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Randomised, placebo-controlled trial and meta-analysis show benefit of ondansetron for irritable bowel syndrome with diarrhoea: The TRITON trial

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Summary

Background: Ondansetron may be beneficial in irritable bowel syndrome with diarrhoea (IBS-D).

Aim: To conduct a 12-week parallel group, randomised, double-blind, placebo-controlled trial of ondansetron 4 mg o.d. (titrated up to 8 mg t.d.s.) in 400 IBS-D patients. Primary endpoint: % responders using the Food and Drug Administration

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(FDA) composite endpoint. Secondary and mechanistic endpoints included stool consistency (Bristol Stool Form Scale) and whole gut transit time (WGTT). After literature review, results were pooled with other placebo-controlled trials in a meta-analysis to estimate relative risks (RR), 95% confidence intervals (CIs) and number needed to treat (NNT).

Results: Eighty patients were randomised. On intention-to-treat analysis, 15/37 (40.5%; 95% CI 24.7%–56.4%) met the primary endpoint on ondansetron versus 12/43 (27.9%; 95% CI 14.5%–41.3%) on placebo ($p = 0.19$). Ondansetron improved stool consistency compared with placebo (adjusted mean difference − 0.7; 95% CI −1.0 to−0.3, $p < 0.001$). Ondansetron increased WGTT between baseline and week 12 (mean (SD) difference 3.8 (9.1) hours, versus placebo −2.2 (10.3) hours, $p = 0.01$). Meta-analysis of 327 patients from this, and two similar trials, demonstrated ondansetron was superior to placebo for the FDA composite endpoint (RR of symptoms not responding = 0.86; 95% CI 0.75–0.98, NNT = 9) and stool response (RR = 0.65; 95% CI 0.52–0.82, NNT = 5), but not abdominal pain response (RR = 0.95; 95% CI 0.74–1.20).

Conclusions: Although small numbers meant the primary endpoint was not met in this trial, when pooled with other similar trials meta-analysis suggests ondansetron improves stool consistency and reduces days with loose stool and urgency.

Trial registration – http://www.isrctn.com/ISRCTN17508514

1 | INTRODUCTION

Irritable bowel syndrome (IBS), which affects 3%–5% of the population,[1] accounts for 2.5% of the 340 million consultations per year in primary care in England and Wales,[2,3] or approximately 8.5 million consultations per year. Patients with IBS report abdominal pain and erratic bowel habit with around one-third meeting criteria for IBS with diarrhoea (IBS-D).[4] Symptoms of IBS-D include frequent loose or watery stools with associated urgency, which if associated with incontinence,[5] can severely limit socialising, travelling and eating out and markedly reduce quality of life and work productivity. When patients with IBS are asked to rank symptoms in order of importance, erratic bowel habit is rated first, followed by abdominal pain and for those with diarrhoea, urgency.[4] Current treatments for patients with IBS-D, such as loperamide, reduce bowel frequency, but often lead to constipation.[6,7]

A previous meta-analysis showed that the 5-hydroxytryptamine-3 receptor antagonists (5-HT_3RAs) alosetron and cilansetron benefited IBS-D patients,[8] improving stool consistency, and reducing both frequency and urgency of defaecation. However, these drugs have serious side effects, including potentially severe constipation in 25% and ischaemic colitis in 0.14% of patients.[9] Alosetron was initially withdrawn and is now only available in the United States with its use restricted to women with severe IBS-D. Cilansetron never came to market, while ramosetron, another 5-HT_3RA is only available in Asia, despite confirmed efficacy.[10,11] Ondansetron is a 5-HT_3RA that, despite 30 years of widespread use for nausea, has never been associated with ischaemic colitis. Generic ondansetron is inexpensive but is currently only licensed for the management of nausea and vomiting induced by cytotoxic chemotherapy, radiotherapy or following anaesthesia. However, a pilot randomised, placebo-controlled cross-over trial showed that 5 weeks of ondansetron was effective in improving both diarrhoea and urgency in IBS-D.[12] More recently, a bimodal release formulation, Bekinda^R, delivering 3 mg of immediate-release and 9 mg delayed-release ondansetron, has been shown to improve stool consistency, but not abdominal pain, in 127 IBS-D patients.[13] Our pilot cross-over study showed the decrease in urgency with ondansetron correlated directly with the reduction in faecal protease,[14] but whether this is important for its effectiveness remains unclear.

The primary aim of the current study was to evaluate the efficacy of ondansetron in IBS-D in a 12-week, multi-centre, parallel group, randomised, placebo-controlled trial. Secondary aims were to assess potential mechanisms of benefit including slowing transit, reducing faecal proteases, and altering rectal sensitivity, which may help design studies of future novel agents for this common condition. Difficulties in recruitment meant we were underpowered. However, since the methodology was similar, we were able to combine the current results with those of two previous studies and perform a meta-analysis, which confirmed ondansetron's effectiveness.

2 | METHODS

The TReatment of IBS with Titrated Ondansetron (TRITON) trial was performed in 18 secondary care centres throughout the UK. The trial

was approved by Yorkshire and the Humber Leeds West Research Ethics Committee (ref 17/YH/0262), the Medicines & Healthcare products Regulatory Agency (EudraCT: 2017-000533-31), and registered with an International Standard Randomised Controlled Trial Number ISRCTN17508514. There were no changes to the endpoints after registration.

2.1 | Patient and public involvement statement

Both the grant application and the design of the study were assisted by our patient participation and involvement (PPI) group, which included patients with IBS-D who supported the original application and subsequently helped with the design of patient-facing documents. Full details of inclusion and exclusion criteria are given in Supplement S1 and in the published protocol.[15] In brief, patients aged ≥18 years were required to meet Rome IV criteria for IBS-D (Supplement S1.1–S1.3),[16] and to have had other likely causes of diarrhoea excluded, namely microscopic colitis, bile acid diarrhoea, coeliac disease or lactose intolerance. Importantly, we also required a threshold for symptom severity as recommended by the Food and Drug Administration (FDA),[17] consisting of a weekly average worst pain score ≥30 on a 0 to 100-point scale and stools with a consistency of 6 or 7 on the Bristol stool form scale (BSFS) for 2 or more days per week. We excluded those with BSFS 6 or 7 on all 7 days per week as our previous experience suggested these patients do not respond. Those unable to stop drugs likely to alter gut motility, such as opioids, were also excluded, although we allowed low-dose tricyclic antidepressants and selective serotonin reuptake inhibitors, provided patients agreed to maintain a stable dose during the trial. Loperamide was allowed as rescue medication, but patients were asked to document each dose in a daily diary and to minimise dosing to no more than one 2 mg tablet per day on a maximum of two separate days per week.

