserod compared with placebo. Due to an increased risk of cardiovascular events tegaserod was taken off of the market in March 2007. Studies of lubiprostone have been published as abstracts only. No evidence is available on docusate calcium, docusate sodium, and lactulose.
Chronic constipation or IBS-C in children	Low Low N/A	The most common adverse events reported in 3 poor quality studies of PEG 3350 without comparison groups were diarrhea (10-13%), bloating/flatulence (6-18%), and pain/cramping (2-5%). No significant laboratory abnormalities were reported. One RCT reported no adverse events were observed in any patient and there were no dropouts for postpubertal adolescents with IBS-C treated with tegaserod. No evidence is available on docusate calcium, docusate sodium, lactulose, lubiprostone, and psyllium
Key Question 3: Comparative Safety		
Chronic constipation or IBS-C in adults	Low Low	**Lactulose vs. PEG 3350:** One poor quality RCT reported lower rates of flatus and abdominal pain, but higher rates of diarrhea for PEG. **Lactulose vs. psyllium:**

	Low	Two poor quality open-label RCTs reported inconsistent results: one reported numerically lower rates of diarrhea and abdominal pain with psyllium; the other reported no differences in abdominal pain or straining and better tolerance with lactulose, due to palatability. **PEG 3350 vs. psyllium:** One fair, open-label RCT reported no significant differences in adverse events between the groups.
Chronic constipation or IBS-C in children	Low	**Lactulose vs. PEG 3350:** Two poor quality studies provided mixed evidence about differences of adverse events between lactulose and psyllium. Neither reported any serious adverse events.
Key Question 4: Subgroups		
Efficacy and harms based on sex	N/A N/A N/A	**Chronic constipation:** One pooled data analysis of lubiprostone published as an abstract only. No evidence is available on docusate calcium, docusate sodium, lactulose, PEG 3350, psyllium or tegaserod. **Constipation associated with IBS:** No evidence is available on docusate calcium, docusate sodium, lactulose, lubiprostone, PEG 3350, psyllium or tegaserod.
Efficacy and harms based on age	N/A N/A N/A	**Chronic constipation:** Two pooled data analyses of lubiprostone in patients $\geq$ 65 years published as abstracts only. No evidence is available on docusate calcium, docusate sodium, lactulose, PEG 3350, psyllium or tegaserod. **Constipation associated with IBS:** No evidence
Efficacy and harms based on race/ethnicity	No evidence	
Efficacy and harms based on co-morbidities	No evidence	

ADDENDUM

As this report was going to press, the first full text study on lubiprostone was published.[76] In this RCT, 129 patients with chronic constipation were randomized to lubiprostone (24, 48, or 72 mcg/day) or placebo. During the 21 days of follow-up, lubiprostone improved spontaneous bowel movement (SBM) rates in a dose-dependent manner. Mean SBM frequencies per week ranged from 5.1 to 6.1 in the lubiprostione groups compared with 3.8 in the placebo group ($P = 0.046$). The most common adverse events were nausea (33%), headache (11%), and diarrhea (11%). Adverse events also occurred in a dose-dependent manner. Overall, 62% - 70% of patients in the lubiprostone groups experienced at least one adverse event (compared with 39% in the placebo group).

Because lubiprostone 72 mcg/d led to higher rates of adverse events, the authors concluded that no clear risk-to-benefit advantage existed compared with lubiprostone 48 mcg/d.

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Appendix A. Search Strategies

#1	Search "Constipation"[MeSH] OR "Irritable Bowel Syndrome"[MeSH]	8148
#3	Search "tegaserod"[Substance Name] OR zelnorm OR "lubiprostone"[Substance Name] OR mitina OR mitina OR "Dioctyl Sulfosuccinic Acid"[MeSH] OR "Psyllium"[MeSH] OR "Polyethylene Glycols"[MeSH] OR "Lactulose"[MeSH]	27912
#4	Search "Cathartics"[MeSH] OR laxative OR "fecal softener" OR "stool softener" OR "Dioctyl Sulfosuccinic Acid"[MeSH] OR colace OR surfak OR "docusate sodium" OR "docusate calcium"	15769
#5	Search #3 OR #4	41964
#6	Search #1 AND #5	1327
#7	Search #1 AND #5 Limits: Publication Date from 1985, Humans	829
#8	Search #1 AND #5 Limits: All Child: 0-18 years, Publication Date from 1985, Humans	230
#9	Search #1 AND #5 Limits: All Adult: 19+ years, Publication Date from 1985, Humans	414
#13	Search ("Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials"[MeSH]) OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH]	327612
#14	Search #8 AND #13	51
#15	Search #9 AND #13	108
#17	Search ("Review Literature"[MeSH] OR "Review"[Publication Type])	1242191
#18	Search #8 AND #17	49
#19	Search #9 AND #17	57
#20	Search #1 AND #5 Limits: All Child: 0-18 years, Publication Date from 1985, Meta-Analysis, Humans	2
#21	Search #1 AND #5 Limits: All Adult: 19+ years, Publication Date from 1985, Meta-Analysis, Humans	7
#23	Search longitudinal studies [mh] OR cohort studies [mh] OR case-control studies [mh] OR comparative study [mh] OR "observational studies" [tw]	857524
#24	Search #8 AND #23	68
#25	Search #9 AND #23	97

Cochrane Reviews = 14
EMBASE = 75
IPA = 70

TOTAL UNDUPLICATE DATABASE = 405

#10	Search "Constipation"[MeSH] OR "Irritable Bowel Syndrome"[MeSH]	8315
#11	Search "tegaserod"[Substance Name] OR zelnorm OR "lubiprostone"[Substance Name] OR mitina OR mitina OR "Dioctyl Sulfosuccinic Acid"[MeSH] OR "Psyllium"[MeSH] OR "Polyethylene Glycols"[MeSH] OR "Lactulose"[MeSH]	28468
#12	Search "Cathartics"[MeSH] OR laxative OR "fecal softener" OR "stool softener" OR "Dioctyl Sulfosuccinic Acid"[MeSH] OR colace OR surfak OR "docusate sodium" OR "docusate calcium"	15906
#13	Search #11 OR #12	42634
#14	Search #10 AND #13	1348
#15	Search #10 AND #13 Limits: added to PubMed in the last 180 days, Humans	24

PUBMED = 20 new records
Cochrane Reviews = 2 = 0 new
EMBASE = 10 = 2 new
IPA = 14 = 10 new

TOTAL = 32 new

Appendix B. Abstract-only Studies

1. Gremse DA. Comparison of polyethylene glycol 3350, NF powder and lactulose and lactulose for treatment of chronic constipation in children. J Pediatr Gastroenterol Nutr 2000;31(Supplement 2):S131.
2. Hamling J, Bang CJ, Tarpila S, Stewart W, al. E. Titration regimen indicates partial 5-HT4 agonist HTF 919 improves symptoms of constipation predominant irritable bowel syndrome (C-IBS). Digestion 1998;59(Suppl 3):735.
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Appendix C. Quality Assessment Methods for Drug Class Reviews for the Drug Effectiveness Review Project

Assessment of Internal Validity

To assess the internal validity of individual studies, the EPC adopted criteria for assessing the internal validity of individual studies from the US Preventive Services Task Force and the NHS Centre for Reviews and Dissemination. To assess the quality of observational studies, we used criteria outlined by Deeks et al., 2003.

For Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
   - Adequate approaches to sequence generation:
     - Computer-generated random numbers
     - Random numbers tables
   - Inferior approaches to sequence generation:
     - Use of alteration, case record numbers, birth dates or week days
   - Not reported

2. Was the treatment allocation concealed?
   - Adequate approaches to concealment of randomization:
     - Centralized or pharmacy-controlled randomization
     - Serially-numbered identical containers
     - On-site computer based system with a randomization sequence that is not readable until allocation
     - Other approaches sequence to clinicians and patients
   - Inferior approaches to concealment of randomization:
     - Use of alteration, case record numbers, birth dates or week days
     - Open random numbers lists
     - Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
   - Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?
11. Is there important differential loss to follow-up or overall high loss to follow-up? (Give numbers in each group.)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?
2. How many patients were recruited?
3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step.)
4. What was the funding source and role of funder in the study?
5. Did the control group receive the standard of care?
6. What was the length of follow-up? (Give numbers at each stage of attrition.)

For Observational Studies:

Assessment of Internal Validity

1. Were both groups selected from the same source population?
2. Did both groups have the same risk of having the outcome of interest at baseline?
3. Were subjects in both groups recruited over the same time period?
4. Was there any obvious selection bias?
5. Were ascertainment methods adequate and equally applied to both groups?
6. Was an attempt made to blind the outcome assessors?
7. Was the time of follow-up equal in both groups?
8. Was overall attrition high ($\geq$ 20%)?
9. Was differential attrition high ($\geq$ 15%)?
10. Did the statistical analysis consider potential confounders or adjust for different lengths of follow-up?
11. Was the length of follow-up adequate to assess the outcome of interest?

Appendix D. Excluded Studies

The full-text of the following studies were considered for inclusion, but failed to meet the particular inclusion criteria for this report.

