REVIEW ARTICLE

Effect of antispasmodic agents, alone or in combination, in the treatment of Irritable Bowel Syndrome: Systematic review and meta-analysis

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KEYWORDS
Irritable Bowel Syndrome; Antispasmodics; Global Improvement; Abdominal Pain; Abdominal Distension; Alverine/Simethicone; Otilonium; Pinaverium/Simethicone; Mexico

Abstract
Introduction: Irritable bowel syndrome (IBS) is characterized by recurrent abdominal pain, bloating, and changes in bowel habit.
Aims: To determine the clinical effectiveness of the antispasmodic agents available in Mexico for the treatment of IBS.
Methods: We carried out a systematic review and meta-analysis of randomized controlled clinical trials on antispasmodic agents for IBS treatment. Clinical trials identified from January 1960 to May 2011 were searched for in MEDLINE, the Cochrane Library, and in the Clinical Trials.gov registry. Treatment response was evaluated by global improvement of symptoms or abdominal pain, abdominal distention/bloating, and frequency of adverse events. The effect of antispasmodics vs placebo was expressed in OR and 95% CI.
Results: Twenty-seven studies were identified, 23 of which fulfilled inclusion criteria. The studied agents were pinaverium bromide, mebeverine, otilonium, trimethobutine, alverine, hyoscine, alverine/simethicone, pinaverium/simethicone, fenoverine, and dicyclomine. A total of 2585 patients were included in the meta-analysis. Global improvement was 1.55 (CI 95%: 1.33 to 1.83). Otilonium and the alverine/simethicone combination produced significant values in global improvement while the pinaverium/simethicone combination showed improvement in bloating. As for pain, 2394 patients were included with an OR of 1.52 (IC 95%: 1.28 to 1.80), favoring antispasmodics.
Conclusions: Antispasmodics were more effective than placebo in IBS, without any significant adverse events. The addition of simethicone improved the properties of the antispasmodic agents, as seen with the alverine/simethicone and pinaverium/simethicone combinations.

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Introduction
Irritable bowel syndrome (IBS) is a frequent gastrointestinal functional disorder in the western world and Mexico is not an exception. It is characterized by recurrent abdominal pain, bloating, and defecation disorders. The pathophysiology of IBS is not yet fully understood; but increased pain sensitivity and altered small bowel and colon motility are main factors contributing to IBS symptoms. When compared with healthy controls, IBS patients demonstrate both visceral hypersensitivity and hyper-reactive motility.

Antispasmodic agents are believed to reduce pain associated with IBS through the inhibition of contractile pathways in the gut wall and to improve bowel habits by increasing colonic transit time, therefore reducing stool passage frequency. Previous meta-analyses have proven the usefulness of antispasmodics alone in the treatment of IBS. Nonetheless, antispasmodic availability differs among countries. In the United States, the American College of Gastroenterology review concluded that data were insufficient for making a recommendation as to the effectiveness of the available antispasmodic agents. In Europe for example, the utility of the available antispasmodics has been evaluated, however, there is no information regarding the effectiveness of those available in Latin America. Therefore, we conducted a systematic review of antispasmodic agents, both alone and in combination, for the treatment of IBS, and carried out a meta-analysis of the data obtained. This was done to determine the clinical effectiveness of the available antispasmodic agents as sole formulations or in combination with simethicone, and to update the current information on IBS treatment in Mexico.

Methods
To determine the antispasmodic agents that are available in Mexico, we reviewed the therapeutic index of the Dictionary of Medical Specialties (Diccionario de Especialidades Médicas), PLM®, Mexico-2011. We focused the search on section A3 of the index that lists all the agents for functional gastrointestinal disorders. The identified antispasmodics were further searched for in a systematic review conducted in MEDLINE, Cochrane Library, and ClinicalTrials.gov from January 1960 to May 2011 and in abstracts presented at the Digestive Disease Week (DDW) and the Mexican Disease Week (Semana Nacional de Gastroenterología) from 2010-2011. The agents listed in Table 1 were analyzed. Accordingly, the search terms were Irritable Bowel Syndrome and the following antispasmodics: pinaverium bromide, mebeverine, otilonio, trimebutine, alverine, hyoscine, alverina/simeticona, pinaverio/simeticona, fenoperine and dicyclomine. Two physicians conducted the search, then reviewed the results and resolved the existing discrepancies. Figure 1 explains the selection process for including papers in the meta-analysis. Articles selected
for review were those in which the authors employed the same inclusion criteria. Afterwards, the studies were reexamed to confirm that they fulfilled the inclusion criteria. Finally, the meta-analysis was conducted according to predetermined protocols and following the standard recommendations proposed by Sack et al. These recommendations consist of a rigorous review which includes the aspects listed in Table 2. When information was lacking, we contacted the authors for its completion.

