Letter

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Letter: placebo run-in for IBS clinical trials—is it useful?

Dear Editors,

We read with interest the paper by Hamatani and Fukudo on the clinical efficacy of the 5-HT4 agonist minesapride in patients with Rome IV irritable bowel syndrome with constipation (IBS-C).[1] The authors applied a run-in period, during which placebo was administered. They followed a similar approach in another recently published trial on minesapride in Rome III IBS-C patients.[2]

While a run-in period is generally customary in all IBS trials, the use of a placebo in this run-in period is neither frequent, nor recommended by the Rome IV consensus on trial design.[3] The authors referred to a systematic review by Pitz et al[4] from 2005 stating "a placebo run-in reduces the placebo response". However, the Pitz paper does not mention the use of placebo in the run-in period specifically. Hamatani and Fukudo even point out that the observed placebo rates were comparable to studies without a run-in period, and it was in fact too high to evaluate efficacy endpoints according to the FDA definition.

The rationale behind using a placebo in the run-in period is to eliminate patients who respond to placebo and, therefore, decrease placebo response rates after randomisation. However, the Rome IV trial design consensus paper[3] references a study that indicates that response selection should not be used when the intention is to determine how best to treat a patient initially, as opposed to randomised withdrawal studies (while the intention is to study withdrawal from an active treatment).[5]

Examining the previous pharmacological trials literature in adult patients with IBS, five trials included a placebo run-in period (Table 1). The median placebo response rate in these trials was 34%, which is in line with placebo response rates observed in previous studies.[6]

In addition, a placebo run-in creates a selection bias and a discrepancy between the trial population and the clinical patient population. Indeed, 55% of the screened population dropped out during the placebo run-in in the current trial[1] and 38% in a similar trial recently published.[2]

Studies in other conditions, such as major depression,[7] have shown that there is no association between a placebo run-in period and the magnitude of the placebo response. This implies that the rationale behind a placebo run-in, which is to decrease placebo response rates and therefore increase the likelihood of demonstrating the efficacy of pharmacological treatment, is not supported by currently available evidence. In addition, these studies point to the unethical aspect of a placebo run-in, as they have an element of deception.

We therefore wonder whether the use of a placebo run-in for IBS trials is sufficiently justified as it otherwise introduces an element of heterogeneity which renders comparison of findings over different trials even more difficult.

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TABLE 1 Pharmacological trials in IBS with a placebo run-in (response rates according to the primary outcome for efficacy of the specific trial)

Study	Year of publication	Duration of placebo run-in	Placebo response rate	Intervention response rate	Therapeutic gain[a]
Hamatani et al[1]	2020	2 wks	13.6% (14/103)	15.9% (49/308)	2.3%
Fukudo et al[2]	2020	2 wks	51.4% (18/35)	77.9% (109/140)	26.5%
Clavé et al[8]	2011	2 wks	54.2% (96/177)	65.7% (117/178)	11.5%
Glende et al[9]	2002	2 wks	22.5% (36/160)	36.9% (58/157)	14.4%
Battaglia et al[10]	1998	2 wks	33.9% (56/165)	42.4% (68/160)	8.4%

[a]Difference in efficacy between active and placebo treatment.

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This article is linked to Hamatani et al papers. To view these articles, visit https://doi.org/10.1111/apt.15907 and https://doi.org/10.1111/apt.16047

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