

# Efficacy of pinaverium bromide in the treatment of irritable bowel syndrome: a systematic review and meta-analysis

Serhat Bor, Philippe Lehert, Adriana Chalbaud<sup>ID</sup> and Jan Tack

## Abstract

**Background:** Spasmolytic agents are an attractive first line treatment option for irritable bowel syndrome (IBS). Pinaverium bromide (pinaverium) has antispasmodic effects on gastrointestinal smooth muscle and can relieve major IBS symptoms, but an up-to-date meta-analysis comparing the efficacy of pinaverium with placebo is lacking. The aim is to perform a systematic review and meta-analysis to assess the efficacy of pinaverium compared with placebo for IBS treatment.

**Methods:** All placebo-controlled trials evaluating pinaverium for IBS treatment were included, up to October 2019. Treatment efficacy was evaluated by overall patient IBS symptoms. Individual symptoms were also evaluated. The effect of pinaverium *versus* placebo was expressed as standardized mean difference (SMD) and risk ratio (RR). Odds ratio (OR) and number needed to treat (NNT) were also calculated.

**Results:** Eight studies were included for analysis. Pinaverium treatment had a beneficial effect on overall IBS symptom relief with a positive SMD of 0.64 [95% confidence interval (CI) 0.45–0.82,  $p < 0.0001$ ] and a positive RR of 1.75 [1.26–2.43,  $p < 0.0008$ ]. No significant difference was found by publication year, gender, age, methodological quality score (MQS), or sample size. No publication bias was detected. OR was 3.43 [2.00–5.88,  $p < 0.0001$ ], and NNT was 4. Pinaverium also demonstrated a beneficial treatment effect for abdominal pain, stool change, and bloating improvement or resolution.

**Conclusion:** Pinaverium is superior to placebo for the treatment of IBS symptoms, irrespective of patient age or gender, study publication year, sample size, or MQS. The NNT in this meta-analysis is amongst the lowest for studies and meta-analyses of antispasmodics *versus* placebo in IBS.

**Keywords:** efficacy, irritable bowel syndrome, meta-analysis, pinaverium bromide, treatment

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## Introduction

Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by recurrent abdominal pain, associated with defecation or a change in bowel habits (i.e., constipation, diarrhea, or both), along with symptoms of abdominal bloating or distention.<sup>1</sup> IBS is considered a multifactorial disorder with a complex pathophysiology not yet fully understood.<sup>1–3</sup>

The worldwide prevalence of IBS is highly variable (1.1–45.0%), depending on the population

and study method, with a pooled prevalence of 11.2% based on a meta-analysis of 80 separate study populations of a total of 260,960 subjects.<sup>4</sup> Reported prevalence rates were higher for women than for men, and in individuals younger than 50 years.<sup>4</sup>

The treatment of IBS is based primarily on type and severity of symptoms. As the etiology and pathogenesis of IBS is not well understood, current treatment targets primarily the main

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symptoms associated with the condition. Although diet and lifestyle modification might be sufficient for some patients, pharmacotherapy is usually needed. Guidelines suggest the use of antispasmodics to improve IBS symptoms in these patients, especially for abdominal pain.<sup>1,5-7</sup> Antispasmodics comprise several classes of drug, including smooth muscle relaxants, anticholinergic agents, and gastrointestinal (GI)-selective calcium channel blockers.<sup>6</sup> Selective calcium channel blockers have a favorable antispasmodic effect on gastrointestinal smooth muscle and can relieve the major symptoms of IBS such as abdominal pain and abdominal distension while they have no clinically relevant anticholinergic side effects.<sup>8</sup>

Pinaverium bromide (pinaverium), a GI-selective calcium channel antagonist, has a highly selective spasmolytic activity in the GI tract. It has a dual mechanism of action that helps treat the discomfort and abdominal pain associated with functional intestinal disturbances such as IBS. As a calcium antagonist inhibits the influx of calcium into intestinal smooth muscle cells. It exerts this effect by blocking the L-type voltage-dependent calcium channels (most common type of voltage-operated calcium channel in the intestinal smooth muscle) at the level of the  $\alpha_1$ -subunit by blocking voltage-dependent calcium channels within the intestinal smooth muscle cells.<sup>9</sup> In addition to being a selective calcium channel blocker, pinaverium also inhibits the contractile effect of digestive hormones and inflammatory mediators such as cholecystokinin, gastrin, and substance P.<sup>9</sup> These compounds play a key role in contraction of intestinal smooth muscles and are linked to defecation-associated abdominal pain and discomfort in patients with IBS.

Pinaverium is used widely in the therapy for IBS patients,<sup>10</sup> but its efficacy is not firmly established in the current literature overview. A variety of systematic reviews and meta-analyses evaluating the efficacy of treatments for IBS have been published over the years. However, these publications tended to evaluate all available IBS treatment interventions (e.g., bulking agents, prokinetics, antispasmodics, and antidepressants), or all antispasmodics (often limited to clinical trials published in English), and no available review has evaluated all published pinaverium clinical trials, irrespective of publication language. In view of this, and given the amount of pinaverium placebo-controlled studies available, a systematic review and meta-analysis was conducted to

evaluate the efficacy of pinaverium bromide compared with placebo for the treatment of IBS.