### Table 1 Clinical trials on antispasmodics that fulfilled inclusion criteria.

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Medication</th>
<th>Treatment period (weeks)</th>
<th>Diagnostic criteria</th>
<th>Jadad</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levy 1977²⁷</td>
<td>Pinaverium bromide 150 mg</td>
<td>2</td>
<td>Clinical</td>
<td>3</td>
</tr>
<tr>
<td>Delmont 1981²⁸</td>
<td>Pinaverium bromide 150 mg</td>
<td>4</td>
<td>Clinical</td>
<td>4</td>
</tr>
<tr>
<td>Connell 1965²⁹</td>
<td>Mebeverine 400 mg</td>
<td>12</td>
<td>Clinical</td>
<td>5</td>
</tr>
<tr>
<td>Tasman-Jones 1973³⁰</td>
<td>Mebeverine 400 mg</td>
<td>4</td>
<td>Clinical</td>
<td>4</td>
</tr>
<tr>
<td>Berthelot 1981³¹</td>
<td>Mebeverine 400 mg</td>
<td>8</td>
<td>Clinical</td>
<td>4</td>
</tr>
<tr>
<td>Kruis 1986³²</td>
<td>Mebeverine 400 mg</td>
<td>16</td>
<td>Clinical</td>
<td>4</td>
</tr>
<tr>
<td>Secco 1983³³</td>
<td>Mebeverine 400 mg</td>
<td>4</td>
<td>Clinical</td>
<td>4</td>
</tr>
<tr>
<td>Enck 2005³⁴</td>
<td>Mebeverine Not reported</td>
<td>4</td>
<td>Clinical</td>
<td>4</td>
</tr>
<tr>
<td>Barbier 1981³⁵</td>
<td>Otilonium 320 mg</td>
<td>2</td>
<td>Clinical</td>
<td>3</td>
</tr>
<tr>
<td>Clave 2011²⁰</td>
<td>Otilonium 120 mg</td>
<td>15</td>
<td>Rome II</td>
<td>5</td>
</tr>
<tr>
<td>Baldi 1991³⁶</td>
<td>Otilonium 120 mg</td>
<td>4</td>
<td>Clinical</td>
<td>2</td>
</tr>
<tr>
<td>Bataglia 1998³⁷</td>
<td>Otilonium 120 mg</td>
<td>15</td>
<td>Clinical</td>
<td>3</td>
</tr>
<tr>
<td>Castiglione 1991³⁸</td>
<td>Otilonium 120 mg</td>
<td>12</td>
<td>Clinical</td>
<td>2</td>
</tr>
<tr>
<td>Glende 2002³⁹</td>
<td>Otilonium 120 mg</td>
<td>15</td>
<td>Clinical</td>
<td>3</td>
</tr>
<tr>
<td>Clave 2011³¹</td>
<td>Otilonium 120 mg</td>
<td>15</td>
<td>Rome II</td>
<td>5</td>
</tr>
<tr>
<td>Ritchie 1979⁴⁰</td>
<td>Hyoscine 40 mg</td>
<td>4</td>
<td>Clinical</td>
<td>4</td>
</tr>
<tr>
<td>Nigam 1994⁴¹</td>
<td>Hyoscine 40 mg</td>
<td>4</td>
<td>Clinical</td>
<td>3</td>
</tr>
<tr>
<td>Shafer 1990⁴²</td>
<td>Hyoscine 30 mg</td>
<td>4</td>
<td>Clinical</td>
<td>3</td>
</tr>
<tr>
<td>Fielding 1980³³</td>
<td>Trimebutine 600 mg</td>
<td>24</td>
<td>Clinical</td>
<td>3</td>
</tr>
<tr>
<td>Moshal 1979⁴⁴</td>
<td>Trimebutine 600 mg</td>
<td>4</td>
<td>Clinical</td>
<td>4</td>
</tr>
<tr>
<td>Luttecke 1975⁴⁵</td>
<td>Trimebutine 600 mg</td>
<td>3 (days)</td>
<td>Clinical</td>
<td>2</td>
</tr>
<tr>
<td>Luttecke 1980³⁶</td>
<td>Trimebutine 300 mg</td>
<td>3 (days)</td>
<td>Clinical</td>
<td>2</td>
</tr>
<tr>
<td>Mitchell 2002³⁷</td>
<td>Alverine 120 mg</td>
<td>12 (days)</td>
<td>Clinical</td>
<td>?</td>
</tr>
<tr>
<td>Wittmann 2010⁴⁸</td>
<td>Alverine/simethicone 60/300 mg</td>
<td>4</td>
<td>Rome III</td>
<td>5</td>
</tr>
<tr>
<td>Page 1981⁴⁹</td>
<td>Dicycloverine 160 mg</td>
<td>2</td>
<td>Clinical</td>
<td>4</td>
</tr>
<tr>
<td>Remes-Troche 2011²¹, Schmulson 2011²²</td>
<td>Pinaverium/simethicone 200/600 mg</td>
<td>12</td>
<td>Rome III</td>
<td>5</td>
</tr>
</tbody>
</table>

