Antispasmodics for Chronic Abdominal Pain: Analysis of North American Treatment Options

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Chronic abdominal pain is a common gastrointestinal (GI) symptom that characterizes many functional GI disorders/disorders of gut-brain interaction, including irritable bowel syndrome, functional dyspepsia, and centrally mediated abdominal pain syndrome. The symptoms of abdominal pain in these highly prevalent disorders are often treated with antispasmodic agents. Antispasmodic treatment includes a broad range of therapeutic classes with different mechanisms of action, including anticholinergic/antimuscarinic agents (inhibition of GI smooth muscle contraction), calcium channel inhibitors (inhibition of calcium transport into GI smooth muscle), and direct smooth muscle relaxants (inhibition of sodium and calcium transport). The aim of this review article was to examine the efficacy and safety of antispasmodics available in North America (e.g., alverine, dicyclomine, hyoscine, hyoscyamine, mebeverine, otilonium, pinaverium, and trimebutine) for the treatment of chronic abdominal pain in patients with common disorders of gut-brain interaction. For the agents examined, comparisons of studies are limited by inconsistencies in treatment dosing and duration, patient profiles, and diagnostic criteria employed. Furthermore, variability in study end points limits comparisons. Risk of selection, performance, detection, attrition, and reporting bias also differed among studies, and in many cases, risks were considered “unclear.” The antispasmodics evaluated in this review, which differ in geographic availability, were found to vary dramatically in efficacy and safety. Given these caveats, each agent should be considered on an individual basis, rather than prescribed based on information across the broad class of agents.

INTRODUCTION

Abdominal pain is the most common gastrointestinal (GI) symptom prompting an office-based outpatient or emergency department visit in the United States (1). Functional GI disorders, now more formally described as disorders of gut-brain interaction (DGBI), such as irritable bowel syndrome (IBS), functional dyspepsia (FD), and centrally mediated abdominal pain syndrome (CAPS), are the underlying cause of abdominal pain in many patients (2). IBS is a chronic disorder characterized by recurring abdominal pain associated with disordered bowel habits (3). According to Rome IV criteria, the diagnosis of IBS requires patients to have abdominal pain ≥1 day per week in the previous 3 months (3). FD is also a pain-prevalent disorder (4). Rome IV diagnostic criteria for FD require patients to present with bothersome epigastric pain (≥1 day per week), epigastric burning (≥1 day per week), postprandial fullness (≥3 days per week), or early satiation (≥3 days per week) during the previous 3 months (5). Centrally mediated abdominal pain syndrome is characterized by persistent abdominal pain that interferes with daily activities; it is not associated with altered bowel habits (6,7).

Functional GI disorders are highly prevalent, resulting in impaired health-related quality of life and increased healthcare utilization (8,9). The prevalence of IBS varies based on the criteria used and the populations studied (10). In Canada and the United States, the prevalence of IBS based on Rome IV criteria has been estimated at 4.7% and 4.8%, respectively; the prevalence of IBS based on Rome III criteria was estimated at 9.7% and 8.8% in the same countries and ranged between 6.5% and 8.7% in Mexico (10,11). The prevalence of FD similarly varies depending on the criteria used to define it (12). In the United States, the prevalence of FD has been estimated at 12% based on Rome IV criteria (9,13). Data for the prevalence of CAPS are currently lacking.

Alterations in GI motility and visceral sensation play a role in the development of abdominal pain in many patients; antispasmodics function as smooth muscle relaxants or antagonists to block excitatory neuromuscular neurotransmission (14,15). Antispasmodics are considered a mainstay treatment option for patients with IBS (Table 1; Figure 1) (16–28); indeed, online survey data indicated that 30% of 1,094 patients with IBS with diarrhea (IBS-D) previously used antispasmodics (29). However, antispasmodic therapies differ in their mechanism(s) of action, with the major classes categorized as anticholinergic/antimuscarinic agents, calcium channel inhibitors, and direct smooth muscle relaxants (30). Anticholinergic/antimuscarinic agents inhibit GI smooth muscle contraction, in part, by blocking calcium transport through calcium channels (31); furthermore, these agents decrease colonic motility (32). Calcium channel inhibitors prevent the influx of calcium into GI smooth muscle, thus inhibiting smooth muscle contraction (33). Direct smooth muscle relaxants affect GI smooth muscle by inhibiting sodium influx through sodium channels and preventing subsequent

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influx of calcium, all of which leads to inhibition of duodenal and colonic contraction (17,34–36).

A 2014 American Gastroenterological Association guideline noted that antispasmodics could be used to treat IBS symptoms; a new guideline is currently under development (37). The American Gastroenterological Association provided a conditional recommendation for antispasmodics based on the low certainty of evidence (e.g., methodologic limitations and publication bias) (37). In addition,
Data were based on continuous, rather than as-needed, use, and not all antispasmodics evaluated are currently available in the United States (37). The 2018 American College of Gastroenterology (ACG) monograph suggested that certain antispasmodic drugs (i.e., dicyclomine, hyoscine, cimetropium, drotaverine, otilonium, and pinaverium) may improve IBS symptoms, although this was a weak recommendation based on the very low quality of evidence (38). Importantly, data are limited for the antispasmodics currently available in the United States. Recently published ACG guidelines (2021) for the treatment of IBS, which used a GRADE approach, do not recommend the use of smooth muscle antispasmodics currently available in the United States for the treatment of IBS (39). Although antispasmodics are frequently prescribed for the treatment of FD, a 2017 joint ACG/Canadian Association of Gastroenterology dyspepsia guideline does not recommend their use for this condition (40,41). There are currently no formal guidelines or recommendations regarding the use of antispasmodics for treating CAPS.