2.2 | Intervention

Eligible patients were randomised on a 1:1 basis to receive either over-encapsulated ondansetron 4 mg capsules or identical appearing over-encapsulated placebo for 12 weeks. The primary outcome measure was the difference in FDA-defined responder rate,[17] compared with placebo. The dose was titrated during the first 2 weeks, starting with one capsule daily, adjusting the dose every third day up to six capsules daily or down to one capsule every third day aiming to achieve a stool consistency type 3–5 on the BSFS (Supplement S1.4). This dose titration was used in the first 2 weeks of the trial to avoid constipation, as previously described with most patients remaining on that dose for the rest of the trial though they were permitted to adjust the dose if neccessary.[12]

2.3 | Trial outcomes

The primary endpoint was the FDA-recommended endpoint of a weekly responder for abdominal pain intensity and stool consistency.[17] This was defined as a patient who recorded both a ≥30% reduction in pain intensity and a >50% decrease in the number of days per week with at least one loose stool (BSFS 6 or 7) for at least 6 weeks of the 12-week treatment period. We also assessed each of these endpoints separately, with an abdominal pain responder defined as a patient who recorded a ≥30% reduction in pain intensity for at least 6 weeks of the 12-week treatment period, and a stool consistency responder defined as a patient who recorded a >50% decrease in the number of days per week with at least one loose stool (BSFS 6 or 7) for at least 6 weeks of the 12-week treatment period.

Secondary outcome measures were as follows: (a) stool consistency and abdominal pain (measured by daily diary and daily text message); (b) stool frequency, urgency of defaecation, use of loperamide rescue medication, and the answer to the question 'Overall, have you had satisfactory relief from your IBS symptoms in the past week'? (measured by diary); (c) IBS symptom severity (measured by the IBS Severity Scoring System (IBS-SSS)),[18] dyspepsia (using the Short-form Leeds Dyspepsia Questionnaire (S-FLDQ)[19]), quality of life and mood (using the IBS Quality of Life (IBSQOL)[20] and Hospital Anxiety and Depression Scale (HADS)[21] questionnaires) and somatic symptoms (using the Patient Health Questionnaire-12 (PHQ-12)[22]) all completed at 12 weeks; (d) stool frequency, stool consistency, urgency and abdominal pain according to the daily diary 4 weeks after the end of treatment and (e) adverse events assessed up to 4 weeks after the end of treatment (Supplement S1.5).

2.4 | Study design

After registration and consent (visit 1) patients completed a 2-week daily diary to confirm eligibility (visit 2), recording stool frequency, stool consistency and loperamide use prior to randomisation (visit 3) (Figure S1). They were instructed on the use of a 12-week paper diary and the daily text messaging system to record whether they had passed a stool of BSFS 6 or 7 and what their worst abdominal pain score was on that day using a 0–100 scale. During the first 2 weeks, patients adjusted the dose of medication, increasing or decreasing to achieve a stool consistency with a BSFS of 3–5. Visit 4 was at 6 weeks and visit 5 after 12 weeks of treatment when patient diaries were collected, and questionnaires were completed. Visit 6 was at 16 weeks when the final symptom diary was collected. Centralised, automated randomisation was performed, and each patient was allocated three bottles of trial medication, each with a unique IMP kit code. Minimisation was used to ensure treatment groups were well balanced with respect to the minimisation factors of registering site and whether the patient had undergone the barostat and colonic manometry mechanistic assessments.

The trial was double-blind; neither the patient nor those responsible for their care and evaluation (treating team and research team) knew the allocation or coding of the treatment allocation. This was achieved by identical packaging and labelling of both the

over-encapsulated ondansetron and matched placebo. Each bottle of ondansetron or placebo was identified by a unique kit code. Randomisation lists containing kit allocation were generated by the safety statistician at the Clinical Trials Research Unit (CTRU) and sent to the clinical supply company who produced the kits and the code break envelopes. Management of kit codes on the kit logistics application, which was linked to the 24-h randomisation system, was conducted by the CTRU safety statistician in addition to maintaining the back-up kit code lists for each site.

Access to the code break envelopes was restricted to the safety statistician and designated safety team. Code breaks were permitted in emergency situations, where treatment allocation knowledge was needed to optimise treatment of the patient. Unblinded interim reports provided to the Data Monitoring and Ethics Committee (DMEC) were provided by the CTRU safety statistician and the reports were securely password-protected.

2.5 | Mechanistic studies

Participation in mechanistic studies was optional to minimise obstacles to recruitment. An abdominal x-ray was performed to assess whole gut transit time (WGTT) both at baseline (visit 3) and on treatment (visit 5), with transit pellet capsules ingested for 6 days prior to each X-ray. Rectal sensitivity was assessed using a dual-drive barostat (Distender series II, G & J Electronic). Rectal pressure/volume relationships were assessed during a phasic isobaric distension with subjects rating sensations from no sensation to pain during each balloon distension. Thresholds for pain, urgency and desire to defaecate were assessed using the ascending method of limits and random phasic distension, as previously described.[23] Stool samples were collected at baseline and at 12 weeks. Faecal water was measured by vacuum drying, proteases using the non-specific proteolysis of azocasein as previously described,[12] and bile acids by liquid chromatography mass spectrometry. For full details for all mechanistic studies see Supplement S1.6.1–S1.6.5.

2.6 | Statistics and sample size estimation

All hypothesis tests were two-sided and used a 5% significance level. Methods to handle missing data are described for each analysis. Analysis and reporting were in line with CONSORT guidelines. The trial statistician was blinded to treatment group allocation throughout the trial, until the database had been locked and downloaded for final analysis. Only the safety statistician, supervising trial statistician, back-up safety statistician and authorised unblinded individuals at the CTRU had access to unblinded treatment group allocation prior to final analysis. Outcome data were analysed once only, at final analysis, although statistical monitoring of safety data was conducted throughout the trial and reported at agreed intervals to the DMEC. Final analysis took place 16 weeks post-last patient randomisation.

All analyses were conducted on the intention-to-treat (ITT) population, defined as all patients randomised, regardless of non-compliance with the intervention. A per-protocol analysis of the primary endpoint was carried out to indicate whether results were sensitive to the exclusion of patients who violated the protocol, for example, those patients randomised but subsequently found to be ineligible. Outcome measures were analysed by regression models appropriate to the data type. Such analyses adjusted for the randomisation minimisation factors (site and completion of manometry or barostat assessment) as well as baseline values where applicable, including age and gender. Baseline characteristics were summarised by randomised group. SAS software version 9.4 was used in the analyses of primary and secondary endpoints.

TRITON planned to recruit 400 patients to provide 90% power at 5% significance to detect a 15% absolute difference between the randomised groups in the proportion of patients achieving the FDA-recommended composite endpoint for abdominal pain and diarrhoea,[17] assuming a placebo response rate of 17% and a 15% attrition rate.

2.6.1 | Primary endpoint

The primary analysis compared the difference in the proportion of patients achieving the FDA-recommended composite endpoint between treatment groups at 12 weeks of post-randomisation using a logistic regression model adjusted for minimisation factors, age and gender. It was planned to assume any missing data were missing at random and they would be imputed for the primary analysis. However, there were only four patients with missing data for the primary endpoint, so complete case analysis was undertaken, with those with insufficient data to evaluate the primary endpoint assumed to be non-responders. With only 5% of patients with an incomplete evaluation of response the impact of these missing data would be small. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were presented.