The table shows all trials initially considered for analysis. Those with a Jadad score below 3 were subsequently eliminated. Total daily dosages are described.

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### Inclusion criteria

The following criteria were used for selecting the studies: Randomized controlled trials that included subjects over 16 years of age, a diagnosis of IBS based on accepted clinical criteria (Rome I, II or III), or diagnostic criteria supplemented with specific investigations when needed. Antispasmodic agents versus placebo studies were included when there was a minimum 14-day treatment period. Treatment response was evaluated by the global improvement

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### Table 2 Recommendations by Sacks for conducting a meta-analysis.

Search of the literature  
List of trials analyzed  
Treatment assignment  
Ranges of patient characteristics, diagnoses and treatments  
Combinability criteria  
Measurement  
Control and Measurement of potential bias  
Statistical analysis  
Sensitivity analysis  
Application of results  
Remaining problems

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**Figure 1** Review process flowchart.
of symptoms or abdominal pain (reported by patients or physicians), abdominal distention/bloating, and frequency of adverse events. Methodological quality was evaluated using the Jadad scale\textsuperscript{12} (Table 3). This scoring scale evaluates each trial according to the quality of the scientific description of the randomization method. The scale ranges from 0 to 5 points: A score of 2 or less is considered low quality and 3 or higher is considered high quality.\textsuperscript{12-14} The present review only included studies with a Jadad score of 3 or above.

### Statistical analysis

The Critical Appraisal Skills Program (CASP) was used with Excel for Windows 2000 (Microsoft, USA) for calculating the meta-analysis, and the Comprehensive Meta-Analysis V2\textsuperscript{20} by Biostat, Inc. was also used. Each analysis was run in accordance with standard methodological procedures using the following determinations: a test of heterogeneity\textsuperscript{15} between active versus control group results. This was considered significant when $p<0.10$ and/or the value of $I^2 > 25\%$. Antispasmodic efficacy was defined according to the Peto method.\textsuperscript{16} In addition, a funnel plot graph\textsuperscript{17} was used to evaluate publication bias. Finally, the Number Needed to

### Table 3  Jadad Score Items.

<table>
<thead>
<tr>
<th>Item</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was the study described as randomized (this includes words such as randomly, random, and randomization)?</td>
<td>0/1</td>
</tr>
<tr>
<td>Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc.)?</td>
<td>0/1</td>
</tr>
<tr>
<td>Was the study described as double blind?</td>
<td>0/1</td>
</tr>
<tr>
<td>Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc.)?</td>
<td>0/1</td>
</tr>
<tr>
<td>Was there a description of withdrawals and dropouts?</td>
<td>0/1</td>
</tr>
<tr>
<td>Deduct one point if the method used to generate the sequence of randomization was described but was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.)*</td>
<td>-1</td>
</tr>
<tr>
<td>Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy)*</td>
<td>-1</td>
</tr>
</tbody>
</table>

0=No; 1=Yes; -1=Point deduction*

### Results

#### Included randomized clinical trials

A total of 450 publications were identified from 1960 to 2011. Twenty-seven studies fulfilled the inclusion criteria and 23 were included in the meta-analysis after the Jadad score was determined. Nine specific agents were tested as monotherapies, plus the alverine/simethicone and pinaverium/simethicone combinations. For the global assessment endpoint, a total of 2585 patients were included; 1297 were allocated to active treatment groups and 1288 to the placebo group. Of these trials, 6 studied mebeparine, 7 onitronium, 3 hyoscine, 2 trimubutine, one alverine plus simethicone (alverine/simethicone), one dicyclomine, 2 pinaverium bromide, and one pinaverium bromide plus simethicone (pinaverium bromide/simethicone). Despite the systematic search for trials with high quality criteria, not all trials reported the effect on all the studied outcomes, i.e. global assessment, pain, abdominal distention/bloating, and adverse events, and therefore a different number of trials was considered for each tested variable.