## Materials and methods

### Search strategy and study selection

A language unrestricted search of Cochrane, EMBASE, Google, MEDLINE, AdisInsight: Safety Reports, Allied & Complementary Medicine, Analytical Abstracts, BIOSIS Previews, EMCare, International Pharmaceutical Abstracts, and ToxFile databases, covering the period from 1 January 1970 to 31 October 2019, was undertaken based on a number of keywords, including “pinaverium bromide” OR “dicetel” OR “eldicet” or “4 6 bromoveratryl 4 2 2 6 6 dimethyl 2 norpinyl ethoxy ethyl morpholinium bromide” OR “blocafer” OR “Colopax” OR “delibs” OR “Nulite” OR “Pinar” OR “Pinaven” OR “pinaverin” OR “Pinaverio” OR “pinav?ri[\*2]” OR “Riginal” OR “Spastec” OR “Sucam” OR “Zerpyco” OR “59995 65 2” OR “53251 94 8” OR “0053251 94 8” AND (“irritable bowel syndrome” OR “colon disease functional” OR “colonospasm” OR “irritable colon” OR “mucomembranous colitis”) OR [(mucous OR spastic OR spasm OR unstable) (colitis OR colon)]. The references were rechecked manually. Printouts from the electronic searches were reviewed, and all treatment trials were selected. An additional manual search was conducted of relevant journals, symposia, and conference proceedings, and relevant trials retrieved; all identified publications were cross-referenced. Non-English publications were translated into English *via* a certified translator.

Eligibility criteria included all randomized clinical trials (RCTs) where pinaverium bromide was compared with placebo, without restriction of language, published either in peer-reviewed journals or abstracts. Study participants were adults, of any age, male or female, of any ethnic group, suffering from IBS. No specific dosage or duration treatment was selected. No treatment combination preparations including pinaverium were included in the analysis. Other exclusion criteria of placebo-controlled RCTs were those with endpoints not related to symptoms assessment or duplicated studies.

### Outcome assessment

Efficacy of treatment was evaluated by patient symptoms improvement or resolution in the

period between first and last drug intake. Improvement was defined as a positive change (amelioration of symptoms) in the scale used at the end of treatment, while resolution was defined as complete disappearance of symptoms at the end of treatment. Symptoms evaluated included overall assessment of IBS symptom relief and specific IBS symptoms such as abdominal pain frequency, severity, and duration; bloating; distension; straining; stool frequency, consistency; transit problems/disturbances including constipation and diarrhea; and additional symptoms. Treatment efficacy on overall IBS symptom relief constituted our primary endpoint. As treatment efficacy on abdominal pain (frequency/severity improvement or resolution), stool change (stool consistency/frequency improvement), and bloating were the main symptoms evaluated in all studies; these were included as a secondary endpoint.

#### *Data extraction*

The different steps of data extraction were acquisition, checking, updating, and file constitution. A pre-project consisted of a careful review of the results of each study.

Data from randomized patients excluded from the final analysis and not contained in the existing results (outcomes of patients who withdrew or were excluded after allocation), were not included in the data file. For studies reporting withdrawals, patient data was included in an “intention to treat” (ITT) analysis.

The available variables identified were:

1. Baseline: Study center, country, treatment, age, gender, weight, education, occupation, abdominal pain frequency, severity and duration, presence and/or severity of bloating, distension and straining, stool frequency and consistency, presence and/or severity of transit problems/disturbances including constipation and diarrhea, any additional symptoms, and overall IBS symptoms.
2. Follow-up: Duration of follow up, duration of medication, and end of trial status. No patients were expected to interrupt the trial prematurely. Data registered were those reported on the final day of treatment.
3. Endpoints: Assessment of overall symptoms and specific symptoms measured at baseline. All symptoms evaluated were recorded at least at the beginning and end of treatment period. Depending on the scales used for symptom evaluation, data included improvement of symptoms (defined as amelioration of symptoms in the established scale at the end of treatment), and/or symptom resolution (defined as complete disappearance of symptoms at the end of treatment).

#### *Assessment of risk of bias in studies (validity assessment)*

The validated domain-based evaluation (DBE) tool recommended in the Cochrane Collaboration Handbook (and still commonly used before the current ROB2 instrument) was used in the current systematic review.<sup>11</sup> During the evaluation of each trial, a qualitative checklist on 17 items evaluating internal and external validity, and statistical analysis was employed and independently completed by each reviewer according to the criteria described by Higgins and Green (2001).<sup>11</sup> Sensitivity analyses were conducted to assess the possible effect of risk of bias level. For this purpose, in addition to the DBE instrument, a methodological quality score (MQS) was calculated as a sum score of the 17 items evaluated. MQS was calculated by three authors independently and the mean between calculations used for this study. Methodological quality of the trials must be assessed for internal (seven variables), external (five variables), and statistical (five variables) validity. For each item, the scoring is 2 = appropriate; 1 = unclear; 0 = inadequate; blank space = undocumented. The sum of the mean value per validity question subgroup constitutes the MQS.

#### *Statistical analysis*

Whenever possible, the full analysis set (FAS), recommended as the best selection for minimizing biases [International Conference on Harmonisation (ICH) E-9], was identified in every publication as it is most similar to the ITT set.

*Data calculation and transformation.* Data values provided as standard error of mean (SEM) were converted into standard deviation (SD) through the expression  $SD = SEM \cdot \sqrt{n}$ .

