Systematic review: FDA-approved prescription medications for adults with constipation

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CRD summary
The authors concluded that there is a lack of high-quality evidence supporting the use of lactulose and polyethylene glycol-3350 in the treatment of chronic constipation, although the data does support use in acute, episodic constipation. High-quality evidence supporting the use of tegaserod was found. Potential publication and language bias, limitations of the evidence, and differences between the studies mean that the authors' conclusions should be interpreted with caution.

Authors' objectives
To evaluate the effectiveness of U.S. Food and Drug Administration (FDA)-approved prescription treatments for adults with constipation.

Searching
MEDLINE (from 1966) and EMBASE (from 1980) were searched to December 2005; the search terms were reported. Only articles published in English were eligible. In addition, abstracts from annual gastroenterology meetings of the American College of Gastroenterology and Digestive Disease Week were handsearched over the previous 4 years. The reference lists of included studies were also screened for additional studies.

Study selection
Randomised controlled trials (RCTs) of FDA-approved prescription treatments for adults with constipation, compared with placebo or a comparator, were eligible for inclusion. Studies of participants with constipation attributed to a secondary cause, such as drug-induced or irritable bowel syndrome, were excluded. In the included studies, the definition of constipation varied. The interventions included in the review were: lactulose compared with ispaghula husk, polyethylene glycol (PEG)-4000 electrolyte solution, bulk laxative plus senna, sorbitol or placebo; PEG-3350 compared with placebo; tegaserod versus placebo; and lubiprostone compared with placebo. The duration of treatment ranged from 1 day to 12 weeks. Outcomes were not clearly defined in the inclusion criteria. The outcome measures differed between the included studies and assessed overall effectiveness, bowel function, stool frequency and consistency, faecal electrolyte content, symptom severity, palatability, acceptability and description of adverse events, among others.

Owing to few published studies being identified for one of the agents of interest (lubiprostone), abstracts were also eligible for inclusion for that agent; for other agents, only full publications were eligible for inclusion.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Validity was assessed using established criteria: prospective design, randomised, double-blinded, parallel design, use of concealed allocation, placebo-controlled, sample size calculated a priori, prospectively defined primary efficacy variable, intention-to-treat analysis, definition of constipation according to Rome criteria for constipation, inclusion of a baseline observation period, follow-up at end of therapy, treatment duration of at least 8 weeks, and use of a validated and patient-derived outcome measure. One point was assigned for the presence of each criterion (maximum of 15 points). Quality was scored as low (0 to 5 points), moderate (6 to 10 points) or high (11 to 15 points).

Two reviewers independently assessed validity. Disagreements were resolved through consensus.

Data extraction
The data extracted included primary and secondary efficacy variables, adverse events and discontinuation due to adverse events. Authors contacted investigators for additional data where relevant.

Two reviewers independently extracted the data onto a standardised form. The methods used to resolve any disagreements were not reported.
Methods of synthesis
The studies were combined in a narrative. The studies were grouped by intervention category and described in the text, with additional descriptive information presented in the tables.

Results of the review
Twenty RCTs (n=3,876) were included in the review.

Lactulose (10 RCTs, n=934).
Study quality scores for lactulose trials were between 3 and 10 points (low to moderate quality). For patients with varying degrees of constipation (mild to chronic), lactulose was more effective than placebo, but less effective than PEG or bulk laxative plus senna, at relieving symptoms. There were no statistically significant differences in adverse events associated with lactulose in comparison with placebo or comparator agents. The adverse events most commonly reported were abdominal pain/griping, bloating, diarrhoea and gas. The reasons for discontinuation, where reported, were depression, concurrent effects (unspecified) and intolerance of lactulose.

PEG-3350 (6 RCTs, n=318).
Study quality scores for PEG 3350 trials were between 7 and 10 points (all moderate quality). Overall, PEG-3350 was found to be significantly more effective than placebo in 4 out of 5 studies (n=203), and modestly more effective than lactulose in one study (n=115), at relieving symptoms of constipation (mild to chronic). The most commonly reported adverse event was diarrhoea, but there were no statistically significant differences in adverse events between PEG-3350 and placebo or comparator. No study reported specific reasons for discontinuation.

Tegaserod (2 RCTs, n=2,133).
Study quality scores for tegaserod trials were 13 and 14 points (high quality). Tegaserod was found to be statistically significantly more effective than placebo in patients with long-term constipation. More episodes of diarrhoea were found in the tegaserod group than in the placebo group. These occurred during the first week of treatment, were transient, and did not result in hospitalisation or electrolyte imbalances. Less than 1% discontinued treatment with tegaserod due to diarrhoea.

Lubiprostone (data from abstracts only) (3 RCTs, n=606).
Study quality scores for lubiprostone trials were between 8 and 13 points (moderate to high quality). Overall, there was a statistically significant benefit of lubiprostone compared with placebo in 3 trials of patients with at least a 6-month duration of symptoms. The incidence of nausea was higher in patients receiving lubiprostone than in those receiving placebo. One study showed no statistically significant differences between groups for discontinuation, with two withdrawals in the intervention and placebo groups. Two studies reported more patients discontinuing lubiprostone treatment compared with placebo. Gastrointestinal adverse events were responsible for 75% of withdrawals.

Authors’ conclusions
The results indicate a lack of methodologically high-quality clinical trials supporting the use of lactulose and PEG 3350 for the treatment of patients with chronic constipation, although the data does support their use in acute, episodic constipation. However, high-quality evidence supporting the use of tegaserod and lubiprostone for the treatment of patients with chronic constipation is available, but conclusions relating to the role of lubiprostone are still in development.

CRD commentary
The inclusion criteria were defined in terms of the study design and intervention, but only broadly defined in terms of the participants; no inclusion criteria were defined for the outcomes. Some relevant sources were searched, though the restriction to studies published in English might have resulted in the loss of some relevant data and the potential for language bias. Unpublished studies were included for one drug only, which means there is the potential for publication bias. Methods were used to minimise reviewer error and bias in the assessment of validity and extraction of data, but it is not clear whether similar steps were taken at the study selection stage. Validity was assessed using specified criteria
and the results of this assessment reported. A narrative synthesis was appropriate given the differences between the studies. In view of the potential for publication and language bias, the methodological limitations of the evidence and the differences between the studies, the authors' conclusions should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.
Research: The authors stated that further research, focusing on studies using recognised and accepted methodological parameters such as a clearly defined patient population (fulfilment of Rome criteria), adequate sample size and trial duration, and patient-derived outcomes, is needed.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.