1. Managing constipation in children. Drug Ther Bull 2000;38(8):57-60.
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EVIDENCE TABLES

Chronic Constipation and IBS-C

STUDY:	**Authors, article #: Andorsky and Goldner**[32] **Year: 1990** **Country:** USA	
FUNDING:	NR	
RESEARCH OBJECTIVE:	Compare clinical efficacy and safety of PEG 3350 vs. placebo	
DESIGN:	**Study design:** double blind randomized cross over trial **Setting:** outpatient **Sample size:** 37	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**PEG 3350** 8 oz per day 5 days 16	**placebo** N/A 5 days 16
INCLUSION CRITERIA:	Men and women age 18 and older; chronic constipation defined as use of laxatives, other than bulk forming agents, at least once every 2 weeks for the previous 3 years, or at least two visits to a physician over the past 3 years for constipation	
EXCLUSION CRITERIA:	Uncorrected metabolic disorder possibly causing constipation evaluated by taking serum electrolytes, calcium, and thyroid-stimulating hormone; history of gastric retention; small bowel obstruction; impaired gag reflex; being prone to aspiration; pregnancy; lactation	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Laxatives and enemas were allowed for intolerable constipation but patients had to record use and cross over to second drug group; all other medications were allowed other than magnesium containing antacids	

Authors: Andorsky and Goldner **Year: 1990**			
POPULATION	**Groups similar at baseline:** Yes		
CHARACTERISTICS:	**PEG 3350 8 oz**	**PEG 3350 16 oz**	
Mean age (years):	62	58	
Patients aged 65 years or older (%):	NR	NR	
Sex (% female):	75%	81.3%	
Ethnicity (% Caucasian):	NR	NR	
Mean body mass index:	NR	NR	
Other germane characteristics:			
• Duration of constipation (mean)	NR	NR	
• Bowel frequency (BM/week)	NR	NR	
• Straining (%)	NR	NR	
• Abdominal pain	NR	NR	
• Hard stools (%)	NR	NR	
• Normal stools (%)	NR	NR	
• Use of laxatives (%)	NR	NR	
• Use of constipation diet (%)	NR	NR	
• Use of bulk-forming agents(%)	NR	NR	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** bowel movement frequency; bowel movement consistency (1= hard, 2=firm, 3=soft, 4=loose, 5=watery); nausea, cramping, abdominal pain, use of laxatives **Secondary Outcome Measures:** **Timing of assessments:** 5 days		
RESULTS:	**Health Outcome Measures:** • **PEG 3350 8 oz per day vs. placebo** • Bowel movement frequency: 5.81 vs. 4.36 *p>0.01* • Bowel movement consistency: 1.91 vs. 1.63 *p>0.01* • Requiring laxatives: 2 patients vs. 3 patients		

Authors: Andorsky and Goldner **Year: 1990**			
ADVERSE EVENTS: **Overall adverse effects reported:**	**PEG 3350**	**PEG 3350**	**placebo**
• diarrhea	NR	NR	NR
• headache	NR	NR	NR
• nausea	8.3%	0%	0%
• abdominal pain	NR	NR	NR
• flatulence	NR	NR	NR
• treatment related upsets	NR	NR	NR
• distension	NR	NR	NR
• gas/cramps	16.7%	75%	0%
Significant differences in adverse events:	P values NR		
Adherence/Compliance:	NR		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	yes		
ATTRITION (*overall*):	**Overall attrition:** 13 % **Differential attrition high:** no		
ATTRITION (*treatment specific*):	**PEG 3350 8 oz per day**	**placebo**	
Total attrition:	4	NR	
Withdrawals due to adverse events:	NR	NR	
QUALITY RATING:	**Fair**		

Chronic Constipation and IBS-C

STUDY:	**Authors, article #: Ashraf et al.**[36, 58] **Year: 1995** **Country:** US		
FUNDING:	Proctor & Gamble Co., USA		
RESEARCH OBJECTIVE:	To determine the effects of psyllium on stool characteristics, colon transit and anorectal function in chronic idiopathic constipation		
DESIGN:	**Study design:** RCT **Setting:** University, subjects responding to invitation to participate in study **Sample size:** 22		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**psyllium** 5 g b.i.d. 8 weeks 11	**placebo** N/A 8 weeks 11	
INCLUSION CRITERIA:	Subjective chronic constipation: defined as passage of <= 3 stools/week for at least 6 months; subjects entered 4-wk baseline phase, and only those who were confirmed on basis of stool diaries to demonstrate constipation were randomized; fully mobile & healthy on basis of medical history & physical exam; 19-85 yrs. old		
EXCLUSION CRITERIA:	Severe constipation requiring continual use of enemas & suppositories; current history of treatment with constipating medication or with unstable doses of thiazides, β-blockers or estrogens; congestive heart failure, unstable angina, inflammatory bowel disease, pancreatitis, diabetes mellitus, or hypothyroidism; history of major GI surgery or major bowel obstruction requiring medical treatment; organic GI lesion causing constipation; current GI, renal, pulmonary, hepatic/biliary disease, or cancer, or history of myocardial infarction or coronary artery bypass or any major surgical procedure in last 6 months; current history of drug or alcohol abuse		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	All laxatives had to be stopped 1 week prior to study		

Authors: Ashraf et al. **Year: 1995**			
POPULATION	**Groups similar at baseline:** No, they differ in sex and duration of constipation		
CHARACTERISTICS:	**psyllium**	**placebo**	
Mean age (years):	52.5	47.3	
Patients aged 65 years or older (%):	NR	NR	
Sex (% female):	72.7	54.5	
Ethnicity (% Caucasian):	NR	NR	
Mean body mass index:	NR	NR	
Other germane characteristics:			
• Duration of constipation (mean years)	33.7	19.6	
• Bowel frequency (BM/week)	NR	NR	
• Straining (%)	NR	NR	
• Abdominal pain	NR	NR	
• Hard stools (%)	NR	NR	
• Normal stools (%)	NR	NR	
• Use of laxatives (%)	72	63	
• Use of constipation diet (%)	NR	NR	
• Use of bulk-forming agents(%)	NR	NR	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Diary reporting stool frequency and occurrence of symptoms related to defecatory function: stool consistency, straining effort, occurrence of pain with defecation and presence of sensation of completeness or incompleteness of evacuation, all scored on visual analog scale ranging from 1-7 **Secondary Outcome Measures:** Colon transit, anorectal manometry **Timing of assessments:** Daily recording in stool diary; colon transit study and ARM at enrollment and weeks 4, 12, and 16		

<table>
<tr><td colspan="4">Authors: Ashraf et al.
Year: 1995</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
Stool frequency increased significantly after 8 wks psyllium treatment (3.8 ± 0.4 vs. 2.9 ± 0.1 stools/wk, P < 0.05), as did stool weight (665.3 ± 95.8 g vs. 405.2 ± 75.9 g, P < 0.05); neither changed on placebo
Stool frequency decreased significantly on stopping psyllium treatment and returned to pre-treatment levels by the end of wash-out phase (week 16 vs. week 12: 2.9 ± 0.2 vs. 3.8 ± 0.4 stool/week, P < 0.05)
All parameters of defecation tended to improve on psyllium, but only stool consistency and pain on defecation demonstrated a significant change; changes in other measures of evacuation did not achieve statistical significance
Subjects reported improvement in stool consistency (stool consistency score: 3.2 ± 0.2 vs. 3.8 ± 0.2, P < 0.05) and pain on defecation (pain score: 2.0 ± 0.4 vs. 2.6 ± 0.5, P < 0.05) on psyllium
Placebo group showed no change in either subjective or objective measures of constipation
Subgroup analysis by gender showed that women reported more straining during the baseline phase (straining score, week 4: F vs. M: 3.8 ± 0.2 vs. 2.4 ± 0.6, P < 0.05) as well as after psyllium treatment (straining score, week 12: F vs. M: 3.2 ± 0.3 vs. 1.8 ± 0.5, P < 0.05)
Colon transit and anorectal manometry parameters were unchanged on psyllium</td></tr>
<tr><td>ADVERSE EVENTS:
Overall adverse effects reported:
diarrhea
headache
nausea
abdominal pain
back pain
bloating/cramping</td><td><u>psyllium</u>
NR
NR
NR
NR
18
9
0</td><td><u>placebo</u>
NR
NR
NR
NR
0
9
0</td><td></td></tr>
<tr><td>Significant differences in adverse events:</td><td colspan="3">Trend toward greater abdominal pain in psyllium group; not statistically significant difference (P = NR) . All AEs were mild, no patient withdrew from the study due to AEs.</td></tr>
<tr><td>Adherence/Compliance:</td><td colspan="3">NR</td></tr>
</table>

ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	yes		
ATTRITION (*overall*):	**Overall attrition:** 0 **Differential attrition high:** No		
ATTRITION (*treatment specific*):	**psyllium**	**placebo**	
Total attrition:	0	0	
Withdrawals due to adverse events:	0	0	
QUALITY RATING:	**Fair**		

