

Meta-analysis of smooth muscle relaxants in the treatment of irritable bowel syndrome

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SUMMARY

Aim: To update previous overviews of placebo-controlled double-blind trials assessing the efficacy and tolerance of smooth muscle relaxants in irritable bowel syndrome.

Methods and trials: A total of 23 randomized clinical trials were selected for meta-analyses of their efficacy and tolerance. Six drugs were analysed: cimetropium bromide (five trials), hyoscine butyl bromide (three trials), mebeverine (five trials), otilium bromide (four trials), pinaverium bromide (two trials) and trimebutine (four trials). The total number of patients included was 1888, of which 945 received an active drug and 943 a placebo.

Results: The mean percentage of patients with global improvement was 38% in the placebo group ($n = 925$) and 56% in the myorelaxant group ($n = 927$), in favour of myorelaxants with a mean odds ratio of 2.13, $P < 0.001$ (95% CI: 1.77–2.58) and a mean risk difference of 22% $P < 0.001$ (95% CI: 13–32%). The percentage of patients with pain improvement was 41% in the placebo group ($n = 568$) and 53% in the myorelaxant group ($n = 567$): odds ratio 1.65, $P < 0.001$ (95% CI: 1.30–2.10) and risk difference 18%, $P < 0.001$ (95% CI: 7–28%). There was no significant difference for adverse events.

Conclusion: Myorelaxants are superior to placebo in the management of irritable bowel syndrome.

INTRODUCTION

In 1994 we published an overview of randomized clinical trials of smooth muscle relaxants in the treatment of patients with irritable bowel syndrome.¹ From this review it was concluded that, contrary to what had been previously stated, five drugs had proved their clinical efficacy without significant adverse reactions: cimetropium bromide, mebeverine, otilium bromide, pinaverium bromide and trimebutine.² In 2000, alosetron, which belongs to a new class of drugs (5-HT₃ receptor antagonists) was approved for the treatment of non-constipated female patients with irritable bowel syndrome due to its efficacy vs. placebo and vs. a

myorelaxant.^{3, 4} However, male and constipated female patients with irritable bowel syndrome still need effective treatment.

Recently, Jailwala *et al.* published a new systematic review of pharmacologic treatment of the irritable bowel syndrome.⁵ Several double-blind trials vs. placebo were missing despite the help of the Cochrane registry. Only 16 randomized trials have been selected for smooth muscle relaxants. Because exhaustiveness is mandatory for meta-analysis, we strongly recommend that the six randomized trials published in a non-English language (four French, one Italian and one German) should be included:^{6, 7} one for hyoscine, including 360 patients, the biggest sample size of their overview; two for mebeverine; one for otilium bromide; and two for pinaverium.^{8–13} We also recommend that sensitivity analysis using other double-blind trials vs. placebo, which were not included in the Jailwala *et al.* overview,

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should also be included at least in a sensitivity analysis.^{5, 14–19} Therefore, we update the meta-analysis of smooth muscle relaxants.

METHODS

Meta-analysis was conducted according to a predetermined protocol and followed the recommendations of Sacks *et al.*, but was not limited to English language randomized clinical trials.⁶ The details of these methods were given in the previous overview.¹ The specific aim was to update the previous meta-analysis, focusing on smooth muscle relaxants without significant adverse effects. MEDLINE and a manual search were combined. The key words 'colonic disease', 'functional', 'irritable bowel syndrome', and 'randomized trial' were used. General reviews, references from published randomized clinical trials, Current Contents and letters to pharmaceutical companies were also used, as well as a recent review of meta-analyses in the Journal Hepatogastroenterology.^{7, 20–22} The quality assessment of randomized trials was made by means of a scoring method including 14 items (range –2 to 14, mean 12).^{23, 24}

Randomized clinical trials had to fulfil the following criteria: published as an article; randomized; included double-blinding vs. placebo; included as least 51% of patients with irritable bowel syndrome in the total study population; carried out an analysis of a drug with potential myorelaxant properties; and used at least one clinical end-point among the following: global assessment of symptoms by the patient or physician, abdominal pain, constipation or abdominal distension. All these endpoints had to be assessed qualitatively or semi-quantitatively in order to be used.

