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TITLE PAGE

Title: Relative Efficacy of Eluxadoline in Irritable Bowel Syndrome.

Authors: Christopher J. Black[1, 2], Lesley A. Houghton[, 2], Alexander C. Ford[1, 2].

[1]Leeds Gastroenterology Institute, St. James's University Hospital, Leeds, UK.

[2]Leeds Institute of Biomedical and Clinical Sciences, University of Leeds, Leeds, UK.

Correspondence: Professor Alexander C. Ford

Leeds Gastroenterology Institute

Room 125

4th Floor

Bexley Wing

St. James's University Hospital

Beckett Street

Leeds

United Kingdom

LS9 7TF

Email: alexf12399@yahoo.com

Telephone: +447887603665

Facsimile: +441132429722

Abbreviations:

5-HT_3	5-hydroxtryptamine-3
BSFS	Bristol stool form scale
FDA	Food and Drug Administration
IBS-D	irritable bowel syndrome with diarrhea
RCT	randomized controlled trial
WAP	worst abdominal pain

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ABSTRACT

Objectives: To update a network meta-analysis of randomized trials of drugs for irritable bowel syndrome with diarrhea (IBS-D) or mixed stool pattern (IBS-M) with new data from an eluxadoline trial. When published previously in abstract form, this trial used more stringent endpoints than the Food and Drug Administration (FDA) recommend; we may therefore have underestimated eluxadoline's efficacy.

Methods: We updated our network meta-analysis, reporting efficacy according to two endpoints.

Results: Eluxadoline's ranking was not improved; it ranked third for the FDA-recommended composite endpoint and sixth for abdominal pain.

Conclusions: 5-hydroxytryptamine-3-receptor antagonists, which have limited availability, were ranked highest for IBS-D and IBS-M.

INTRODUCTION

We recently published a systematic review and network meta-analysis of randomized controlled trials (RCTs) examining the relative efficacy of licensed drugs for irritable bowel syndrome with diarrhea (IBS-D) and mixed stool pattern IBS, (1) including alosetron, eluxadoline, ramosetron, and rifaximin. We incorporated data from the recent paper by Brenner *et al.*, (2) reporting a placebo-controlled phase 4 study of eluxadoline 100mg b.i.d. in patients with IBS-D who had inadequate symptom response to loperamide, based on the published abstract of this trial, (3) in our analysis. In this network meta-analysis, the 5-hydroxytryptamine (5-HT)-3 receptor antagonists alosetron 1mg b.i.d. and ramosetron 2.5mcg o.d. were ranked first and second for efficacy using a composite endpoint to define treatment response, as recommended by the Food and Drug Administration (FDA), with eluxadoline ranked third. In terms of effect on abdominal pain, ramosetron 2.5mcg o.d., ramosetron 5mcg o.d., and alosetron 1mg b.i.d. were ranked first, second, and third respectively, with eluxadoline fifth.

The analyses in the published abstract of the trial by Brenner *et al.* were based on a composite endpoint of a ≥40% improvement in worst abdominal pain (WAP) on ≥50% of days and a daily Bristol stool form scale (BSFS) score of <5 as the primary outcome, and also reported the effect on abdominal pain using a ≥40% improvement in WAP on ≥50% of days. (3) These are more stringent endpoints than those required by the FDA, and may have led to an underestimation of the relative efficacy of eluxadoline in our network meta-analysis. In the fully published article, Brenner and colleagues also report a *post hoc* analysis of efficacy, using a composite endpoint of a ≥30% improvement in WAP on ≥50% of days and a daily BSFS score of <5. This is in line with FDA recommendations, and is identical to the endpoint used in the other RCTs included in our network. They also reported effect on abdominal pain using a ≥30% improvement in WAP on ≥50% of days.

