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RESEARCH LETTERS

Efficacy of Drugs Acting on Histamine 1 Receptors in Irritable Bowel Syndrome: Systematic Review and Meta-Analysis

There is increasing evidence that a subset of patients with irritable bowel syndrome (IBS) have an organic explanation for their symptoms. Some patients exhibit evidence of mast cell activation,[1,2] although the cause is unknown. Recent evidence suggests this could relate to a break in oral tolerance to a dietary antigen after an acute enteric infection.[3] Degranulation of mast cells results in mucosal release of tryptase and histamine[1] and, hence, immune activation and visceral afferent neuron hyperexcitability. This has led to emerging interest in a potential role for histamine 1 receptor antagonists (H_1RAs) as a treatment for IBS. A recent randomized controlled trial (RCT) of ebastine, a nonsedating H_1RA, suggested a benefit of the drug in nonconstipated IBS,[4] but only for a composite endpoint of improvement in global symptoms and abdominal pain, not either endpoint separately. We, therefore, undertook a systematic review and meta-analysis to examine the efficacy of drugs acting on histamine 1 receptors in IBS.

We searched the medical literature using MEDLINE (January 1, 1946, to January 31, 2024), Embase and Embase Classic (January 1, 1947, to January 31, 2024) and the Cochrane central register of controlled trials for RCTs of drugs acting on histamine 1 receptors in IBS. We also searched conference proceedings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week) to identify potentially eligible trials published only in abstract form, as well as bibliographies of all obtained articles. The search is detailed in the Supplementary Materials.

There were no language restrictions. We evaluated abstracts identified by the search for appropriateness to the study question, and all potentially relevant papers were obtained and evaluated in detail. Two reviewers (M.K. and A.C.F.) assessed articles independently using predesigned eligibility forms, according to the a priori eligibility criteria (Supplementary Table 1). We resolved disagreements between investigators by consensus.

We assessed the efficacy of drugs acting on histamine 1 receptors in IBS compared with placebo, in terms of failure to respond to therapy, according to the proportion of patients failing to achieve an improvement in either global IBS symptoms or abdominal pain at trial completion. Other outcomes assessed included the total number of people experiencing any adverse event. All data were extracted independently by 2 reviewers (M.K. and A.C.F.) onto a Microsoft Excel spreadsheet (XP Professional Edition Microsoft Corp) as dichotomous outcomes (e.g., global IBS symptoms improved or not improved) using intention-to-treat analyses, with dropouts classed as treatment failures.

We pooled data using a random effects model to provide a more conservative estimate of the effect of drugs acting on histamine 1 receptors in IBS. We expressed the impact of drugs acting on histamine 1 receptors as a relative risk (RR) of global IBS symptoms or abdominal pain not improving compared with placebo with 95% confidence intervals (CIs), where, if the RR was less than 1 and the 95% CI did not cross 1, there was a significant benefit of drugs acting on histamine 1 receptors over placebo. We assessed heterogeneity using the I^2 statistic, which ranges between 0% and 100%. Values of 25% to 49% are considered low, 50% to 74% moderate, and $\geq$75% high heterogeneity.[5]

The search identified 225 citations. Four RCTs were eligible for inclusion, containing 433 patients.[4,6–8] Two trials used ebastine,[4,6] and 2 used ketotifen.[7,8] Detailed trial characteristics are provided in Supplementary Table 2. There were 217 patients receiving active treatment. All 4 RCTs reported global symptom data, and 2 trials reported abdominal pain data.[4,6] When data for global IBS symptoms were pooled, there was no statistical heterogeneity (I^2 = 0%), and drugs acting on histamine 1 receptors were significantly more effective than placebo (RR of global IBS symptoms not improving, 0.88; 95% CI, 0.82–0.95) (Figure 1). This effect was observed for both ebastine (RR, 0.90; 95% CI, 0.82–0.98) and ketotifen (RR, 0.84; 95% CI, 0.74–0.96). When data for abdominal pain from the 2 trials of ebastine were pooled, there was a significant effect of the active drug (RR of abdominal pain not improving, 0.82; 95% CI, 0.71–0.95; I^2 = 0%). Adverse events were reported by all 4 trials and were no more common with the active drug than with placebo (RR, 1.26; 95% CI, 0.80–1.99).

