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TITLE PAGE

Title: Invited Editorial: Understanding differences in patient response to ondansetron in irritable bowel syndrome with diarrhoea: Are we any closer?

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Abbreviations:

IBS-D	irritable bowel syndrome with diarrhoea
RCT	randomised controlled trial
5-HT	5-hydroxytriptamine
5-HIAA	5-hydroxyindoleacetic acid
SERT	serotonin re-uptake transporter

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5-hydroxytryptamine 3 (HT_3) receptor antagonists, are effective treatments for patients with irritable bowel syndrome with diarrhoea (IBS-D).[1] Lack of availability of alosetron and ramosetron in Europe has led to attention turning to ondansetron, which, although not currently licensed for the treatment of IBS-D, is widely available. A recent trial showed ondansetron to significantly improve bowel habit and transit.[2] However, not all patients responded, whilst some appeared more sensitive to ondansetron than others, requiring only a low dose to achieve improvement.

In the paper by Gunn et al,[3] the original investigators explore whether certain factors predicted response to ondansetron and, in an attempt to understand possible mechanisms, report an analysis of 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) concentrations in colorectal biopsies in a subset of patients. They also looked for the presence of known polymorphisms in genes associated with 5-HT synthesis and reuptake, and the structure of the 5-HT_3 receptor.

Stool form responders to ondansetron were younger, with lower anxiety and depression, less pain and urgency, and slower whole gut transit (WGT). Despite slower WGT, stool consistency and frequency did not predict response. In contrast to previous studies,[4] there was no difference in 5-HT concentrations in biopsies from IBS-D patients and healthy controls. However, 5-HT concentrations were lower in responders compared with non-responders. Analysis by dose, highlighted that patients on <4mg ondanstron were more commonly female with slightly firmer stools, and showed a greater increase in WGT, compared with placebo, than those on a higher dose (15.6 vs.3.9 hrs). 5-HT concentrations in biopsies from those taking <4mg were lower compared with those on higher doses (21.3 vs. 37.7 pmol/mg protein), a finding the authors speculated may relate to higher 5-HT turnover, as suggested by 5-HT release from biopsies being increased in this group. However, 5-HT concentrations in biopsies from those on <4mg were similarly reduced compared with healthy controls and, given that 5-HT release appeared similar between these groups, this casts doubt on their interpretation.

Surprisingly, no differences in the serotonin re-uptake transporter (SERT) or tryptophan hydroxylase polymorphisms were found between responders and non-responders, despite the original

trial reporting that patients with the sl genotype of SERT had a trend towards greater improvements in stool form with ondansetron, and a larger increase in WGT, compared with the ll genotype.[2] Stool consistency responders were more likely to carry the CC genotype (SNP p.N163K rs6766410) of the HTR3C gene encoding the 3C subunit of the 5-HT_3 receptor, although the implications of this are unclear. Despite genes encoding subunits HTR3A,[5] HTR3B,[6] and HTR3E[5, 7] having shown an association with IBS-D previously, no associations were detected in this study.

Important limitations, include lack of correction for multiple testing, and the small and varying numbers of patients used in the study, which may have influenced interpretation. Nonetheless, this study advances our understanding of factors that may influence patient sensitivity to ondansetron. This issue will have important clinical implications, should the drug become more widely used for IBS-D. Ongoing trials should help resolve this.[8]

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Guarantor of the article: LAH

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