Chronic Constipation and IBS-C

STUDY:	**Authors, article #: Attar et al.**[43] **Year: 1999** **Country:** France and U.K.		
FUNDING:	NR		
RESEARCH OBJECTIVE:	To compare the efficacy of PEG and lactulose in chronic constipation		
DESIGN:	**Study design:** single blind RCT—as the treatments differed in appearance and taste, patients may know which they received **Setting: Multi-center,** multicenter, 10 centers in France and Scotland, patients recruited from outpatient gastroenterology and geriatric institutions **Sample size:** 115		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**PEG 3350 (with electrolytes)** 13.12 grams (1.8 sachets/day for first 2 weeks, 1.6 for last 2 weeks) 1 month 60	**lactulose** 10 grams (1.9 sachets/day for first 2 weeks, 2.1 for last 2 weeks) 1 month 55	
INCLUSION CRITERIA:	age ≥ 18; chronic constipation defined as 3 months with less than three stools per week or straining, if above age 45 colonic disease was excluded by colonoscopy or barium enema		
EXCLUSION CRITERIA:	Patients taking concomitant medications that could modify bowel habit (except microenemas/suppositories as below), severe liver; renal; or cardiac disease; pregnant, breastfeeding women		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	microenemas, suppositories		

Authors: Attar et al. **Year: 2004**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes		
	PEG 3350	**lactulose**	
Mean age (years):	55	55	
Patients aged 65 years or older (%):	41.7	32.7	
Sex (% female):	85	78.2	
Ethnicity (% Caucasian):	NR	NR	
Mean body mass index:	NR	NR	
Other germane characteristics:			
• Duration of constipation (mean)	NR	NR	
• Bowel frequency (BM/week)	NR	NR	
• < 3 stools per week (%)	38.3	47.3	
• Straining (%)	10	14.5	
• Abdominal pain	NR	NR	
• Hard stools (%)	NR	NR	
• Normal stools (%)	NR	NR	
• Use of laxatives (%)	NR	NR	
• Use of constipation diet (%)	NR	NR	
• Use of bulk-forming agents(%)	NR	NR	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** daily number of stools, daily symptoms of straining, liquid stools, abdominal pain, bloating, flatus, rumbling all scored from 0 (absence) to 3(severe), at week 4 overall improvement of symptoms was assessed on a visual analog scale 0 (no change) to 19 (excellent improvement) **Secondary Outcome Measures:** **Timing of assessments:** daily, 4 weeks		
RESULTS:	**Health Outcome Measures:** • Mean stool frequency 1.3/day (peg 3350) vs. 0.9/day (lactulose) *p=0.005* • Median daily score of straining 0.5 (peg 3350) vs. 1.2 (lactulose) *p=0.0001* • Mean visual analog scale ratings at 4 weeks 7.4 (PEG 3350) vs. 5.2 (lactulose) *p=<0.001* • Need for suppositories or microenemas 16% (peg 3350) vs. 34% (lactulose) *p=0.04*		

Authors: Attar et al. **Year: 1999**			
ADVERSE EVENTS: **Overall adverse effects reported:** **Median daily episodes of:** • diarrhea • headache • nausea • abdominal pain • flatulence • bloating • rumbling	**PEG 3350** NR 0.3 NR NR 0.4 0.8 0.7 0.2	**lactulose** NR 0.2 NR NR 0.7 1.0 0.9 0.4	
Significant differences in adverse events:	• flatus (3.8 vs. 9.2; *P* = 0.01); reporting # of days with score >1 • abdominal pain (3.9 vs. 6.8; *P* = 0.08). • mean # of liquid stools (2.4 vs. 0.6; *P* = 0.001). • slight decrease in sodium in the lactulose group from 140 to 139 (*P* = 0.02). • 4 AEs lead to drug withdrawal during the additional 2 months: acute diarrhea with fever (1), abdominal pain (2), and vomiting (1).		
Adherence/Compliance:	NR		
ANALYSIS:	**ITT:** no **Post randomization exclusions:** NR		
ADEQUATE RANDOMIZATION:	yes		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	De facto "no" because patients may have known the drug due to taste/appearance, the outcome assessors and providers may have learned that as well		
ATTRITION (*overall*):	**Overall attrition:** 13% **Differential attrition high:** no		
ATTRITION (*treatment specific*): **Total attrition:** **Withdrawals due to adverse events:**	**PEG3350** 10 2	**lactulose** 6 1	
QUALITY RATING:	**Poor**		

Chronic Constipation and IBS-C

STUDY:	**Authors, article #: Cleveland et al.**[33] **Year: 2001** **Country:** USA		
FUNDING:	Braintree laboratories		
RESEARCH OBJECTIVE:	Compare clinical efficacy and safety of PEG 3350 with placebo		
DESIGN:	**Study design:** cross over double blind RCT **Setting:** a "busy New Hampshire practice" **Sample size:** 23		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**PEG 3350 (w/o electrolytes)** 17 g per day 2 weeks NR	**placebo** N/A 2 weeks NR	
INCLUSION CRITERIA:	Men and women age 18 and over; history of constipation; Must have had 3 or fewer BMs during a 7 day placebo control period to enter [no mention of "chronic" constipation—to enter must have had a history of constipation and 3 or fewer BMs during 7 day entry period]		
EXCLUSION CRITERIA:	Organic cause of constipation verified with colonoscopy or barium enema; pregnancy; weight <100 pounds; previous gastric surgery; more than 3 bowel movements during the run-in period		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Patients instructed not to take any other laxatives		

Authors: Cleveland et al. **Year: 2001**	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** NR
	Overall
Mean age (years):	47.7 years
Patients aged 65 years or older (%):	NR
Sex (% female):	95.7%
Ethnicity (% Caucasian):	NR
Mean body mass index:	NR
Other germane characteristics:	NR
• Duration of constipation (mean)	NR
• Bowel frequency (BM/week)	
• Straining (%)	NR
• Abdominal pain	NR
• Hard stools (%)	NR
• Normal stools (%)	NR
• Use of laxatives (%)	NR
• Use of constipation diet (%)	NR
• Use of bulk-forming agents(%)	NR
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** overall effectiveness measured by the investigator; overall effectiveness measured by the investigator; Flatus score 0=none, 1= moderate, 2=occasional, 3= frequent, 4= very frequent; Cramping score 0=none, 1=mild, 2=moderate, 3=severe, 4=have to discontinue **Timing of assessments:** 2 weeks, and 2 weeks after cross over
RESULTS:	**Health Outcome Measures:** • PEG 3350 vs. placebo • Patient rated overall effectiveness 83% vs. 35% *P<0.01* • Investigator rated effectiveness 72% vs. 35% *P<0.025* • Cramping score 2.0 vs. 1.9 *P=.25* • Flatus score 0.9 vs. 0.6 *P<0.001*

Authors: Cleveland et al. **Year:2001**			
ADVERSE EVENTS: **Overall adverse effects reported:** • Diarrhea ("loose stools or mild diarrhea") • headache • nausea • abdominal pain • flatulence • heartburn • serious AEs	**PEG 3350** NR N=3 (13.0%) NR N=2 (8.7%) NR NR NR 0	**placebo** NR NR N=1 (4.3%) NR NR N=1 (4.3%) 0	
Significant differences in adverse events:	Note: they report no "clinically significant differences in blood chemistry, CBC, or urinalysis were observed between the active treatment and placebo patients" "scores" (0-4 scales rated by patients) reported for cramping, rectal irritation, and flatus—these scores were used more as effectiveness, but: PEG vs. placebo:: Cramping: 0.6 vs. 0.9, P <0.001; Rectal irritation: 0.4 vs. 0.6, P < 0.001; Flatus: 1.9 vs. 2.0, P = 0.25.		
Adherence/Compliance:	A total of 56% of the study population requested termination; 11 patients (44%) requested early termination during placebo vs. 3 (11%) during PEG		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	yes		
ATTRITION (*overall*):	**Overall attrition:** 56% **Differential attrition high:** yes		
ATTRITION (*treatment specific*): **Total attrition:** **Withdrawals due to adverse events:**	**PEG 3350** 12% NR	**placebo** 44% NR	
QUALITY RATING:	**Poor**		

Chronic Constipation and IBS-C

STUDY:	**Authors, article #: Dettmar et al.**[65] **Year: 1998** **Country:** UK		
FUNDING:	In part by Ricketts and Coleman Products, Ltd		
RESEARCH OBJECTIVE:	Compare clinical efficacy and safety of psyllium versus lactulose or other laxatives		
DESIGN:	**Study design:** open RCT **Setting:** multicenter, outpatient but this point is somewhat unclear **Sample size:** 394		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**psyllium** 3.5 g bid 4 weeks 224	**lactulose** 4 weeks 91	**bisacodyl, docusate sodium, senna, magnesium sulfate** 4 weeks 79
INCLUSION CRITERIA:	Patients presenting to general physicians; age≥18; with simple constipation defined as a change in bowel habits resulting in straining; or passage of hard stools. Note: duration of constipation was not a criteria. Duration ranged from 7 days or less in 37 patients to more than 90 days in 36 patients.		
EXCLUSION CRITERIA:	Pregnancy; required hospitalization; passing blood in rectum; gastrointestinal carcinoma; those already taking bulking agents; patients who a history of laxative abuse; those taking drugs that can alter bowel habits; those with unstable diabetes; those with other gastrointestinal diseases		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Laxatives or drugs altering bowel habits not allowed		

