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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.

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/B987

Am J Gastroenterol 2021;116:1587–1600. https://doi.org/10.14309/ajg.0000000000001266

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-predominant 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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Received February 7, 2021; accepted March 18, 2021; published online May 17, 2021

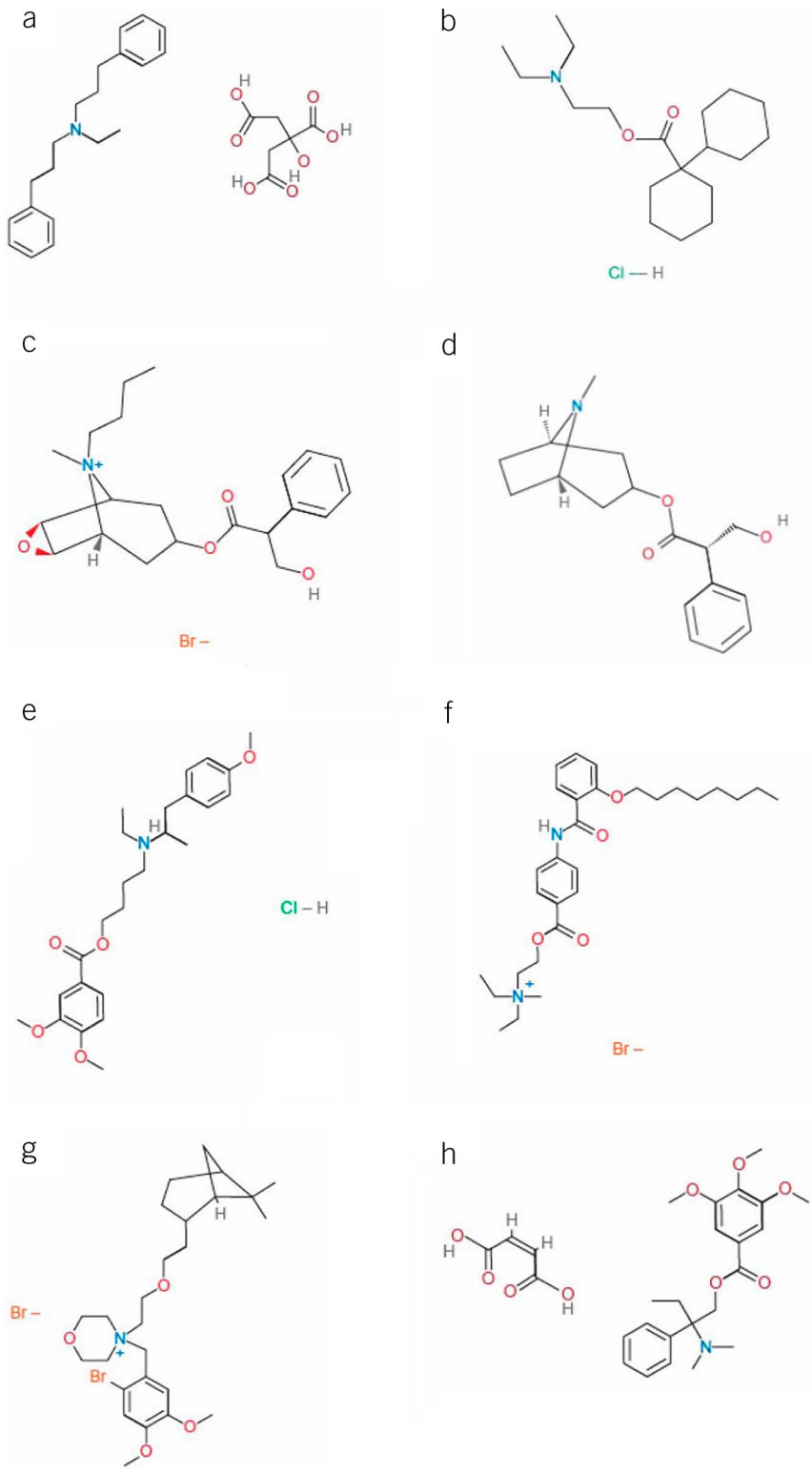

Figure 1. Chemical structure for antispasmodic agents available in North America. (**a**) alverine, (**b**) dicyclomine, (**c**) hyoscine, (**d**) hyoscyamine, (**e**) mebeverine, (**f**) otilonium, (**g**) pinaverium, (**h**) trimebutine. Chemical structures reprinted from PubChem, https://pubchem.ncbi.nlm.nih.gov

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,

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

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

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, hyoscyamine, 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," "hyoscyamine," "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).