Given the discrepancies in recent recommendations, the aim of this review was to examine the efficacy and safety of individual antispasmodics available in North America (i.e., alverine, dicyclomine, hyoscine, hyoscymine, mebeverine, otilonium, pinaverium, and trimebutine; Table 1; Figure 1) for the treatment of chronic abdominal pain in patients with these pain-predominant disorders.

**METHODS**

PubMed and Embase were searched electronically for full-length articles available through December 2020 (start date, 1963 [PubMed] or 1947 [Embase] to allow complete database review) that reported the results of randomized, placebo-controlled, parallel, or crossover studies of antispasmodics conducted in adults with abdominal pain because of IBS, dyspepsia/FD, and CAPS. Antispasmodics currently available in North America (United States, Canada, and Mexico) were included in this search. Search terms were “abdominal pain,” “irritable bowel syndrome,” “dyspepsia,” “centrally mediated abdominal pain syndrome,” “antispasmodic,” “parasympatholytic,” “alverine,” “dicyclomine,” “hyoscine,” “hyoscymine,” “mebeverine,” “otilonium,” “pinaverium,” and “trimebutine.” Reference lists from relevant review articles and the Cochrane Central Register for Controlled Trials were searched for additional references. Relevant articles published in languages other than English were translated using Google Translate. Articles eligible for inclusion examined improvement in chronic abdominal pain as an efficacy outcome in functional GI disorders in adults. Studies evaluating peppermint oil formulations were excluded from this review, as peppermint oil is considered a unique treatment class for these disorders. Trials of <10 days’ treatment duration were also excluded.

The Cochrane Collaboration’s “Risk of Bias” tool was used to assess the risk of bias in articles included in the review (42). Briefly, risk of bias was rated as “low,” “high,” or “unclear” for random allocation sequence generation and concealment; blinding of patients, personnel, and outcome assessments; adequately addressing incomplete outcome data; and selective outcome reporting (42).

**Table 1. Mechanisms of action for antispasmodic agents available in North America**

| Agent            | Anticholinergic/antimuscarinic activity | Calcium channel inhibitor | Opioid receptor agonist | Potassium channel blocker | Smooth muscle relaxant | Geographic availability |
|------------------|----------------------------------------|---------------------------|-------------------------|---------------------------|------------------------|-------------------------|
| Alverine (19)    | ✓                                      |                           |                         |                           |                        | Mexico                  |
| Dicyclomine (18) | ✓                                      |                           |                         |                           |                        | Canada, the United States |
| Hyoscine (20–22) | ✓                                      |                           |                         |                           |                        | Canada, the United States |
| Hyoscymine (23)  | ✓                                      |                           |                         |                           |                        | The United States       |
| Mebeverine (17)  | ✓                                      |                           |                         |                           |                        | Mexico                  |
| Otilonium (24)   | ✓                                      | ✓                         |                         |                           |                        | Mexico                  |
| Pinaverium (25,26)| ✓                                      |                           |                         |                           |                        | Canada, Mexico          |
| Trimebutine (27,28) | ✓                                      | ✓                         | ✓                      | ✓                         | ✓                      | Canada, Mexico          |

