



# DRUG EFFECTIVENESS REVIEW PROJECT

## P&T Committee Brief Constipation Drugs

Alison Little, MD

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### P&T Committee Brief Disclaimer

This brief was written by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). It is a summary of certain material matters contained in the Drug Effectiveness Review Project (DERP) report "Drug Class Review on Constipation Drugs" dated September 2007, which is a product of the RTI-UNC Evidence-based Practice Center at the university of North Carolina at Chapel Hill. You can find the original report online at the following web address:

[http://www.ohsu.edu/drugeffectiveness/reports/documents/CONST\\_Final\\_Report\\_Original1.pdf](http://www.ohsu.edu/drugeffectiveness/reports/documents/CONST_Final_Report_Original1.pdf) .

Although at least one of the authors of this report reviewed and commented on the brief, its content and conclusions are those of the CEBP and not those of the authors or reviewers of the DERP report. The Center is a policy resource and is not providing any legal or business advice. This Brief is subject to the information and conclusions contained in the DERP report, and readers of this Brief are advised to review the DERP report. This Brief is intended for the benefit of the participant organizations and their constituent decision-making bodies.

## Center for Evidence-based Policy

Oregon Health & Science University

2611 SW 3<sup>rd</sup> Ave, MQ 280 Portland OR 97201-4950 503.494.2182 Fax 503.494.3807

[www.ohsu.edu/policy/drugeffectiveness](http://www.ohsu.edu/policy/drugeffectiveness)

## P & T COMMITTEE BRIEF

### Drugs for Chronic Constipation: A Comparative Drug Class Review Summary

#### 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. Constipation can stand on its own as a distinct diagnosis or be part of another functional bowel disorder, Irritable Bowel Syndrome (IBS). IBS is the most common functional gastrointestinal (GI) disorder. It is defined as a combination of chronic or recurrent GI symptoms not explained by structural or biochemical abnormalities. 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.

Pharmacologic treatments for chronic constipation include a chloride channel activator (lubiprostone), a 5-HT<sub>4</sub> serotonin receptor agonist (tegaserod maleate), osmotic laxatives (polyethylene glycol [PEG] and lactulose), bulking agents (psyllium, calcium polycarbophil, methylcellulose, and bran), stool softeners (docusate), and stimulant laxatives (senna and bisacodyl). Lubiprostone was most recently approved by the US Food and Drug Administration (FDA) for the treatment of chronic idiopathic constipation in adults. It is not yet available in Canada. Tegaserod maleate is a pre-synaptic 5-HT<sub>4</sub> serotonin receptor agonist that stimulates the peristaltic reflex, increases colonic motility, decreases visceral hypersensitivity, and facilitates secretion into the colonic lumen. Its marketing was suspended in the US and Canada in March of 2007 because of concerns regarding serious cardiovascular events. Osmotic laxatives, such as PEG and lactulose, are poorly absorbed ions or molecules and create an osmotic gradient within the intestinal lumen, drawing water into the lumen and making stools soft and loose. Bulking agents, such as psyllium, are organic polymers that retain water in the stool thereby increasing the frequency of stool and producing fewer hard stools. Stool softeners, like docusate sodium and docusate calcium, are surface-active agents or detergents that facilitate water interacting with the stool in order to soften the stool for easy passage. This review covers the use of the following drugs 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:

Generic Name	Trade Names	Generic Name	Trade Names
docusate calcium	Surfak®, others	PEG 3350	Colyte®*, others
docusate sodium	Colace®*, others	psyllium	Metamucil®, others
lactulose	Cephulac®, others	tegaserod	Zelnorm®**
Lubiprostone*	Amitiza®		

\* not available in Canada \*\*withdrawn from market in March 2007

The purpose of this review is to compare the effectiveness and safety of the different drugs for constipation listed above.

#### Methodology:

The Drug Effectiveness Review Project (DERP) reviews all pertinent studies, solicits and accepts public input and updates reviews frequently. This is the first DERP review on drugs used for the treatment of chronic constipation. Searches identified 535 citations.

Study eligibility is determined by pre-set criteria. Studies which did not meet these criteria with respect to study design or duration, patient population, interventions, or outcomes were excluded. Additionally, studies not in English were excluded. The quality of all included studies was appraised.

