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RESEARCH LETTER

Belief of Allocated Treatment and Symptom Response to Amitriptyline in Irritable Bowel Syndrome

TENDER, a randomized controlled trial (RCT) of nortriptyline, a tricyclic antidepressant (TCA), in functional dyspepsia (FD), reported no benefit of active drug over placebo.[1] This is in contrast to previous RCTs in this field[2,3] and meta-analyses,[4,5] which suggest TCAs are efficacious for FD. Participants' belief of whether they received active treatment appeared to exert a stronger effect on symptom improvement than actual treatment allocation, suggesting expectancy bias. Expectations of benefit have also been reported as potentially important in irritable bowel syndrome (IBS).[6] We examined this issue in the largest RCT of a TCA in IBS to date,[7–9] according to dichotomous outcome measures, as per TENDER.

We conducted an exploratory post hoc analysis of ATLANTIS (Clinical trial registration: ISRCTN48075063), a double-blind RCT of 6 months of treatment with low-dose amitriptyline for IBS, titrated from 10 mg to 30 mg once daily, vs placebo in primary care in England. An exit poll was undertaken, asking all participants which treatment they believed they had received either at completion of treatment at 6-month follow-up or, for those withdrawing before 6-month follow-up, at the point of treatment discontinuation.

Analyses were conducted on the trial's key secondary outcome, subjective global assessment (SGA) of relief of IBS symptoms, and the exploratory outcome, a ≥30% improvement in abdominal pain from baseline, at 6 months, as these were dichotomous outcomes. We compared rates of symptom response in each trial arm according to actual treatment allocation and belief as to whether amitriptyline or placebo was received.

Analyses were performed in all participants completing 6 months of treatment and answering the exit poll. All statistical testing used 2-sided 5% significance levels and was performed in SAS, version 9.4. We analyzed both outcomes using logistic regression with fixed effects for true values of minimization variables, Irritable Bowel Syndrome Symptom Severity Scale score at baseline (for a ≥30% improvement in abdominal pain from baseline only), belief of treatment received (amitriptyline or placebo), actual treatment allocation, and belief of treatment × actual treatment allocation interaction. We imputed missing outcomes data (ie, SGA of relief of IBS symptoms or a ≥30% improvement in abdominal pain) via multiple imputation, as described previously.[7] We conducted a sensitivity analysis including participants answering the exit poll question at the point of treatment discontinuation for those withdrawing before 6 months.

The P value for the interaction term was used to assess for differential treatment effectiveness across groups (ie, a significant P value suggests the intervention is more or less effective according to actual treatment allocation and belief as to which treatment was received). Simple effects, together with 95% confidence intervals (CIs) and P values, of the adjusted odds ratio (OR) summarized treatment effect within each category (actual allocation to amitriptyline or placebo vs participant belief as to which they received). There was no adjustment for multiple testing.

Of 338 participants completing 6 months of treatment, 334 answering the exit poll question were included. Among participants allocated to amitriptyline, symptom response rates for both SGA of IBS symptoms (OR, 7.83; 95% CI, 3.54–17.3; $P < .0001$) and a ≥30% improvement in abdominal pain (OR, 3.30; 95% CI, 1.57–6.95; $P = .0016$) were significantly higher in those believing they received amitriptyline, compared with those believing they received placebo (Figure 1). Similarly, among those allocated to placebo, symptom response rates for both SGA of IBS symptoms (OR, 12.3; 95% CI, 5.56–27.3; $P < .0001$) and a ≥30% improvement in abdominal pain (OR, 2.15; 95% CI, 1.10–4.19; $P = .025$) were significantly higher in those believing they received amitriptyline, compared with those believing they received placebo. These results differ from the main trial,[7,8] where response rates were significantly higher with amitriptyline for both outcomes, because this is a report from a subset of participants completing 6 months of treatment and answering the exit poll question, and the analysis was adjusted for belief of treatment.

Among participants believing they received amitriptyline, there was no significant difference in symptom response rates, irrespective of allocation to amitriptyline or placebo, for SGA of IBS symptoms (OR, 1.02; 95% CI, 0.48–2.16; $P = .96$), although there was for a ≥30% improvement in abdominal pain (OR, 1.87; 95% CI, 1.01–3.48; $P = .046$) (Figure 1). There were no significant

