



Drugs for Constipation Draft

December 2008

Produced by:
The Health Resources Commission
Office for Oregon Health Policy & Research
1225 Ferry Street SE Salem, OR 97301 Phone: 503.373.1629

Health Resources Commission

Chair: James MacKay, MD
Vice Chair: Dan Kennedy, RPh
Manny Berman
Dean Haxby, PharmD
Justin Leonard, JD.
Diane Lovell
John Muench, MD
Katherine Merrill, MD
William Origer, MD
George Waldman M.D.

Subcommittee Members

Bill Origer, MD
Ruth Medak, MD
Tracy Klein, FNP
Nicole O’Kane, PharmD
Rich Clark, MD
Cydreese Aebi, PhD, RPh

Health Resources Commission Staff

Director: David Pass M.D.
Assistant: Tina Huntley

Health Resources Commission

The State of Oregon’s Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative; two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the commission subject to approval by a majority of the commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.

Overview

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-managed Prescription Drug Plan (PMPDP). The statute specifically directs the Health Resources Commission (HRC) to advise the Oregon Medical Assistance (OMAP) Department of Human Services (DHS) on this Plan.

In 2007 the Oregon Health Resources Commission (HRC) appointed a pharmaceutical subcommittee to perform evidence-based reviews of pharmaceutical agents. Members of the subcommittee consisted of three Physicians, a Nurse Practitioner, a PhD, RPh and a PharmD. All meetings were held in public with appropriate notice provided. The HRC

director worked with the Center for Evidence-based Policy (Center) and the Oregon Health and Science University's (OHSU) Evidence-based Practice Center (EPC) to develop and finalize key questions for this drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities. Using standardized methods, the EPC reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

The EPC's report, *Drugs for Constipation*, August 2007, was circulated to subcommittee members and posted on the web. The subcommittee met to review the document and this report is the consensus result of those meetings. Time was allotted for public comment, questions and testimony.

This report does not recite or characterize all the evidence that was discussed by the OHSU EPC, the Subcommittee or the HRC. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the HRC in providing recommendations to the Department of Human Services. The HRC, working together with the EPC, the Center for Evidence Based Policy, DMAP, and the Oregon State University College of Pharmacy, will monitor medical evidence for new developments in this drug class. Approximately once per year new pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PMPDP will be made. For pharmaceuticals on the plan, significant new evidence will be assessed and Food and Drug Administration changes in indications and safety recommendations will be evaluated. This report will be updated if indicated. Substantive changes will be brought to the attention of the Health Resources Commission, who may choose to approve the report, or reconvene a subcommittee.

The full OHSU Evidence-based Practice Center's draft report, "*Drugs for Constipation*" is available via the Office for Oregon Health Policy & Research, Practitioner-Managed Prescription Drug Plan website:

www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml

Information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Office for Oregon Health Policy & Research website: <http://www.oregon.gov/DAS/OHPPR/HRC/index.shtml>

You may request more information including copies of the draft report from:

David Pass, MD

Director, Health Resources Commission

Office for Oregon Health Policy & Research

1225 Ferry St. SE

Salem, Oregon 97301

Phone: 503-373-1629 (HRC Assistant)

Fax: 503-378-5511

Email: HRC.info@state.or.us

Information dossiers submitted by pharmaceutical manufacturers are available upon request from the OHSU Center for Evidence-based Policy by contacting:

Alison Little, MD

Assistant Director for Health Projects

Oregon Health & Science University

Center for Evidence-based Policy

2611 SW Third Avenue, MQ280

Portland, OR 97201-4950

Phone: 503-494-2691

E-mail: littlea@ohsu.edu

There will be a charge for copying and handling in providing documents from both the Office of Oregon Health Policy & Research and the Center for Evidence Based Policy.

Critical Policy

Senate Bill 819

– “The Department of Human Services shall adopt a Practitioner-managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price.”

Health Resources Commission

- “Clinical outcomes are the most important indicators of comparative effectiveness”
- “If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed.”

