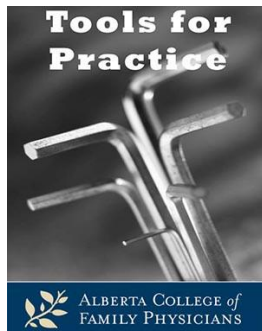


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Moving along the management of constipation predominant IBS – Is it worth the cost?

Clinical Question: What is the efficacy and safety of linaclotide in constipation predominant irritable bowel syndrome (IBS-C)?

Bottom Line: Compared to placebo, for every seven patients treated with linaclotide one more will be a “responder” [30% improvement in pain and one additional “complete” spontaneous bowel movement (CSBM) per week for six weeks in 12]. Overall, patients experience ~3 additional “spontaneous” bowel movements (BM) per week, at the price of \$15 per BM. For every 21 patients treated, one will stop due to diarrhea. Post-marketing surveillance should help clarify long-term safety.

Evidence:

- Two multicentre, Randomized Controlled Trials (RCTs) (803 and 805 patients)^{1,2} comparing linaclotide 290 mcg to placebo in IBS-C, and three systematic reviews.³⁻⁵
 - Both RCTs had strikingly similar baseline demographics and outcomes at 12 weeks:^{1,2}
 - Mean age 44, ~ 90% female, ~78% white.
 - Baseline abdominal pain ~5.6 on 0-10 point scale, CSBM 0.2/week.
 - Primary outcome:
 - “Responder”: ≥30% reduction in abdominal pain and increase of one CSBM per week for six of the 12 weeks.^{1,2}
 - 34% linaclotide versus 14-21% placebo.^{1,2}
 - Combined number needed to treat=7.^{3,4}
 - Secondary outcomes:
 - ~3 additional spontaneous BM per week (above placebo).^{1,2}
 - Average pain reduction in both trials was 1.9 linaclotide versus 1.1 placebo (0-10 scale).
 - Minimally clinically important difference=2.2.⁶
 - Adverse outcomes:
 - Diarrhea resulting in discontinuation:^{1,2}
 - 4-6% linaclotide versus 0.2-0.3% placebo.
 - Combined Number Needed to Harm=21.

- Limitations: Unclear recruitment, run in excluded >40% of patients.
- Over 40 publications (abstract and peer-reviewed) on two RCTs with common author (employee of linaclotide manufacturer). Some inconsistent data between abstracts and peer-reviewed publications.^{3,7}
- One smaller RCT reported similar outcomes.⁸

Context:

- Publication bias likely: Two open-label, 52 and 78-week safety studies with 1,557 and 1,743 patients completed in 2012 and 2013 not fully published⁹⁻¹¹ but have been evaluated by the FDA.¹²
- At least two other IBS-C drugs have been withdrawn due to safety concerns:
 - Tegaserod: 5-HT₄ antagonist due cardiovascular risk.¹³
 - Alosetron: 5-HT₃ antagonist due to ischemic colitis.¹⁴
- Linaclotide costs approximately \$180 per month or ~\$15 per additional BM.

Authors:

Brent Turner MD, Michael R. Kolber BSc MD CCFP MSc, Christina Korownyk MD CCFP

Disclosure:

Authors do not have any conflicts of interest to declare.

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