METHODS

We re-ran the network meta-analysis using these new data. The methodology is as in our previous network meta-analysis. (1) Briefly, we performed a network meta-analysis using the frequentist model, with the statistical package "netmeta" (version 0.9-0, https://cran.r-project.org/web/packages/netmeta/index.html) in R (version 3.4.2), to explore indirect treatment comparisons of efficacy of each medication. We used a relative risk of failure to achieve the FDA-recommended composite endpoint for efficacy in treatment trials in IBS, as well as failure to achieve improvement in abdominal pain. We ranked treatments according to their P-score, which is a value between 0 and 1. P-scores are based solely on the point estimates and standard errors of the network estimates, and measure the extent of certainty that a treatment is better than another treatment, averaged over all competing treatments. We also included data from two 12-week trials of cilansetron, another 5-HT_3-receptor antagonist, (4, 5) which never reached the market, in order to examine whether the higher ranking of 5-HT_3-receptor antagonists seen in our original network meta-analysis, (1) in terms of effect on abdominal pain, was consistent across different drugs within this class.

RESULTS

When data were pooled from 10 trials, recruiting 5517 patients, according to failure to achieve the FDA-recommended endpoint to define treatment response, there was no global statistical heterogeneity ($I^2 = 0\%$). The findings were similar; all drugs were significantly more effective than placebo, and alosetron 1mg b.i.d. and ramosetron 2.5mcg o.d. were ranked first and second, respectively (P-scores 0.97 and 0.79) (Figure 1). After indirect comparison of active treatments, significant differences were seen with alosetron 1mg b.i.d. compared with all other treatments, except ramosetron 2.5mcg o.d. (Table 1).

When data were pooled from 19 RCTs, recruiting 10,527 patients, according to failure to achieve an abdominal pain response, again, there was no global statistical heterogeneity (I^2 = 0%). Ramosetron 2.5mcg and 5mcg o.d., cilansetron 2mg t.i.d., alosetron 1mg b.i.d., and eluxadoline 100mg b.i.d. were all significantly more effective than placebo. When findings were compared to our original meta-analysis, ramosetron 2.5mcg o.d. was still the top-ranked treatment (P-score 0.91), with cilansetron 2mg t.i.d. now ranked second (P-score 0.88). Eluxadoline 100mg b.i.d. was ranked sixth. On indirect comparison of active treatments, significant differences were seen with ramosetron 2.5mcg o.d. compared with eluxadoline 75mg b.i.d., eluxadoline 100mg b.i.d., and rifaximin 550mg t.i.d. Other significant differences are detailed in Table 2.

DISCUSSION

Updating the network meta-analysis with the fully published data from Brenner *et al.* did not improve the ranking of eluxadoline; (2) the drug was still ranked third for the FDA-recommended composite endpoint for efficacy, and was ranked sixth in terms of effect on abdominal pain. Moreover, for both endpoints studied, after indirect comparison of active treatments, some 5-HT_3-receptor antagonists were significantly better than either dose of eluxadoline. To some extent, these updated analyses seem to confirm our hypothesis with 5-HT_3-receptor antagonists, as a class, not only having the best overall rankings for each of the endpoints studied, but also out-performing both eluxadoline and rifaximin, irrespective of individual drug and dosage.

The FDA-recommended composite endpoint was identical in all included RCTs, so it is highly likely that the results we observed are robust, and that eluxadoline is less effective than alosetron 1mg b.i.d. However, it should be pointed out that in terms of the effect on

abdominal pain, several of the trials used more old-fashioned, and less stringent, endpoints than that used in the trials of eluxadoline, based on adequate relief of symptoms, although this was the accepted outcome measure at the time these RCTs were conducted. (6) Nevertheless, our findings suggest that the efficacy of eluxadoline in IBS is modest. Improving access to licensed 5-HT_3-receptor antagonists may produce benefit for a greater proportion of patients with IBS.