Studies Included/Excluded

A complete discussion of inclusion and exclusion criteria can be found in the DERP review and will not be repeated here.

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.

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.

Clinical Overview

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 weeks¹. The diagnosis is primarily symptom-based, relying on the patient’s self report of symptoms. While physicians traditionally defined constipation as fewer than three bowel movements per week², 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 constipation¹

Rome II Criteria	ACG CC Task Force
<p>At least 12 weeks, need not be consecutive, in past 12 months of > 2 of:</p> <ul style="list-style-type: none"> • 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 	<p>Symptoms for at least 3 of the last 12 months consisting of:</p> <ul style="list-style-type: none"> • Infrequent stools: less than 3 per week, or • Difficult stool passage, which may include: <ul style="list-style-type: none"> • 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 age². 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.

Approximately 2.5 million US physician visits are attributed to constipation each year³; assuming an average cost of approximately \$3,000 per patient (in 2007 dollars)⁵, 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.

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.

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)⁶. 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. This report focuses on functional constipation and does not cover other IBS associated symptoms such as abdominal pain/discomfort, diarrhea, and bloating.

Pharmacologic treatments for chronic constipation

Pharmacologic treatments for chronic constipation (Table 2) 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.

This review covers the use of the following drugs (Table 2) in adults and children with chronic constipation or IBS-C; drugs for intermittent or short-term constipation, such as stimulant laxatives are not included in this review.

Table 2: Included Drugs

Class	Generic Name	Brand name	Rx/OTC
5-HT ₄ Serotonin Agonist	Tegaserod maleate*	Zelnorm	Rx
	Psyllium (ispaghula)	Metamucil	OTC
		Fiberall	
		GenFiber	
		Natural Psyllium Fiber	
		Hydrocil	
		Konsyl	
		Reguloid	
		Natural Fiber laxative	
		Syllact serutan	
Chloride Channel Activator	Lubiprostone	Amitiza	Rx

Osmotic Laxatives	Polyethylene glycol 3350 (PEG 3350)	Glycolax	PEG 3350: OTC
		MiraLax	
		Generic	
	Lactulose	Chronulac	Lactulose: Rx
		Generic	
Stool Softeners	Docusate Sodium	Docusate Sodium	OTC
		Ex-lax	
		Dioclyn	
		Colace	
		D-S-S	
		Dulcolax	
		Silace	
		Stool Softener	
		Regulan SS	
		Genasoft	
		Sof-lax	
		Dioclo	
		Docu	
		D.O.S.	
	Docusate Calcium	Docusate Calcium	
		Stool Softener	
		Sulfolax	
		Surfax Liquigels	
		DC Softgels	

Quality of the Evidence

For quality of evidence the EPC and subcommittee took into account the number of studies, the total number of patients in each study, the length of the study period and the endpoints of the studies. Statistical significance was an important consideration. The subcommittee utilized the EPC's ratings of "good, fair or poor" for grading the body of evidence. Overall quality ratings for an individual study were based on the internal and external validity of the trial.

Internal validity of each trial was based on:

- 1) Methods used for randomization
- 2) Allocation concealment and blinding
- 3) Similarity of compared groups at baseline and maintenance of comparable groups
- 4) Adequate reporting of dropouts, attrition, and crossover
- 5) Loss to follow-up
- 6) Use of intention-to-treat analysis

External validity of trials was assessed based on:

- 1) Adequate description of the study population

- 2) Similarity of patients to other populations to whom the intervention would be applied
- 3) Control group receiving comparable treatment
- 4) Funding source that might affect publication bias.

Weighing the Evidence

A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the body of evidence relevant to that question.

Scope and Key Questions

In this report, we review the general and comparative effectiveness, safety, and tolerability of drugs for chronic constipation.

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 medication⁷. The FDA reported that in clinical studies 0.1% (total n = 13) of patients treated with tegaserod experienced serious and life-threatening cardiovascular adverse events, compared with 0.01% (total 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 serious 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 (KQs) to guide this review:

KQ 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?

KQ 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?

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

KQ 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?