2.6.2 | Secondary endpoints

The difference in the proportion of patients with satisfactory relief of IBS symptoms between the treatment groups at 12 weeks' post-randomisation was compared using logistic regression models, adjusting for minimisation factors, age and gender. ORs and corresponding 95% CIs were presented. Any missing data were assumed missing at random and imputed. The differences between the two treatment groups for the continuous secondary endpoints at 12 weeks post-randomisation were compared using linear regression models, adjusted for minimisation factors, baseline values, where applicable, age and gender. These endpoints included urgency of defaecation over the last month, stool frequency over the last month, number of days per week with at least one loose stool (BSFS >5) over the last month, average stool consistency, number of days

rescue medication used over 12 weeks, abdominal pain score, HADS depression and anxiety scores, S-FLDQ score, IBS-QOL score and subscales, PHQ-12 scores and IBS-SSS severity scores. Any missing data were assumed missing at random.

2.6.3 | Safety analyses

All patients who received at least one dose of trial treatment were included in the safety analysis set. The number of patients reporting a serious adverse event (up to 28 days after the last dose of treatment), and details of all serious adverse events, were reported for each treatment group. The number of patients withdrawing from trial treatment was summarised by treatment arm, along with reasons for withdrawal. All safety analyses performed prior to final analysis were undertaken by the safety statistician, rather than the trial statistician, thus ensuring that the trial team remained blinded.

2.6.4 | Mechanistic studies

The differences between treatment groups for changes in whole gut transit times, rectal compliance and thresholds for urgency and pain, measured using the barostat, and faecal bile acid concentrations were assessed using a Mann–Whitney U test as data were non-normally distributed.

2.7 | Meta-analysis methodology

We searched MEDLINE (1946 to 16th August 2022), EMBASE and EMBASE Classic (1947 to 16th August 2022), and the Cochrane central register of controlled trials along with clinicaltrials.gov (1964 to present), for unpublished trials. Randomised controlled trials (RCTs) comparing ≥4 weeks of treatment with ondansetron with placebo in adult patients (≥18 years) with IBS were eligible for inclusion, including the first period of cross-over RCTs, prior to cross-over to the second treatment. Trials were only eligible if they reported efficacy according to FDA-recommended endpoints for IBS-D. The medical literature was searched using the following terms: *irritable bowel syndrome* and *functional diseases*, *colon* (both as medical subject heading and free text terms), and *IBS*, *spastic colon*, *irritable colon* or *functional* adj5 *bowel* (as free text terms). These were combined using the set operator AND with studies identified with the terms: *ondansetron* or *Bekinda* (as free text terms). The eligibility criteria are provided in Supplement S2.

The outcomes assessed were the effects of ondansetron compared with placebo on FDA-recommended endpoints (composite response, abdominal pain response, stool consistency response) for IBS-D at study end, as well as a ≥30% improvement in faecal urgency scores. We used an ITT analysis, with dropouts assumed to be treatment failures (i.e. no response to therapy) and pooled data using a random effects model.[24] We expressed the impact of ondansetron versus placebo as a relative risk (RR) of each outcome not being achieved separately, along with 95% CIs, where if the RR was less than 1 and the 95% CI did not cross 1, there was a significant benefit of ondansetron over placebo. We assessed heterogeneity using the I^2 statistic, using a value >50% to denote statistically significant heterogeneity. Review Manager version 5.4.1 (The Cochrane Collaboration 2020) was used to generate Forest plots for all outcomes.

2.8 | Role of the funding source

This project was funded by the National Institute for Health Research Efficacy and Mechanism Evaluation Programme (Grant Ref: 15/74/01). The funding source had no role in the running of the trial nor its analysis or interpretation of the data.

3 | RESULTS

3.1 | Recruitment

Participants were randomised over 23 months from July 2018 until May 2020 when the COVID-19 pandemic prevented further recruitment. The trial had proved difficult to recruit to prior to the pandemic and the funder, therefore, took the decision to close the trial. Details of recruitment are provided in the Consort diagram (Figure 1). As can be seen, many patients initially considered for the trial failed to meet the criteria for entry, particularly the Rome IV criteria, which require pain at least 1 day per week and the requirement for an average worse daily pain to exceed a score of ≥30 on a 0–100 scale.

Of those who met all the criteria, 37 (46.3%) participants were randomised to ondansetron and 43 (53.8%) to placebo. Recruitment by site is provided in Supplement S3.1 Table S1. All patients had bile acid diarrhoea excluded by Selenium homocholic acid taurine scanning or serum C4, other than four patients at one site who had a therapeutic trial of a bile acid sequestrant. The demographics are shown in Table 1. As in our previous trial,[12] dose titration led to a wide range of doses, from 4 mg every 3 days to 8 mg t.d.s., with the most common dose being 4 mg b.d.

Subjects in the two treatment groups were similar. The mean abdominal pain score was in the moderate to severe range. Most days were associated with loose stools and moderate to severe urgency. The IBS-SSS score showed most patients had moderate or severe symptoms, while psychological parameters showed high anxiety and depression scores, 44% and 23%, respectively, being above the upper limit of normal of 7. The proportion of males was 43.2%.

Treatments were generally well tolerated, and dose titration was successful with a median of one capsule daily for those taking ondansetron and six for those on placebo by the second week.

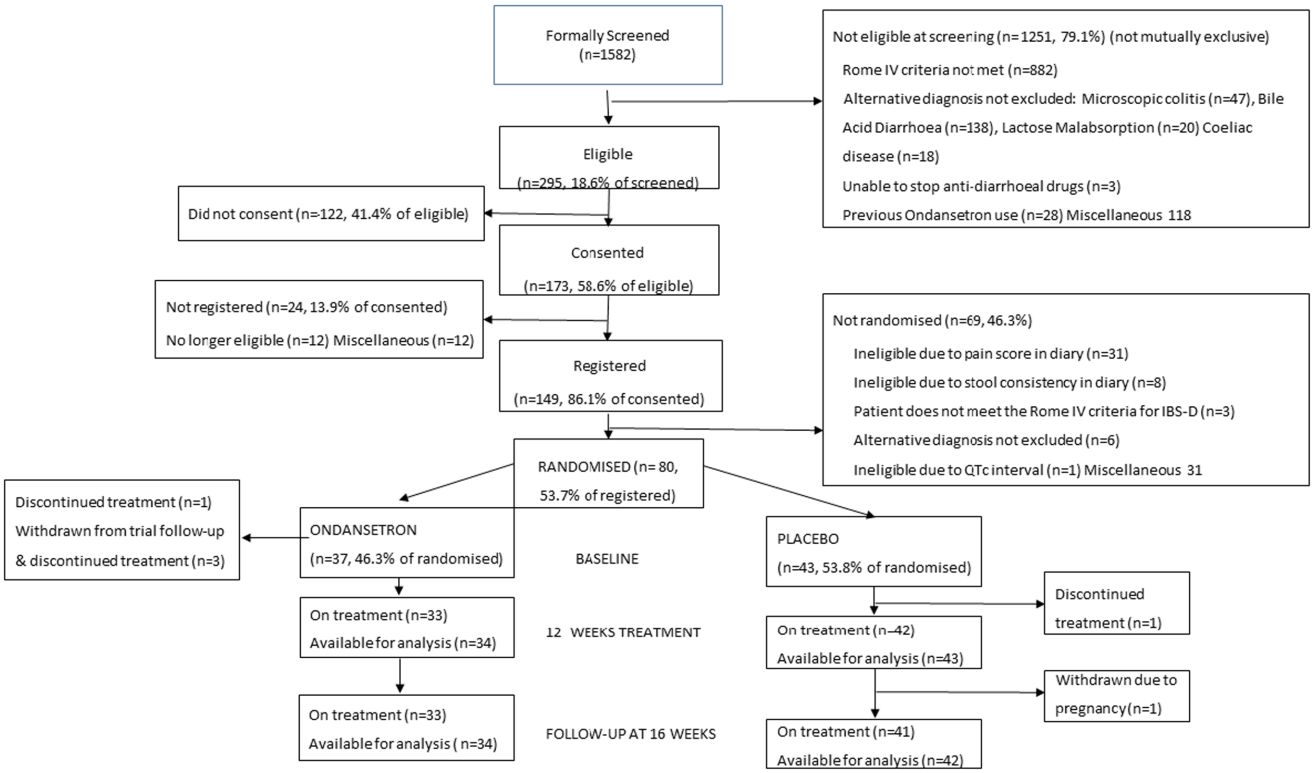


FIGURE 1 Consort diagram showing recruitment and patient disposition.