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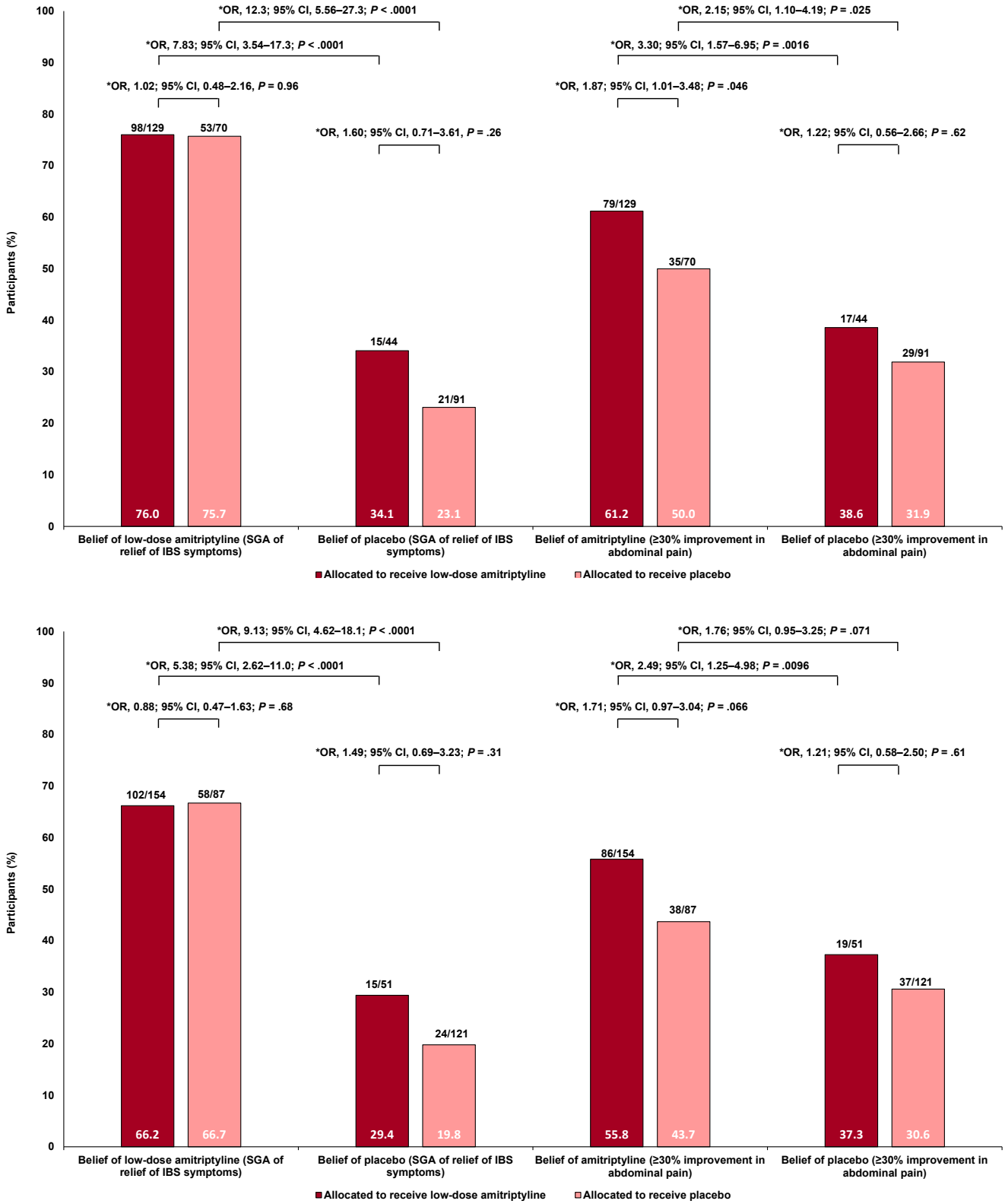

Figure 1. Subjective global assessment (SGA) of relief of irritable bowel syndrome (IBS) symptoms or a ≥30% improvement in abdominal pain among 334 ATLANTIS participants completing 6 months of treatment and answering the exit poll question, according to actual treatment allocation and belief as to which treatment was received. *All odds ratios (ORs) estimated using logistic regression with fixed effects for true values of minimization variables, Irritable Bowel Syndrome Symptom Severity Scale score at baseline (for a ≥30% improvement in abdominal pain from baseline only), belief of treatment received (amitriptyline or placebo), actual treatment allocation, and belief of treatment × actual treatment allocation interaction. CI, confidence interval.

differences in symptom response rates for either SGA of IBS symptoms (OR, 1.60; 95% CI, 0.71–3.61; $P = .26$) or a ≥30% improvement in abdominal pain (OR, 1.22; 95% CI, 0.56–2.66; $P = .62$) among participants believing they received placebo irrespective of allocation to low-dose amitriptyline or placebo.

Similar results were obtained in the sensitivity analysis of 413 participants, including 79 people discontinuing treatment prior to 6 months but answering the exit poll question at the time of treatment cessation (Supplementary Figure 1).

Our findings resonate with those from the TENDER trial, although based on a larger number of participants. In TENDER, response rates, according to a ≥30% decrease in mean daily FD composite symptom scores in ≥50% of weeks 3 to 12, were higher among those allocated to nortriptyline believing they received nortriptyline (72%), compared with those believing they had received placebo (0%), and among those receiving placebo believing they had received nortriptyline (85%), compared with those believing they had received placebo (50%). Belief about assigned treatment, and possible expectation of benefit arising from it, appears important in RCTs in both FD and IBS.

However, it is important to point out that, in both trials, belief of treatment was measured during an exit poll at the end of the RCT. At this point, although still blinded, participants would have come to their own conclusions as to whether their symptoms had improved, which will have influenced their belief of whether they received active treatment. In addition, if the active treatment is more effective than placebo, one would expect belief of treatment to be highly correlated with actual treatment received. Hence, belief of treatment received may be a proxy for the observed outcome of treatment response, rather than an independent predictor of it. ATLANTIS had a nested qualitative study exploring participants' perspectives around treatment beliefs within a blinded trial,[10] which, when analyzed, should further our understanding of these effects.

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ATLANTIS TRIALISTS

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2026.06.015.

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Conflicts of interest

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