Conclusions:

I. Limitations of the evidence

- 1. The evidence on the general efficacy for most drugs is sparse, fraught with methodological issues, or entirely missing.***
- 2. Docusate sodium, docusate calcium, lactulose, and psyllium were marketed prior to the need for FDA approval. Therefore there is little information on these medications regarding their general or comparative efficacy/ effectiveness or harms.***
- 3. There is insufficient evidence to draw conclusions about general or comparative efficacy/ effectiveness or harms of PEG 3350, lubiprostone or tegaserod maleate.***
- 4. This review covers the use of the drugs listed in Table 2 (page 7) in adults and children with chronic constipation or IBS-C; drugs for intermittent or short-term constipation, such as stimulant laxatives are not included in this review.***

II. Conclusions

A. Chronic Constipation in Adults

- 1. No controlled evidence is available for efficacy/effectiveness of docusate calcium, docusate sodium and lactulose.***
- 2. There is insufficient evidence to determine the efficacy/effectiveness of lubiprostone, PEG 3350, tegaserod maleate, or psyllium for the treatment of chronic constipation in adults.***
- 3. There were no studies on the general tolerability and safety of docusate calcium, docusate sodium, or lactulose.***
- 4. Poor quality evidence suggests that lubiprostone treatment is associated with a higher incidence of nausea compared to treatment with placebo.***
- 5. The FDA withdrew tegaserod maleate from the market after reporting 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. 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.***

Conclusions (continued)

B. Chronic Constipation in Children

- 1. There was no evidence on the general efficacy or effectiveness of any of the included drugs when used for chronic constipation in children.*
- 2. We found no studies on the general tolerability and safety of docusate calcium, docusate sodium, lactulose, lubiprostone, and psyllium that met the expanded eligibility criteria.*

C. IBS-C in Adults

- 1. No controlled evidence is available for docusate calcium, docusate sodium, lactulose, PEG 3350, and psyllium for the treatment of IBS-C in adults.*
- 2. Poor quality studies suggest the general efficacy of tegaserod in this population.*

D. IBS-C in Children

- 1. No controlled evidence is available for docusate calcium, docusate sodium, lactulose, PEG 3350, or psyllium for the treatment of IBS-C in children.*
- 2. Poor quality evidence suggests the general efficacy of tegaserod for the treatment of IBS-C in adolescents, particularly in reduction in pain.*

E. Treatment Duration

- 1. There was no evidence found that addressed the effect of treatment duration on effectiveness.*
- 2. No evidence was found that addressed when treatment should be switched in patients not responding to a given drug.*

F. Subgroups

- 1. No evidence on efficacy or harms is available for docusate calcium, docusate sodium, lactulose, PEG 3350 or psyllium for the treatment of chronic constipation or IBS-C based on gender.*
- 2. There is insufficient evidence for tegaserod to determine any differences in efficacy based on gender. The majority of the patients in these studies were female (83%-100%).*
- 3. There was no evidence on differences in the general efficacy or harms of docusate calcium, docusate sodium, lactulose, PEG 3350, psyllium, or tegaserod for the treatment of chronic constipation or IBS-C based on age.*
- 4. There was no evidence on differences in the general or comparative efficacy, effectiveness or harms of included drugs for the treatment of chronic constipation or IBS-C based on race, ethnicity or co-morbidities.*

Supporting Evidence

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. Most of the included efficacy studies were conducted in narrowly defined populations and/or were limited to less than 2 months of follow-up.

Chronic constipation in adults

General efficacy and effectiveness

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

The literature search, however, detected 12 published abstracts. 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 abstract of an open-label study over 24 weeks suggested a durable response of lubiprostone⁸. These abstracts do not provide enough information to critically appraise methods of these individual studies

Polyethylene Glycol (PEG 3350)

Three RCTs determined the general efficacy of PEG 3350. 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 period⁹. 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.^{10,11}

An uncontrolled before-after study¹² 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

One study was of fair methodological quality; however, only 22 patients were enrolled in this RCT¹³. Therefore chance findings (random error) cannot be ruled out. 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 limitations of this study, results must be interpreted cautiously.