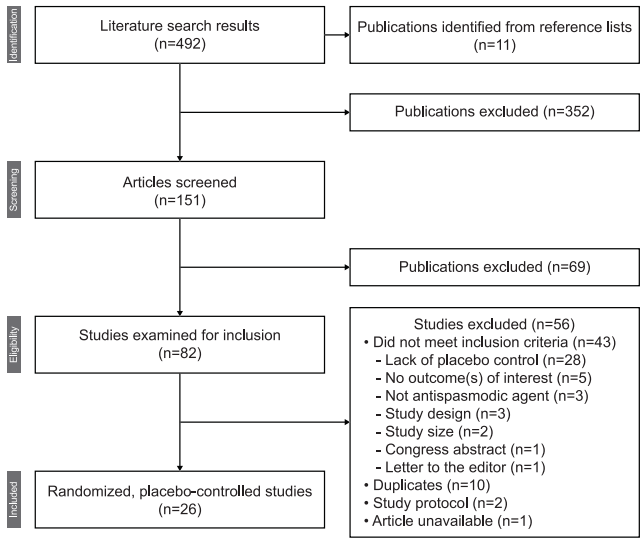

Figure 2. Summary of literature search.

Table 2. Efficacy and safety of anticholinergic/antimuscarinic antispasmodics and smooth muscle relaxants in IBS studies

Study details	Patient population	Treatment	Efficacy outcome(s)	Safety outcome(s)	Study limitation(s)[a]
			Dicyclomine		
Matts, 1967(43) R, DB, C, crossover	Pts with IBS Age not reported The United Kingdom	Dicyclomine 10 mg t.i.d. (n = 72) vs PBO (n = 72) Duration: 10 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 • Diagnostic criteria not reported • 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, 1981 (18) R, DB, C, P	Pts with IBS Pt age inclusion criterion: 18–65 yr The United States	Dicyclomine 40 mg q.i.d. (n = 34) vs PBO (n = 37) Duration: 2 wk	Dicyclomine improved (completely well/gone, better) PGA vs PBO at 2 wk: overall[b], 94% vs 54%; abdominal pain[b], 94% vs 57%; abdominal tenderness[c], 94% vs 62%; bowel habits[c], 85% vs 54% Dicyclomine improved (completely well/gone, better) general condition by pt self-assessment vs PBO[d] 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%	AEs were reported by 69% of pts (n = 33) receiving dicyclomine 160 mg/d for 2 wk AEs reported in 16% of pts receiving PBO Most common AEs with dicyclomine: blurred vision, dizziness, and dry mouth Dicyclomine led to tx discontinuation in 7 pts	• Small sample size • Pts not subgrouped by the type of IBS • Short treatment duration • High rates of AEs
			Hyoscine		
Ritchie and Truelove, 1979 (44) R, DB, C	Pts with IBS Pt age range: 16–69 yr England	Hyoscine 10 mg q.i.d. (n = 48) vs PBO (n = 48) Duration: 3 mo	Hyoscine improved symptoms from baseline vs PBO at 3 mo: 46% vs 29%	NR	• Single center • Small sample size • Diagnostic criteria not reported • Pts not subgrouped by the type of IBS • Abdominal pain not assessed separately
Nigam et al., 1984 (45) R, DB, C	Pts with IBS Pt age range: 16–68 yr India	Hyoscine (n = 84) vs PBO (n = 84) Duration: 12 wk	Hyoscine improved (rating of better) symptoms from baseline vs PBO at 12 wk: 45.3% vs 29.7% ($P < 0.05$)	Most common AEs with hyoscine: dry mouth (25%), blurring of vision (11.9%), and palpitations and/or hallucinations (5.9%)	• Single center • Pts not subgrouped by the type of IBS • Abdominal pain not assessed separately