**Figure 2. Summary of literature search.**
| Study details          | Patient population               | Treatment                  | Efficacy outcome(s)                                                                 | Safety outcome(s)                                                                 | Study limitation(s)                      |
|-----------------------|----------------------------------|----------------------------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-----------------------------------------|
| Dicyclomine           |                                  |                            |                                                                                      |                                                                                 |                                         |
| Hass, 1967(43)         | Pts with IBS                     | Dicyclomine 10 mg t.i.d.   | Pts receiving dicyclomine had greater preference for dicyclomine vs PBO related to symptom improvement (symptoms not specified; no statistics) | No significant difference in AE rates between dicyclomine and PBO               | Single center                           |
| R, DB, C, crossover    | Age not reported                 | (n = 72) vs PBO (n = 72)   | Duration: 10 d                                                                       |                                                                                  | Diagnostic criteria not reported        |
| The United Kingdom     |                                  |                            |                                                                                      |                                                                                  | Pts not subgrouped by the type of IBS  |
|                       |                                  |                            |                                                                                      |                                                                                  | Abdominal pain not assessed separately |                                         |
|                       |                                  |                            |                                                                                      |                                                                                  | Crossover study design                 |
|                       |                                  |                            |                                                                                      |                                                                                  | washout period not reported            |
|                       |                                  |                            |                                                                                      |                                                                                  | Short treatment duration               |
| Page and Dirnberger,   | Pts with IBS                     | Dicyclomine 40 mg q.i.d.   | Hyoscine improved (completely well/gone, better) PGA vs PBO at 2 wk: overall: 94%  | Hyoscine were reported by 69% of pts (n = 33) receiving dicyclomine 160 mg/d for 2 wk | Single center                           |
| 1981 (18)             | Pt age inclusion criterion: 18-65 | (n = 34) vs PBO (n = 37)   | 94% vs 54%; abdominal pain: 94% vs 57%; abdominal tenderness: 94% vs 62%; bowel | AEs reported in 16% of pts receiving PBO Most common AEs with hyoscine: blurred | Small sample size                       |
| R, DB, C, P           | yr                               | Duration: 2 wk             | habits: 85% vs 54% Dicyclomine improved (completely well/gone, better) general condition by self-assessment vs PBO at 2 wk: 84% vs 54% Greater percentage of pts receiving dicyclomine experienced a clinically meaningful (>75%) decrease from baseline in daily abdominal pain duration vs PBO at 2 wk: 56% vs 41% | disconnection in 7 pts                 | Pts not subgrouped by the type of IBS  |
|                       | England                          |                            |                                                                                      |                                                                                  | Abdominal pain not assessed separately |
|                       |                                  |                            |                                                                                      |                                                                                  |                                         |
| Ritchie and Truelove,  | Pts with IBS                      | Hyoscine 10 mg q.i.d.      | Hyoscine improved symptoms from baseline vs PBO at 3 mo: 46% vs 29%                  |                                                                                  |                                         |
| 1979 (44)             | Pt age range: 16-69 yr           | (n = 48) vs PBO (n = 48)   | Duration: 3 mo                                                                       |                                                                                  |                                         |
| R, DB, C              | England                          |                            |                                                                                      |                                                                                  |                                         |
|                       |                                  |                            |                                                                                      |                                                                                  |                                         |
| Nigam et al., 1984    | Pts with IBS                      | Hyoscine (n = 84) vs PBO   | Hyoscine improved (rating of better) symptoms from baseline vs PBO at 12 wk:        |                                                                                  |                                         |
| (45)                  | Pt age range: 16-68 yr           | (n = 84) vs PBO (n = 84)   | 45.3% vs 29.7% (P < 0.05)                                                            |                                                                                  |                                         |
|                       | India                            | Duration: 12 wk            |                                                                                      |                                                                                  |                                         |
|                       |                                  |                            |                                                                                      |                                                                                  |                                         |
Each author independently evaluated risk of bias, with authors reaching consensus on any disagreements in ratings.

RESULTS
The PubMed and Embase database searches identified 492 publications (Figure 2). Eleven additional references were identified from reference lists in relevant review articles and the Cochrane Central Register for Controlled Trials. A total of 26 studies, including 23 IBS and 1 FD, were included. In addition, 2 studies of recurrent abdominal pain with cramping (APC) met criteria for inclusion. No studies evaluating antispasmodics in patients with CAPS were identified.

### Antispasmodics for IBS

#### Anticholinergic/antimuscarinic antispasmodics.

**Dicyclomine.** In 2 randomized, placebo-controlled studies, dicyclomine improved symptoms of IBS relative to placebo (Table 2) (18,43–49). One study reported no difference in adverse event (AE)
### Table 3. Efficacy and safety of calcium channel inhibitors in IBS studies

| Study details                  | Patient population                  | Treatment                  | Efficacy outcome(s)                                                                 | Safety outcome(s)                  | Study limitation(s)* |
|-------------------------------|-------------------------------------|----------------------------|-------------------------------------------------------------------------------------|------------------------------------|----------------------|
| **Alverine**                  |                                     |                            |                                                                                     |                                    |                      |
| Mitchell et al., 2002 (50)    | Pts with IBS (Rome II criteria)      | Alverine 120 mg t.i.d.     | Comparable % of pts with improvement (scale range, 0–3 (absence of symptoms to severe/very frequent symptoms)) in symptom intensity and frequency from baseline to week 12 vs PBO: abdominal pain intensity (66.0% vs 57.7%) and frequency (67.9% vs 69.2%); bloating intensity (47.2% vs 51.9%) and frequency (45.3% vs 53.8%); overall well-being intensity (50.9% vs 44.2%) and frequency (49.1% vs 42.3%) P < NS for all comparisons | Pts with ≥1 AE with alverine vs PBO: 39.6% vs 48.1%; 5 nervous system-related mild AEs with alverine (not tx related) | Pts not subgrouped by the type of IBS |
| Wittmann et al., 2010          | Pts with IBS (Rome III criteria)     | Alverine 60 mg/           | Alverine/simethicone improved abdominal pain intensity based on 100-mm VAS vs PBO at week 4: 40.0 mm vs 50.0 mm (P = 0.047) Alverine/simethicone had greater % of abdominal pain responders (i.e., pts with decrease from baseline ≥50% in VAS score at week 4) vs PBO: 46.8% vs 34.3% (OR, 1.3; 95% CI, 1.1–1.6; P = 0.01) | AEs with alverine/simethicone vs PBO: 17.9% vs 24.4%; 1 serious AE with alverine (traumatic tendon rupture (not tx related)) Tx-related AEs: 3.4% vs 5.9% AEs leading to study withdrawal with alverine/simethicone: eye swelling (n = 1); with PBO: dizziness (n = 1) and pain in extremities (n = 1) | Pts not subgrouped by the type of IBS |
| Baldi et al., 1991 (52)        | Pts with IBS                         | Otilonium 40 mg t.i.d.    | Otilonium numerically improved abdominal pain intensity (assessed by 10-mm VAS) vs PBO (P = NS) and significantly improved frequency (episodes/d) vs PBO (P < 0.05) during weeks 3–4 Otilonium improved bloating intensity, assessed by 10-mm VAS, from baseline through week 4 vs PBO (P < 0.01) Daily bowel movement frequency did not differ between groups | 1 AE (mild nausea) with otilonium and no AEs with PBO | Small sample size Pts not subgrouped by the type of IBS |
| Battaglia et al., 1998 (53)    | Pts with IBS                         | Otilonium 40 mg t.i.d.    | Otilonium improved abdominal pain intensity (rating of absent, mild/moderate) from baseline to week 15 vs PBO (% of pts): 42.4% vs 34.0% (OR, 1.4; 95% CI, 0.9–2.2; P = NS) | 3 AEs leading to study withdrawal: otilonium (n = 2; dizziness and prostate disturbance); PBO (n = 1; skin rash) | Pts not subgrouped by the type of IBS |
Table 3. (continued)