Tegaserod maleate

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. Because tegaserod has been taken off the market in the US, we (DERP) did not rate the internal validity of individual studies. A summary of these studies is below in Table 3

Table 3. Summary of trials assessing the general efficacy of tegaserod maleate 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 > 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

Docusate sodium vs. psyllium

There was one RCT (n= 187) however this study¹⁴ was rated poor quality because of a high rate of post-randomization exclusions (9%) and the lack of an ITT analysis.

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 constipation¹⁵. 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.

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.^{16,17} 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%, $P = 0.005$).

Chronic constipation in children

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.

Comparative efficacy and effectiveness

PEG 3350 vs. lactulose

A double-blinded RCT¹⁸ 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. This study was rated as poor quality because of a lack of ITT analysis and a high rate of post-randomization exclusions (9%).

Constipation associated with IBS in adults

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.

Tegaserod maleate

Five RCTs support the general efficacy of tegaserod for the treatment of IBS-C. These studies are presented in Table 15 in the DERP report. However, as mentioned above,

tegaserod is currently not available in the US or Canada because of safety concerns. Because tegaserod has been taken off the market in the US, we (DERP) did not rate the internal validity of individual studies

Lubiprostone

Only one study, published as an abstract only, examined the efficacy of lubiprostone in patients with IBS-C¹⁹. 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.

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.

Constipation associated with IBS in children

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.

Tegaserod maleate

One RCT randomized²⁰ postpubertal adolescents with constipation predominant IBS to laxative only or laxative plus tegaserod (6mg/bid)²¹. However, as mentioned above, tegaserod is currently not available in the US or Canada because of safety concerns. 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.

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, and 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.

Chronic constipation and constipation associated with IBS in adults

General risk of harms

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. Most studies were conducted in patients with chronic constipation; only one abstract enrolled patients with IBS-C¹⁹. Most trials were of relatively short durations (3 to 4 weeks), but two were long-term studies of 24 and 48 weeks^{22,23}. 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.

The FDA CDER medical review of lubiprostone²⁴ 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 and one open-label observational study¹² 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 events⁹. The PEG 3350 patients had lower rates of severe cramping and severe gas. The other two RCTs were cross-over studies^{10, 11} 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 RCT⁹ 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 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.

Tegaserod maleate

Fifteen studies, including 9 RCTs, 1 systematic review²⁵, 2 pooled analyses, 2 open-label prospective cohort studies, and 1 uncontrolled extension of an RCT report data on the general safety and harms of tegaserod for the treatment of chronic constipation and IBS-C in adults. Because tegaserod has been taken off the market in the US, we did not rate the internal validity of individual studies. In general the incidence of adverse events was similar between all groups except for diarrhea which was more common in patients taking tegaserod vs. placebo with the incidence higher in patients taking 6mg bid vs. 2 mg bid.

Cardiac adverse events with tegaserod maleate were specifically reported in 4 studies. In an open label placebo controlled study by Fried et al 2005²⁶ (n=843; 8 weeks) in adults with IBS-C (72% female), taking tegaserod 6mg BID, there were 0.9% serious AEs, 1 was cardiovascular (chest pain); no deaths. Morganroth et al. 2002²⁷ evaluated 3 RCTs

which were pooled for safety analysis (n= 2516; 12 weeks). Using doses of Tegaserod (2 mg and 6 mg BID) vs. placebo in Adults with IBS-C, (84% female) there was 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. Nyhlin et al. 2004²⁸ studied adults with constipation predominant IBS-C (n= 647; 12 weeks; 86% female) comparing Tegaserod 6 mg BID vs. placebo reported 1 death in the tegaserod group due to acute myocardial infarction. An open label placebo controlled study by Tougas et al. 2002²⁹ in adults with constipation predominant IBS-C (n= 579 (53% completed trial); 12 months; 90% female) evaluating Tegaserod 2 or 6 mg BID, flexible dose titration found significant adverse events in 4.4% including chest pain in 2 patients.