Table 2. (*continued*)

Study details	Patient population	Treatment	Efficacy outcome(s)	Safety outcome(s)	Study limitation(s)[a]
Schäfer and Ewe, 1990 (46) R, DB, C, P	Pts with IBS Pt age range: 18–79 yr Germany	Hyoscine 10 mg t.i.d. (n = 182) vs PBO (n = 178) Duration: 4 wk	Hyoscine resulted in marked or some improvement in symptoms (abdominal pain, bloating, constipation, cramping, gas, and nausea) from baseline at 4 wk vs PBO: 76% vs 64%	AEs with hyoscine (n = 9) vs PBO (n = 6)	• Pts not subgrouped by the type of IBS
		Hyoscyamine			
Carling et al., 1989 (47) R, DB, C, crossover	Pts with IBS Pt age range: 18–65 yr Sweden	Hyoscyamine 0.2 mg t.i.d. (n = 30) vs PBO (n = 13) Duration: 2 wk Pts began the second round of tx if IBS symptoms continued after first tx or recurred	Hyoscyamine did not significantly improve abdominal symptom score[e] (constipation diarrhea, distension, flatulence, nausea, and pain) from baseline to week 2 (hyoscyamine [score 32.4–27.8] vs PBO [score 27.4–28.8]; P = NS)	AEs with hyoscyamine vs PBO: overall, 86.7% vs 7.1% ($P < 0.001$); dry mouth, 70% vs 7.1%; blurred vision, 46.7% vs 0%	• Small sample size • Pts not subgrouped by the type of IBS • Abdominal pain not assessed separately • Short treatment duration
		Mebeverine			
Kruis et al., 1986 (48) R, DB, C	Pts with IBS Pt age range: 19–71 yr Germany	Mebeverine 100 mg q.i.d. (n = 40) vs PBO (n = 40) for 16 wk	Mebeverine and PBO resolved or improved symptoms from baseline to week 16 (% pts): abdominal pain, 22.5% vs 27.5%; irregular bowel habits, 12.5% vs 25.0%; flatulence, 2.5% vs 7.5%	No clinically relevant AEs observed	• Small sample size • Pts not subgrouped by the type of IBS
Everitt et al., 2013 (49) R, DB, C	Pts with IBS (Rome III criteria) Pt age inclusion criterion: 16–60 yr The United Kingdom	Mebeverine 135 mg t.i.d. (n = 44), methylcellulose (3 tablets b.i.d.; n = 46), or PBO (n = 46) for 6 wk Pts also randomly assigned to 1 of 3 groups for website self-management: website with nurse telephone session (30 min), website with minimal support, or no website	No significant differences between medication tx groups in change from baseline in IBS-SSS score and IBS-QOL at 6 and 12 wk; Patient Enablement Questionnaire at 6 wk and 12 wk; SGA of relief at 12 wk; and HADS score at 6 and 12 wk	NR	• Small sample size • Abdominal pain not assessed separately

AE, adverse event; b.i.d., twice daily; C, controlled; DB, double-blind; HADS, Hospital Anxiety and Depression Scale; IBS, irritable bowel syndrome; IBS-QOL, irritable bowel syndrome quality of life questionnaire; IBS-SSS, Irritable Bowel Symptom Severity Scale; NR, not reported; P, parallel; PBO, placebo; PGA, physicians' global assessment; pts, patients; q.i.d., 4 times daily; R, randomized; SGA, subjects global assessment; t.i.d., 3 times daily; tx, treatment.
[a]Sample size of <50 patients per treatment arm considered small, and treatment duration of ≤15 days considered short.
[b]$P < 0.001$ for overall comparison of dicyclomine vs placebo (18).
[c]$P = 0.003$ for overall comparison of dicyclomine vs placebo (18).
[d]$P = 0.006$ for overall comparison of dicyclomine vs placebo (18).
[e]Symptom scores were calculated by adding individual symptom scores (scale range, 0 [asymptomatic] to 3 [severe symptoms]) (47).