Authors: Dettmar et al. **Year: 1998**			
POPULATION	**Groups similar at baseline:**		
CHARACTERISTICS:	**psyllium**	**lactulose**	**other**
Mean age (years):	NR	NR	NR
Patients aged 65 years or older (%):	NR	NR	NR
Sex (% female):	63%(4 unknown)	63%	65%(1 unknown)
Ethnicity (% Caucasian):	NR	NR	NR
Mean body mass index:	NR	NR	NR
Other germane characteristics:			
• Duration of constipation	NR	NR	NR
(mean)	NR	NR	NR
• Bowel frequency (BM/week)	NR	NR	NR
• Straining (%)	NR	NR	NR
• Abdominal pain	NR	NR	NR
• Hard stools (%)	NR	NR	NR
• Normal stools (%)	NR	NR	NR
• Use of laxatives (%)	NR	NR	NR
• Use of constipation diet (%)	NR	NR	NR
• Use of bulk-forming agents(%)	NR	NR	NR
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** drug effectiveness; palatability; acceptability; bowel function compared with pretreatment (diary cards used to record each day) **Timing of assessments:** after 2 and 4 weeks, adverse events assessed between weeks 1-2 and 3-4		
RESULTS:	**Health Outcome Measures: psyllium vs. lactulose** • Psyllium/lactulose/other • Bowel function: Much better: 32.6%, 26.8%, 18.6%; Better: 58.7, 49.3, 61.4 $P \leq 0.01$ *(authors report that "there was a difference between all three treatments at the 1% level" but it is not clear specifically what the difference was between)* • Overall effectiveness: Excellent: 20.6%, 15.5%, 10.0%; good: 56.0%, 45.1%, 38.6% $P \leq 0.01$ *(as above)* • Palatability: Excellent: 13.1%, 11.3%, 7.1%; Good 48.9%, 38.0%, 42.9% $P \leq 0.05$ *(as above, but at the 5% level)* • Acceptability: Excellent: 21.4%, 11.3%, 4.3%; Good: 51.7%, 38.0%, 45.7% $P \leq 0.01$ *(as above)*		

Authors: Dettmar et al. **Year: 1998**			
ADVERSE EVENTS: **Overall adverse effects reported:**	**psyllium**	**lactulose**	**other**
• diarrhea	1.5% of days	2.2% of days	4.4% of days
• headache	NR	NR	NR
• nausea	8.0	7.7	6.4
• abdominal pain or griping	15.1	22.0	29.5
• flatulence	28.0	22.0	28.2
• treatment related upsets	4.4%	4.2%	10.0%
• distension	15.5%	13.2%	15.45
Significant differences in adverse events:	• Diarrhea • Abdominal pain or griping, numbers above		
Adherence/Compliance:	NR		
ANALYSIS:	**ITT:** no **Post randomization exclusions:** NR		
ADEQUATE RANDOMIZATION:	**Procedure NR**		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	no		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):**	**Overall attrition:** NR, if a patient was lost to follow up, "a new patient was recruited to the same treatment group to maintain randomization" **Differential attrition high:** NR		
Total attrition:	**psyllium**	**lactulose**	**Other**
Withdrawals due to adverse events:	NR NR	NR NR	NR NR
QUALITY RATING:	**Poor**		

Chronic Constipation and IBS-C

STUDY:	**Authors, article #: DiPalma et al.**[31] **Year: 2000** **Country:** US		
FUNDING:	Braintree laboratories		
RESEARCH OBJECTIVE:	To determine the efficacy and safety of a new laxative, PEG 3350		
DESIGN:	**Study design:** placebo-controlled, double-blind, multicenter, RCT **Setting:** multi-center **Sample size:** 151		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**PEG 3350 (w/o electrolytes)** 17 g per day 2 weeks 80	**placebo** 17 g per day 2 weeks 71	
INCLUSION CRITERIA:	History of constipation; less than two bowel movements per week during 7 day qualification		
EXCLUSION CRITERIA:	Allergy to PEG 3350; prior GI surgery; known or suspected GI obstruction; ileus; heart failure; ascites; other known chronic bowel, liver, renal or cardiopulmonary disorders; pregnancy; lactation; weight < 100 lb		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

Authors: DiPalma et al. **Year: 2000**			
POPULATION	**Groups similar at baseline:** NR		
CHARACTERISTICS:	**PEG 3350**	**placebo**	
Mean age (years):	46.7	45.8	
Patients aged 65 years or older (%):	NR	NR	
Sex (% female):	83.8%	90.1%	
Ethnicity (% Caucasian):	NR	NR	
Mean body mass index:	NR	NR	
Other germane characteristics:			
• Duration of constipation (mean)	NR	NR	
• Bowel frequency (BM/week)	NR	NR	
• Straining (%)	NR	NR	
• Abdominal pain	NR	NR	
• Hard stools (%)	NR	NR	
• Normal stools (%)	NR	NR	
• Use of laxatives (%)	NR	NR	
• Use of constipation diet (%)	NR	NR	
• Use of bulk-forming agents(%)	NR	NR	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** patient global assessment score; investigator global assessment score; treatment failure <3 bowel movements per week, need for laxatives, enema, withdrawal from the study **Timing of assessments:** 2 weeks		
RESULTS:	**Health Outcome Measures:** • PEG 3350 vs. placebo • Percentage Satisfactory stools 68% vs. 48% *P<0.05* • Difficult stool passage 13.8% vs. 46.4% *P=0.001* • Bowel movements per week 4.5 vs. 2.7 *P=0.001* • Severe gas 24% vs. 40.2% *P=0.001* • Severe cramps 12% vs. 22.6% *P=0.001*		

Authors: DiPalma et al. **Year: 2000**			
ADVERSE EVENTS: **Overall adverse effects reported:**	**PEG 3350**	**placebo**	
• diarrhea	NR	NR	
• headache	NR	NR	
• nausea	NR	NR	
• abdominal pain	NR	NR	
• flatulence	NR	NR	
• severe cramp	12	22.6	
• severe gas	24	40.2	
Significant differences in adverse events:	Patient subjective observations: Severe cramping: Pretreatment; PEG 35.5% vs. placebo 39.2%, P 0.61. During treatment period; 12.0% vs.22.6%, P = 0.001. Severe gas: Pretreatment; PEG 49.5% vs. placebo 60.7%, P = 0.13. During treatment period; 24% vs. 40.2%, P = 0.001. --No statistically or clinically significant differences between groups for laboratory measurements or AEs. Data NR.		
Adherence/Compliance:	4.6% noncompliant or admitted to the study from erroneous lab tests		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** yes(7)		
ADEQUATE RANDOMIZATION:	No		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	yes		
ATTRITION (*overall*):	**Overall attrition:** 11% **Differential attrition high:** NR		
ATTRITION (*treatment specific*):	**drug 1**	**drug 2**	**drug 3**
Total attrition:	NR	NR	
Withdrawals due to adverse events:	NR	NR	
QUALITY RATING:	**Fair**		

Chronic Constipation and IBS-C

STUDY:	**Authors, article #: Fenn et al.**[35] **Year: 1986** **Country:** UK	
FUNDING:	Searle Pharmaceuticals	
RESEARCH OBJECTIVE:	To evaluate the efficacy and safety of psyllium in functional constipation	
DESIGN:	**Study design:** RCT, blinding status is NR **Setting:** UK, multi-site study conducted by 17 general practitioners **Sample size:** 201	
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**psyllium** 3.6 g tid (patients able to vary the dose if stools became watery) 2 weeks 104	**placebo** tid 2 weeks 97
INCLUSION CRITERIA:	Men and women between ages 18 -70 years; mobile; functional constipation (definition not offered); willing and able to complete a diary card	
EXCLUSION CRITERIA:	Taking other laxatives or gastrointestinal drugs; taking Regulan immediately prior to the study; intestinal obstruction; intestinal narrowing; organic causes of constipation; fecal impaction; pregnancy; lactation; known sensitivity to psyllium or sucrose	
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	No other gastrointestinal drugs	

Authors: Fenn et al. **Year: 1986**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:**		
	psyllium	**placebo**	
Mean age (years):	50	48	
Patients aged 65 years or older (%):	NR	NR	
Sex (% female):	74%	76%	
Ethnicity (% Caucasian):	NR	NR	
Mean body mass index:	NR	NR	
Other germane characteristics:			
• Duration of constipation (mean)	Median 2 years	Median 3 years	
• Bowel frequency (BM/week)	2.3	2.3	
• Straining (%)	NR	NR	
• Abdominal pain	NR	NR	
• Hard stools (%)	67	76	
• Normal stools (%)	NR	NR	
• Use of laxatives (%)	NR	NR	
• Use of constipation diet (%)	NR	NR	
• Use of bulk-forming agents(%)	NR	NR	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** straining; abdominal pain or discomfort; number and consistency of bowel movements; symptom improvement **Timing of assessments:** 2 weeks		
RESULTS:	**Health Outcome Measures: psyllium vs. placebo** • Bowel movements: 14 vs. 9 *P<0.001* • Patient assessment of constipation improvement: Better: 90% vs. 46% *P<0.001* • Investigator assessment of constipation improvement: Better: 87% vs. 48% *P<0.001*		