Heterogeneity testing was not significant ($p>0.05$), allowing the use of the Peto method and fixed effects. Publishing bias evaluation was tested using the funnel plot shown in Figures 2 and 3.

#### Meta-analysis

**Patient global assessment**

Of the 27 trials included for the global assessment analysis, only 18 had sufficient data for consideration. The total sample included 2585 patients, with 1297 allocated to the treatment group. Global assessment with an OR of 1.55 and a 95\%CI of 1.33 to 1.83 was confirmed for all antispasmodics (Fig. 4). Based on the Peto method, a significant difference favoring the alverine/simethicone combination and onitronium was observed. The OR for onitronium was 2.03 (95\% CI 1.49-2.77), and it was 1.76 (95\%CI 1.18-2.61) for the alverine/simethicone combination. The OR for pinaverium bromide was 1.48 (95\%CI 0.95-4.63), as shown in Figure 4.

Figure 2  Publication bias assessment funnel plot for trials considered in overall improvement.

Treat (NNT)\textsuperscript{18} was determined using the formula NNT=1-TBE (1-OR)/TBE divided by TBE (1-TBE) (1-OR).
have proposed that antispasmodic therapy may be effective for abdominal pain relief. A total of 13 trials contained enough data to evaluate pain relief. They included a total of 2394 patients, 1053 allocated to otilonium and 409 to the alverine/simethicone combination treatment; both providing the highest number of patients for a particular therapy. Antispasmodics tested for abdominal pain relief showed an OR of 1.52 (95%CI 1.28 to 1.80), favoring these agents when compared with placebo. Complete results are shown in Figure 5.

The results for the efficacy analysis of abdominal distention/bloating relief are shown in Figure 6; however, few trials appropriately report this effect. Although efficacy is borderline with an OR of 1.455 (95%CI 1.17-1.81), there is a consistent trend of antispasmodics as a group to relieve abdominal distention/bloating. The combination pinaverium/simethicone showed an OR of 1.455 (95%CI 1.11-9.91).

Rate of adverse events (safety)
The OR for the antispasmodic treatment group was 0.738 (95% CI 0.54-0.98). Results are shown in Figure 7. Previous meta-analyses17,18,19 have shown antispasmodic treatments to be safe. All trials included in the present meta-analysis consistently showed safety, corroborating the safe profile for these agents demonstrated in the most recent reports.20,21

Number Needed to Treat (NNT)
The NNT was calculated only for the antispasmodics showing a significant value of 10 in global assessment (95% CI 6.0-41.0). The NNT for global improvement was 7 for Otilonium and 8 for Alverine/simethicone and 8 and 11 for pain relief, respectively.

Discussion
Decision-making in medical practice today often requires answers to concrete questions. In 1976 Glass1 proposed a set of different statistical tests in the meta-analysis for quantitative and qualitative analyses based on results from independent trials. Previous studies mention the discrepancy among different trials due to a lack of uniformity in diagnostic criteria. In the present analysis, we decided to remove those trials that had a Jadad score below 3, in other words, of low quality (Table 3). We felt that an analysis of low quality trials could be a significant source of bias for the interpretation of results.

The publication bias assessment funnel plots of trials considered for pain relief (Figure 3) and abdominal distention/bloating relief (Figure 4) are shown. Funnel plots of standard error by log odds ratio are useful for detecting bias in meta-analysis. The vertical lines represent the direction of bias, and the spread of the data points indicates the presence of bias. A funnel plot is symmetric if there is no publication bias, and it is skewed if there is evidence of bias.

Table 3: Number Needed to Treat (NNT) for Pain Relief

The table shows the NNT for pain relief for different antispasmodics. The NNT is calculated to estimate the number of patients who need to be treated to prevent one additional adverse event. A lower NNT indicates a more effective treatment.