A high fibre diet or fibre supplementation, when taken in all randomized groups, was not considered a source of exclusion. Randomized clinical trials which were published as abstracts or letters, had not been clearly randomized, had not been double-blind, had not used a placebo, had used a combination of drugs, had compared different treatments without control groups, or had used only quantitative end-points, were excluded. Randomized clinical trials which had analysed drugs with only a pharmacologic effect on motility, such as metoclopramide, domperidone or cisapride, were excluded; randomized clinical trials which had analysed hydrotryptamine receptor antagonists or octeotide, or drugs with central action (central nervous system action), were excluded. Randomized clinical trials which

had analysed dicyclomide bromide and peppermint oil were excluded because there had been significant adverse events in a previous meta-analysis.¹ When a high fibre diet or fibre supplementation had been given in only one arm, the trial was excluded. When a drug had been evaluated by only one randomized clinical trial, it was excluded. This meta-analysis was supported in part by SOLVAY pharmaceutical company, which manufactures mebeverine and pinaverium bromide.

Statistical methods

All analyses were performed according to the intention-to-treat method. No randomized patient was excluded. For all end-points, patients with truncated data were considered failures, whatever the cause. For each end-point the following strategy was used: (a) assessment of heterogeneity of results between the control groups; (b) assessment of drug efficacy according to the Peto *et al.* method;²⁵ and (c) assessment of drug efficacy according to the Der Simonian and Laird method.²⁶ When a significant difference was observed, sensitivity analyses were performed according to the type of drug, the treatment duration (less than 3 weeks, between 3 and 8 weeks, more than 8 weeks), the prevalence of constipated patients (less or more than 50%) and according to methodological quality (more or less than the median 9).

The main end-point was the percentage of patients with a global improvement in symptoms during the treatment period. The other end-points analysed were: the percentage of patients with abdominal pain improvement, constipation improvement, transit improvement, abdominal distention improvement; and the percentage of patients without adverse events.

RESULTS

Randomized clinical trials identified and selected

A total of 216 trials were identified (Table 1), 148 between 1959 and 1992 and 68 between 1993 and 1999. A total of 23 smooth muscle relaxant randomized clinical trials were selected for meta-analyses of their efficacy in treating irritable bowel syndrome. A total of six drugs were analysed: cimetropium bromide (five trials among four articles);^{27–30} hyoscine butyl bromide (three trials);^{8, 18, 19} mebeverine (five trials);^{9, 10, 31–33} otilium bromide (four trials);^{11, 17, 34, 35} pinaverium bromide (two trials);^{12, 13} and trimebutine (four trials).^{15–17, 36}