Authors: Fenn et al. **Year: 1986**			
ADVERSE EVENTS: **Overall adverse effects reported:**	**psyllium**	**placebo**	
• diarrhea	NR	NR	
• headache	NR	NR	
• nausea	NR	NR	
• abdominal pain	51.4	67.4	
• flatulence	NR	NR	
• treatment related upsets	NR	NR	
• distension	NR	NR	
• straining	48.5	74.7	
Significant differences in adverse events:	Abdominal pain was better in 44 and worse in 11 subjects on the psyllium group and better in 27 and worse in 15 in the placebo group ($p < 0.035$). Reduction in moderate or severe straining on defecation was greater in the ispaghula group ($p = 0.003$) (from 70 subjects at baseline to 11 vs. from 63 to 27 for placebo) Five subjects in each treatment group named side effects as reason for withdrawal from study. Reasons included abdominal pain, wind, bubbly stomach, nausea vomiting, nausea, vomiting, diarrhea, pyrexia, and feeling unwell, malaise.		
Adherence/Compliance:	91% adherence		
ANALYSIS:	**ITT:** no **Post randomization exclusions:** yes (5)		
ADEQUATE RANDOMIZATION:	**Procedure NR**		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	No		
ATTRITION (*overall*):	**Overall attrition:** 9% attrition **Differential attrition high:** no		
ATTRITION (*treatment specific*):	**psyllium**	**placebo**	
Total attrition:	6.7%	11.3%	
Withdrawals due to adverse events:	4.8%	5.2%	
QUALITY RATING:	**Poor**		

Chronic Constipation and IBS-C

STUDY:	**Authors, article #: Loening-Baucke et al.**[68] **Year: 2004** **Country:** USA
FUNDING:	NR
RESEARCH OBJECTIVE:	To evaluate the safety of PEG 3350 in children under 2 for the treatment of constipation.
DESIGN:	**Study design:** Retrospective chart review **Setting:** outpatient **Sample size:** 75
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**PEG 3350** Started at 1 mg/kg/day adjusted by parents to produce 2 soft stools per day as needed 6 months 75
INCLUSION CRITERIA:	All children < 2 years of age at time they started PEG; idiopathic constipation defined by NASPGHAN criteria; seen between 2000 and 2003
EXCLUSION CRITERIA:	Hirschsprung's disease; chronic intestinal pseudo-obstruction or previous surgery on the colon or anus; disease states placing limits on the act of defecation like hypotonia, cerebral palsy, severe mental retardation
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR

Authors: Loening-Baucke et al. **Year: 2004**	
POPULATION	**Groups similar at baseline:** N/A
CHARACTERISTICS:	**PEG 3350**
Mean age (years):	17 months
Patients aged 65 years or older (%):	0
Sex (% female):	52.0
Ethnicity (% Caucasian):	NR
Mean body mass index:	NR
Other germane characteristics:	
• Duration of constipation (mean)	10 months
• Bowel frequency (BM/week)	4.2
• Straining (%)	NR
• Abdominal pain	NR
• Hard stools (%)	85
• Normal stools (%)	NR
• Use of laxatives (%)	24
• Use of constipation diet (%)	100
• Use of bulk-forming agents(%)	NR
• Pain with stools (%)	73
• Blood with stools (%)	40
• Rectal impaction (%)	53
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Any adverse effects of PEG **Timing of assessments:** 6 months
RESULTS:	**Health Outcome Measures:** N/A—Adverse Events only (see below)

Authors: Loeing-Baucke et al. **Year: 2004**			
ADVERSE EVENTS: **Overall adverse effects reported:** • diarrhea • headache • nausea • abdominal pain • flatulence • treatment related upsets • distension	**PEG 3350 (treatment 4 months or less)** NR 7	**PEG 3350 (treatment 6 months or more)** NR 2	
Significant differences in adverse events:	AEs were not defined, some were pre-specified. No description of how AE data obtained. "Parents did not report" increased flatus, abdominal distention, vomiting, or new onset abdominal pain. Lab tests—CBC, electrolytes, LFTs performed occasionally and all checked were normal.		
Adherence/Compliance:	Noncompliance 1% short-term and 2% long term		
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A		
ADEQUATE RANDOMIZATION:	**N/A**		
ADEQUATE ALLOCATION CONCEALMENT:	N/A		
BLINDING OF OUTCOME ASSESSORS:	N/A		
ATTRITION (*overall*):	**Overall attrition:** N/A **Differential attrition high:** N/A		
ATTRITION (*treatment specific*): **Total attrition:** **Withdrawals due to adverse events:**	**PEG 3350** None reported		
QUALITY RATING:	**Poor**		

Chronic Constipation and IBS-C

STUDY:	**Authors, article #: McRorie et al.**[42] **Year: 1998** **Country:** USA		
FUNDING:	Proctor and Gamble Company and the Oklahoma Foundation for Digestive Research		
RESEARCH OBJECTIVE:	Compare clinical efficacy and safety of psyllium and docusate sodium		
DESIGN:	**Study design:** double blind RCT **Setting:** NR, multi-center **Sample size:** 187		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**psyllium** 5.1 g twice a day 2 weeks NR	**docusate sodium** 100 mg twice a day 2 weeks NR	
INCLUSION CRITERIA:	3 "productive" stools or less per week; more frequent but non-productive stools based on size and segments measured in the run-in phase		
EXCLUSION CRITERIA:	Laxative abuse; obstructive or metabolic cause for constipation; history of regular stimulant laxative use (more than 1 per week); pregnancy		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

<table>
<tr><td colspan="4">Authors: McRorie et al.
Year: 1998</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: NR</td></tr>
<tr><td></td><td><u>psyllium</u></td><td><u>docusate</u></td><td><u>Overall</u></td></tr>
<tr><td>Mean age (years):</td><td></td><td></td><td>37.2 years</td></tr>
<tr><td>Patients aged 65 years or older (%):</td><td></td><td></td><td>91.8%</td></tr>
<tr><td>Sex (% female):</td><td></td><td></td><td>64.1%</td></tr>
<tr><td>Ethnicity (% Caucasian):</td><td></td><td></td><td>NR</td></tr>
<tr><td>Mean body mass index:</td><td></td><td></td><td>NR</td></tr>
<tr><td>Other germane characteristics:</td><td></td><td></td><td></td></tr>
<tr><td>• Duration of constipation (mean)</td><td></td><td></td><td>NR
NR</td></tr>
<tr><td>• Bowel frequency (BM/week)</td><td>3.08</td><td>3.07</td><td></td></tr>
<tr><td>• Straining (%)</td><td></td><td></td><td>NR</td></tr>
<tr><td>• Abdominal pain</td><td></td><td></td><td>NR</td></tr>
<tr><td>• Hard stools (%)</td><td></td><td></td><td>NR</td></tr>
<tr><td>• Normal stools (%)</td><td></td><td></td><td>NR</td></tr>
<tr><td>• Use of laxatives (%)</td><td></td><td></td><td>NR</td></tr>
<tr><td>• Use of constipation diet (%)</td><td></td><td></td><td>NR</td></tr>
<tr><td>• Use of bulk-forming agents(%)</td><td></td><td></td><td>NR</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Bowel movement frequency; measured on a 7 point scale (1=good 7 bad) straining; pain with defecation; overall feeling of constipation; completeness of evacuation

Timing of assessments: 2 weeks</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures: (all statistical test one sided)
• Psyllium vs. docusate sodium
• Bowel movements per week 3.51 vs. 2.87 P=0.021
• Straining 2.81 vs. 2.05 P=0.152
• Pain with BM 2.04 vs. 2.27 P=0.116
• Evacuation completeness 3.53 vs. 3.74 P=0.018</td></tr>
</table>

Authors: McRorie et al. **Year: 1998**			
ADVERSE EVENTS: **Overall adverse effects reported:** • diarrhea • headache • nausea • abdominal pain • flatulence • X • Y	**psyllium** NR NR NR NR NR	**docusate sodium** NR NR NR NR NR	
Significant differences in adverse events:			
Adherence/Compliance:	NR		
ANALYSIS:	**ITT:** no **Post randomization exclusions:** yes (9%)		
ADEQUATE RANDOMIZATION:	NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	Yes		
ATTRITION (*overall*):	**Overall attrition:** NR **Differential attrition high:** NR		
ATTRITION (*treatment specific*): **Total attrition:** **Withdrawals due to adverse events:**	**psyllium** NR NR	**docusate sodium** NR NR	
QUALITY RATING:	**Poor**		