TABLE 1 Demographics, mean IBS severity, and psychological scores (mean, SD).

Demographics	Ondansetron ($n = 37$)	Placebo ($n = 43$)
Mean age in years	45.0 (15.7)	43.0 (16.3)
Male/female *N* (% female)	16/21 (56.8%)	17/26 (60.5%)
Mean daily worse abdominal pain score (0–100)	61.4 (19.7)	55.2 (16.7)
Mean days per week with loose stool	5.9 (1.3)	5.4 (1.2)
Mean urgency score (0–100)	67.5 (19.6)	60.4 (17.8)
IBS-SSS (0–500)	387.6 (89.0)	336.5 (82.2)
PHQ-12 score Male (0–33)	7.5 (4.63)	7.5 (3.54)
PHQ-12 score Female (0–36)	10.3 (4.32)	9.6 (4.63)
HADS anxiety score (0–21)	9.9 (5.0)	10.2 (4.5)
HADS depression score (0–21)	8.0 (4.2)	6.9 (4.0)

3.2 | Primary outcome

Analyses were conducted on the ITT population and all 80 participants were included in the primary analysis (Table 2). Four participants (two in each arm) did not provide sufficient data to evaluate the primary endpoint. Both arms showed an improvement in symptoms over the 12 weeks of the trial with a marked response in the first 4 weeks (Table 2, Figure 2A,B). There was no evidence of a statistically significant difference in the FDA-defined primary endpoint responder rate between arms. The adjusted OR from the logistic regression model was 1.93 (95% CI 0.73–5.11, $p = 0.19$). A higher proportion of patients used loperamide in the placebo arm during treatment (17 (39.5%) with placebo compared with 7 (18.9%) with ondansetron). Loperamide use was, therefore, added as an interaction term with the treatment allocation. However, the findings were similar (Table 2). Assessment of the primary outcome by use of loperamide is provided in Supplement S3.2 Table S2.

3.3 | Secondary outcomes

Ondansetron significantly improved stool consistency compared with placebo during the 12 weeks (adjusted mean (SE) difference −0.7 (0.19); 95% CI −1.0 to −0.3, $p = 0.0013$). The differences in stool consistency were obvious within the first week and persisted over the 12 weeks, promptly returning to baseline on cessation of ondansetron (Figure 2A). There was no significant difference in pain intensity, with both arms showing a rapid fall in the first few weeks and then remaining stable over the ensuing 8 weeks ($p = 0.64$) (Figure 2B). Assessment of these outcomes by use of loperamide is provided in Supplement S3.2 Table S2, which shows around half the placebo stool consistency responders (10/22) took loperamide compared with only 2 of 15 ondansetron responders (Fisher exact test, $p = 0.03$).

TABLE 2 Responder rates using FDA criteria.

	Ondansetron $n = 37$	Placebo $N = 43$	Adjusted p for difference[a]	Adjusted p for difference[b]
FDA responder: combined endpoint n (%; 95% CI)	15 (40.5;24.7–56.4)	12 (27.9; 14.5–41.3)	0.19	0.36
FDA responder: abdominal pain n (%; 95% CI)	17 (46.0; 29.9–62.0)	16 (37.2; 22.8–51.7)	0.32	0.35
FDA responder: stool consistency n (%; 95% CI)	25 (67.6; 52.5–82.7)	22 (51.2; 36.2–66.1)	0.07	0.06

[a]Derived from the odds ratio from the logistic regression model using complete cases adjusted for the treatment group, the minimisation variables (undergoing barostat study, age, and gender).

[b]Derived from the odds ratio from the logistic regression model using complete cases adjusted for the treatment group, the minimisation variables (undergoing barostat study, age, and gender), and loperamide use.

There was also a striking fall in the number of days with loose stool in those taking ondansetron, which increased on cessation of drug intake (Figure 3). Considering the entire 12-week study period, ondansetron was associated with significantly firmer stools and significantly fewer days per week with loose stool than with placebo (mean (SE) 1.0 (0.45) days; 95% CI −1.0 to −0.3 days, $p = 0.036$) (Table 3).

However, there was no significant difference in abdominal pain scores, stool frequency or rated severity of urgency on ondansetron compared with placebo. The mean global IBS-SSS fell during the trial in both arms but not significantly more on ondansetron versus placebo, adjusted mean difference (SE) −26.5 (32.5), $p = 0.4$ (Table 4). Satisfactory relief showed no difference, being reported by 40.5% on ondansetron and 39.5% on placebo.

After 12 weeks of treatment, there were similar falls in both anxiety and depression scores (Supplement S3.3 Table S3). However, the reduction of dyspepsia, as assessed by the SFLDQ, was significantly greater with ondansetron (adjusted mean difference (SE) −3.2 points (1.43); 95% CI −6.1 to −0.4 points, $p = 0.0275$).

3.4 | Correlation between anxiety and depression and bowel symptoms

Anxiety at baseline did not correlate with urgency, pain scores, bowel consistency or number of loose motions per day. By contrast, depression did correlate significantly with number of loose motions per day and abdominal pain ($r = 0.30$ and 0.33, $p < 0.003$ and <0.008 respectively). Both were significant even after Bonferroni correction.

3.5 | Mechanistic outcomes

Transit studies before and during treatment were completed on 64 participants (27 on ondansetron, 37 on placebo). Ondansetron significantly increased WGTT (Table 5), with a significant prolongation in the rectosigmoid, but not the right or left colon (Supplement S3.4 Table S4). Stool samples allowed analysis of bile acids in 53 participants and, where enough sample remained, we measured stool water (16 placebo, 16 ondansetron) and protease (17 placebo, 13 ondansetron). Faecal bile acid concentrations (Supplement S3.5 Table S5) were 3.9 (2.1) mM/L at baseline in those providing stool samples ($n = 53$), with none meeting criteria for bile acid malabsorption. Faecal proteases were assessed at baseline and week 12 and showed no significant change by visit or treatment ($p = 0.8$).