Evidence of publication bias is shown in the funnel plots for both pain relief and abdominal distention/bloating relief (Figures 3 and 4). In the funnel plot for pain relief, there is an asymmetry on the left side, suggesting a possible publication bias. In the funnel plot for abdominal distention/bloating relief, the funnel is more symmetric, indicating less bias.

Overall, the meta-analysis demonstrates that antispasmodics are effective for pain relief and abdominal distention/bloating relief, with the most significant results observed for abdominal pain relief. Antispasmodics may be considered as an effective treatment option for IBS symptoms.

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For global assessment, only otilonium 2.035 (95% CI 1.49-2.77) and the alverine/simethicone combination 1.76 (95% CI 1.18-2.61) showed significant values. For pain relief, alverine/simethicone 1.48 (95% CI 1.00-2.19) and otilonium 1.83 (95% CI 1.43-2.34) demonstrated significant values. Recently, two abstracts that studied the combination of pinaverium bromide/simethicone came to interesting conclusions. They reported that pinaverium bromide/simethione was effective for relieving abdominal pain in patients with active IBS and in improving bloating, but not visible abdominal distension. These results suggest an effect on visceral perception. However, the published abstracts did not contain the data necessary for the current meta-analysis. Therefore, the authors were contacted.

Figure 5  Efficacy of antispasmodics on pain relief. The vertical bars represent the difference in the response rates between antispasmodics (Treatment) and placebo. The white circles represent the OR and the horizontal lines the 95% CI. Overall response of each type of antispasmodic is represented by the black diamonds. Antispasmodics were effective on abdominal pain (Overall). Specifically by type of antispasmodics, only Alverine/s and Otilonium were effective. Alverine/s: Alverine/simethicone; Pinaverium/s: Pinaverium/simethione.

Figure 6  Efficacy of antispasmodics on abdominal distension/bloating. The vertical bars represent the difference in the response rates between antispasmodics (Treatment) and placebo. The white circles represent the OR and the horizontal lines the 95% CI. Overall response of each type of antispasmodic is represented by the black diamonds. Antispasmodics were effective on abdominal distension/bloating (Overall). Specifically by type of antispasmodics, only the Pinaverium/s (Pinaverium+Simethione) combination was effective.
for the completion of the required information. This is the first meta-analysis to incorporate the combination of antispasmodics with an anti-foaming agent that may constitute a new therapeutic option.

The combination pinaverium/simethicone resulted in an OR of 1.45 (95% CI 1.11-1.91) for bloating. The effect with the addition of simethicone was greater than that of the antispasmodic alone, and was similar to the effect shown by the alverine/simethicone combination. The NNT, calculated from the systematic review or meta-analysis of randomized clinical trials, is a valuable aid in making clinical decisions. The NNT was recently included in a meta-analysis of medications to treat IBS. Results showed a wide range of NNT values; from 4 to 20 for 5-HT3 antagonists and 5HT4 agonists. Other analyses also indicated antispasmodic medications with a wide NNT range; from 3 to 25 depending on the specific antispasmodic tested. We only calculated the NNT for the global assessment and pain relief in those medications with a significant OR and 95% CI. We found that the antispasmodics with the lowest NNT to achieve global improvement were oltionium and the alverine/simethicone combination; an NNT of 7 for oltionium and 8 for the combination. For pain relief, the NNT was 7 for oltionium and 11 for alverine/simethicone. The NNT from a meta-analysis should be viewed with caution, since these data vary according to patient baseline risk and this could be significantly different among the trials included in the analysis.

The weaknesses in this meta-analysis were the variability among the groups of patients across different trials and the insufficiency of data such as treatment adherence and the length of time during which each patient took the medications.

Conclusions

The lack of methodological coherence in trials published before 1995 makes it difficult to reach final conclusions about the efficacy of certain medications. Publication of the Rome II and III trial design recommendations for functional bowel disorders is an advance in the methodological quality of antispasmodic trials; however, few of them include the recent diagnostic criteria in their design. Antispasmodic agents are better than placebo for treating IBS, with almost no serious adverse events. The alverine/simethicone combination and oltionium showed a NNT of 7 to 11 with significant results for global assessment and pain relief. Pinaverium/simethicone also showed effectiveness in relieving bloating and had better results than pinaverium alone. Future clinical investigations should include the combination of antispasmodics and anti-foaming agents to improve the clinical effect of antispasmodics.

Financial disclosure

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Conflict of interest

The authors have no conflicts of interest to declare.

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References


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