| Study details                  | Patient population            | Treatment                          | Efficacy outcome(s)                                                                 | Safety outcome(s)                                      | Study limitation(s)  |
|-------------------------------|-------------------------------|-----------------------------------|------------------------------------------------------------------------------------|-------------------------------------------------------|-----------------------|
| Clavé et al., 2011 (54)       | Pts with IBS (Rome II criteria) | Otilonium 40 mg t.i.d. (n = 179) vs PBO (n = 177) for 15 wk | Otilonium improved abdominal pain frequency (rating scale, 0 [0 episodes], 1 [1–3 episodes]) from baseline to week 15 vs PBO: −0.9 vs −0.6 (P = 0.04) Otilonium and PBO improved symptom intensity (abdominal pain, bloating, stool consistency, and presence of mucus; rating of excellent) from week 5 to week 15 (all comparisons, P < 0.0001) Otilonium improved stool frequency from baseline to week 15 (P = 0.004) Otilonium and PBO improved pt judgment of global efficacy (abdominal pain intensity, bloating intensity, stool consistency and frequency; rating of excellent) from week 5 to week 15 (both P < 0.0001 vs baseline; otilonium vs PBO at week 15, P = 0.047) | Pts with ≥1 AE with otilonium vs PBO: 24% vs 17% Tx-related AEs: 3 with otilonium (dry mouth [n = 2] and nausea [n = 1]) vs 0 with PBO AEs leading to study withdrawal: 1 in each tx group | • Pts not subgrouped by the type of IBS |
| Chmielewska-Wilkoń et al., 2014 (55) | Pts with IBS (Rome II criteria) | Otilonium 20 mg t.i.d. (n = 24), 40 mg t.i.d. (n = 23), or 80 mg t.i.d. (n = 23) vs PBO (n = 23) for 4 wk | Otilonium (any dose) and PBO reduced the intensity or frequency of abdominal discomfort, bloating, or pain from baseline to week 4; however, no significant differences were seen between groups at week 4 Otilonium 80 mg improved intensity of abdominal discomfort, bloating, or pain from baseline to week 4; however, no significant differences were seen between groups at week 4 | Tx-related AEs: 3 with otilonium (dry mouth, headache, nausea); 1 with PBO (headache) No serious AEs reported | • Small sample size • Pts not subgrouped by the type of IBS |
| Study details         | Patient population | Treatment                  | Efficacy outcome(s)                                                                 | Safety outcome(s) | Study limitation(s) |
|----------------------|--------------------|----------------------------|------------------------------------------------------------------------------------|-------------------|---------------------|
| Levy et al., 1997 (56) | R, DB, C           | Pts with IBS               | Pinaverium 50 mg t.i.d. (n = 25) vs PBO (n = 25) Duration: 15 d                   | Pinaverium        | Small sample size   |
|                      |                    |                            | Pinaverium improved global symptoms (rating of good) after 15 d vs PBO: 60% vs 16% |                   | Single center       |
|                      |                    |                            | Pinaverium improved symptoms from baseline to day 15 vs PBO for abdominal pain     |                   | Diagnostic criteria not reported |
|                      |                    |                            | (P < 0.01), abdominal symptoms (P < 0.05), and GI transit (P < 0.01)               | Constipation:     | Pts not subgrouped by the type of IBS |
|                      |                    |                            |                                                                                   | pinaverium        | Short study duration |
|                      |                    |                            |                                                                                   | (n = 2); PBO (n = 3) |                     |
| Delmont, 1981(57)    | R, DB, C           | Pts with IBS               | Pinaverium t.i.d. (n = 30) vs PBO (n = 30) Duration: 30 d                         | Pinaverium:       | Small sample size   |
|                      |                    |                            | More pts indicated a pain intensity of 0 in the pinaverium group vs pts in the PBO | dry mouth         | Single center       |
|                      |                    |                            | group: 66.7% vs 30.8%; fewer pts reported a pain intensity of 2 or 1 (range 0 [no | (n = 1), and epigastralgia (n = 1) | Pts not subgrouped by the type of IBS |
|                      |                    |                            | pain] to 2 [strong pain]) in the pinaverium group vs PBO: 25.9% vs 65.4%           | PBO: leg cramps   |                     |
|                      |                    |                            |                                                                                   | (n = 1), fatigue (n = 1), and malaise (n = 1) |                     |
| Awad et al., 1995 (58)| R, DB, C           | Pts with IBS               | Pinaverium 50 mg t.i.d. (n = 19) vs PBO (n = 19) Duration: 3 wk                   | Pinaverium:       | Small sample size   |