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)[a]
			Alverine		
Mitchell et al., 2002 (50) R, DB, C	Pts with IBS (Rome II criteria) Pt age range: 19–73 yr The United Kingdom	Alverine 120 mg t.i.d. (n = 53) vs PBO (n = 54) for 12 wk	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 (51) R, DB, C	Pts with IBS (Rome III criteria) Pt age inclusion criterion: 18–75 yr Hungary and Poland	Alverine 60 mg/simethicone 300 mg t.i.d. (n = 207) vs PBO (n = 205) for 4 wk	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
			Otilonium		
Baldi et al., 1991 (52) R, DB, C, P	Pts with IBS Pt age range: 19–66 yr Italy	Otilonium 40 mg t.i.d. (n = 34) vs PBO (n = 37) for 4 wk	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) R, DB, C, P	Pts with IBS Pts >18 yr included Italy	Otilonium 40 mg t.i.d. (n = 160) vs PBO (n = 165) for 15 wk	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)[a]
			Otilonium improved abdominal pain frequency (episodes/wk) from baseline to week 15 vs PBO (% of pts): 55.3% vs 39.9% (OR, 1.9; 95% CI, 1.2–2.9; $P < 0.01$) Otilonium and PBO improved pt well-being, assessed by 10-mm VAS, from baseline to week 15 ($P < 0.001$ for both groups); otilonium had greater improvement vs PBO at week 15 ($P < 0.05$) Otilonium improved investigators' global judgment of efficacy (good, excellent) from baseline to week 15 vs PBO: 65.2% vs 49.6% (OR, 1.9; 95% CI, 1.2–3.1; $P < 0.01$)		
Clavé et al., 2011 (54) Phase 4, R, DB, C, P	Pts with IBS (Rome II criteria) Pt age inclusion criterion: >18 yr Belgium, Germany, Greece, Portugal, Romania, Russia, Spain, Turkey	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 $P < 0.00001$ 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) Phase 1/2, R, DB, C, P	Pts with IBS (Rome II criteria) Pt age inclusion criterion: 18–65 yr Poland	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	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

Table 3. (*continued*)

Study details	Patient population	Treatment	Efficacy outcome(s)	Safety outcome(s)	Study limitation(s)[a]
			baseline to week 1 vs PBO: −19.7% vs −4.8% ($P < 0.05$) Otilonium 80 mg improved bowel movement frequency from baseline to week 4 vs PBO: −41.9% vs −8.4% ($P < 0.01$)		
			Pinaverium		
Levy et al., 1997 (56) R, DB, C	Pts with IBS Pt age range: 22–77 yr France	Pinaverium 50 mg t.i.d. (n = 25) vs PBO (n = 25) Duration: 15 d	Pinaverium improved global symptoms (rating of good) after 15 d vs PBO: 60% vs 16% Pinaverium improved symptoms from baseline to day 15 vs PBO for abdominal pain ($P < 0.01$), abdominal symptoms ($P < 0.05$), and GI transit ($P < 0.01$)	Constipation: pinaverium (n = 2); PBO (n = 3)	• Small sample size • Single center • Diagnostic criteria not reported • Pts not subgrouped by the type of IBS • Short study duration
Delmont, 1981(57) R, DB, C	Pts with IBS Pt age range: 15–89 yr France	Pinaverium t.i.d. (n = 30) vs PBO (n = 30) Duration: 30 d	More pts indicated a pain intensity of 0 in the pinaverium group vs pts in the PBO group: 66.7% vs 30.8%; fewer pts reported a pain intensity of 2 or 1 (range 0 [no pain] to 2 [strong pain]) in the pinaverium group vs PBO: 25.9% vs 65.4%	Pinaverium: dry mouth (n = 2), epigastric burns (n = 1), and epigastralgia (n = 1) PBO: leg cramps (n = 1), fatigue (n = 1), and malaise (n = 1)	• Small sample size • Single center • Pts not subgrouped by the type of IBS
Awad et al., 1995 (58) R, DB, C	Pts with IBS Pt age range: 17–52 yr Mexico	Pinaverium 50 mg t.i.d. (n = 19) vs PBO (n = 19) Duration: 3 wk	Pinaverium and PBO improved the duration of abdominal pain[b] from baseline to week 3: 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: $P = 0.02$ 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; $P = 0.01$)	Pinaverium: headache (n = 1) PBO: no AEs reported	• Small sample size • Single center • Pts not subgrouped by the type of IBS
Zheng et al., 2015 (15) R, DB, C	Pts with IBS-D (Rome III criteria) Pt age inclusion criterion: 18–70 yr China	Pinaverium 50 mg t.i.d. (n = 218) vs PBO (n = 209) Duration: 4 wk	Abdominal pain and stool consistency response[c] 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 response[c] 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%)	• Included only pts with IBS-D