*Endpoint calculation and effect size.* Given the heterogeneity of the studies in their clinical definition, direction and measurement also needed the following transformations: (a) with the objective to compare the studies, severity scores (higher values meaning higher severity) were converted into improvement scores. (b) Two alternative methods were used to aggregate scales based on quantitative values or proportions: converting the proportions  $x/n$  into quantitative values in assimilating this value to a normal approximation of mean  $p = x/n$  and standard deviation  $SD = \sqrt{(p(1-p))/n}$ . Conversely, the conversion of quantitative difference distributed according a normal distribution  $N(m, \sigma)$  assumes the success proportion (SP) = 0.5 for the tested drug, whereas SP on the control arm was calculated as  $\text{Prob}(N(0, s) < -m) = P(N(0, 1) < -m/s) = F(-m/s)$ .

Based on these calculations, the primary endpoint was based on the mean score of all the IBS symptoms used in each study, and the pooling of these values was calculated following the standardized mean difference (SMD) as the endpoints did not use the same measurement scale and were characterized by non-comparable heterogeneity needing standardization.

For sensitivity purposes, and as secondary analysis, the analyses were repeated based on proportions, and the risk ratio RR was considered as the main calculation of effect size [Odds ratio (OR) and number needed to treat (NNT) were also mentioned for the main results].

Secondary endpoints symptoms were regrouped into three main classes: abdominal pain, stool change (consistency/frequency) and bloating. OR and NNT were mentioned for the abdominal pain results. The classification of these symptoms was obtained through a principal components analysis followed by clinical discussion.

For the main and secondary analyses, the meta-analytical model was similar. Considering that the number of trials may be limited and have unequal sample sizes, the random effects model was systematically used [calculated both by the restricted maximum likelihood (REML) and the DerSimonian and Laird approach] with the most conservative statistics retained.<sup>12,13</sup> The fixed effects model was used only for sensitivity purposes and only when a non-significant heterogeneity between studies was found (chi-square heterogeneity test,  $p > 0.05$  and  $I^2 < 0.25$ ). The

pooling principle was invariably based on mean difference weighted by the inverse of its variance.

*Meta-regressions.* The over-arching goal of the current meta-analysis was to include the maximum number of studies that met the inclusion and exclusion criteria. Contrary to previous meta-analyses separating specific subgroups, any attempt in the current meta-analysis to assess a subgroup effect was analyzed by meta-regression on the whole data set by considering one or more covariates. This approach allowed for a better comparison between the results by keeping the power more comparable. The Knapp and Hartung method was used as an adjustment to the standard errors of the estimated coefficients.<sup>14</sup>

Meta-regressions were conducted using the following differentiating descriptions known to potentially influence the results of a meta-analysis: publication year, gender, age, MQS, and sample size. Due to the non-availability of individual patient data, the number of covariates in the meta-regression was limited. The combined effect of two covariates is difficult to measure and depends on the variety of combinations found for each separate covariate.

Knowing that missing data imputation may introduce bias, a measure of the magnitude of bias was determined by means of meta-regression analysis in estimating the effect of missing data compared with existing data. This was done for each endpoint where data imputation was used and is reported in the results for each endpoint.

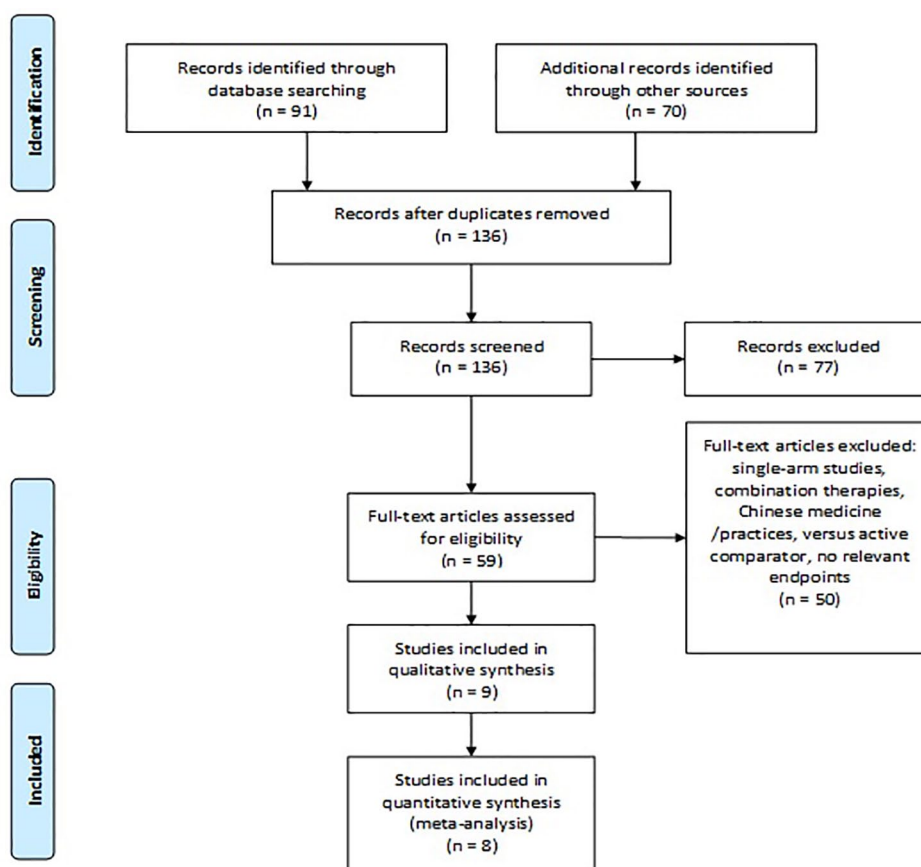
*Publication bias and consistency varying with precision.* The risk of publication bias was graphically illustrated with the funnel plot method and statistically examined with a linear regression test, determining the linear regression coefficient between log odds ratio and its standard error.