|                      |                    |                            | Pinaverium and PBO improved the duration of abdominal painb from baseline to week 3: | headache          | Single center       |
|                      |                    |                            | pinaverium ("several hours" to "a few minutes"); score 5.2–2; P = 0.01; PBO ("several hours" to "about a half hour"); score 5.2–3.1; P = NS; and pinaverium vs PBO at week 3: P = 0.02 | PBO: no AEs reported | Pts not subgrouped by the type of IBS |
|                      |                    |                            | Abdominal pain severity improved from baseline to week 3: pinaverium ("severe" to  |                   |                     |
|                      |                    |                            | "slight"); score 4.9–2.3; P = 0.01; PBO ("severe" to "moderate"); and score 5.0–3.0; |                   |                     |
|                      |                    |                            | P = 0.01)                                                                               |                   |                     |
|                      |                    |                            | Abdominal pain responsec for pinaverium vs PBO (% pts) at week 2: 13.3% vs 6.2% (OR, 2.3; 95% CI, 1.2–4.6; P < 0.05); at week 4: 38.1% vs 16.7% (OR, 3.1; 95% CI, 1.9–4.8; P < 0.001) |                   |                     |
|                      |                    |                            | Abdominal pain responsec for pinaverium vs PBO (% pts) at week 2: 40.4% vs 16.7% (OR, 3.4; 95% CI, 2.1–5.3); Pts with ≥1 AE (pinaverium vs PBO): 18.3% vs 15.3% |                   |                     |
|                      |                    |                            | Most common AEs (pinaverium vs PBO): nausea (3.7% vs 1.9%); dizziness (3.2% vs 0.5%); abdominal discomfort (2.3% vs 1.0%); and increased blood pressure (2.3% vs 1.0%) |                   |                     |
| Zheng et al., 2015 (15) | R, DB, C           | Pts with IBS (Rome III criteria) | Pinaverium 50 mg t.i.d. (n = 218) vs PBO (n = 209) Duration: 4 wk |                  | Included only pts with IBS-D |
| Study details | Patient population | Treatment | Efficacy outcome(s) | Safety outcome(s) | Study limitation(s) |
|---------------|--------------------|-----------|--------------------|------------------|--------------------|
| Schmulson *et al.*, 2020 (59) | Pts with IBS (Rome III) Pt age inclusion criterion: 18–50 yr Mexico | Pinaverium 100 mg plus simethicone 300 mg b.i.d. (n = 140) vs PBO (n = 145) Duration: 12 wk | Pinaverium and PBO achieved 20% tx difference in overall symptom improvement at week 12 (P = 0.1) Pinaverium improved (≥30% effect size) individual symptoms, each assessed by 10-cm VAS “nothing” to “extremely intense” vs PBO at week 12: abdominal pain intensity (effect size 30%; P = 0.04), bloating intensity (effect size 33%; P = 0.02) Pinaverium improved (≥30% effect size) abdominal pain intensity (provider assessment using the 6-point Likert scale [nothing to very severe]) vs PBO at week 12 (effect size 36%; P = 0.009); no significant difference in bloating intensity for pinaverium vs PBO (effect size 26%; P = 0.09) | AEs: pinaverium, 3.3%; PBO, 4.0% SAEs: pinaverium, acute pancreatitis with hypertriglyceridemia (n = 1); PBO, brain aneurysm (n = 1) | – Primary efficacy end point of improvement in overall IBS symptoms not met – Pts aged >50 yr were excluded |
| Moshal *et al.*, 1979 (60) | Pts with IBS Pt age range: 21–42 yr South Africa | Trimebutine 200 mg t.i.d. (n = 20) vs PBO (n = 20) Duration: 4 wk | Abdominal pain, assessed using the 4-point scale (none to severe), was improved in significantly more pts treated with pinaverium vs PBO at the end of the second tx period (P < 0.001) | No AEs related to trimebutine tx were reported | – Small sample size – Single center – Diagnostic criteria not reported – Pts not subgrouped by the type of IBS – Crossover study design washout period not reported |
| Fielding, 1980 (61) | Pts with IBS Pt age range: 15–53 yr Ireland | Trimebutine 200 mg t.i.d. (n = 24) vs PBO (n = 29) Duration: 6 mo | Trimebutine and PBO did not differ in % of pts with improvement (decrease, absent) of abdominal pain at 1 mo (58% vs 55%); at 6 mo, 75% and 66% of pts had abdominal pain with trimebutine vs PBO, respectively Trimebutine and PBO resulted in improvement from baseline in or normal bowel habits at 1 mo | AEs: trimebutine, n = 10 pts; PBO, n = 7 pts Most common AEs with trimebutine: nausea (n = 2), upset stomach and shaky hands (n = 2); with PBO: dizziness (n = 2), rash (n = 2), and tiredness (n = 2) | – Small sample size – Diagnostic criteria not reported – Pts not subgrouped by the type of IBS |
rates with dicyclomine vs placebo (43), whereas the other reported that AEs occurred in a greater percentage of patients (69%) receiving dicyclomine 160 mg/d continuously for 2 weeks vs patients receiving placebo (16%; Table 2) (18). Although efficacy data were generally favorable, these studies used different doses of dicyclomine and had a short treatment duration (10 days–2 weeks) (18,43). Furthermore, 1 study had a high risk of allocation bias (see Supplementary Table, Supplementary Digital Content, http://links.lww.com/AJG/B987) because of AEs (15,18,43–66).

