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TITLE PAGE

Title: Lubiprostone is effective in treating functional bowel disease with constipation.

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Abbreviations:

CIC	chronic idiopathic constipation
IBS-C	irritable bowel syndrome with constipation
RCT	randomized controlled trial

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Editor;

We read the two studies by Fukudo et al. reported in a single paper with interest.¹ Although lubiprostone has been shown to be effective in both IBS with constipation (IBS-C) and chronic idiopathic constipation (CIC),²⁻⁶ more data to confirm the efficacy of the drug in other populations are welcome. However, there are some aspects of their study that warrant further discussion.

Firstly, the authors state in their methods that they recruited a broad group of patients into both studies, including patients with functional bowel disease with constipation, and therefore presumably encompassing both CIC and IBS-C. Testing the efficacy of drugs in heterogeneous patient populations, which may resemble usual clinical practice more closely, is to be commended, and is something we have called for previously.^{7,8} However, we remain confused as to the exact characteristics of the subjects included in study 1 because, from the information provided in the supplementary materials, it appears that only CIC patients were recruited into the randomized controlled trial (RCT).

Secondly, the duration of the RCT was relatively short. IBS-C and CIC are chronic conditions, a fact reinforced by the average duration of constipation symptoms of 16 years for patients entering this trial. However, study 1 ran for only 4 weeks, and the primary endpoints were assessed after 1 week of therapy. The efficacy of the drug appeared to wane over the entire 4-week duration for some of the endpoints of interest, including their dichotomous assessment of response to treatment, with a response rate of 75.4% with lubiprostone compared to 29.0% for placebo ($P < 0.001$) at week 1, decreasing to 54.2% vs. 36.7% at week 4 ($P = 0.066$).

Thirdly, the authors demonstrated in study 2 that lubiprostone led to significant improvements in quality of life and a significant increase in spontaneous bowel movements. It is important to point out that this study was not a double-blind placebo-controlled trial, but rather an observational study of the effect of long-term open-label lubiprostone treatment, and therefore the placebo effect cannot be discounted. Worryingly, the authors appear to have extrapolated findings from the effect of open-label lubiprostone on quality of life from study 2 inappropriately into the conclusions in their abstract concerning the efficacy of the drug in study 1, where no such effect on quality of life was demonstrated.

Despite these limitations, this study provides more evidence of the efficacy of lubiprostone in patients with CIC and IBS-C. When data from all trials in either condition are pooled, ⁶ the drug is superior to placebo, although its effect in IBS-C appears more modest. We now need head-to-head trials of the drug against available and effective osmotic or stimulant laxatives, in order to assess the most cost-effective approach to managing patients with chronic constipation.

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