*Generalities.* All tests were conducted at two-sided 0.05 significance level. For statistical calculations, R (Version 2.6.2) was used, and, in particular, the Metafor Library to conduct meta-analyses and meta-regressions.

## Results

### Screening selection

A total of 136 citations on pinaverium were identified. Studies evaluated during the screening



**Figure 1.** PRISMA flow diagram.  
PRISMA, preferred reporting items for systematic review and meta-analysis.

selection steps are included in the Prisma flow diagram (Figure 1). Ultimately, a total of eight distinct placebo-controlled RCTs were identified and included in the meta-analysis (Table 1).<sup>15–22</sup> Data were available for all selected trials. A total of 757 patients were included in the meta-analysis. Detailed characteristics of the eight included studies are provided in Table 1.

#### *Overall IBS symptom relief assessment*

The SMD was based on the eight selected studies,<sup>15–22</sup> and the pooling performed by the random meta-analytical model (RE). As shown in Figure 2, a beneficial effect of treatment on the overall IBS symptom relief was found in the pinaverium treatment group with a positive SMD of 0.64 (95% CI 0.45–0.82,  $p < 0.0001$ ). A non-significant ratio of total heterogeneity among studies on the total variability ( $I^2$  statistics) was 16.3%, ( $\chi^2 = 8.36$ ,  $df = 7$ ,  $p = 0.30$ ). The consistency of this effect was reviewed through meta-regressions. No significant difference

was found by publication year [−0.004 per year of publication (−0.02, 0.01),  $p = 0.60$ ], gender [−0.41 for female patients, (−1.46, 0.80),  $p = 0.55$ ], age [0.02 per year, (−0.02, 0.03),  $p = 0.87$ ], MQS [−0.01 per score unit, (−0.11, 0.08),  $p = 0.09$ ], or sample size [0.01 per 10 patients, (−0.26, 0.28),  $p = 0.94$ ]. Visual inspection of the funnel plot (Figure 3) did not detect abnormal values for any of the studies outside the confidence interval assuming the calculated effect size, and no asymmetry around the effect size was observed which suggests absence of no publication bias in particular for non-published non-positive studies.

As a secondary analysis, and based on the proportions of success, the RR was compared across studies (Figure 4). A beneficial effect of treatment on the overall IBS symptom relief was found in the pinaverium treatment group with a positive RR of 1.75 (1.26, 2.43,  $p < 0.0008$ ). The ratio of total heterogeneity among studies on the total variability ( $I^2$  statistics) was 60.4%. Some



**Table 1.** Characteristics of selected studies.

Study (Country)	Sample size (pinaverium, placebo) <sup>a</sup>	Mean age (years)	Proportion of female patients	Medication dosage (schedule)	Diagnostic criteria	Treatment duration (days)	MQS	Outcome assessed	Primary outcome
Awad <i>et al.</i> (Mexico) <sup>15</sup>	40 (20, 20)	31	1	50 mg (tid)	Rome I	21	8.11	OSR, API, ADI, SFI, SCI, ASI	Significant API ( $p < 0.01$ )
Delmont (France) <sup>16</sup>	60 (30, 30)	56	0.67	50 mg (tid)	Clinical	28	5.72	OSR, API, ADI, TPN	Significant OSR ( $p < 0.01$ ) and API ( $p < 0.05$ )
Dubarry and Quinton (France) <sup>17</sup>	20 (10, 10)	40	0.5	50 mg (tid)	Clinical	6	4.86	APR	Significant APR ( $p < 0.01$ )
Levy <i>et al.</i> (France) <sup>18</sup>	44 (22, 22)	50	0.59	50 mg (tid)	Clinical	15	6.63	OSR, API, ADI, TPN	Significant OSR ( $p < 0.01$ )
Virat <i>et al.</i> (France) <sup>19</sup>	78 (39, 39)	44	0.51	50 mg (tid)	Clinical	7	6.98	OSR, API, ADI, SFI	Significant API ( $p < 0.05$ )
Zhang <i>et al.</i> (China) <sup>20</sup>	28 (18, 10)	40	0.5	50 mg (tid)	Rome III	28	6.06	OSR, API, ADI, SFI, ASI	Significant API, ADI and SFI ( $p < 0.05$ )
Zhao <i>et al.</i> (China) <sup>21</sup>	60 (30, 30)	37	0.5	50 mg (tid)	Rome II	28	2.50	OSR, APR, ADI, TPN	Significant OSR ( $p < 0.01$ )
Zheng <i>et al.</i> (China) <sup>22</sup>	427 (218, 209)	37	0.47	50 mg (tid)	Rome III	28	9.24	OSR, APR, ADI, SFI, SCI	Significant APR ( $p < 0.01$ )

<sup>a</sup>Sample size: number of patients in the pinaverium group and placebo group.

ADI, abdominal distension improvement; API, abdominal pain improvement; APR, abdominal pain resolution; ASI, additional symptoms improvement; MQS, overall methodological quality score; OSR, overall symptoms response; SCI, stool consistency improvement; SFI, stool frequency improvement; tid, three times daily; TPN, transit problems normalization.

heterogeneity across studies was found ( $\chi^2 = 20.17$ ,  $df = 7$ ,  $p = 0.005$ ). Similarly to the analysis by mean-scores, no significant difference was found by publication year [RR = 0.99 per year of publication (0.99, 0.99),  $p = 0.52$ ], gender [RR = 0.73 for female patients, (0.8, 6.19),  $p = 0.77$ ], age [1.01 per year, (0.97, 1.06),  $p = 0.51$ ], methodological quality score [1.06 per score unit, (0.96, 1.17),  $p = 0.25$ ], or sample size [RR = 1.00 per patient, (0.99, 1.01),  $p = 0.64$ ].