Comparative risk of harms

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 constipation¹⁵. 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. One RCT funded by the makers of psyllium³⁰ reported numerically lower rates of diarrhea and abdominal pain with psyllium. The other RCT³¹ 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 study³⁰ 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 RCT³¹ 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^{17, 18}. 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%).

Chronic constipation in children

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.

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. Two studies^{32,33} were funded by the makers of PEG without electrolytes. The other study³⁴ 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.

Tegaserod maleate

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 events⁷. We found one RCT that reported on the safety and harms of tegaserod for the treatment of postpubertal adolescents with constipation predominant IBS²¹. 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.

Comparative risk of harms

PEG 3350 vs. lactulose

We found one poor quality RCT¹⁸ 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 PEG¹⁸. The authors did not define serious adverse events or how these were assessed. The study was rated poor for several reasons including: lack of an ITT analysis and adverse events were not pre-specified and defined. The results should be interpreted cautiously due to the poor quality of this study.

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?

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.

Lubiprostone

This published abstract compared the efficacy of lubiprostone and placebo for treating chronic constipation in men versus women³⁵. 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. For example, in two RCTs on tegaserod 90%³⁶ and 86%³⁷ 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.

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.

Two published abstracts examined the efficacy of lubiprostone in patients > 65 years. 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 ($P < 0.0001$)³⁸. In the second study, mean changes from baseline in SBM rates were significantly improved among lubiprostone elderly subjects compared to their placebo counterparts during weeks 1,2, and 4 ($P < 0.0286$)³⁹. 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.

References-(Footnotes in red are keyed to the DERP report)

¹ American College of Gastroenterology Functional Gastrointestinal Disorders Task Force. An evidence-based approach to the management of chronic constipation in North America. *Am J Gastroenterol.* 2005;100 Suppl 1:S1-4.

²Higgins PD, Johanson JF. Epidemiology of constipation in North America: a systematic review. *Am J Gastroenterol.* 2004 Apr;99(4):750-9.

³Johanson JF, Sonnenberg A, Koch TR. Clinical epidemiology of chronic constipation. *J Clin Gastroenterol.* 1989 Oct;11(5):525-36.

⁴ Stewart WF, Liberman JN, Sandler RS, Woods MS, Stemhagen A, Chee E, et al. Epidemiology of constipation (EPOC) study in the United States: relation of clinical subtypes to sociodemographic features. *Am J Gastroenterol.* 1999 Dec;94(12):3530-40.

⁵ Rantis PC, Jr., Vernava AM, 3rd, Daniel GL, Longo WE. Chronic constipation--is the work-up worth the cost? *Dis Colon Rectum.* 1997 Mar;40(3):280-6.

⁶ Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. In: Drossman DA, Corazziari E, Delvaux M, Spiller RC, Talley NJ, Thompson WG, et al., eds. *Rome III: The Functional Gastrointestinal Disorders, 3rd edition.* McLean, VA: Degnon Associates, Inc. 2006.

⁷ FDA. Public Health Advisory: Tegaserod maleate (marketed as Zelnorm). <http://www.fda.gov/cder/drug/advisory/tegaserod.htm>. 2007.

⁸ Johanson JF, Panas R, Holland PC, Ueno R. Long-term efficacy of lubiprostone for the treatment of chronic constipation [Abstract M1171]. *Gastroenterology.* 2006;130(Supplement 2):A-317.

⁹DiPalma JA, DeRidder PH, Orlando RC, Kolts BE, Cleveland MB. A randomized, placebo-controlled, multicenter study of the safety and efficacy of a new polyethylene glycol laxative. *Am J Gastroenterol.* 2000 Feb;95(2):446-50.

¹⁰ Andorsky RI, Goldner F. Colonic lavage solution (polyethylene glycol electrolyte lavage solution) as a treatment for chronic constipation: a double-blind, placebo-controlled study. *Am J Gastroenterol.* 1990 Mar;85(3):261-5.

