Constipation Drugs

Final Report

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RTI-UNC Evidence-based Practice Center
for the Drug Effectiveness Review Project

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Included Medications

- Docusate calcium
- Docusate sodium
- Lactulose
- Lubiprostone (Amitiza®)
- Polyethylene glycole 3350 (PEG 3350)
- Psyllium
- Tegaserod (Zelnorm®)*

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

Included Populations

Pediatric and adult patients with

- Chronic functional constipation (Rome II criteria: symptoms occurring at least 12 weeks in past 12 months)
- Irritable bowel syndrome with constipation (IBS-C)

Included Outcomes

- **Health outcomes**
  - Quality of life
  - Relief of specific gastrointestinal (GI) symptoms (e.g. bloating, straining…)
  - Number of spontaneous bowel movements
  - Time to effectiveness
- **Adverse events**
  - Overall rate of adverse events
  - Withdrawals because of adverse events
  - Specific adverse events (e.g. electrolyte abnormalities, nausea, dehydration…)

Rating the Strength of the Evidence: Modified GRADE

- HIGH: future research is very unlikely to change the confidence in the estimate of effect
- MODERATE: future research is likely to have an important impact on our confidence and may change the estimate
- LOW: Future research is very likely to have an important impact on our confidence and is likely to change the estimate

Key Questions/Included Design

1. **General and comparative effectiveness (efficacy)**
   - Any prospective controlled study
2. **Influence of treatment duration on effectiveness**
   - Any prospective controlled study
3. **Comparative safety**
   - Any study design except case reports
4. **Subgroups**
   - Any prospective controlled study

Results

- 33 studies included
  - 7 head-head trials
  - 16 placebo controlled trials
  - 1 meta-analysis
  - 7 observational studies
  - 2 pooled data analyses
- Remarkable lack of high quality evidence
- 78 percent of studies received poor quality ratings
- Scientific evidence on some drugs entirely missing

Key Question 1

1a: What is the general efficacy and effectiveness of drugs used to treat chronic constipation and IBS-C?

1b: Given the general efficacy, what is the comparative efficacy and effectiveness of constipation drugs?

Chronic Constipation - Adults: General Efficacy

- No prospective, controlled evidence on: docusate calcium, docusate sodium, lactulose
- All studies on lubiprostone have been published as abstracts only

Chronic Constipation - Adults: General Efficacy

- **PEG 3350**
  - 3 RCTs (1 poor) provide moderate strength evidence that PEG 3350 is more efficacious than placebo (210 patients)
  - None of these studies had a follow-up of more than 2 weeks
  - No inferences on long-term efficacy can be drawn

Chronic Constipation - Adults: General Efficacy

- **Psyllium**
  - 2 studies (1 poor) provide low strength evidence that psyllium is more efficacious than placebo (201 patients)
  - Smaller study (22 patients) had an 8 week follow-up
  - No inferences on long-term efficacy can be drawn

Chronic Constipation - Adults: General Efficacy

- **Tegaserod**
  - Multiple well-conducted studies provide evidence of the general efficacy of tegaserod (3234 patients)

Chronic Constipation - Adults: Comparative Efficacy

- **Docusate sodium vs. psyllium**
  - 1 poor, 2-week RCT did not detect any differences in subjective outcome measures (170 patients)
- **Lactulose vs. PEG 3350**
  - 1 poor ,4-week, open-label RCT found less improvement (VAS score) for lactulose than for PEG 3350 (115 patients)

Strength of evidence for both comparisons is low

Chronic Constipation - Adults: Comparative Efficacy

- **PEG 3350 vs. Psyllium**
  - 1 fair, 2-week, open-label RCT reported a higher rate of improvements in patients on PEG 3350 than on psyllium (126 patients)

Strength of evidence is low

Chronic Constipation - Children: General Efficacy

No evidence

Chronic constipation-children: comparative efficacy

- **Lactulose vs. PEG 3350**
  - 1 poor, 8-week RCT reported no differences in efficacy (100 patients)

Strength of evidence is low

IBS-C in Adults: General Efficacy

- No prospective, controlled evidence on: docusate calcium, docusate sodium, lactulose, PEG 3350, and psyllium
- One study on lubiprostone has been published as an abstract only
- 5 RCTs support the general efficacy of tegaserod

IBS-C in Adults: Comparative Efficacy

No evidence

IBS-C in Children: General Efficacy

- No prospective, controlled evidence on: docusate calcium, docusate sodium, lactulose, lubiprostone, PEG 3350, and psyllium
- 1 RCT supported the general efficacy of tegaserod

IBS-C in Children: Comparative Efficacy

No evidence

Key Question 2

Does treatment duration influence the effectiveness of drugs?

No evidence

When should treatments be switched in patients not responding?

No evidence

Key Question 3

What is the comparative tolerability and safety of constipation drugs?

Comparative Tolerability and Safety in Adults

- Evidence is limited to 4 poor trials comparing:
  - Lactulose vs. PEG 3350 (115 patients)
  - Lactulose vs. psyllium (2 trials, 518 patients)
  - PEG 3350 vs. Psyllium (126 patients)

Comparative Tolerability and Safety in Adults

- No substantial differences in harms
- Study durations are between 2 and 4 weeks
- Serious methodological problems

Strength of evidence is low

Comparative Tolerability and Safety in Children

- 1 poor study compared lactulose with PEG 3350
- No substantial differences in harms
- Better palatability for lactulose

Strength of evidence is low

Key Question 4

Are there subgroups of patients for which one treatment is more efficacious or associated with fewer adverse events?

Subgroups

- 1 study on lubiprostone, published as abstract only, did not detect any differences between men and women.
- Tegaserod has not been approved for men with IBS-C
- No evidence on age, race or ethnicity, and comorbidities

Summary

- Existing evidence is poor in *quantity* and *quality*
- For some drugs, evidence on the general efficacy is entirely missing

Summary

- Evidence is insufficient to draw conclusions about the comparative efficacy and safety of constipation drugs

The information in this slide show is based on the drug class review report written by

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