Table 1. Characteristics of trials included

First author	Year of publication	Drug	Number of patients active group	Number of patients placebo group	Treatment duration	Sex ratio female/male	Median age	Methodological score
Piai ²⁷	1987	Cimetropium 150 mg	15	15	12 weeks			20
Centonze ²⁸	1988	Cimetropium 150 mg	24	24	24 weeks	7/16 15/6	34 32	21
Passaretti ²⁹	1989	Cimetropium 150 mg	13	12	4 weeks	19/6	36	15
Passaretti ²⁹	1989	Cimetropium 150 mg	7	8	4 weeks	5/10	42	15
Dobrilla ³⁰	1990	Cimetropium 150 mg	35	35	12 weeks	23/12 24/11	45 45	21
Ritchie ¹⁸	1979	Hyoscine 40 mg	48	48	4 weeks	74/22	38	15
Nigam ¹⁹	1984	Hyoscine 40 mg	84	84	4 weeks	76/92	35	19
Schafer ⁸	1990	Hyoscine 30 mg	182	178	4 weeks	113/69 121/57	49 49	19
Connell ³¹	1965	Mebeverine 400 mg	22	22	12 weeks	13/7 12/8	40 40	21
Tasman-Jones ³²	1973	Mebeverine 400 mg	12	12	4 weeks	7/5 7/5	43 43	12
Berthelot ⁹	1981	Mebeverine 400 mg	36	33	8 weeks	74/37	56	16
Secco ¹⁰	1983	Mebeverine 405 mg	15	15	4 weeks	15/15	45	12
Kruis ³³	1986	Mebeverine 400 mg	40	40	16 weeks	23/17	43 41	17
Barbier ¹¹	1981	Otilonium 320 mg	36	36	2 weeks	27/9 27/9	55 55	15
Baldi ³⁴	1983	Otilonium 120 mg	15	15	4 weeks	9/6 10/5	42 41	15
Castiglione ³⁸	1991	Otilonium 120 mg	30	30	12 weeks			6
Battaglia ³⁵	1998	Otilonium 120 mg	160	165	15 weeks	111/49 114/51	47 48	20
Levy ¹²	1977	Pinaverium 150 mg	25	25	2 weeks	12/13 11/14	50 46	12
Delmont ¹³	1981	Pinaverium 150 mg	30	30	4 weeks	19/11 21/9	57 57	21
Luttecke ¹⁴	1978	Trimebutine 600 mg	40	40	3 days	21/18	45	17
Moshal ³⁶	1979	Trimebutine 600 mg	20	20	4 weeks	13/7 13/7	27 27	19
Luttecke ¹⁵	1980	Trimebutine 300 mg	26	26	3 days	25/19	47	12
Fielding ¹⁶	1980	Trimebutine 600 mg	30	30	24 weeks	17/7 23/6	26 26	13

The total number of patients included was 1888, of which 945 received an active drug and 943 a placebo. The largest trial included 360 patients, the smallest 15, with a mean of 77 patients per trial. Methodological scores ranged from 10 to 21.

Meta-analysis

Percentage of patients with improved global assessment (Figure 1). A total of 21 randomized clinical trials involving six different drugs were available for this end-point. The mean percentage of patients with global improvement was 38% in the placebo group ($n = 925$) and 56% in the myorelaxant group ($n = 927$). According to the Peto method, there was a significant difference in favour of myorelaxants, with a mean odds ratio of 2.13, $P < 0.001$ (95% CI: 1.77–2.58). According to the Der Simonian method, the risk difference was 22% $P < 0.001$ (95% CI: 13–32%).

The ranking of the six drugs according to their odds ratio was: trimebutine 3.45 (95% CI: 2.03–5.86), cimetropium 2.87 (95% CI: 1.61–5.13), otilonium

2.33 (95% CI: 1.60–3.40), pinaverium 2.15 (95% CI: 0.96–4.83), mebeverine 2.04 (95% CI: 1.15–3.63) and hyoscine 1.56 (95% CI: 1.14–2.15). The ranking according to risk difference was very similar: cimetropium 31% (95% CI: 15–47%), trimebutine 30% (95% CI: 13–47%), otilonium 21% (95% CI: 11–30%), pinaverium 16% (95% CI: 0–33%), mebeverine 16% (95% CI: 2–30%) and hyoscine 11% (95% CI: 3–20%). All differences were significant vs. placebos ($P < 0.05$), although without significant differences between drugs.

Meta-analyses which were stratified according to treatment duration, prevalence of constipation among patients, quality of trials, and randomized clinical trial design (parallel or crossover), showed similar results (data not shown).

Percentage of patients with pain improvement (Figure 2). A total of 11 randomizations involving six different drugs were available for this end-point. The mean percentage of patients with pain improvement was 41% in the placebo group ($n = 568$) and 53% in the myorelaxant group ($n = 567$). According to the Peto method, there