**Hyoscine.** Hyoscine, also known as scopolamine, is an anticholinergic/antimuscarinic agent and smooth muscle relaxant (20). In 3 studies,

| Study details | Patient population | Treatment | Efficacy outcome(s) | Safety outcome(s) | Study limitation(s)a |
|---------------|--------------------|-----------|--------------------|-------------------|---------------------|
| Ghidini et al., 1986 (62) R, DB, C Pts with IBS Pt age range: 23–66 yr Italy | Trimebutine 100 mg t.i.d. (n = 30) vs PBO (n = 30) Duration: 60 d | Trimebutine improved pain symptoms in more pts vs PBO: total relief, 53.3% vs 30.0%; partial relief, 43.3% vs 40.0% (P < 0.05) at 60 d | No clinical or biochemical AEs reported | • Small sample size • Single center • Pts not subgrouped by the type of IBS |
| Dumitras¸cu and St˘anculete, 2006 (63) R, C Pts with IBS (Rome II criteria) Pt age range: 22–71 yr Romania | Trimebutine 100 mg t.i.d. (n = 25) vs PBO (n = 25) Duration: 2 wk | Trimebutine and PBO improved intensity and frequency of GI symptoms: abdominal pain (13.1 vs 2.7 [P < 0.000] and 12.5 vs 7.7 [P < 0.05]; trimebutine vs PBO, P < 0.001) constipation (10.6 vs 7.2 [P < 0.05] and 11.4 vs 10.5 [P = NS]; trimebutine vs PBO, P < 0.001) diarrhea (6.0 vs 2.3 [P < 0.01] and 6.5 vs 5.5 [P = NS]; trimebutine vs PBO, P < 0.01) Emesis (2.2 vs 0.5 [P < 0.01] and 3.6 vs 2.8 [P = NS]; trimebutine vs PBO, P < 0.001) Nausea (8.1 vs 4.0 [P < 0.01] and 7.9 vs 5.3 [P = NS]; trimebutine vs PBO, P < 0.05) | NR | • Small sample size • Single center • Double-blind methodology not described • Pts not subgrouped by the type of IBS • Short study duration |

AE, adverse event; b.i.d., twice daily; C, controlled; CI, confidence interval; DB, double-blind; GI, gastrointestinal; IBS, irritable bowel syndrome; IBS-D, irritable bowel syndrome with diarrhea; NR, not reported; NS, not significant; OR, odds ratio; P, parallel; PBO, placebo; pts, patients; R, randomized; SAEs, serious adverse events; t.i.d., 3 times daily; tx, treatment; VAS, visual analog scale.

aSample size of <50 patients per treatment arm considered small, and treatment duration of ≤15 days considered short.

bDetermined by patient response to the statement, “How long does the pain last?”, using a 7-point scale (0 [nonexistent], 1 [a few seconds], 2 [a few minutes], 3 [about a half hour], 4 [about an hour], 5 [several hours], and 6 [all day]) (58).

cDefined as decrease from baseline ≥30% in weekly average worst abdominal pain and decrease from baseline ≥50% in days per week with Bristol Stool Scale type 6 or 7 stool (15).

dDetermined by patient response to the statement, “The treatment helped to improve my bowel problems,” using a 5-point Likert scale (0 [strongly disagree], 1 [disagree], 2 [neither agree nor disagree], 3 [agree], and 4 [strongly agree]) (59).

eOverall score range for each symptom, 0–16; based on a combination of individual symptom intensity and frequency assessed at baseline and week 2: 0 [neither agree nor disagree], 1 [slightly agree], 2 [agree], 3 [agree strongly], and 4 [strongly agree] (59).

fDetermined by patient response to the statement, “The treatment helped to improve my bowel problems.”

#15 days considered short.