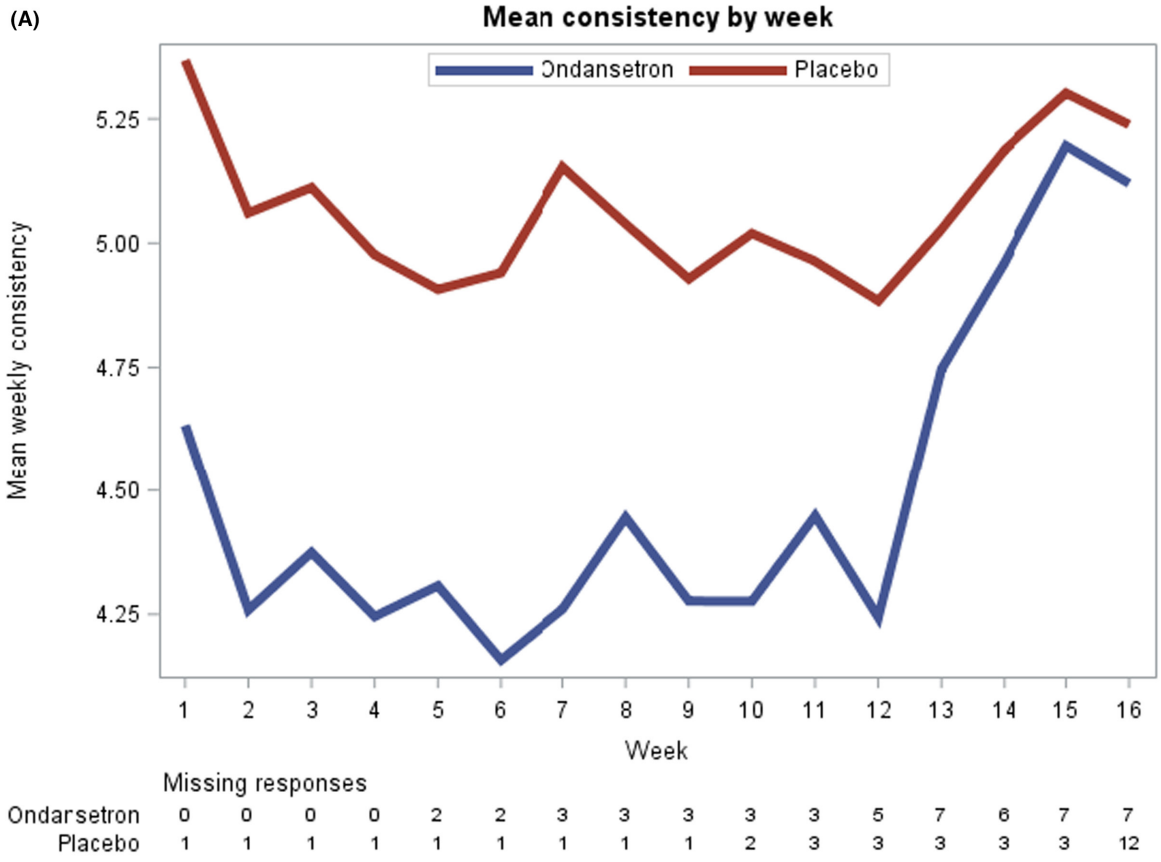
Seven patients on ondansetron and six on placebo completed the barostat study. Using the ascending method of limits, the mean (SD) volumes to reach thresholds for urgency were 84 mL (27 mL) versus 38 mL (21 mL) ($p = 0.16$) and for pain 57 mL (24 mL) versus 24 mL (12 mL) ($p = 0.3$), on ondansetron versus placebo respectively. Using the random phasic distension method, ondansetron treatment was associated with an approximate halving of the severity of the sensation of urgency as judged by the area under the curve of the visual analogue scale over the range 8–24 mmHg which was 829 (122) units on placebo but significantly lower at 387 (285) units on ondansetron ($p = 0.035$). For full details see Supplement S3.6, Figure S3, and Tables S6–S8.

3.6 | Adverse events

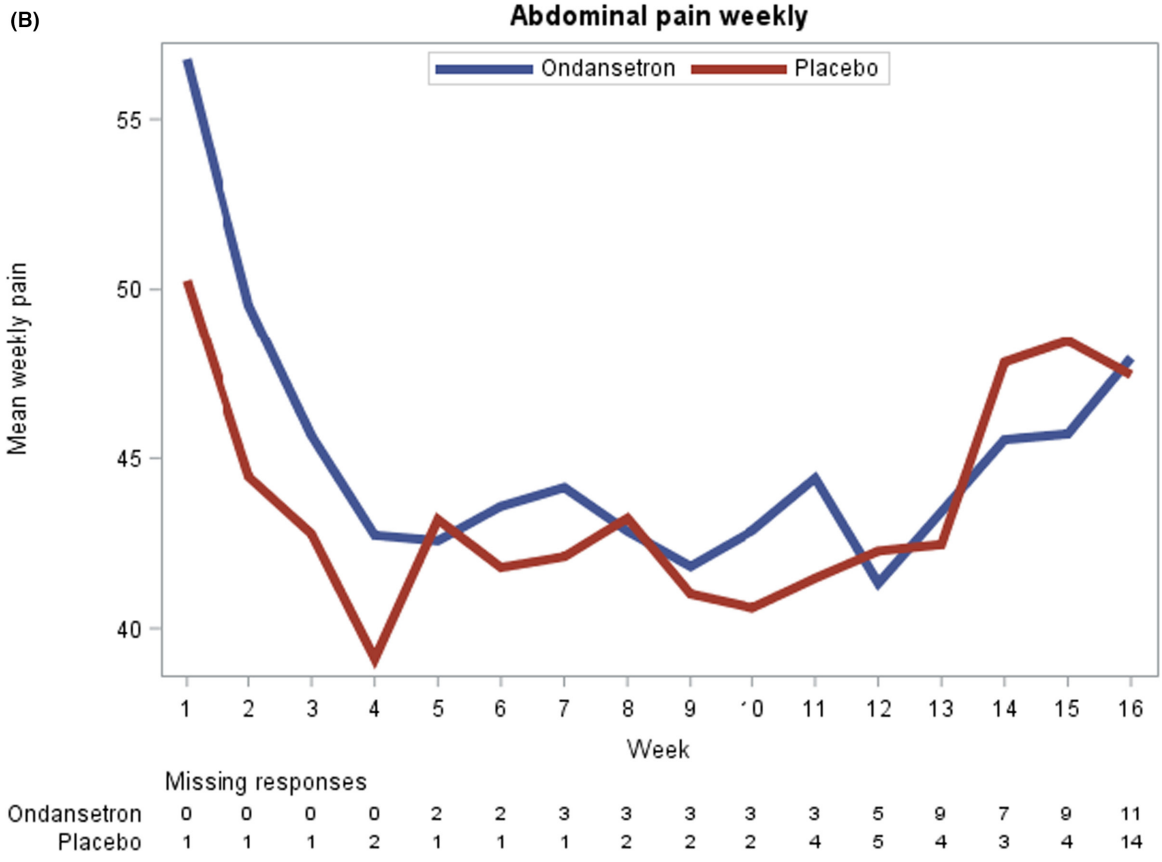
There were no serious adverse events. More patients on ondansetron reported constipation (45.9% vs. 25.6%), but this was mostly mild and only one (3%) patient on ondansetron and none on placebo reported severe constipation. One patient on ondansetron and one on placebo discontinued treatment because of constipation. Rectal bleeding, which was specifically sought by direct questioning, was reported by three (3%) patients on ondansetron and seven (17%) on placebo but all cases were judged as minor adverse events except for one case, which was in a placebo-treated patient. In no cases was it considered necessary to perform a sigmoidoscopy.

