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Title: Ondansetron and Irritable Bowel Syndrome.

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Abbreviations: 5-HT 5-hydroxytryptamine

FDA Food and Drug Administration

GI gastrointestinal

IBS-D diarrhoea-predominant irritable bowel syndrome

Keywords: Irritable bowel syndrome

5-hydroxytryptamine

Ondansetron

Word count: 469

Editor;

We read the paper by Garsed *et al,*[1] which revives interest in 5-hydroxytryptamine (5-HT) receptor antagonists as treatment for diarrhoea-predominant irritable bowel syndrome (IBS-D). As a highly prevalent functional gastrointestinal (GI) disorder, [2] without a known organic pathology to target, IBS continues to be challenging to treat. Interest in agents acting on 5-HT receptors selectively is not novel, with alosetron, the most well studied 5-HT_3 antagonist, demonstrating efficacy in treating IBS-D. [3] However, cases of severe constipation and ischaemic colitis led to the withdrawal of the drug. Ondansetron first demonstrated effects on GI transit over twenty years ago. [4] Given the known clinical effectiveness of 5-HT_3 antagonists in IBS, and the good safety profile of ondansetron, it is perhaps surprising that no randomised controlled trial has been conducted previously.

At a time when licensed treatment options for IBS-D are lacking, we would like to congratulate the authors for performing this trial. The study demonstrated a significant improvement in stool form, the primary endpoint, a reduction in the number of days with urgency, and reduced urgency scores with ondansetron, compared with placebo. When applying the Food and Drug Administration (FDA) guidelines for assessing pharmacological agents in treating IBS, [5] ondansetron achieved a greater percentage of stool and pain responders (41%), than placebo (17%), although this result was not statistically significant. Unfortunately, there was no significant effect on abdominal pain, with FDA pain response criteria met by 43% with ondansetron, and 40% with placebo. Adverse events were limited with both treatments, although rates of constipation were higher with ondansetron. Reassuringly, no cases of ischaemic colitis were seen, although this is not surprising given the relatively small sample size.

Whilst the findings are important and may alter clinical practice, there are some limitations of the study. As with all crossover studies, there is the problem of carryover and order effects between crossover periods, which often cannot be completely adjusted for. Despite the 2 to 3-week washout period between treatments, the heterogeneous, fluctuating nature of IBS, along with high placebo response rates, [6] makes it difficult to be sure that there is no carryover between treatment periods. In addition, patient dropout rates were almost double in the arm receiving active treatment first, as compared to the arm receiving placebo first, suggesting an order effect, where patient dropout may be influenced by the sequence of treatment. These dropouts were omitted from the final analysis of the study, and hence a true intention-to-treat analysis was not carried out.

With this in mind, we feel the efficacy of ondansetron in treating IBS-D could be better judged if the authors had presented dichotomous data for pain and stool response for all 61 patients receiving ondansetron, and all 59 receiving placebo in the first treatment period, prior to crossover, with all dropouts assumed to be treatment failures.

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Competing Interests:

None.

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