Chronic Constipation and IBS-C

STUDY:	**Authors, article #: Michail et al.**[77] **Year: 2004** **Country:** USA
FUNDING:	NR
RESEARCH OBJECTIVE:	Evaluate the safety of PEG 3350 in children aged less than 18 months or less with chronic constipation
DESIGN:	**Study design:** retrospective cohort **Setting:** NR **Sample size:** 28
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**PEG 3350** 17g/240 mL water (titrated after 24 hours to produce one nonformed bowel movement per day) 3 weeks to 21 months 28
INCLUSION CRITERIA:	Male and female children less than 18 months; constipation defined by Rasquin-Weber et al. for infants and pre-school aged children; 2 weeks with majority of stools being hard or having firm stools two or fewer times a week (stool consistency scale 1=hard, 2=firm, 3=soft, 4=loose, 5=watery)
EXCLUSION CRITERIA:	Organic etiology of constipation including Hirschsprung's disease, anorectal malformation, bowel obstruction, systemic illness, hypothyroidism, cystic fibrosis, lead poisoning; taking medications that can change the frequency or consistency of bowel movements
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	No medications affecting bowel movement frequency or consistency

Authors: Michail et al. **Year: 2004**	
POPULATION CHARACTERISTICS:	**Groups similar at baseline:**
	PEG 3350
Mean age (years):	NR
Patients aged 65 years or older (%):	NR
Sex (% female):	NR
Ethnicity (% Caucasian):	NR
Mean body mass index:	NR
Other germane characteristics:	
• Duration of constipation (mean)	NR
	NR
• Bowel frequency (BM/week)	2.2
• Straining (%)	NR
• Abdominal pain	NR
• Hard stools (%)	NR
• Normal stools (%)	NR
• Use of laxatives (%)	NR
• Use of constipation diet (%)	NR
• Use of bulk-forming agents(%)	NR
• Mean stool consistency	1.7
• Children experiencing discomfort with defecation	71.9%
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** effective maintenance dose; side effects; duration of therapy; compared to baseline - response to therapy; mean stools per week; mean stool consistency score **Timing of assessments:** every 8- 12 weeks
RESULTS:	**Health Outcome Measures:** • Mean effective dose: 0.78 g/kg/day • 96.4% of patients were effectively treated • mean stool frequency 8.4 per week *P<0.001* • mean stool consistency score 3.8 *P<0.001* • parent report that discomfort during defecation in infants improved: 95%

Authors: Michail et al. **Year: 2004**	
ADVERSE EVENTS: **Overall adverse effects reported:** • diarrhea • headache • nausea • abdominal pain • flatulence	**PEG 3350** 14.2% NR NR NR 3.6%
Significant differences in adverse events:	N/A
Adherence/Compliance:	Authors suggested that compliance was good due to high resolution of symptoms
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ADEQUATE RANDOMIZATION:	**N/A**
ADEQUATE ALLOCATION CONCEALMENT:	N/A
BLINDING OF OUTCOME ASSESSORS:	N/A
ATTRITION (*overall*):	**Overall attrition:** N/A **Differential attrition high:** N/A
ATTRITION (*treatment specific*): **Total attrition:** **Withdrawals due to adverse events:**	**PEG 3350** N/A N/A
QUALITY RATING:	**Poor**

Chronic Constipation and IBS-C

STUDY:	**Authors, article #: Pashankar et al.**[67] **Year: 2003** **Country:** USA		
FUNDING:	Braintree Labs		
RESEARCH OBJECTIVE:	To assess the long-term safety profile and acceptance of PEG 3350 in children with chronic constipation.		
DESIGN:	**Study design:** Prospective cohort study **Setting:** Pediatric clinics at a referral center **Sample size:** 83		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**PEG 3350 w/o electrolytes** 0.8 mg/kg/day (changed with symptoms) 3-30 months (mean 8.7 months) 83	**No Comparison**	
INCLUSION CRITERIA:	All children > 2 yrs. old treated with PEG more than 3 months were eligible; chronic constipation based on symptoms of ≥ 3 months duration, including at least 2 of the following: hard stools, painful defecation, encopresis, or < 3 BMs per week.		
EXCLUSION CRITERIA:	Children included in 2 other studies conducted by the authors; history of Hirschsprung's disease; anorectal malformation; systemic disease leading to constipation		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	NR		

Authors: Pashankar et al. **Year: 2006**	
POPULATION	**Groups similar at baseline:** N/A
CHARACTERISTICS:	**PEG 3350 w/o electrolytes**
Mean age (years):	7.4
Patients aged 65 years or older (%):	0
Sex (% female):	42.2
Ethnicity (% Caucasian):	NR
Mean body mass index:	NR
Other germane characteristics:	
• Duration of constipation (mean)	28.8 months
• Bowel frequency (BM/week)	NR
• Straining (%)	NR
• Abdominal pain	NR
• Hard stools (%)	NR
• Normal stools (%)	NR
• Use of laxatives (%)	NR
• Use of constipation diet (%)	NR
• Use of bulk-forming agents(%)	13
• Prev. therapy attempted (%)	82
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Safety: questionnaire for parents asking about possible adverse effects of PEG, including excessively loose or frequent stools, abdominal pain, flatulence, bloating, and nausea; serum samples evaluated hemoglobin, hematocrit, serum electrolytes, blood urea nitrogen, serum creatinine, osmolality, albumin, aspartate aminotransferase, and ALT; abnormal results were repeated in 8 weeks while therapy continued; Acceptance: questionnaire included compliance, ease of mixing. **Timing of assessments:** Variable, not standardized
RESULTS:	**Health Outcome Measures:** • N/A

Authors: Pashankar **Year: 2003**			
ADVERSE EVENTS: **Overall adverse effects reported:** • diarrhea • headache • nausea • abdominal pain • flatulence or bloating • fatigue • thirst • elevated ALT • elevated AST	**PEG 3350 w/o electrolytes** 10% NR 1% 2% 6% 1% 1% 11 4		
Significant differences in adverse events:	All lab results were normal except 9 patients (11%) with abnormal ALTs and 3 (4%) with elevated aspartate aminotransferase.		
Adherence/Compliance:	Acceptance/tolerability: PEG liked by 93% of the treated children; all children (n = 62, 82%) who had used other therapies preferred PEG to other laxatives; daily compliance, assessed by parents' recall and diary was "good" (not defined) in 90% of group.		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ADEQUATE RANDOMIZATION:	N/A (not randomized)		
ADEQUATE ALLOCATION CONCEALMENT:	N/A		
BLINDING OF OUTCOME ASSESSORS:	N/A		
ATTRITION (*overall*):	**Overall attrition:** 0 **Differential attrition high:** N.A		
ATTRITION (*treatment specific*): **Total attrition:** **Withdrawals due to adverse events:**	**PEG 3350 w/o electrolytes** 0 0		
QUALITY RATING:	**Poor**		

Chronic Constipation and IBS-C

STUDY:	**Authors, article #: Rouse et al.**[66] **Year: 1991** **Country:** UK		
FUNDING:	NR		
RESEARCH OBJECTIVE:	Compare clinical efficacy and safety of psyllium versus lactulose		
DESIGN:	**Study design:** open RCT **Setting:** Multicenter, outpatient but this point is somewhat unclear **Sample size:** 124		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**psyllium** 3.5 g bid 4 weeks 45	**lactulose** 15 ml b.i.d. (up to 60 b.i.d. ml as needed) 4 weeks 48	
INCLUSION CRITERIA:	Men and women older than 18 years; 3 weeks of having 3 or less stools per week Entered the study via 21 general practitioners		
EXCLUSION CRITERIA:	Lactose intolerance; organic causes of constipation; laxative abuse; galactosemia		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	Yes but not listed		

Authors: Rouse, et al. **Year: 1991**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:**		
	psyllium	**lactulose**	
Mean age (years):	49.5	51.8	
Patients aged 65 years or older (%):	NR	NR	
Sex (% female):	NR	NR	
Ethnicity (% Caucasian):	NR	NR	
Mean body mass index:	NR	NR	
Other germane characteristics:			
• Duration of constipation (mean)	NR NR	NR NR	
• Bowel frequency (BM/week)	2.03	1.96	
• Straining (%)	NR	NR	
• Abdominal pain	NR	NR	
• Hard stools (%)	NR	NR	
• Normal stools (%)	NR	NR	
• Use of laxatives (%)	NR	NR	
• Use of constipation diet (%)	NR	NR	
• Use of bulk-forming agents(%)	NR	NR	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** straining; abdominal pain; clinical global improvement (not defined); palatability **Timing of assessments:** 4 weeks		
RESULTS:	**Health Outcome Measures: psyllium vs. lactulose** • Straining: None/Mild/Moderate/Severe • 46.7%/40.0%/13.3%/0% vs. 31.2%/54.1%/12.5%/2.1% *P=NR* • Abdominal pain: None/Mild/Moderate/Severe • 68.9%/28.9%/0/2.1% vs. 70.8%22.9%.4.2%/2.1% *P=NR* • Clinical Global improvement: Much improved/Slightly improved/No change/Slightly worse/ Much worse • 64.4%/31.1%/4.4%/0/0 vs. 68.8%/27.1%/2.1%/2.1%/0 *P=NR* • Palatability: At day 7: 18.5% vs. 5.7%, *P=0.04; At day 28: 15.6% vs. 4.2%, P= 0.063*		