FIGURE 2 (A) Weekly average stool consistency score (BSFS scale 1–7) from week 1–16 showing ondansetron significantly improved stool form score (adjusted mean (SE) difference −0.7 (0.19); 95% CI −1.0, −0.3, $p < 0.001$). (B) Average abdominal pain score (0–100 scale) from week 1–16, showing no significant difference between treatments ($p = 0.64$).

(A)



(B)



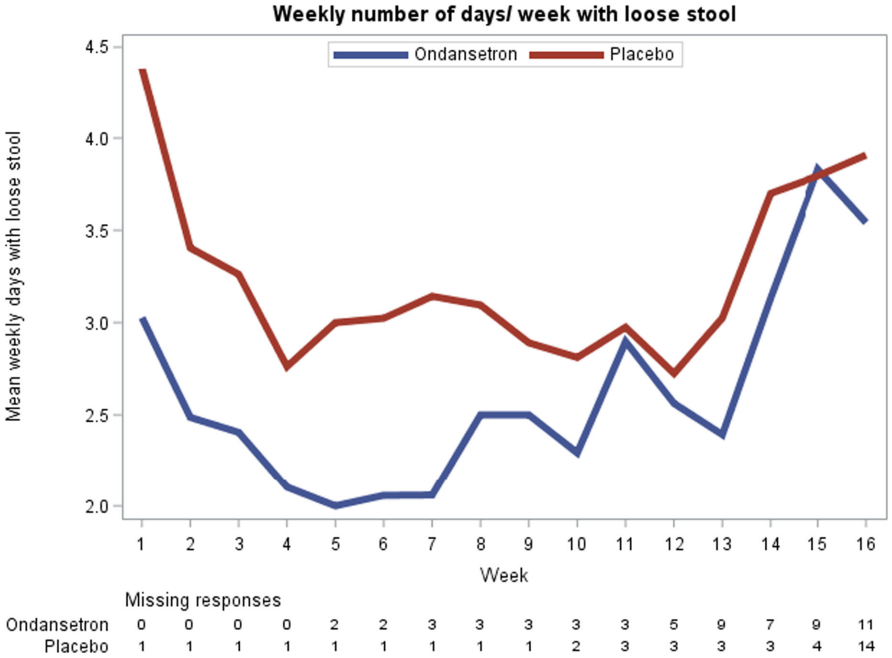


FIGURE 3 Days per week with loose stool over the 16-week trial period. Ondansetron use was associated with significantly fewer days per week with loose stool than placebo (mean (SE) difference 1.0 (0.45) days; 95% CI −1.0 to −0.3 days, $p = 0.036$).

TABLE 3 Effect of ondansetron versus placebo on symptoms of IBS during weeks 1–12.

Analysis (linear models)—weeks 1–12	Adjusted mean ondansetron	Adjusted mean placebo	Difference in adjusted means	SE	*p*-value	95% CI lower	95% CI upper	N
Abdominal pain score (0–100)	41.6	43.5	−1.8	3.88	0.64	−9.6	5.9	77
Stool consistency (BSFS) (1–7)	4.4	5.0	−0.7	0.19	0.0013	−1.0	−0.3	75
Stool urgency (0–100)	38.4	44.9	−6.5	4.8	0.18	−16.1	3.1	76
Stool frequency (number of stools/day)	2.5	2.8	−0.3	0.25	0.20	−0.8	0.2	76
Days/week with loose stool	2.3	3.2	−1.0	0.45	0.036	−1.9	−0.1	79

TABLE 4 IBS-SSS score at baseline and at 12 weeks (median, IQR).

	Ondansetron	Placebo
Baseline	385 (155, 500)	335 (190, 500)
Week 12	270 (0, 500)	260 (30, 475)

TABLE 5 Whole gut transit time in hours (median, IQR).

	Baseline		Week 12: Change from baseline	
	n	WGTT	*n*	Change from baseline
Ondansetron	28	4.8 (2.7, 9.3)	27	3.6 (−2.4, 8.4)*
Placebo	37	7.2 (3.0, 11.4)	37	−1.2 (−7.8, 3.0)

Note: Ondansetron versus placebo.

*$p = 0.01$ Mann Whitney U test.

3.7 | Meta-analysis

The search identified 392 citations. In addition to the current study, we identified two eligible RCTs that met our criteria (Table 6).[12,13] One of these was a 10-week crossover trial,[12] but we obtained original data from the first 5 weeks of treatment, prior to crossover. There were 327 subjects in these three trials. Ondansetron was superior to placebo for the FDA composite endpoint (RR of symptoms not responding = 0.86; 95% CI 0.75–0.98, NNT = 9; 95% CI 5–65, $I^2 = 0\%$), FDA stool consistency response (RR = 0.65; 95% CI 0.52–0.82, NNT = 5; 95% CI 4–10, $I^2 = 0\%$) and for a ≥30% improvement in urgency score (RR = 0.74; 95% CI 0.59–0.93, NNT = 7; 95% CI 4 to 26, $I^2 = 45\%$), but not FDA abdominal pain response (RR = 0.95; 95% CI 0.74–1.20, $I^2 = 0\%$) (Figure 4). There was no significant heterogeneity between studies in any analysis.

4 | DISCUSSION

Although the trial did not meet its primary endpoint, due to small patient numbers, when pooled together in a meta-analysis of all trials conducted to date, there appeared to be a benefit of ondansetron in IBS-D for managing urgency and loose stools, key symptoms which can severely impair quality of life. A major novelty compared with most trials in IBS was using dose titration against stool consistency in the first 2 weeks of the trial as previously described,[12] an approach which substantially reduces the adverse effect of constipation, which is otherwise common with all 5-HT_3RAs.[8] The patients recruited appear typical of those

TABLE 6 Characteristics of Randomised Controlled Trials of Ondansetron Versus Placebo in IBS-D.

Study	Country and number of Centres	Diagnostic criteria used for IBS	Number of patients (% female)	Number of patients assigned to active drug, dosage, schedule, and duration of therapy
Garsed 2014[14]	UK, 2 sites	Rome III criteria	120 (72.5)	61 patients received titrated ondansetron commencing at a dose of 4 mg o.d. for 5 weeks
Plasse 2021[13]	USA, 16 sites	Rome III criteria	127 (69.8)	75 patients received modified release ondansetron 12 mg o.d. for 8 weeks
Gunn 2022	UK, 18 sites	Rome IV criteria	80 (58.8)	37 patients received titrated ondansetron commencing at a dose of 4 mg o.d. for 12 weeks

Abbreviation: o.d., once daily.