Table 3. (*continued*)

Study details	Patient population	Treatment	Efficacy outcome(s)	Safety outcome(s)	Study limitation(s)[a]
			$P < 0.001$); at week 4: 62.4% vs 29.7% (OR, 3.9; 95% CI, 2.6–5.9; $P < 0.001$) Stool consistency response[c] for pinaverium vs PBO (% pts) at week 2: 22.9% vs 11.5% (OR, 2.3; 95% CI, 1.4–3.9; $P < 0.005$); and at week 4: 53.2% vs 20.6% (OR, 4.4; 95% CI, 2.9–6.7; $P < 0.001$)		
Schmulson et al., 2020 (59) R, DB, C, P	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[d] 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
			Trimebutine		
Moshal et al., 1979 (60) R, DB, C Crossover	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) R, DB, C	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

Table 3. (*continued*)

Study details	Patient population	Treatment	Efficacy outcome(s)	Safety outcome(s)	Study limitation(s)[a]
			(79% vs 86%) and at 6 mo (32% vs 32%)	AEs leading to study withdrawal with trimebutine: depressed and high (n = 1), dry and sour mouth (n = 1); with PBO: depressed and high (n = 1)	
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
Dumitraşcu and Stănculete, 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[e] from baseline to week 2: Abdominal pain (13.1 vs 2.7 [$P < 0.000$] and 12.5 vs 7.7 [$P < 0.05$]; trimebutine vs PBO, $P < 0.001$) Anorexia (8.9 vs 4.4 [$P < 0.001$] and 9.8 vs 6.7 [$P < 0.05$]; trimebutine vs PBO, $P < 0.05$) Bloating (10.3 vs 2.6 [$P < 0.000$] and 10.5 vs 8.8 [P = NS]; 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, $P < 0.02$) 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.

[a]Sample size of <50 patients per treatment arm considered small, and treatment duration of ≤15 days considered short.

[b]Determined 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).

[c]Defined 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).

[d]Determined 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).

[e]Overall score range for each symptom, 0–16; based on a combination of individual symptom intensity and frequency assessed at baseline and week 2: 0 (never) to 4 (daily) (63).

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,

Table 4. Efficacy and safety of antispasmodics for abdominal pain in studies of non-IBS functional GI disorders