Authors: Rouse, et al. **Year: 1991**			
ADVERSE EVENTS: **Overall adverse effects reported:** • diarrhea • headache • nausea • abdominal pain • flatulence • treatment related upsets • distension	**psyllium** NR NR NR NR NR NR NR	**lactulose** NR NR NR NR NR NR NR	
Significant differences in adverse events:	Abdominal pain		
Adherence/Compliance:	9.6% had protocol violations and were excluded in the final analysis, 16.1% left the study		
ANALYSIS:	**ITT:** No **Post randomization exclusions:** Yes		
ADEQUATE RANDOMIZATION:	Procedure NR		
ADEQUATE ALLOCATION CONCEALMENT:	NR		
BLINDING OF OUTCOME ASSESSORS:	No		
ATTRITION (*overall*):	**Overall attrition:** 25.8% **Differential attrition high:** No		
ATTRITION (*treatment specific*): **Total attrition:** **Withdrawals due to adverse events:**	**psyllium** NR NR	**lactulose** NR NR	
QUALITY RATING:	**Poor**		

Chronic Constipation and IBS-C

STUDY:	**Authors, article #: Tran et al.**[34] **Year: 2005** **Country:** USA		
FUNDING:	NR		
RESEARCH OBJECTIVE:	To extend the treatment and safety experience with PEG 3350 and to evaluate any lasting effectiveness during a 30-day post-treatment observational period		
DESIGN:	**Study design:** open uncontrolled trial **Setting:** outpatient, university gastroenterology practice **Sample size:** 50		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**PEG 3350** 17 grams per day 2 weeks 50		
INCLUSION CRITERIA:	Men and women over age 19; satisfactory stools less than 3 times a week; meet Rome II-based criteria for constipation for at least 12 weeks in the preceding 12 months (straining or lumpy or hard stools or the sensation of incomplete or the need for manual maneuvers to defecate or the sensation of ano-rectal blockage in more than 25% of defecations)		
EXCLUSION CRITERIA:	Those qualifying for a diagnosis for IBS; pregnancy; breastfeeding; stool occult blood which has been unevaluated; known or suspected bowel perforation; obstruction; fecal impaction; gastric retention; inflammatory bowel disease; bowel resection; colostomy; using medications known to cause constipation; allergy to PEG 3350		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	None		

Authors: Tran et al. **Year: 2005**			
POPULATION	**Groups similar at baseline:** N/A		
CHARACTERISTICS:	**PEG 3350 8 oz**		
Mean age (years):	52.1		
Patients aged 65 years or older (%):	NR		
Sex (% female):	94%		
Ethnicity (% Caucasian):	60%		
Mean body mass index:	NR		
Other germane characteristics:			
• Duration of constipation (mean)	22.6 months		
• Bowel frequency (BM/week)	NR		
• Straining (%)	NR		
• Abdominal pain	NR		
• Hard stools (%)	NR		
• Normal stools (%)	NR		
• Use of laxatives (%)	NR		
• Use of constipation diet (%)	NR		
• Use of bulk-forming agents(%)	NR		
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** percentage of satisfactory defecations; percentage of complete bowel movements; discontinuation due to adverse events; percentage achieving successful treatment (no longer meeting Rome-II criteria for constipation); need for laxatives **Timing of assessments:** 2 weeks		
RESULTS:	**Health Outcome Measures:** • **71% of bowel movements were satisfactory** • **80% achieved treatment success** • 57.3% of reported bowel movements were noted to be complete		

Authors: Tran et al. **Year: 2005**			
ADVERSE EVENTS: **Overall adverse effects reported:** • diarrhea • headache • nausea • abdominal pain • flatulence • treatment related upsets • distension • constipation • chest congestion • high blood pressure	**PEG 3350** NR 4% 2% NR NR NR NR 2% 2% 2%		
Significant differences in adverse events:	N/A		
Adherence/Compliance:	4% of subjects dropped out		
ANALYSIS:	**ITT:** yes **Post randomization exclusions:** N/A		
ADEQUATE RANDOMIZATION:	**N/A**		
ADEQUATE ALLOCATION CONCEALMENT:	N/A		
BLINDING OF OUTCOME ASSESSORS:	N/A		
ATTRITION (*overall*):	**Overall attrition:** 12% **Differential attrition high:** N/A		
ATTRITION (*treatment specific*): **Total attrition:** **Withdrawals due to adverse events:**	**PEG 3350 8 oz per day** 6 4		
QUALITY RATING:	**Poor**		

Chronic Constipation and IBS-C

STUDY:	**Authors, article #: Voskuijl et al.**[46] **Year: 2004** **Country:** Netherlands		
FUNDING:	NR		
RESEARCH OBJECTIVE:	Compare clinical efficacy and safety of PEG with electrolytes with lactulose in pediatric constipation and evaluate clinical efficacy/side effects.		
DESIGN:	**Study design:** Double blind RCT **Setting:** Multi-center, referral population (children referred to peds GI by GPs, school doctors, and pediatricians) **Sample size:** 100		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**PEG 3350 w/ electrolytes** 1 sachet (2.95 g) for age <6, 2 sachets (5.9 g) for age >6 8 weeks 50	**lactulose** 1 sachet (6 g) for age <6, 2 sachets (12 g) for age >6 8 weeks 50	
INCLUSION CRITERIA:	Children aged 6 months to 15 years; constipation defined as having 2 of the following 4 for the last 3 months: < 3 bowel movements per week, encopresis for more than a week, large amounts of stool every 7-30 days, palpable abdominal or rectal mass on physical exam.		
EXCLUSION CRITERIA:	Hypothyroidism, spina bifida occulta, Hirschsprung's, and other organic causes for disease		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	No oral laxatives were allowed during the 1 week run-in; stimulant laxatives were prescribed during treatment phase if treatment they were randomized to was unsuccessful at maximum dose allowed by the protocol.		

Authors: Voskuijl et al. **Year: 2004**			
POPULATION	**Groups similar at baseline:** Yes		
CHARACTERISTICS:	**PEG 3350**	**lactulose**	
Mean age (years):	6.5	6.5	
Patients aged 65 years or older (%):	0	0	
Sex (% female):	46%	44%	
Ethnicity (% Caucasian):	NR	NR	
Mean body mass index:	NR	NR	
Other germane characteristics:			
• Duration of constipation (mean)	NR	NR	
• Bowel frequency (BM/week)	64	60	
• Straining (%)	NR	NR	
• Abdominal pain	NR	NR	
• Hard stools (%)	NR	NR	
• Normal stools (%)	NR	NR	
• Use of laxatives (%)	NR	NR	
• Use of constipation diet (%)	NR	NR	
• Use of bulk-forming agents(%)	NR	NR	
• Encopresis > once/week	58	60	
• Large amounts of stool	60	50	
• Fecal impaction	48	52	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Frequency of stools, frequency of encopresis, overall success of treatment **Timing of assessments:** 8 weeks		
RESULTS:	**Health Outcome Measures: PEG 3350 vs. lactulose** • All ages 7.12 versus 6.43 defecations per week $P \leq 0.01$ • Age < 6 7.18 versus 5.22 defecations/per week $P \leq 0.01$ • Age ≥ 6 7.08 versus 7.70 defecations per week $P = 0.01$ • All ages 3.11 versus 2.8 encopresis per week $P \leq 0.01$ • Age < 6 3.54 versus 3.56 encopresis/per week $P \leq 0.172$ • Age ≥ 6 2.72 versus 2.08 encopresis per week $P = 0.01$ • Overall success percentage 56% versus 29% $P = 0.02$ • Medication sachets per day 1.99 vs. 2.4 $P = 0.03$		

Authors: Voskuijl et al. **Year: 2004**			
ADVERSE EVENTS: **Overall adverse effects reported:** • diarrhea • headache • nausea • abdominal pain • flatulence	**PEG 3350** All data reported in bar graph	**lactulose** All data reported in bar graph	
Significant differences in adverse events:	Statistically significantly more patients with a weekly score > 1 for abdominal pain, pain at defecation, and straining at defecation in the lactulose group (%'s NR, shown in graph only; $P < 0.05$); more patients with weekly score > 1 for bad palatability in PEG group (%'s NR, shown in graph; $P < 0.05$).		
Adherence/Compliance:	1 PEG subject withdrew due to bad palatability vs. 0 in lactulose group		
ANALYSIS:	**ITT:** No **Post randomization exclusions:** Yes (9)		
ADEQUATE RANDOMIZATION:	Method NR		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	Yes, but method NR		
ATTRITION (*overall*):	**Overall attrition:** 9% **Differential attrition high:** No		
ATTRITION (*treatment specific*): **Total attrition:** **Withdrawals due to adverse events:**	**PEG 3350** 8% 0%	**lactulose** 10% 0%	
QUALITY RATING:	**Poor**		