-
- ¹¹ Cleveland MV, Flavin DP, Ruben RA, Epstein RM, Clark GE. New polyethylene glycol laxative for treatment of constipation in adults: a randomized, double-blind, placebo-controlled study. *South Med J*. 2001 May;94(5):478-81.
- ¹² Tran LC, Di Palma JA. Lack of lasting effectiveness of PEG 3350 laxative treatment of constipation. *J Clin Gastroenterol*. 2005 Aug;39(7):600-2.
- ¹³ Ashraf W, Park F, Lof J, Quigley EM. Effects of psyllium therapy on stool characteristics, colon transit and anorectal function in chronic idiopathic constipation. *Aliment Pharmacol Ther*. 1995 Dec;9(6):639-47.
- ¹⁴ McRorie JW, Daggy BP, Morel JG, Diersing PS, Miner PB, Robinson M. Psyllium is superior to docusate sodium for treatment of chronic constipation. *Aliment Pharmacol Ther*. 1998 May;12(5):491-7.
- ¹⁵ Attar A, Lemann M, Ferguson A, Halphen M, Boutron MC, Flourie B, et al. Comparison of a low dose polyethylene glycol electrolyte solution with lactulose for treatment of chronic constipation. *Gut*. 1999 Feb;44(2):226-30.
- ¹⁶ Wang HJ, Liang XM, Yu ZL, Zhou LY, Lin SR, Geraint M. A Randomised, Controlled Comparison of Low-Dose Polyethylene Glycol 3350 plus Electrolytes with Ispaghula Husk in the Treatment of Adults with Chronic Functional Constipation. *Clinical Drug Investigation*. 2004;24(10):569-76.
- ¹⁷ Wang HJ, Liang XM, Yu ZL, Zhou LY, Geraint M. A randomised, controlled comparison of low-dose polyethylene glycol 3350 plus electrolytes with ispaghula husk in the treatment of adults with chronic functional constipation. *Drugs R D*. 2005;6(4):221-5.
- ¹⁸ Voskuil W, de Lorijn F, Verwijs W, Hogeman P, Heijmans J, Makel W, et al. PEG 3350 (Transipeg) versus lactulose in the treatment of childhood functional constipation: a double blind, randomised, controlled, multicentre trial. *Gut*. 2004 Nov;53(11):1590-4.
- ¹⁹ Johanson JF, Panas R, Holland PC, Ueno R. A dose-ranging, double-blind, placebo-controlled study of lubiprostone in subjects with irritable bowel syndrome and constipation (c-ibs) [Abstract 131]. *Gastroenterology*. 2006;130(Supplement 2):A-25.
- ²⁰ Kellow J, Lee OY, Chang FY, Thongsawat S, Mazlam MZ, Yuen H, et al. An Asia-Pacific, double blind, placebo controlled, randomised study to evaluate the efficacy, safety, and tolerability of tegaserod in patients with irritable bowel syndrome. *Gut*. 2003;52(5):671-6.
- ²¹ Khoshoo V, Armstead C, Landry L. Effect of a laxative with and without tegaserod in adolescents with constipation predominant irritable bowel syndrome. *Aliment Pharmacol Ther*. 2006 Jan 1;23(1):191-6.
- ²² Johanson JF, Gargano MA, Holland PC, Patchen ML, Ueno R. Multicenter open-label study of oral lubiprostone for the treatment of chronic constipation. *Am J Gastroenterol*. 2005;100(Supplement 9):S331.
- ²³ Ueno R, Wahle A, Panas R, Joswick TR, Rivera E. Evaluation of safety and efficacy in a twelve-month study of lubiprostone for the treatment of chronic idiopathic constipation [Abstract 1269]. *Am J Gastroenterol*. 2006;101(Supplement 2):S491.
- ²⁴ FDA Center for Drug Evaluation and Research. Medical Review NDA 21-908 of RU-0211 (lubiprostone). http://www.fda.gov/cder/foi/nda/2006/021908s000_Amitiza_MEDR.pdf. 2006.
- ²⁵ Evans BW, Clark WK, Moore DJ, Whorwell PJ. Tegaserod for the treatment of irritable bowel syndrome. *Cochrane Database Syst Rev*. 2004(1):CD003960.