Study details	Patient population	Treatment	Efficacy outcome(s)	Safety outcome(s)	Study limitation(s)[a]
			Hyoscine		
Mueller-Lissner et al., 2006 (64) R, DB, C, P	Pts with recurrent APC Pt age range: 17–76 yr Germany	Hyoscine 10 mg t.i.d. (n = 400) vs PBO (n = 394) Duration: 3 wk	Hyoscine significantly decreased abdominal pain intensity on the 100-mm VAS from baseline vs PBO (mean change from baseline, 2.3 mm vs 1.9 mm; $P < 0.0001$) Pain frequency (verbal rating scale; 0 [not at all] to 3 [≥5 times]) showed significant decrease from baseline with hyoscine vs PBO (0.7/d vs 0.5/d; $P < 0.0001$)	Pts with ≥1 AE (hyoscine vs PBO): 15.9% vs 10.9%	• Pts with different underlying physiologies contributing to APC grouped in 1 category
Lacy et al., 2013 (65) R, DB, C, P	Pts with recurrent APC Pt age range: 18–73 yr The United States	Hyoscine 20–100 mg (n = 88) vs PBO (n = 87) on demand Duration: 2 separate episodes of APC during 4-wk period	Hyoscine tx resulted in a significant decrease in pain intensity vs PBO over 4 hr during APC episode 1 but not separate episode 2 (adjusted mean difference in change from baseline NPRS [11-point scale]: −0.7 for episode 1 [$P = 0.02$] and −0.6 for episode 2 [P = NS]) Pts in hyoscine group reported a ≤2-point improvement in NPRS (~30% pain relief) earlier than pts in the PBO group (45 vs 60 min)	No difference in AE rates for hyoscine (10.2%) vs PBO (10.3%) Most common AEs with hyoscine: abdominal pain (2.3%), diarrhea (2.3%), and joint sprain (2.3%)	• Pts with different underlying physiologies contributing to APC grouped in 1 category • Treatment effect for second episode missed statistical significance
			Trimebutine		
Walters et al., 1980 (66) R, DB, C Crossover	Pts with functional dyspepsia Pt age range: 18–70 yr Ireland	Trimebutine 200 mg t.i.d. (n = 24) vs PBO (n = 24) Duration: 4 wk	No significant overall symptomatic improvement with trimebutine vs PBO	Trimebutine: feeling tired (n = 3) and penile rash (n = 1) PBO: no AEs reported	• Small sample size • Abdominal pain not assessed separately • Crossover design washout period not reported

AE, adverse event; APC, abdominal pain with cramping; C, controlled; DB, double-blind; GI, gastrointestinal; NPRS, numeric pain rating scale; NS, not significant; P, parallel; PBO, placebo; pts, patients; R, randomized; t.i.d., 3 times daily; tx, treatment; VAS, visual analog scale.
[a]Sample size of <50 patients per treatment arm considered small, and treatment duration of ≤15 days considered short.

hyoscine taken for a duration of 4 weeks to 3 months was more efficacious than placebo at improving IBS symptoms (Table 2) (44–46). Only 1 study adequately reported AEs (45). Although all 3 studies reported favorable efficacy, they differed in treatment duration and definitions of IBS, and 2 studies lacked separate assessments of abdominal pain (44–46). However, the risk of bias was mostly low (44,45).

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

(Table 3) (50,51). 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 (50). 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 most of these antispasmodic studies, the US Food and Drug Administration (FDA) has provided guidance for defining treatment response in clinical trials of IBS. Importantly, of all the 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 physiologies 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.

Specific author contributions: Both authors contributed equally to the design, research, writing, and editing of this review.

Financial support: Technical editorial and medical writing assistance was provided, under direction of the authors, by Mary Beth Moncrief, PhD, and Sophie Bolick, PhD, Synchrony Medical Communications, LLC, West Chester, PA. Funding for this assistance was provided by Salix Pharmaceuticals, Bridgewater, NJ.

Potential competing interests: D.M.B. reports serving as a consultant, advisor, and/or speaker for Alnylam, Alphasigma, Arena, Salix Pharmaceuticals, Allergan (Abbvie), Ironwood, and Takeda Pharmaceuticals. D.M.B. was also supported in research by an unrestricted grant from the Irene D. Pritzker Foundation. B.E.L. reports serving as an advisory board member for Ironwood Pharmaceuticals, Salix Pharmaceuticals, Arena Pharmaceuticals, Alphasigma, and Allakos; he also has provided consulting services to Viver and Urovant Sciences.

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