Chronic Constipation and IBS-C

STUDY:	**Authors, article #: Wang et al.**[44, 45] **Year: 2004** **Country:** China		
FUNDING:	Norgine, Ltd UK		
RESEARCH OBJECTIVE:	Compare clinical efficacy of PEG 3350 vs. psyllium in treating chronic constipation		
DESIGN:	**Study design:** open-label RCT **Setting**: China**,** 2 centers, outpatient **Sample size:** 126		
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**PEG 3350** 13.8 g two times per day 2 weeks 63	**psyllium** 3.5 g two times per day 2 weeks 63	
INCLUSION CRITERIA:	Males and females; age 18 to 75; 3 months of constipation prior to the study; 3 or less stools per week; Bristol stool for 1, 2 or 3		
EXCLUSION CRITERIA:	Anatomical pathology ruled in by colonoscopy or barium enema; abdominal pain of unknown cause; serious abdominal disease; serious systemic disease; impaired renal, hepatic or cardiac function; prior abdominal surgery; pregnancy; sensitivity to psyllium or PEG 3350; anyone who had taken laxatives within 7 days of the start of the study; anyone deemed likely to take drugs effecting intestinal motility and pregnant women		
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	No other medications affecting intestinal mobility		

Authors: Wang **Year: 2004**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** yes		
	PEG 3350	**psyllium**	Overall
Mean age (years):	51.23	50.00	50
Patients aged 65 years or older (%):	NR	82.9%	NR
Sex (% female):	72.5%	80.0%	NR
Ethnicity (% Caucasian):	NR	NR	Chinese
Mean body mass index:	NR	NR	NR
Other germane characteristics:			
• Duration of constipation (mean)	10.26	11.76	11
• Bowel frequency (BM/week)	1.33	1.18	1
• Straining (%)	NR	NR	83
• Abdominal pain	NR	NR	37
• Hard stools (%)	NR	NR	NR
• Normal stools (%)	NR	NR	NR
• Use of laxatives (%)	NR	NR	NR
• Use of constipation diet (%)	56	56	56
• Use of bulk-forming agents(%)	NR	NR	NR
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** overall efficacy Secondary Outcome Measures: weekly defecation rate; stool form type; severity of flatulence, abdominal pain, difficulty with defecation, pain on defecation; **Timing of assessments:** 1 and 2 weeks		
RESULTS:	**Health Outcome Measures:** • PEG 3350 vs. psyllium • Overall efficacy 92.1 vs. 73.0 *P = 0.005* • Defecations per week: 8.48 vs. 5.33 *P<0.001* • Normal stool forms: 87.3% vs. 66.7% *P<0.001* • Resolving rates for abdominal pain: 87.5% vs. 56.35 *P=0.059* • Resolving rate for pain on defecation: 94.1% vs. 83.3% *P=0.55* • Resolving rate for difficulty on defecation: 92.0% vs. 79.2% *P=0.087* • Resolving rates for flatulence 86.4% vs. 76.7% *P=0.28* • Resolving rates for passing gas 42.9% vs. 64.3% *P=0.18*		

Authors: Wang et al. **Year: 2004**			
ADVERSE EVENTS: **Overall adverse effects reported:**	**PEG 3350**	**psyllium**	
• diarrhea	0%	1.7%	
• headache	1.7%	1.7%	
• nausea	NR	NR	
• abdominal pain	NR	NR	
• flatulence	NR	NR	
• dry mouth	1.7%	5%	
• dizziness	5%	0%	
• fatigue	3.3%	0%	
• weakness	1.7%	0%	
• back pain	1.7%	0%	
• borborygmus	1.7%	0%	
• insomnia	1.7%	0%	
• oliguria	0%	1.7%	
Significant differences in adverse events:	No		
Adherence/Compliance:	4.8%		
ANALYSIS:	**ITT:** yes for efficacy, no for safety **Post randomization exclusions:** no for efficacy, no for safety		
ADEQUATE RANDOMIZATION:	**Yes**		
ADEQUATE ALLOCATION CONCEALMENT:	Yes		
BLINDING OF OUTCOME ASSESSORS:	No		
ATTRITION (*overall*):	**Overall attrition:** 6 **Differential attrition high:** no		
ATTRITION (*treatment specific*):	**PEG 3350**	**psyllium**	
Total attrition:	3	3	
Withdrawals due to adverse events:	1	0	
QUALITY RATING:	**Fair**		

Chronic Constipation and IBS-C

STUDY:	**Authors, article #: Youssef et al.**[69] **Year: 2002** **Country:** USA			
FUNDING:	Braintree Laboratories			
RESEARCH OBJECTIVE:	To investigate the efficacy and safety of PEG 3350 in the treatment of childhood fecal impaction			
DESIGN:	**Study design:** prospective, DB, parallel, randomized study of 4 doses of PEG **Setting:** university pediatric gastroenterology clinic **Sample size:** 40			
INTERVENTION: **Dose:** **Duration:** **Sample size:**	**PEG 3350 0.25** 0.25 g/kg/d 3 days 10	**PEG 3350 0.5** 0.5 g/kg/d 3 days 10	**PEG 3350 1.0** 1 g/kg/d 3 days 10	**PEG 3350 1.5** 1.5 g/kg/d 3 days 10
INCLUSION CRITERIA:	New patient referred to a pediatric gastroenterology clinic for evaluation of constipation with evidence of fecal impaction; Rome criteria including difficulty passing stools > 3 months (straining, grunting, stool "getting stuck") and passage of stools < 3 times per week; age 3 to 18 years; no previous GI surgery, no allergy/sensitivity to PEG or phosphates; fecal impaction defined as a palpable mass in the left lower abdomen and/or dilated rectum filled with a large amount of hard stool on rectal examination			
EXCLUSION CRITERIA:	Signs and symptoms suggestive of obstruction such as vomiting, abdominal distention, or abdominal mass extending beyond the umbilicus.			
OTHER MEDICATIONS/ INTERVENTIONS ALLOWED:	All medications for constipation had to be discontinued 7 days before examination			

Authors: Youssef et al. **Year: 2002**				
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** No, difference for mean age, weight, % previously on medication for constipation); 0.5g/kg/d group had lower mean age than other groups; the 1.5 g/kg/d group had higher significantly higher mean weight (over 10kg higher than other groups)			
	PEG 3350 0.25	**PEG 3350 0,5**	**PEG 3350 1.0**	**PEG 3350 1.5**
Mean age (years):	7.98	5.7	7.8	8.6
Patients aged 65 years or older (%):	0	0	0	0
Sex (% female):	7	7	8	7
Ethnicity (% Caucasian):	NR	NR	NR	NR
Mean body mass index:	NR	NR	NR	NR
Mean weight (kg)	27.3	25.7	26.8	37.9
Other germane characteristics:				
• Duration of constipation (mean) months	36	33.8	48.3	42
• Bowel frequency (BM/week)				
• Previous medication (%)	50			
• Constipation score	10.7	70 13	20 9.4	50 11.5
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Success of disimpaction **Secondary Outcome Measures:** Number of BMs; Straining, consistency, stool amount, gas, or cramping—used VAS from 0 to 10 for each; Adverse events—see below **Timing of assessments:** 5 days after beginning treatment			
RESULTS:	**Health Outcome Measures:** • Greater success of disimpaction with higher doses (1 and 1.5g/kg/d) than lower doses (0.25 and 0.5g/kg/d) (95% vs. 55%; $P < 0.005$) • 83% of all subjects had > 3 BMs during the 5 day study • All doses lead to an increase in the # of stools • Trend for less straining and looser consistency with increasing dosed but not statistically sig. No statistically significant difference between any of the groups for straining, consistency, stool amount, gas or cramping			

Authors: Youssef et al. **Year: 2002**					
ADVERSE EVENTS: **Overall adverse effects reported:** • Diarrhea • headache • nausea • pain/cramping • bloating/flatulence • vomiting	**PEG 3350 (0.25 and 0.5 combined)** 25			**PEG 3350 (1 and 1.5 combined)** 10	**Total** NR 13 NR 5 5 18 5
Significant differences in adverse events:	Diarrhea was more prevalent in the high dose groups than the low dose groups (25% vs. 10%; $P < 0.02$). No patients had clinically significant abnormal laboratory values aft the use of PEG 3350.; fecal soiling occurred in 35 children 91% of them were daily				
Adherence/Compliance:	Tolerability: 95% of children took the medication on the first attempt; All children said that they would repeat a 3-day regimen of PEG 3350 to help treat a future fecal impaction.				
ANALYSIS:	**ITT:** No, analyzed the 40/41 that followed up. **Post randomization exclusions:** 1, did not follow up (in the 1.5g/kg/d group)				
ADEQUATE RANDOMIZATION:	Yes				
ADEQUATE ALLOCATION CONCEALMENT:	Yes				
BLINDING OF OUTCOME ASSESSORS:	Yes				
ATTRITION (*overall*):	**Overall attrition:** 1/41= 2.4% **Differential attrition high:** No				
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:**	**PEG 3350** 2.4% None reported				
QUALITY RATING:	**Poor**				