**Evidence Available:**

Relevant information for this topic consists of 33 publications: seven head-to-head randomized controlled trials (RCT), one observational extension of an RCT, 16 placebo-controlled trials, one systematic review/meta-analysis, six observational studies, and two pooled data analyses. In addition, 75 articles were retrieved for background information. Outcome measures evaluated include general subjective measures (overall relief of GI symptoms, symptom composite score), specific GI symptoms (straining, bloating, abdominal pain, ease of defecation, spontaneous bowel movement), physiologic measures (frequency of bowel movements, stool consistency), quality of life (QOL), time to effectiveness, switching in patients not responding, and influence of treatment duration on effectiveness. Safety outcomes include overall rate of adverse effects (AEs), withdrawals due to AEs, serious AEs and specific AEs (electrolyte abnormalities, diarrhea, bloating, nausea, flatulence, dehydration, hypovolemia).

**Key Questions and Findings:**

Question # 1: What is the general efficacy and effectiveness of drugs used to treat chronic constipation? Given general efficacy and effectiveness, what is the comparative effectiveness of drugs used to treat chronic constipation?

Chronic Constipation in Adults

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. Three trials provide moderate strength of evidence on the general efficacy of PEG 3350 for the treatment of chronic constipation. Results of these three studies consistently support a statistically significant increase in bowel movements in patients on PEG 3350 compared with those on placebo. None of these studies, however, had a follow-up of more than two 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 one small RCT and one open-label RCT. In terms of quality, the first one was rated fair whereas the second study was rated poor. Although both studies indicate a beneficial treatment effect for psyllium, both have methodological limitations. Studies assessing the efficacy of lubiprostone for the treatment of chronic constipation have been published as abstracts only, limiting the ability to critically appraise the underlying methods and draw firm conclusions. Results from these abstracts, however, suggest that lubiprostone is an efficacious treatment for chronic constipation. Multiple studies provide evidence on the general efficacy of tegaserod for the treatment of chronic constipation in men and women.

Regarding comparative efficacy and effectiveness, no head-to-head evidence is available for most comparisons of constipation drugs. Available evidence is limited to three head-to-head trials comparing docusate sodium versus psyllium, lactulose versus PEG 3350,

and PEG 3350 versus psyllium. Two of the three studies had severe methodological limitations; their quality was rated as poor (for docusate sodium versus psyllium, there was no difference in subjective outcomes, and for lactulose versus PEG 3350, there was greater improvement of symptoms for patients on PEG 3350 compared to those on lactulose). The only fair quality rated trial compared PEG 3350 with psyllium; it found a statistically significantly greater rate of improvement in patients on PEG 3350, compared to those on psyllium.

#### Chronic constipation in children

There was no evidence on the general efficacy or effectiveness of any of the included drugs when used for chronic constipation in children. The evidence on the comparative efficacy of constipation drugs is limited to one poor quality RCT comparing PEG 3350 with lactulose. This study found significant improvement in both treatment groups in primary outcomes (weekly defecation and encopresis frequency), although a significantly higher number of patients in the PEG 3350 group were reported to have been “successfully treated”, compared with those in the lactulose group.

#### IBS-C in adults

No controlled evidence is available for docusate calcium, docusate sodium, lactulose, PEG 3350, and psyllium for the treatment of IBS-C in adults. Multiple RCTs support the general efficacy of tegaserod in this population. Only one study examined the efficacy of lubiprostone in patients with IBS-C. Because it was published as an abstract only, the information was insufficient to critically appraise the methods of this study; it was therefore not formally included in the analysis. Results, however, suggest that lubiprostone is an efficacious treatment for IBS-C. There was no evidence on the comparative efficacy and effectiveness of included drugs for the treatment of IBS-C.

#### IBS-C in children

No controlled evidence is available for docusate calcium, docusate sodium, lactulose, PEG 3350, or 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. There was no evidence on the comparative efficacy and effectiveness for any of the included drugs for the treatment of IBS-C in children.

Question #2: Does treatment duration influence the effectiveness of drugs used to treat chronic constipation? When should treatments be switched in patients not responding to a given drug?

No evidence was found that addressed this key question.

Question #3: What is the comparative tolerability and safety of drugs used to treat chronic constipation?