$2 week.
Hyoscyamine. Hyoscyamine, an L-isomer of atropine racemate, is, like hyoscine, an anticholinergic/antimuscarinic agent and smooth muscle relaxant (23). One small crossover study (N = 40) reported that hyoscyamine 0.2 mg 3 times daily (t.i.d.) for a 2-week period (dose increased if IBS symptoms persisted) improved IBS symptoms (including pain) from baseline numerically, but not significantly, compared with placebo (P = NS; Table 2) (47). Study limitations included short treatment duration and lack of analysis by IBS subtype or abdominal pain alone. According to the authors, patients might also have been aware of treatment assignment, given the nature of the AEs reported (47).

Direct smooth muscle relaxant.

Mebeverine. The efficacy of mebeverine was examined in 2 randomized, placebo-controlled trials (Table 2) (48,49). In 1 study, 16 weeks of treatment with mebeverine 100 mg 4 times daily was less effective for patients with IBS than placebo for improving symptoms of abdominal pain and flatulence, and irregular bowel habits. No clinically relevant AEs occurred in either treatment group (48). In a second study, a 6-week treatment with mebeverine 135 mg t.i.d. in conjunction with or without use of a self-management website had no greater efficacy than placebo for improving IBS symptoms; AEs were not reported in this study (49). Limitations included small sample sizes and lack of data for IBS subtypes (48,49). Risk of bias was mostly unclear for 1 study (48), whereas another indicated a potential placebo effect on efficacy results (49).

Calcium channel inhibitors.

Alverine. Efficacy and safety were examined for alverine, a calcium channel blocker (19), in 2 randomized, placebo-controlled studies...
A comparable percentage of patients receiving alverine 120 mg t.i.d. or placebo for 12 weeks experienced improvements from baseline in the intensity and frequency of abdominal pain, bloating, and overall well-being at week 12; differences between groups did not achieve statistical significance. A lower percentage of patients receiving alverine reported ≥1 AE, compared with placebo (50). In a second study, alverine 60 mg/simethicone 300 mg t.i.d. was significantly more efficacious than placebo at improving abdominal pain in patients with IBS (P = 0.047) (51). The safety profile of alverine/simethicone was generally comparable with that of placebo (51); however, this study potentially excluded patients with more severe symptoms (51).

**Otilonium.** The efficacy and safety of otilonium were examined in 4 randomized, controlled studies (Table 3) (52–55). In 3 studies, otilonium 40 mg t.i.d. decreased abdominal pain frequency compared with placebo during weeks 3–4 (52) and at week 15 (53,54). Otilonium was associated with mild nausea in 1 study, whereas no AEs were reported with placebo (52). In another study, prostate disturbance and dizziness were reported with otilonium, and skin rash with placebo; these AEs led to study withdrawal (53). In a dose-ranging study, otilonium 20, 40, and 80 mg t.i.d. decreased the intensity and frequency of abdominal pain and bloating from baseline to 4 weeks; however, no differences between otilonium and placebo were observed after treatment (55). Treatment-related AEs with otilonium were generally comparable with placebo (55). Few details regarding treatment allocation, blinding, and participant attrition were provided for 2 of the studies (52,53); thus, the risks of bias were mostly unclear. One study was at high risk of bias for selective outcome reporting because of a lack of economic data (a prespecified outcome) (54).

**Pinaverium.** Pinaverium efficacy and safety were reported in 5 randomized placebo-controlled IBS studies (Table 3) (15,56–59). Three small, single-center studies published in 1995 or earlier reported that pinaverium 50 mg t.i.d. improved abdominal pain in patients with IBS (56–58). The safety profile of pinaverium in these small studies was generally comparable with that of placebo (56–58).

Two larger, multicenter, double-blind, placebo-controlled studies evaluated the efficacy and safety of pinaverium in patients with IBS diagnosed per Rome III criteria (15,59). Zheng reported that patients with IBS-D receiving pinaverium 50 mg t.i.d. experienced significant improvements in composite abdominal pain and stool consistency response versus placebo at weeks 2 and 4 (P < 0.05 and P < 0.001, respectively) (15). The most common AEs reported were nausea, dizziness, abdominal discomfort, and hypertension (15). Schmulson reported that the combination of pinaverium 100 mg plus simethicone 300 mg twice daily compared with placebo significantly improved the intensity of abdominal pain (P = 0.04) and bloating (P = 0.02); the individual contribution of each agent cannot be determined (59). The safety profile of pinaverium/simethicone was generally comparable with that of placebo.

Analysis of risk of bias in the 5 pinaverium studies was mostly unclear (15,56–59).

**Trimebutine.** Across 4 small studies of trimebutine 100 or 200 mg t.i.d. administered for 2 weeks to 6 months, improvement in abdominal pain was inconsistently observed (Table 3) (60–63). Of these 4 studies, 1 evaluating trimebutine 200 mg t.i.d. did not show improvement in abdominal pain versus placebo (61). Nausea, shaky hands, and upset stomach, the most common AEs experienced with trimebutine, were not reported by any patients receiving placebo (61). The other 3 studies (100 and 200 mg t.i.d.) reported improvement in abdominal pain versus placebo (60,62,63). Safety data were not consistently presented in the 4 studies, and the risk of bias was mostly unclear (60–63).

**Antispasmodics for abdominal pain in other functional GI disorders**

Three non-IBS functional GI disorder studies were included in this review (Table 4) (64–66).