Alternative measurements of effect size were conducted. OR was 3.43 [(2.00, 5.88),  $p < 0.0001$ ] (Figure 5), the absolute risk difference (ARD) was 0.26 [(0.16, 0.35),  $p < 0.0001$ ], and the corresponding NNT was 3.84 (2.85, 17.8).

### Secondary endpoints

All studies contained enough data to evaluate abdominal pain separately.<sup>15–22</sup> Similarly to the

overall IBS symptoms results, the pinaverium treatment group showed a beneficial effect of treatment on abdominal pain improvement/resolution over placebo, with a positive SMD of 0.82 [95% CI 0.62, 1.02,  $p < 0.0001$ , and RR of 1.98 (1.46, 2.69),  $p \leq 0.0001$ , Supplemental Figure S1]. The ratio of total heterogeneity among studies on the total variability ( $I^2$  statistics) was 23.31% and 51.51%, respectively. No significant heterogeneity was found when evaluating the SMD.

Seven of the eight included studies contained data to evaluate stool change (consistency/frequency) and bloating as individual symptoms.<sup>15,16,18–22</sup> Pinaverium treatment showed a beneficial effect of treatment for the management of stool frequency and consistency disorders with a positive SMD of 0.53 [95% CI 0.33, 0.72,  $p < 0.001$ , and a RR of 1.57 (1.08, 2.28),  $p = 0.0179$ , Supplemental Figure S2]. The analysis on bloating improvement showed a beneficial effect of treatment in the

Pinaverium treatment group with a positive SMD of 0.52 [95% CI 0.37, 0.67,  $p < 0.001$ , and a RR of 1.52 (1.15, 2.00),  $p = 0.0033$ , Supplemental Figure S3]. For both symptoms, some heterogeneity across studies was found only when evaluation proportion of success ( $\chi^2 = 22.2234$ ,  $df = 6$ ,  $p = 0.0011$ ) and ( $\chi^2 = 14.4026$ ,  $df = 6$ ,  $p = 0.0254$ ), respectively.

For all individual symptoms evaluated, no significant difference in the treatment effect of pinaverium was found by publication year, gender, age, MQS, or sample size. Only when evaluating abdominal pain by proportion of success (RR), was this analysis characterized by an effect of the MQS [1.08 per score unit, (1.03, 1.14),  $p = 0.008$ ]; thus, the proportion of success under pinaverium treatment was higher for studies of better quality. Similarly, a significant effect on sample size was found when evaluating proportion of success of pinaverium for bloating [1.001 per patient, (1.00, 1.001),  $p = 0.0028$ ].

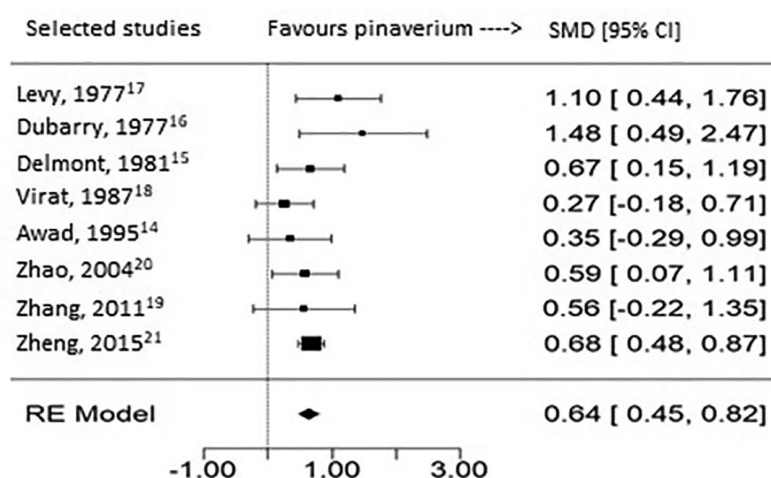
No publication bias was detected when evaluating any individual symptom (Supplemental Figures S4–S6).

For the abdominal pain results, alternative measurements of effect size were also conducted. OR was 4.67 [(3.33, 6.54),  $p < 0.0001$ ; Supplemental Figure S7], ARD was 0.34 [(0.27, 0.41),  $p < 0.0001$ ], and the corresponding NNT was 2.94 (2.46, 3.70).