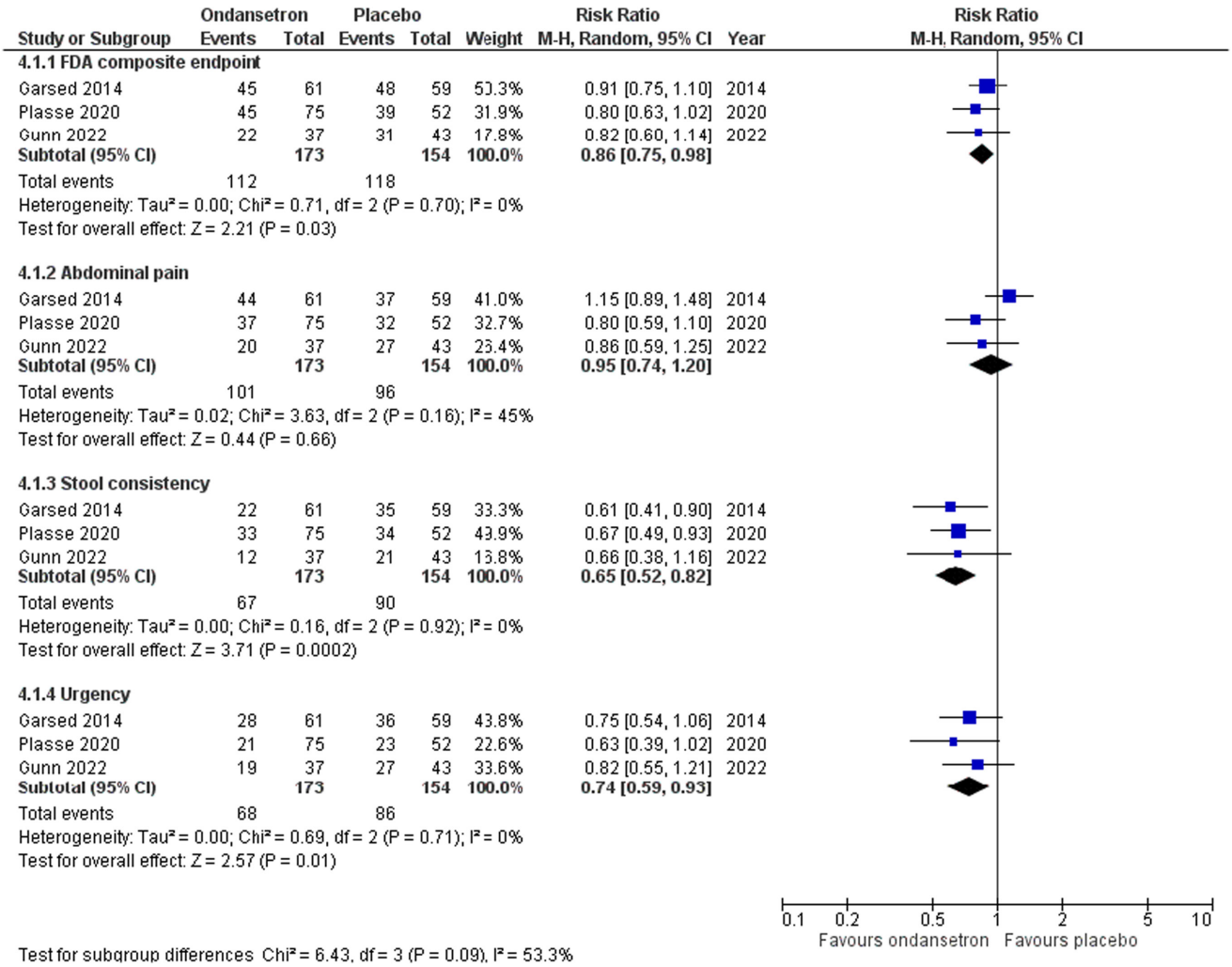


FIGURE 4 Forest plot of randomised, placebo-controlled trials of ondansetron in the treatment of IBS with diarrhoea. Events are patients failing to meet either the FDA composite endpoint, the individual components of the composite endpoint (abdominal pain, loose stools) or urgency.

attending outpatients with severe IBS-D symptoms, having loose stools most day with urgency and recurrent abdominal pain. The effect of ondansetron on stool form was rapid, being seen in the first week with an improvement in stool consistency and reduction in the number of days with loose stool. Thus, 51.4% were stool consistency responders on ondansetron at week 1, compared with 16.3% on placebo. It is worth noting that both in this trial and our previous one,[12] the placebo effect was much less for stool

consistency than abdominal pain, for which it was substantial. The effect on stool consistency was maximal in week 1 and persisted for 12 weeks. Stool consistency relapsed promptly on discontinuing ondansetron and was back to baseline levels within 1–2 weeks, repeating the pattern seen in our previous trial.[12] Interpretation is complicated in one in five patients who took loperamide as rescue medication. This was greater in the placebo group, which would have tended to minimise treatment differences. We found the abdominal pain response was rapid for both active drug and placebo, but it appears from this, and other studies,[13] that ondansetron does not add to this effect. Likewise, currently licensed drugs for IBS-D, such as eluxadoline, while improving bowel habit do not seem to provide much benefit over placebo for abdominal pain.[25] A recent meta-analysis of 17 placebo-controlled trials in IBS-D showed a much higher placebo response (40.2%) for abdominal pain than stool response (16.2%), thus, requiring much larger numbers to show significant effects for pain compared with stool response in IBS-D.[26] Despite this apparent lack of effect on pain, in our previous cross-over study patients were more than four times as likely to prefer ondansetron to placebo,[12] suggesting that patient preference puts control of urgency and bowel frequency as more important than control of pain.

Our trial differed from most IBS trials in mimicking clinical practice and using dose titration to optimise drug effect. Most patients took one or two 4 mg tablets daily but there has been a wide range of final doses in our trials and there is a subgroup who are very sensitive to the drug,[12,27] who would develop constipation if given a standard 4 mg o.d. dose. Only one patient out of 33 receiving ondansetron in the current trial developed severe constipation, paralleling our pilot study when constipation was reported by just 9%,[12] compared with 33% with fixed-dose alosetron,[28] and more recently 13% with delayed-release fixed dose ondansetron.[13] We suggest that future trials should also use this method, as it avoids early dropout due to unacceptable constipation.

A major limitation of our trial was the failure to achieve the planned numbers. This was in part due to the COVID-19 pandemic and partly due to the widespread introduction of faecal calprotectin screening, which markedly reduced the referral of IBS-D patients to exclude inflammatory bowel disease.[29,30] The more restrictive nature of the Rome IV criteria also meant that many patients who were felt to have IBS by a physician did not meet the minimum pain threshold required, suggesting their use may hamper recruitment to clinical trials. There was also a slight imbalance in randomisation between groups, even though minimisation was used. Minimisation according to the 18 sites and whether the patients chose to participate in mechanistic studies meant there were a possible 72 combinations of stratifiers. With only 80 patients randomised, however, imbalance is still possible. Our use of an adapted method to study transit may have exaggerated the effect of ondansetron on WGTT. The current study, on its own, as well as the two previous trials, lacked power to demonstrate the efficacy of ondansetron using the current FDA-recommended composite endpoint, although it showed a clear effect on stool consistency, transit time and IBS-SSS. However, when combined with the two other studies our meta-analysis suggests ondansetron meets efficacy criteria according to FDA-recommended endpoints. Nevertheless, the trials are somewhat heterogeneous in terms of their design, with varying durations of treatment, setting (two being conducted in the United Kingdom and one in the United States), and drug used (two using titrated generic ondansetron and one using a bimodal release formulation). The fact that efficacy for the FDA composite endpoints was observed in the meta-analysis, but not in any of the individual trials, probably relates to there being more patients in the meta-analysis, so the power to detect a significant difference over placebo is increased, and because the more stringent combined endpoint tends to reduce the placebo response rate. This is supported by a recent meta-analysis of response rates for FDA endpoints in trials of licensed drugs for IBS with diarrhoea or IBS with constipation, in which the placebo response rate for the FDA composite endpoint was 16.2%, compared with 33.9% for abdominal pain alone or 24.4% for stool consistency alone.[26]