Global assessment

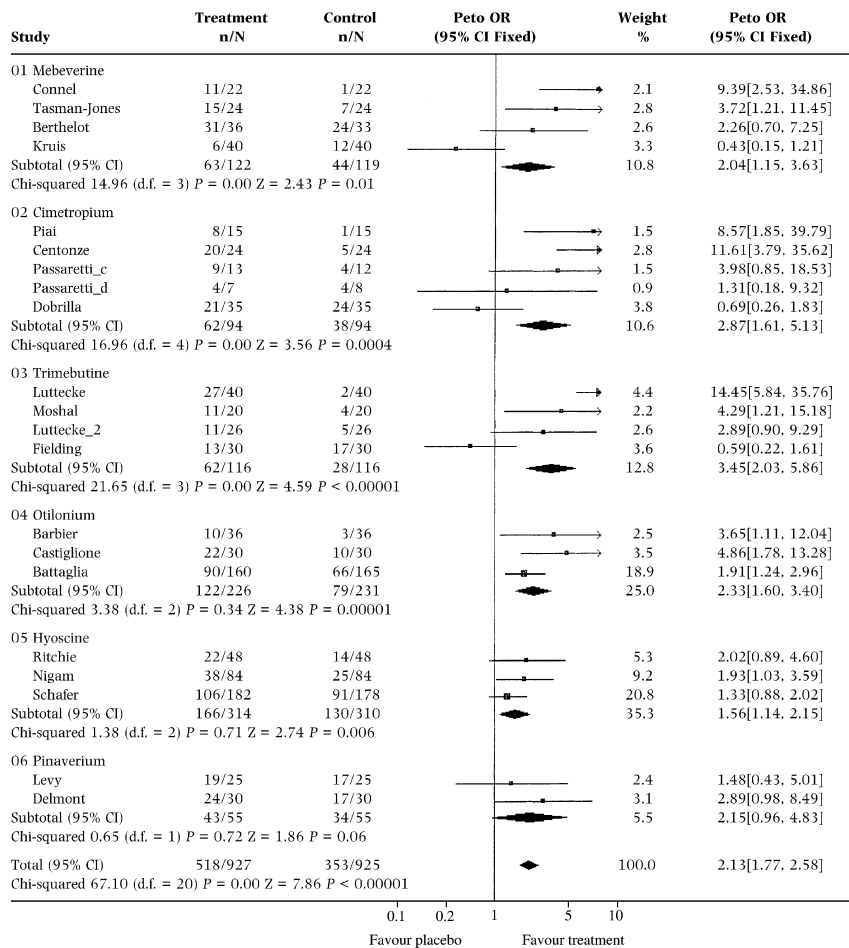


Figure 1. Meta-analysis of the efficacy of myorelaxant on the global assessment. The difference in rates between myorelaxant- and placebo-treated patients is represented by the vertical bar, with the 95% confidence interval shown by a horizontal line. When the odds ratio or the risk difference is at the right of the vertical, the difference is in favour of the myorelaxant. When the horizontal line does not cross the vertical line, a significant difference exists between the myorelaxant and placebo.

was a significant difference in favour of myorelaxants, with a mean odds ratio of 1.65, $P < 0.001$ (95% CI: 1.30–2.10). According to the Der Simonian method, the risk difference was 18%, $P < 0.001$ (95% CI: 7–28%).

Percentage of patients with abdominal distension improvement (Figure 3). A total of six randomizations involving five different drugs were available for this end-point. The mean percentage of patients with global improvement was 35% in the placebo group ($n = 443$) and 44% in the myorelaxant group ($n = 442$). According to the Peto method, there was a significant difference in favour of myorelaxants, with a mean odds ratio of 1.46, $P = 0.008$ (95% CI: 1.10–1.94). According to the Der Simonian method, the risk difference was 14%, $P = 0.04$ (95% CI: 0–27%).

Percentage of patients with constipation improvement. Only four trials (490 total patients) gave results concerning

the percentage of patients without constipation. There was no significant difference in favour of myorelaxants, with a mean odds ratio of 0.89, $P = 0.60$ (95% CI: 0.60–1.31).

Percentage of patients with transit improvement. Only four trials (230 total patients) gave results concerning the percentage of patients with transit improvement. There was no significant difference in favour of myorelaxants, with a mean odds ratio of 1.04, $P = 0.90$ (95% CI: 0.58–1.87).