## Discussion

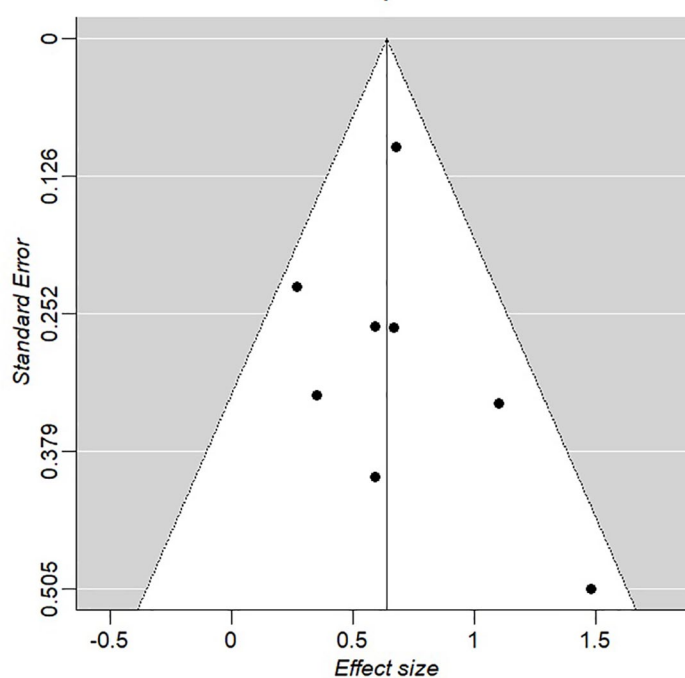
After a systematic review, eight placebo-controlled trials evaluating the efficacy of pinaverium in the treatment of IBS symptoms fulfilled the inclusion criteria and were included in the present meta-analysis.<sup>15–22</sup> All trials individually showed positive results in favor of pinaverium for the treatment of IBS. Nonetheless, study characteristics varied widely with, for instance, four of the included studies being dated between 1977 and 1987, and three studies being published over the last 15 years, justifying the need for an updated meta-analysis to compare all available studies to date. The effect of the studied drug was found to be homogeneous, without significant difference or heterogeneities between studies; furthermore, no differences were found across studies regarding publication year, or any other possible moderator in meta-regressions.

Previous meta-analyses have been published evaluating IBS treatment options. Apart from the



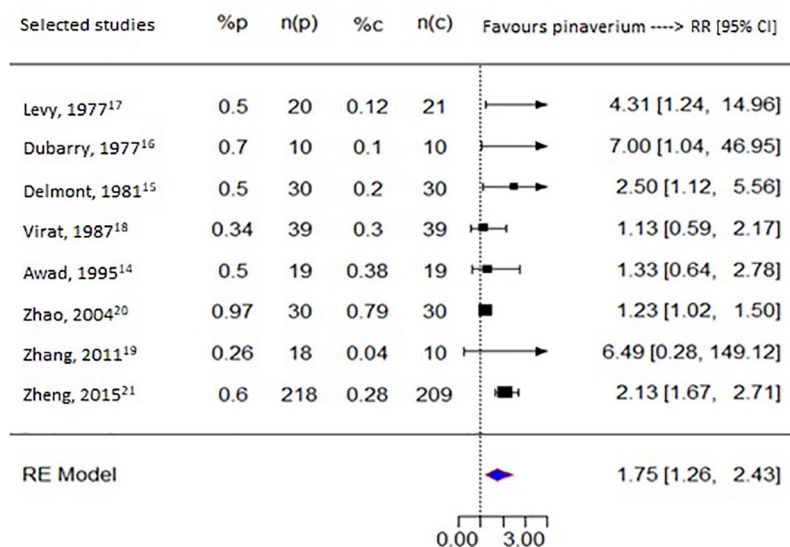
**Figure 2.** Forest plot of SMD of placebo-controlled trials of pinaverium versus placebo in IBS (overall symptoms), based on eight selected studies, pooling performed by the RE.

CI, confidence interval; IBS, irritable bowel syndrome; RE, random meta-analytical model; SMD, standardized mean difference.

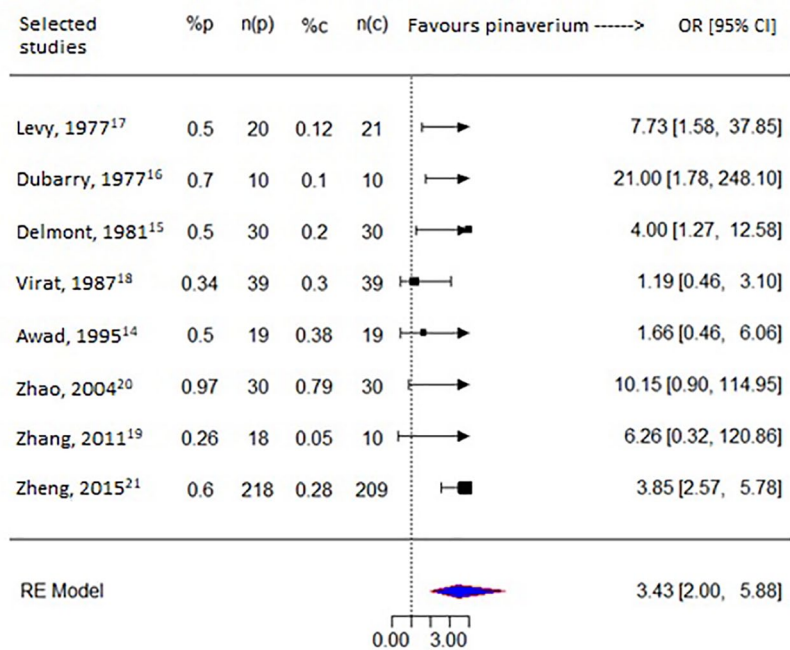


**Figure 3.** Funnel plot of the main analysis. No abnormal value or asymmetry of effect size of each study with respect of the mean pooled effect (0.64) was found.

Cochrane review by Ruepert *et al.*,<sup>23</sup> 12 systematic reviews of antispasmodics and other drug treatments for IBS have been published.<sup>8,24–34</sup> Although the different meta-analyses showed the benefit of antispasmodics for the treatment of IBS symptoms, considering the quality and methodological



**Figure 4.** Forest plot of proportion of success (RR) of placebo-controlled trials of pinaverium versus placebo in IBS (overall symptoms), based on eight selected studies, pooling performed by the RE. %p, n(p), %c and n(c) being the proportions and sample sizes of the treatment groups for Pinaverium and control, respectively. CI, confidence interval; IBS, irritable bowel syndrome; RE, random meta-analytical model; RR, risk ratio.