-
- ²⁶ Fried M, Beglinger C, Bobalj NG, Minor N, Coello N, Michetti P. Tegaserod is safe, well tolerated and effective in the treatment of patients with non-diarrhoea irritable bowel syndrome. *Eur J Gastroenterol Hepatol*. 2005 Apr;17(4):421-7.
- ²⁷ Morganroth J., Rüegg PC, Dunger-Baldauf C, Appel-Dingemanse S, Bliesath H, Lefkowitz M. Tegaserod, a 5-hydroxytryptamine type 4 receptor partial agonist, is devoid of electrocardiographic effects. *The American journal of gastroenterology*. 2002;97(9):2321-7.
- ²⁸ Nyhlin H, Bang C, Elsborg L, Silvennoinen J, Holme I, Ruegg P, et al. A double-blind, placebo-controlled, randomized study to evaluate the efficacy, safety and tolerability of tegaserod in patients with irritable bowel syndrome. *Scand J Gastroenterol*. 2004 Feb;39(2):119-26.
- ²⁹ Tougas G, Snape WJ, Jr., Otten MH, Earnest DL, Langaker KE, Pruitt RE, et al. Long-term safety of tegaserod in patients with constipation-predominant irritable bowel syndrome. *Aliment Pharmacol Ther*. 2002 Oct;16(10):1701-8.
- ³⁰ Dettmar PW, Sykes J. A multi-centre, general practice comparison of ispaghula husk with lactulose and other laxatives in the treatment of simple constipation. *Curr Med Res Opin*. 1998;14(4):227-33.
- ³¹ Rouse M, Chapman N, Mahapatra M, Grillage M, Atkinson SN, Prescott P. An open, randomised, parallel group study of lactulose versus ispaghula in the treatment of chronic constipation in adults. *Br J Clin Pract*. 1991 Spring;45(1):28-30.
- ³² Pashankar DS, Loening-Baucke V, Bishop WP. Safety of polyethylene glycol 3350 for the treatment of chronic constipation in children. *Arch Pediatr Adolesc Med*. 2003 Jul;157(7):661-4.
- ³³ Youssef NN, Peters JM, Henderson W, Shultz-Peters S, Lockhart DK, Di Lorenzo C. Dose response of PEG 3350 for the treatment of childhood fecal impaction. *J Pediatr*. 2002 Sep;141(3):410-4.
- ³⁴ Loening-Baucke V, Krishna R, Pashankar DS. Polyethylene glycol 3350 without electrolytes for the treatment of functional constipation in infants and toddlers. *J Pediatr Gastroenterol Nutr*. 2004 Nov;39(5):536-9.
- ³⁵ Ueno R, Joswick TR, Wahle A, Zhu Y, Holland PC. Efficacy and safety of lubiprostone for the treatment of chronic constipation in male vs. female subjects [Abstract M1195]. *Gastroenterology*. 2006;130(4, Supplement 2):A322.
- ³⁶ Johanson JF, Wald A, Tougas G, Chey WD, Novick JS, Lembo AJ, et al. Effect of tegaserod in chronic constipation: a randomized, double-blind, controlled trial. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2004;2(9):796-805.
- ³⁷ Kamm MA, Muller-Lissner S, Talley NJ, Tack J, Boeckstaens G, Minushkin ON, et al. Tegaserod for the treatment of chronic constipation: a randomized, double-blind, placebo-controlled multinational study. *Am J Gastroenterol*. 2005 Feb;100(2):362-72.
- ³⁸ Ueno R, Panas R, Wahle A, Zhu Y, Holland PC. Long-term safety and efficacy of lubiprostone for the treatment of chronic constipation in elderly subjects [Abstract S1260]. *Gastroenterology*. 2006;130(Supplement 2):A-188.
- ³⁹ Ueno R, Joswick TR, Wahle A, Zhu Y, Holland PC. Efficacy and safety of lubiprostone for the treatment of chronic constipation in elderly vs. non-elderly subjects [Abstract S1262]. *Gastroenterology*. 2006;130(4, Supplement 2):A-189.