**Hyoscine for recurrent abdominal pain.** Two multicenter studies assessed the efficacy and safety of hyoscine for the treatment of recurrent APC not linked to altered bowel habits (64,65). Mueller-Lissner et al. reported a significant decrease from baseline in abdominal pain intensity with hyoscine 10 mg t.i.d. compared with placebo (P < 0.0001) after 3 weeks of treatment; in addition, abdominal pain frequency was significantly reduced with hyoscine compared with placebo (P < 0.0001) (64). Lacy et al. reported that, during a 4-week period of study, on-demand hyoscine 20–100 mg treatment over 4 hours decreased abdominal pain intensity versus placebo during the first APC episode (P = 0.02), but not during a second, separate APC episode (65). Hyoscine was well tolerated in both studies (64,65).

**Trimebutine for patients with FD.** A small crossover study with trimebutine 200 mg t.i.d. in patients with FD reported no significant improvement in overall dyspeptic symptoms (including abdominal pain) compared with placebo after 4 weeks of treatment (66). Tiredness and transient penile rash were AEs reported during trimebutine treatment, whereas no AEs were reported during placebo treatment (66).

**DISCUSSION**

Dicyclomine, hyoscine, and hyoscyamine are anticholinergic/antimuscarinic agents available in the United States. Although placebo-controlled efficacy and safety data related to the use of these antispasmodics in patients with IBS seem favorable, the studies of dicyclomine (18,43) and hyoscine (44–47) identified in this review were published in 1990 or earlier and used different doses, treatment durations, and outcome assessments. Furthermore, in these relatively small studies, patients with IBS were not subgrouped by IBS subtype, and definitions of IBS were inconsistent. Consequently, comparisons that can be made across studies are limited. Risk of bias was variable among studies (e.g., AEs with dicyclomine and hyoscyamine could have revealed treatment allocation) (18,47).

Two randomized, placebo-controlled studies demonstrated that the direct smooth muscle relaxant mebeverine did not improve IBS symptoms compared with placebo (48,49). However, these trials were limited by small sample sizes (48,49). Furthermore, the risk of bias was unclear in 1 of the 2 studies (48).

Calcium channel inhibitors for the treatment of chronic abdominal pain are currently available in Canada and/or Mexico, but not the United States. The efficacy of alverine was variable in 2 randomized, controlled studies, with 1 study achieving a statistically significant improvement in abdominal pain compared with placebo (50,51). Both studies had a risk of...
bias related to patient selection (50,51). Otilonium was evaluated in 4 clinical studies that varied in dosing and treatment duration (52–55) and also treatment allocation, blinding, and patient attrition (52,53). The high placebo response observed in 1 study was potentially because of patient selection and/or the patient-provider relationship (54). Pinaverium was examined in 5 randomized, placebo-controlled studies that differed in treatment duration, dosing, and outcomes; furthermore, 1 study included only patients with IBS-D (15,56–59). Studies generally had an unclear risk of bias (15,56–59). Trimebutine was examined in 4 clinical trials of patients with IBS with inconsistent results: in 2 studies, trimebutine 100 mg t.i.d. improved multiple IBS symptoms, a finding that differed significantly from placebo; however, 2 studies that examined trimebutine treatment at a higher dose showed the drug was no more efficacious than placebo for improving abdominal pain or bowel habits (60–63). Limitations included the absence of patient populations from multiple centers, which potentially limited the generalizability of results, and small, underpowered studies. Risk of bias in studies of trimebutine was unclear.

The definition of IBS has changed over time, and studies of antispasmodics are inconsistent in this regard. For example, Rome IV criteria no longer include abdominal discomfort as a hallmark symptom because of its ambiguous nature and a lack of the term in some languages; in addition, duration of symptom frequency increased from ≥3 d/mo with Rome III criteria to ≥1 d/wk with Rome IV (67). Furthermore, since the publication of the current US FDA guidance (68), antispasmodic trials reviewed herein, only one (15) is consistent with the current US FDA guidance (68).

Studies supporting the use of specific antispasmodics for non-IBS DGBI are limited. Hyoscine was examined in 2 studies of patients with recurrent APC (64,65), and trimebutine in 1 small study of patients with FD (66). Hyoscine improved abdominal pain frequency and intensity versus placebo in patients with recurrent APC, with a fixed dosing schedule or on-demand use; however, patients with different underlying pathologies contributing to APC were grouped in 1 broad category in these studies (64,65). Trimebutine did not show overall symptomatic improvement versus placebo in patients with FD (66).

In summary, data supporting the use of antispasmodics for the treatment of chronic abdominal pain in patients with DGBI, including IBS and FD, are limited. Limited sample size, short duration of therapy, heterogeneity in outcomes, and concerns over potential bias with study design make it difficult to recommend these agents for clinical use, especially when compared with the data sets available from large, randomized, controlled trials that characterize the current US FDA-approved IBS medications. This highlights the need to use other therapies to treat chronic abdominal pain (e.g., neuromodulators and cognitive behavioral therapy) and to develop agents to treat this debilitating symptom.

**CONFLICTS OF INTEREST**

Guarantor of the article: Darren M. Brenner, MD, FACG.

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