#### Chronic constipation and IBS-C in adults

The tolerability and safety evidence is generally sparse. When available, it was rated as poor quality evidence. There were no studies on the general tolerability and safety of

docusate calcium, docusate sodium, or lactulose. Studies assessing the tolerability and safety of lubiprostone have been published as abstracts only, providing insufficient information to critically appraise these studies 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 AEs reported were nausea, headache, diarrhea, and bloating. Discontinuations due to AEs 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, found no significant differences in AEs. The other three studies were rated as poor quality; they were consistent in reporting only minor AEs for subjects taking PEG 3350. All four studies were funded by the makers of PEG formulations. There were only two poor quality RCTs that examined the general tolerability and safety of psyllium. Both enrolled subjects with constipation and were funded by the makers of psyllium preparations. These studies consistently reported that psyllium was well tolerated. Neither study reported significant differences in rates of AEs between psyllium and placebo; no serious AEs were reported. Tegaserod was taken off the market in March 2007 because a recent analysis of data from 29 RCTs including 11,614 patients treated with tegaserod found an increased risk of myocardial infarction, stroke, and unstable angina in patients taking this medication. The FDA reported that in clinical studies 0.1% (n = 13) of patients treated with tegaserod experienced serious and life-threatening cardiovascular AEs, compared with 0.01% (n = 1) of patients on placebo. The current review found 16 studies that reported data on the general tolerability and safety of tegaserod for the treatment of chronic constipation or IBS in adults. Most report a greater incidence of diarrhea with tegaserod than placebo.

Regarding comparative evidence on AE, no head-to-head evidence is available for most comparisons of the included medications. The evidence is limited to four head-to-head trials on comparisons of PEG 3350 versus lactulose, lactulose versus psyllium (two trials), and PEG 3350 versus psyllium. All of these studies had severe methodological limitations and were rated as poor quality for assessment of AEs.

#### Chronic constipation and IBS-C in children

The evidence is sparse; the quality was rated as poor. There were no studies on the general tolerability and safety of docusate calcium, docusate sodium, lactulose, lubiprostone, and psyllium. All of the studies found for general tolerability and safety in children were rated poor quality for the assessment of AEs (three studies for PEG 3350, one for tegaserod). No head-to-head evidence is available for most comparisons of the included medications. The evidence is limited to one poor quality head-to-head trial that compared PEG 3350 with lactulose. It did not report any serious AEs, but did report more abdominal pain, pain at defecation, and straining at defecation in those treated with lactulose, and worse palatability with PEG 3350.

Question #4: Are there subgroups of patients based on demographics (age, racial or ethnic groups, and gender), other medications, or co-morbidities, including IBS, for which one symptomatic treatment is more effective or associated with fewer AEs?

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 sex. Only one pooled data analysis, published as an abstract only, examined the differences in the general efficacy of lubiprostone for chronic constipation in women versus men. Response rates were slightly higher for men. However, because the reported information was insufficient to critically appraise the methods of this study, it was not formally included in the analysis. 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 differences in efficacy between men and women existed.

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. Only two pooled data analyses, published as abstracts only, examined the differences in the general efficacy of lubiprostone for chronic constipation in patients > 65 years. Because the reported information was insufficient to critically appraise the underlying methods of these studies, they were not formally included. Lubiprostone was well tolerated by elderly patients, and mean changes in spontaneous bowel movements were significantly improved in lubiprostone patients compared to their placebo counterparts. 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.

#### **Conclusion:**

Although chronic constipation is a disorder with a high prevalence and an important burden of disease, objective evidence from well-conducted studies on the efficacy, effectiveness and safety is largely missing. There were no studies on docusate calcium, docusate sodium, and lactulose for the treatment of chronic constipation or IBS-C. Likewise, no evidence is available for the treatment of IBS-C with psyllium or PEG 3350. Most of the studies that support the efficacy, effectiveness or safety of psyllium and PEG 3350 for the treatment of chronic constipation in adults and children have significant methodological problems. We found no published full-text studies assessing the efficacy, effectiveness or safety of lubiprostone. High quality evidence supports the efficacy of tegaserod for the treatment of chronic constipation and IBS with predominant constipation in adults and children. The comparative evidence is similarly sparse. For the comparative efficacy or effectiveness on chronic constipation in adults, there were three head-to-head trials, all less than four weeks in duration and with considerable methodological limitations. For comparative safety in adults there were four head-to-head trials, all rated as poor quality for assessment of AEs. For pediatric populations, there were no studies on the general efficacy, effectiveness, tolerability, or safety of docusate calcium, docusate sodium, lactulose, lubiprostone, and psyllium. For comparative evidence of general efficacy or effectiveness in pediatric populations, the evidence was limited to one poor quality study comparing PEG 3350 with lactulose. 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, there were no studies specifically designed to compare the effect of constipation drugs in particular subpopulations.