This meta-analysis summarizes all evidence, to date, for the use of drugs acting on histamine 1 receptors in IBS. There appear to be benefits for these types of drugs for both global symptoms and abdominal pain. Repurposing drugs that are cheap and widely available is an attractive treatment strategy for IBS,[9] particularly in patients with IBS with diarrhea or mixed bowel habits where there are few or no licensed therapies.[10] However, there are some limitations. Three trials emanated from a single group of researchers, meaning that the efficacy of these drugs in other centers and countries is uncertain. It is important to point out that ketotifen has mixed effects because it is not only a H_1RA but also a mast cell stabilizer. Hence, it also prevents leukotriene and cytokine release from mast cells. Additionally, it inhibits phosphodiesterase. Ketotifen is lipophilic, crossing the blood-brain barrier, meaning drowsiness can be a side effect and that an impact on IBS symptoms due to central effects cannot be excluded. Finally, the effect on both global

Abbreviations used in this paper: CI, confidence interval; H_1RA, histamine 1 receptor antagonist; IBS, irritable bowel syndrome; RCT, randomized controlled trial; RR, relative risk.

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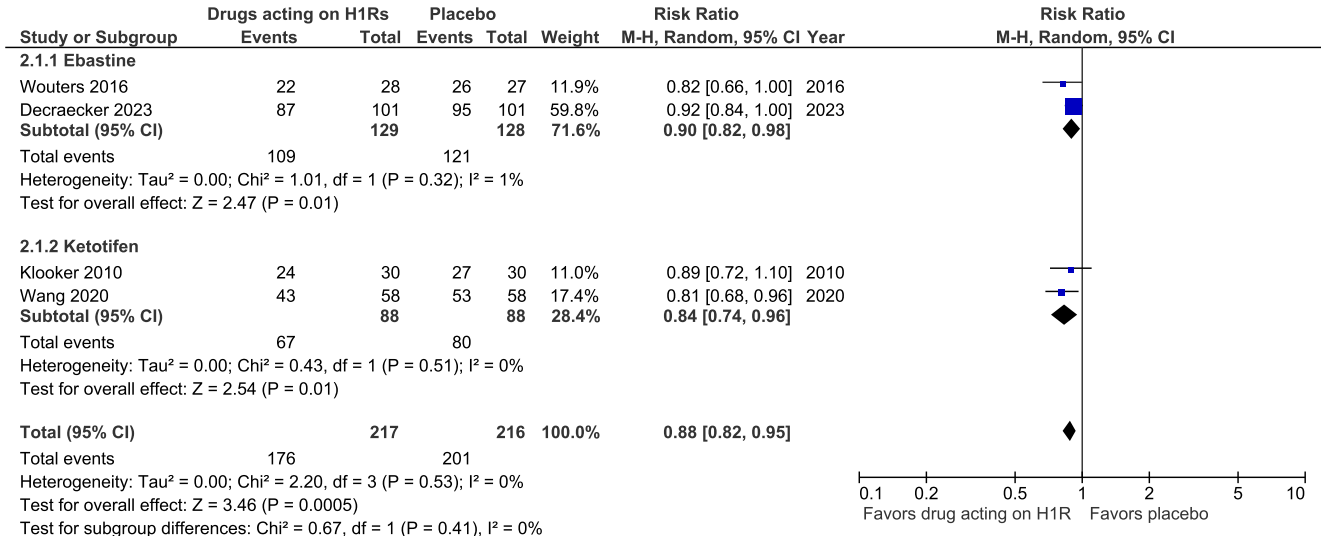

Figure 1. Forest plot of RCTs of drugs acting on histamine 1 receptors in terms of effect on global symptoms in IBS. M-H, Mantel–Haenszel.

symptoms and abdominal pain was modest, and only 2 trials reported data for the latter endpoint.

Some of these RCTs confirmed the mechanistic effects of these drugs, in terms of improvement in visceral hypersensitivity on barostat testing[6,7] and a reduction in mucosal mast cell counts and the proportion of degranulated mast cells.[8] However, none examined the ability of these mechanisms to predict response. Both drugs have potent antihistaminergic effects. Histamine may, therefore, be a therapeutic target in IBS. Interestingly, other drugs that have beneficial effects in IBS, such as tricyclic and tetracyclic antidepressants, also act as H_1RAs. Further trials of drugs acting on histamine 1 receptors are, therefore, required. Our literature search identified one protocol for an RCT of fexofenadine and another of loratadine. There is also a trial of ebastine vs mebeverine underway.

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Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2024.03.014.

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Conflicts of interest
The authors disclose no conflicts.

Search Strategy

1 IBS.mp.

2 irritable colon.mp.

3 spastic colon.mp.