**Figure 5.** Forest plot of OR of placebo-controlled trials of pinaverium versus placebo in IBS (overall symptoms), based on eight selected studies, pooling performed by the RE. %p, n(p), %c and n(c) being the proportions and sample sizes of the treatment groups for Pinaverium and control, respectively. CI, confidence interval; IBS, irritable bowel syndrome; OR, odds ratio; RE, random meta-analytical model.

variability of the included studies, the overall efficacy of antispasmodics was not well established and there were only very limited data for individual antispasmodics. Of note, only a few pinaverium trials were included in the different analyses, up to five studies, including combination therapies as opposed to the eight studies included in the present meta-analysis.

The Cochrane review of bulking agents, antispasmodics, and antidepressants for the treatment of IBS included 10 categories of antispasmodics.<sup>23</sup> The authors reported a beneficial effect for antispasmodics over placebo for global assessment (RR 1.49; 95% CI 1.25–1.77;  $p < 0.0001$ ; NNT=5), and for improvement of abdominal pain (RR 1.32; 95% CI 1.12–1.55;  $p < 0.001$ ; NNT=7). In a subgroup analysis, pinaverium showed a statistically significant benefit for abdominal pain with a RR of 1.57 (95% CI 1.08–2.26) from three studies (Delmont<sup>16</sup>; Dubarry and Quinton<sup>17</sup>; Virat *et al.*<sup>19</sup>), and a SMD of 0.44 (95% CI -0.20 to 1.08; 114 patients) (Awad *et al.*<sup>15</sup>; Virat *et al.*<sup>19</sup>). Similar results were observed when evaluating the improvement in global assessment (RR 1.66; 95% CI 1.25–2.19; 308 patients). The authors supported the use of antispasmodics, although, it was not entirely clear whether one antispasmodic was more effective than another.<sup>23</sup>

Following the Cochrane review, Martinez-Vasquez *et al.*,<sup>33</sup> published a systematic review and meta-analysis focusing on the effect of antispasmodics in the treatment of IBS. The review included 23 studies of eight antispasmodic agents, including combination therapies. Only three pinaverium trials were included, amongst them one in combination with simethicone.<sup>16,18,35,36</sup> Only otilonium bromide and alverine/simethicone demonstrated a significant effect for global assessment. The OR for pinaverium in the global assessment analysis was 2.15 (95% CI, 0.95–4.83,  $p = 0.063$ ). The authors discussed that, for pinaverium, only with the addition of simethicone could a statistically significant effect in relieving bloating be demonstrated. The NNT for global improvement was calculated for only otilonium bromide and alverine/simethicone, reaching 7 and 8, respectively. The authors concluded that antispasmodics were more effective than placebo for the treatment of IBS.<sup>33</sup>

In a systematic review and meta-analysis in Chinese, Chen and Wang focused on the efficacy and safety



of selective calcium channel blockers otilonium bromide and pinaverium *versus* placebo for IBS.<sup>8</sup> Meta-analysis of overall response rate of IBS patients treated with calcium channel blockers or placebo reported a RR = 2.06 (95% CI 1.56–2.73;  $p < 0.00001$ ; NNT = 3). A subgroup analysis of five pinaverium placebo-controlled studies, one of them not identified and found for this meta-analysis, showed a RR of 2.35 (1.51–3.66,  $p = 0.0001$ ). When evaluating the abdominal distension remission rate, defined in this meta-analysis as bloating, subgroup analysis showed that the remission rate associated with pinaverium was statistically significantly higher compared with placebo [RR = 1.25 (1.03–1.52),  $p = 0.03$ ], but not statistically significant for otilonium bromide *versus* placebo [RR = 2.05 (0.84–4.96),  $p = 0.11$ ].<sup>8</sup>

Although the meta-analysis by Chen and Wang showed more positive results than previous meta-analyses,<sup>8</sup> only two non-Chinese clinical studies were included.<sup>16,18</sup> Additionally, in 2015, Zheng *et al.* published a high quality, large sample size, placebo-controlled multicenter RCT to evaluate the effectiveness and safety of pinaverium in IBS treatment.<sup>22</sup> Considering the variability in the amount of pinaverium trials included in previous meta-analyses evaluating efficacy on IBS treatment, and the publication of Zheng *et al.*,<sup>22</sup> it was important to reevaluate the efficacy of pinaverium for the treatment of IBS *via* meta-analysis. Our systematic review showed that none of the Asian trials (in Chinese) were included in any of the meta-analyses published to date.<sup>20,21</sup> It also showed that a meta-analysis including studies of pinaverium *versus* an active comparator would provide inconclusive results as only eight RCTs were found, and there were as many as four different active comparators amongst these eight studies.