Recent studies have emphasised that bile acid diarrhoea may account for up to 25% of patients with IBS-D, but our careful screening ensured that none of our patients' values for concentration of total bile acids were above the mean reported by Peleman and colleagues.[31] Interestingly, we did not find any correlation between anxiety and pain, urgency, bowel frequency or stool consistency in this highly selected group of patients but did find a correlation between abdominal pain and stool frequency with depression as others have recently reported.[32]

The related 5-HT_3RA, alosetron, which like ondansetron improves urgency,[33] has been shown in a barostat study to increase rectal compliance.[34] Ondansetron has been shown to reduce colonic tonic response to feeding,[35] but its effect on sensation remains unclear.[36] Our barostat analysis was underpowered, so the findings should also be interpreted with caution. Nevertheless, ondansetron reduced the sensation of urgency during rapid phasic distension significantly. Although there was a tendency for ondansetron to be associated with higher threshold volumes to cause urgency this was not significant and the pressure at half maximum volume did not differ from placebo, suggesting that ondansetron is acting on the sensory pathway rather than increasing compliance, as was reported for alosetron.[34] This idea is supported by animal and human studies demonstrating that ondansetron can inhibit 5-HT_3-mediated descending facilitation of nociceptive pathways,[37] as well as acting on central interoceptive circuitry.[38]

This study was ended prematurely because of a combination of slow recruitment and the COVID-19 pandemic. Recruitment of patients with IBS-D in secondary care had not been a problem in previous trials,[12,39] so the current failure is most likely due to changes in referral practice, with screening of patients with diarrhoea in primary care using faecal calprotectin markedly reducing the numbers of IBS-D patients referred to secondary care.[30] This means that most patients are now being managed in primary care so it will be important to perform a larger more definitive trial in this setting to confirm that this is an effective way of ameliorating symptoms in this very large patient group with a persistent unmet need.

Current alternatives to ondansetron include loperamide and the recently introduced eluxadoline. There are only a few very small historical trials of loperamide in patients with IBS-D, which show its effectiveness in controlling diarrhoea, but not pain.[6,7] Anecdotally, most patients have already tried loperamide and often report dissatisfaction because of constipation, bloating and discomfort. Although 45% of patients treated with titrated ondansetron experienced some constipation in this trial, in most cases it was mild, and only one patient discontinued treatment as a result. A randomised, placebo-controlled trial comparing these two treatments would be valuable to confirm its superiority. Eluxadoline, a combined μ-opioid agonist and δ-opioid antagonist, has been shown to increase the proportion of responders from 5.7% on placebo to 11% to 14% in a dose–response study.[25] However, the main effect was on stool consistency with no obvious effect on pain. Unfortunately, this drug has been associated with acute pancreatitis and sphincter of Oddi dysfunction, which is an unacceptable side effect for most patients with IBS.

5 | CONCLUSIONS

Although this trial was underpowered, it does show that titrated ondansetron is well tolerated in IBS-D and significantly improves stool consistency compared with placebo. When data from this trial and two others were pooled in a meta-analysis, ondansetron appeared efficacious for the FDA composite endpoint, stool consistency and urgency. The meta-analysis tends to confirm the known efficacy of 5-HT_3RAs for IBS-D. However, although both alosetron and ramosetron are efficacious, and ramosetron has not been associated with ischaemic colitis, these drugs are unavailable outside of the United States and Japan respectively. Generic titrated ondansetron, therefore, is a widely available and inexpensive alternative. That said, it is unlicensed, and a drug's licence status may influence its prescription and reimbursement. Many patients with IBS-D have only mild or moderate pain and for them, control of diarrhoea would be sufficient to justify the use of ondansetron. We believe, therefore, further large pragmatic trials of this safe and inexpensive generic drug should be conducted to prove efficacy. If efficacious, it could be made available to the large group of patients who suffer from IBS-D, not only reducing patient symptoms, but also reducing healthcare costs of repeated unnecessary investigations.

AUTHOR CONTRIBUTIONS

David Gunn: Data curation (equal); investigation (equal); project administration (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Rabia Topan:** Data curation (supporting); investigation (supporting); project administration (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Lorna Barnard:** Data curation (supporting); investigation (supporting); project administration (equal); writing – original draft (supporting). **Ron Fried:** Data curation (supporting); investigation (supporting); project administration (supporting). **Ivana Holloway:** Formal analysis (equal); investigation (supporting); methodology (supporting); project administration (supporting); writing – original draft (equal). **Richard Brindle:** Data curation (supporting); formal analysis (supporting); investigation (supporting); methodology (supporting); project administration (supporting). **Maura Corsetti:** Investigation (supporting); methodology (supporting); project administration (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Mark Scott:** Conceptualization (supporting); funding acquisition (supporting); investigation (supporting); methodology (supporting); resources (supporting); supervision (supporting). **Adam Farmer:** Funding acquisition (supporting); investigation (supporting); writing – review and editing (supporting). **Kapil Kapur:** Investigation (supporting); writing – review and editing (supporting). **David Sanders:** Investigation (supporting); writing – review and editing (supporting). **Maria Eugenicos:** Investigation (supporting); writing – review and editing (supporting). **Nigel Trudgill:** Investigation (supporting); writing – review and editing (supporting). **Peter Whorwell:** Funding acquisition (supporting); investigation (supporting); writing – review and editing (supporting). **John McLaughlin:** Funding acquisition (supporting); investigation (supporting); writing – review and editing (supporting). **Ayesha Akbar:** Investigation (supporting); writing – review and editing (supporting). **Lesley Houghton:** Investigation (supporting); methodology (supporting); writing – review and editing (supporting). **Phil G. Dinning:** Conceptualization (supporting); formal analysis (supporting); funding acquisition (supporting); investigation (supporting); methodology (supporting); writing – review and editing (supporting). **Qasim Aziz:** Conceptualization (supporting); funding acquisition (supporting); investigation (supporting); methodology (supporting); project administration (supporting); supervision (supporting); writing – review and editing (supporting). **Alexander C. Ford:** Conceptualization (supporting); formal analysis (supporting); funding acquisition (supporting); investigation (supporting); methodology (supporting); project administration (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Amanda J. Farrin:** Conceptualization (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); writing – original draft (equal); writing – review and editing (supporting). **Robin Spiller:** Conceptualization (equal); formal analysis (supporting); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); supervision (equal); writing – original draft (equal); writing – review and editing (lead).

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MacLennan (University of Aberdeen) and Karen Andrews (PPI representative). Data monitoring and Ethics Committee: Dr Charlie Murray, DMEC Chair (Royal Free London NHS Foundation Trust), Dr James Turvill (York Teaching Hospitals NHS Foundation Trust) and Natalie Rowland (Birmingham Clinical Trials Unit). Patient and Public Involvement: Karen Andrews and Peter Rutherford.

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CONFLICT OF INTEREST STATEMENT

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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