Percentage of patients without adverse effects (Figure 4). A total of 18 randomizations involving six different drugs were available for this end-point. The mean percentage of patients without adverse events was 90% in the placebo group ($n = 691$) and 86% in the myorelaxant group ($n = 693$). According to the Der Simonian method, there was no overall significant difference,

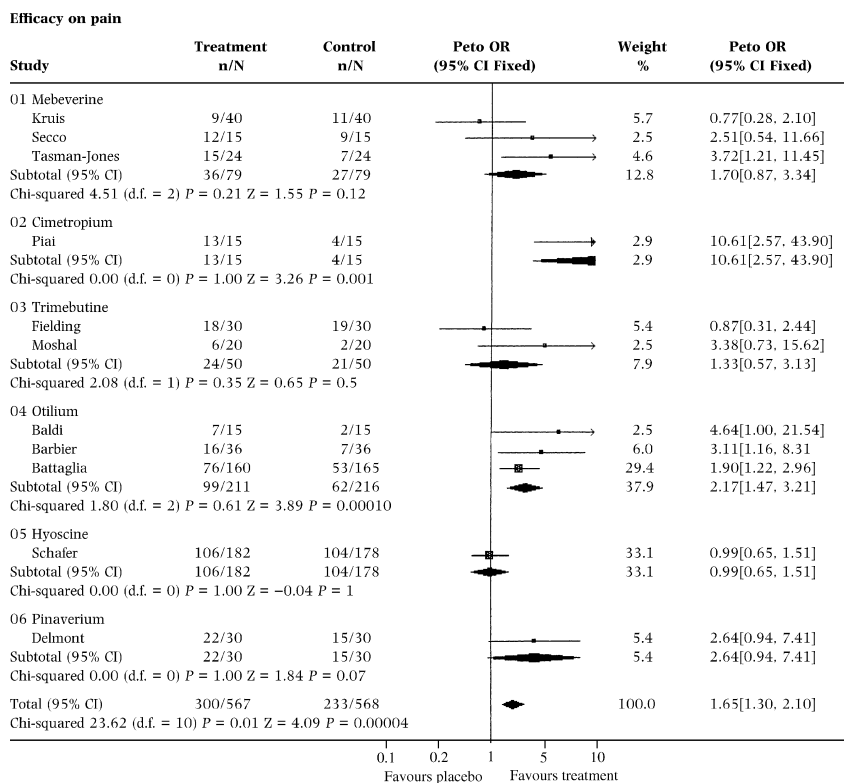


Figure 2. Meta-analysis of the efficacy of myorelaxant on pain improvement.

with a mean risk difference of - 2%, P = 0.08 95% CI: - 5% to + 1%) in favour of placebo. Only one single trial had a significant difference in favour of placebo. No drug had a significant difference, although two were nearly significant; cimetropium (mean risk difference of - 8% P = 0.08 95% CI: - 17% to + 2%) and hyoscine (mean risk difference of - 6% P = 0.10 95% CI: - 15% to + 3%).

DISCUSSION

In contrast to the previous study, the present meta-analysis focused on six active drugs without significant adverse effects, and therefore peppermint oil and

dicycloverine had to be excluded.¹ Two new randomized clinical trials were identified, including a large one which included 325 patients.^{35, 36} This last trial fulfilled most of the recent standards and restated the conclusions of the former overview which had been based on smaller trials.^{36, 37} This update completes the recent meta-analysis by Jailwala *et al.*, which was of good methodological quality but did not included the randomized trials published in a non-English language.⁵

This update confirms the efficacy of myorelaxants in the treatment of irritable bowel syndrome. These drugs showed significant efficacy on the global assessment despite a high placebo effect (38% global improvement), with a range of difference from 31% for cimetropium to

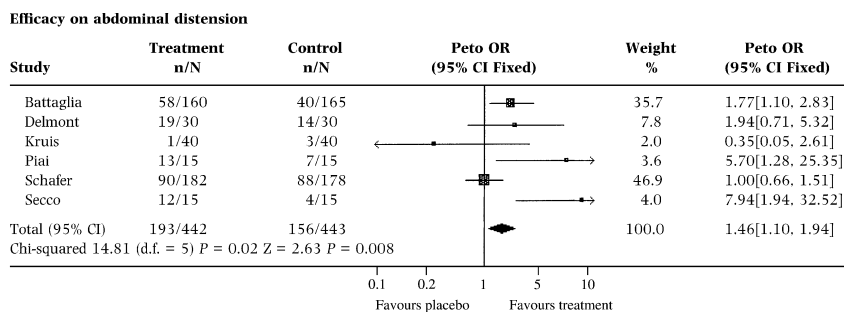


Figure 3. Meta-analysis of the efficacy of myorelaxant on abdominal distension improvement.