Of the eight RCTs comparing the effect of pinaverium *versus* other antispasmodics in the treatment of IBS symptoms, comparators were either otilonium (three studies),<sup>37–39</sup> trimebutine (three studies),<sup>40–42</sup> mebeverine (one study),<sup>43</sup> or N-butyl hyoscine bromide (one study).<sup>44</sup> Similar to the studies included in the present meta-analysis, four of these studies dated between 1983 and 1991,<sup>37,38,40,44</sup> with no study being published in the last 15 years. Of the three studies evaluating otilonium *versus* pinaverium, only one found otilonium to be more effective than pinaverium in the treatment of IBS, but only for the number of pain

episodes; severity of pain, frequency of bowel movements and side effects were comparable between drugs.<sup>37</sup> Regarding trimebutine, two of the three studies found were done in Asian populations.<sup>41,42</sup> Wang *et al.* randomized 72 IBS-D patients (1:1) to pinaverium or trimebutine for 3 months.<sup>41</sup> In the third month, the total efficacy rate of the pinaverium group was significantly higher than that of the trimebutine group ( $p < 0.05$ ).<sup>41</sup> The second Asian study evaluated IBS-C and IBS-D patients, showing no significant difference in the improvement of IBS symptoms between the two groups.<sup>42</sup> Both studies comparing pinaverium with mebeverine or hyoscine, showed similar therapeutic effects on all IBS symptoms evaluated.<sup>43,44</sup> As shown here and as mentioned earlier, comparison of RCT evaluating pinaverium *versus* other antispasmodics *via* meta-analysis would have provided inconclusive results.

Most recently, in a systematic review and network meta-analysis of current therapies in IBS (soluble fiber, antispasmodic drugs, and gut-brain neuromodulators),<sup>34</sup> 51 RCTs with data from 4644 patients were eligible to assess the efficacy of treatments (4–12 weeks) in IBS management. A total of 18 studies on antispasmodics were included and divided in two groups: antimuscarinic agents only (cimetropium, hyoscine, pirenzepine, rociverine, and trimebutine), and a second group with different mechanisms of action (alverine, drotaverine, mebeverine, otilonium, pinaverium, and pargeverine). Only 13 of the included trials were at low risk of bias, 1 with pinaverium.<sup>22</sup> Peppermint oil and tricyclic antidepressants (TCAs) ranked first for efficacy when evaluating the improvement in global IBS symptoms and abdominal pain, respectively. Nonetheless, based on an endpoint of failure to achieve improvement in abdominal pain at 4–12 weeks, a sub-analysis by antispasmodic group showed that the group of other antispasmodics (which included two pinaverium studies<sup>16,22</sup>) were ranked first for efficacy (RR 0.48, 95% CI 0.35–0.64,  $p$  score 0.93) followed by tricyclic antidepressants (RR 0.54, 95% CI 0.36–0.80,  $p$  score 0.84).<sup>34</sup> The authors concluded that, because of the lack of methodological rigor of some RCTs analyzed, there is likely to be considerable uncertainty around these findings.<sup>34</sup>

Differently from Ruepert *et al.* and the more recent Black *et al.*, in the present study, data transformations were made to allow the analysis

of all pinaverium trials in one meta-analysis using either the mean-scores or the proportions of success,<sup>23,34</sup> leading to the calculation of SMD and RR, followed by OR, ARD, and NNT.

NNT is a valuable tool in daily clinical practice, supporting physicians in selecting therapeutic interventions. To our knowledge, the present meta-analysis is the first to calculate the overall NNT for the global assessment of pinaverium treatment alone (NNT=4). Given the relevance of abdominal pain in IBS symptomatology, we have also calculated the NNT for this specific symptom (NNT=3). Most recent published NNTs for antispasmodic treatment options for IBS, as mentioned in the previous meta-analyses varied from 3 to 8.<sup>8,23,33</sup> The NNT in the present study are two of the lowest reported for studies comparing antispasmodics with placebo.

Even though there is a high variability between study characteristics, no publication bias was found. Previous meta-analyses have discussed the difficulty in evaluating clinical trials on the efficacy of treatments for IBS, especially due to the methodological quality of studies. In the present study, a sub analysis to evaluate study characteristics that could potentially influence the results of the meta-analysis, was performed. The evaluation of publication date, MQS, gender, age, and sample size demonstrated that there is no significant difference between studies.

This meta-analysis has certain limitations. Firstly, there is a limited number of RCTs evaluating the efficacy of pinaverium *versus* placebo for the treatment of IBS; a thorough analysis was able to identify only eight separate trials, but this is more than in the previous meta-analyses. Secondly, the variability in treatment duration was not evaluated in the current meta-analysis. Finally, based on the data from the included studies, it was unfortunately not possible to analyze safety in the present meta-analysis.

In conclusion, this systematic review and meta-analysis demonstrates, through two different models, a highly significant ( $p < 0.001$ ) benefit of pinaverium treatment over placebo in relieving/resolving symptoms in patients with IBS. Furthermore, through meta-regressions, we showed that patient age or gender, or study publication year, sample size, or MQS had no impact on our main results ( $p > 0.05$ ). Both NNT reported in

this study, for overall symptoms and for abdominal pain, were of the lowest amongst studies comparing antispasmodics *versus* placebo.

### Conflict of interest statement

SB has served as a speaker for Reckitt Benckiser, Abbott, and has given scientific advice and received research funding from Neutec.

PL has served as a consultant for Abbott.

AC is an employee of Abbott.

JT has given Scientific advice to Alfa Wassermann, Allergan, Christian Hansen, Danone, Grünenthal, Ironwood, Janssen Pharmaceuticals, Kiowa Kirin, Menarini, Mylan, Neutec, Novartis, Noventure, Nutricia, Shionogi, Shire, Takeda, Theravance, Tramedico, Truvion, Tsumura, Zealand and Zeria Pharmaceutical Co. Ltd and has served on the Speaker's bureau for Abbott, Allergan, AstraZeneca, Janssen, Kyowa Kirin, Menarini, Mylan, Novartis, Shire, Takeda, Truvion and Zeria Pharmaceutical Co. Ltd.

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### Supplemental material

Supplemental material for this article is available online.

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