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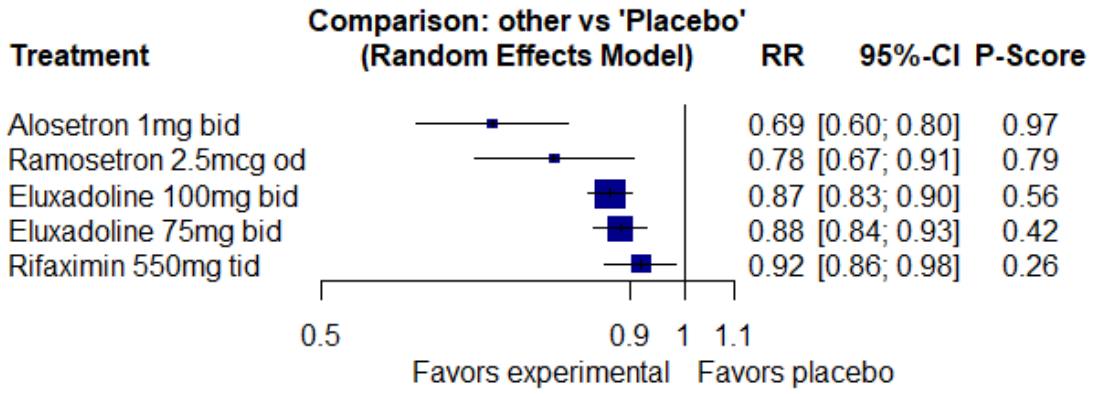
Figure 1. Forest Plot of the Indirect Evidence for Failure to Achieve the FDA-recommended Endpoint to Define Treatment Response.



Note: the P-score is the probability of each treatment being ranked first in the network meta-analysis, averaged across all competing treatments. A higher score equates to a greater probability of being ranked first.

RR: relative risk

Table 1. League Table for Failure to Achieve the FDA-recommended Endpoint to Define Treatment Response.

Alosetron 1mg bid					
0.89 (0.72; 1.10)	**Ramosetron 2.5mcg od**				
0.80 (0.69; 0.93)	0.90 (0.77; 1.05)	**Eluxadoline 100mg bid**			
0.78 (0.67; 0.91)	0.88 (0.75; 1.03)	0.98 (0.93; 1.04)	**Eluxadoline 75mg bid**		
0.75 (0.64; 0.88)	0.85 (0.72; 1.00)	0.94 (0.87; 1.02)	0.96 (0.89; 1.05)	**Rifaximin 550mg tid**	
0.69 (0.60; 0.80)	0.78 (0.67; 0.91)	0.87 (0.83; 0.90)	0.88 (0.84; 0.93)	0.92 (0.86; 0.98)	**Placebo**

Note: Relative risk with 95% CIs in parentheses. Comparisons, column versus row, should be read from left to right and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as first after the network meta-analysis of indirect effects.

Boxes shaded green denote a statistically significant difference.

Table 2. League Table for Failure to Achieve an Abdominal Pain Response.

Ramosetron 2.5mcg od								
0.98 (0.83; 1.15)	**Cilansetron 2mg tid**							
0.91 (0.78; 1.06)	0.93 (0.82; 1.06)	**Ramosetron 5mcg od**						
0.90 (0.78; 1.04)	0.92 (0.82; 1.03)	0.99 (0.89; 1.10)	**Alosetron 1mg bid**					
0.86 (0.67; 1.09)	0.88 (0.70; 1.10)	0.95 (0.76; 1.18)	0.95 (0.78; 1.17)	**Alosetron 0.5mg bid**				
0.83 (0.72; 0.97)	0.85 (0.76; 0.96)	0.92 (0.82; 1.03)	0.93 (0.84; 1.02)	0.97 (0.78; 1.21)	**Eluxadoline 100mg bid**			
0.79 (0.68; 0.93)	0.81 (0.71; 0.92)	0.87 (0.78; 0.98)	0.88 (0.79; 0.98)	0.92 (0.74; 1.15)	0.95 (0.87; 1.03)	**Eluxadoline 75mg bid**		
0.78 (0.68; 0.91)	0.80 (0.71; 0.90)	0.86 (0.78; 0.96)	0.87 (0.80; 0.95)	0.91 (0.74; 1.13)	0.94 (0.85; 1.03)	0.99 (0.89; 1.10)	**Rifaximin 550mg tid**	
0.74 (0.65; 0.85)	0.76 (0.69; 0.84)	0.82 (0.75; 0.89)	0.83 (0.78; 0.88)	0.87 (0.71; 1.06)	0.89 (0.83; 0.96)	0.94 (0.86; 1.02)	0.95 (0.89; 1.01)	**Placebo**

Note: Relative risk with 95% CIs in parentheses. Comparisons, column versus row, should be read from left to right and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as first after the network meta-analysis of indirect effects.

Boxes shaded green denote a statistically significant difference.