Meta-analysis of adverse events

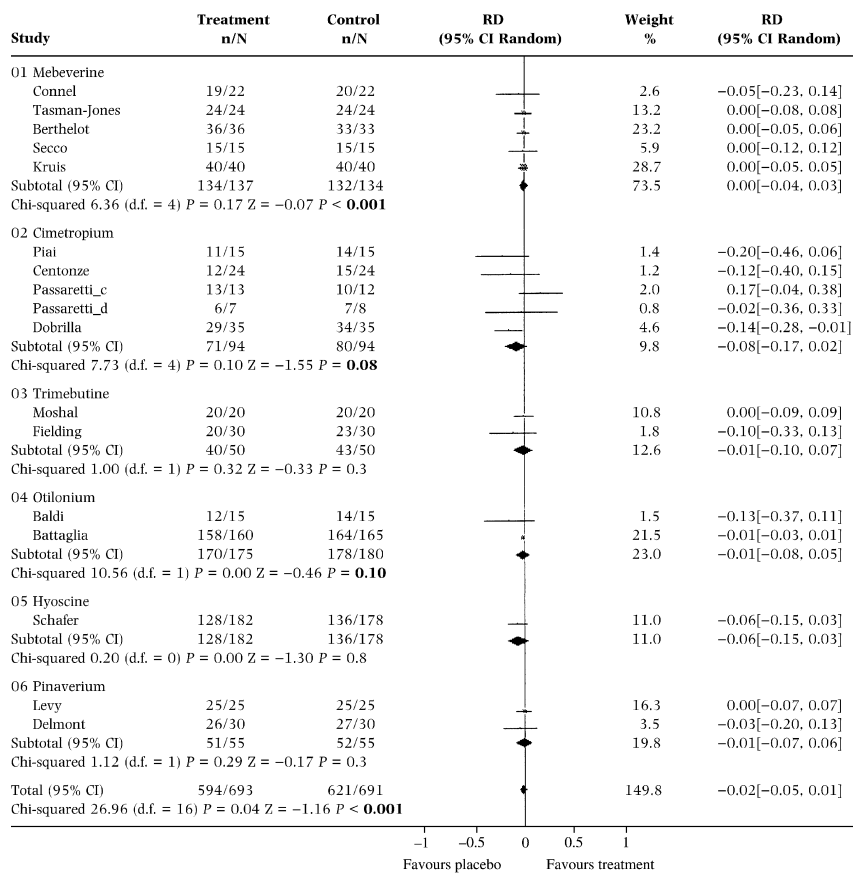


Figure 4. Meta-analysis of myorelaxants vs. placebo: percentage of patients without adverse events.

11% for hyoscine. The efficacy was also significant and in the same range for pain relief, as well as for abdominal distension relief, although lower. The efficacy on abdominal distension was not found by Jailwala *et al.* and this could be a consequence of the fewer number of trials included.⁵ There was no significant difference for transit abnormalities, diarrhoea or constipation. One weakness of our meta-analysis was to have no individual data, making it impossible to identify patients with 'pure' irritable bowel syndrome as defined by the Rome criteria.

Recent trials have demonstrated that alosetron, a 5-HT₃ receptor antagonist, is effective in the treatment of irritable bowel syndrome in non-constipated females vs. placebo and vs. mebeverine.^{3, 4} Myorelaxants however, can still be useful particularly in treating males and constipated females with irritable bowel syndrome. In non-constipated females, the combination of an anti-diarrheal and a myorelaxant could also be an alternative to the 5-HT₃ receptor antagonist.

In conclusion, this overview demonstrates that there is still a need for myorelaxants in the management of

irritable bowel syndrome. There is also a need for including non-English language trials in any meta-analysis.

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