4 irritable bowel syndrome.mp. or Colonic Diseases, Functional/ or Irritable Bowel Syndrome/

5 (functional adj5 bowel).mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw, tn, dm, mf, dv, kf, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]

6 Acrivastine.mp. [mp=ti, ot, ab, tx, kw, ct, sh, fx, hw, tn, dm, mf, dv, kf, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx]

7 Astemizole.mp. [mp=ti, ot, ab, tx, kw, ct, sh, fx, hw, tn, dm, mf, dv, kf, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx]

8 Bepotastine.mp. [mp=ti, ot, ab, tx, kw, ct, sh, fx, hw, tn, dm, mf, dv, kf, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx]

9 Bilastine.mp. [mp=ti, ot, ab, tx, kw, ct, sh, fx, hw, tn, dm, mf, dv, kf, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx]

10 Cetirizine.mp. [mp=ti, ot, ab, tx, kw, ct, sh, fx, hw, tn, dm, mf, dv, kf, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx]

11 Desloratadine.mp. [mp=ti, ot, ab, tx, kw, ct, sh, fx, hw, tn, dm, mf, dv, kf, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx]

12 Ebastine.mp. [mp=ti, ot, ab, tx, kw, ct, sh, fx, hw, tn, dm, mf, dv, kf, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx]

13 Fexofenadine.mp. [mp=ti, ot, ab, tx, kw, ct, sh, fx, hw, tn, dm, mf, dv, kf, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx]

14 Ketotifen.mp. [mp=ti, ot, ab, tx, kw, ct, sh, fx, hw, tn, dm, mf, dv, kf, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx]

15 Levocetirizine.mp. [mp=ti, ot, ab, tx, kw, ct, sh, fx, hw, tn, dm, mf, dv, kf, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx]

16 Loratadine.mp. [mp=ti, ot, ab, tx, kw, ct, sh, fx, hw, tn, dm, mf, dv, kf, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx]

17 Mizolastine.mp. [mp=ti, ot, ab, tx, kw, ct, sh, fx, hw, tn, dm, mf, dv, kf, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx]

18 Quifenadine.mp. [mp=ti, ot, ab, tx, kw, ct, sh, fx, hw, tn, dm, mf, dv, kf, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx]

19 Rupatadine.mp. [mp=ti, ot, ab, tx, kw, ct, sh, fx, hw, tn, dm, mf, dv, kf, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx]

20 Terfenadine.mp. [mp=ti, ot, ab, tx, kw, ct, sh, fx, hw, tn, dm, mf, dv, kf, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx

21 1 or 2 or 3 or 4 or 5

22 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (44623)

23 21 and 22

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e3. Wang J, et al. Eur J Gastroenterol Hepatol 2020;32:706–712.

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Supplementary Table 1. Eligibility Criteria

RCTs
Adults (aged ≥18 years)
Diagnosis of IBS based on either a clinician's opinion or meeting specific diagnostic criteria,[a] supplemented by negative investigation findings where trials deemed this necessary
Compared drugs acting on histamine 1 receptors with placebo
Minimum duration of therapy of 4 weeks
Dichotomous assessment of response to therapy in terms of effect on either global IBS symptoms or abdominal pain after treatment[b]

[a]Manning criteria; Kruis score; Rome I, II, III, or IV criteria.
[b]Preferably patient reported, but if this was not available then as assessed by a physician or questionnaire data.

Supplementary Table 2. Characteristics of RCTs of Drugs Acting on Histamine 1 Receptors vs Placebo in IBS

Study	Country and setting	Diagnostic criteria used for IBS and percentage with each subtype	Endpoint(s) used	Sample size (% female)	Drug used	Duration of therapy
Klooker et al (2010)[e1]	The Netherlands, tertiary care	Rome II 15% IBS-C, 37% IBS-D, 48% IBS-M	Considerable relief of global IBS symptoms	60 (72)	Ketotifen 2 mg twice daily for 2 weeks, titrated to 4 mg twice daily for 2 weeks, then 6 mg twice daily for 4 weeks	8 weeks
Wouters et al (2016)[e2]	Belgium, tertiary care	Rome III 20% IBS-C, 47% IBS-D, 17% IBS-M	Considerable relief of global IBS symptoms for ≥6 of 12 weeks Considerable relief of abdominal pain for ≥6 of 12 weeks	55 (62)	Ebastine 20 mg once daily	12 weeks
Wang et al (2020)[e3]	China, tertiary care	Rome IV 100% IBS-D	Improvement in global IBS symptoms by ≥75%	116 (53)	Ketotifen 1 mg twice daily	8 weeks
DeCraecker et al (2024)[e4]	Belgium and the Netherlands, secondary and tertiary care	Rome III 66% IBS-D, 17% IBS-M, 17% IBS-U	Considerable relief of global IBS symptoms for ≥6 of 12 weeks ≥30% decrease in abdominal pain for ≥6 of 12 weeks	202 (68)	Ebastine 20 mg once daily	12 weeks

IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, mixed-type IBS; IBS-U, IBS unclassified.