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REVIEW

Targeted therapies for diarrhea-predominant irritable bowel syndrome

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Abstract: Irritable bowel syndrome (IBS) causes gastrointestinal symptoms such as abdominal pain, bloating, and bowel pattern abnormalities, which compromise patients' daily functioning. Common therapies address one or two IBS symptoms, while others offer wider symptom control, presumably by targeting pathophysiologic mechanisms of IBS. The aim of this targeted literature review was to capture clinical trial reports of agents receiving the highest recommendation (Grade 1) for treatment of IBS from the 2009 American College of Gastroenterology IBS Task Force, with an emphasis on diarrhea-predominant IBS. Literature searches in PubMed captured articles detailing randomized placebo-controlled trials in IBS/diarrhea-predominant IBS for agents receiving Grade I (strong) 2009 American College of Gastroenterology IBS Task Force recommendations: tricyclic antidepressants, nonabsorbable antibiotics, and the 5-HT_3 receptor antagonist alosetron. Studies specific for constipation-predominant IBS were excluded. Tricyclic antidepressants appear to improve global IBS symptoms but have variable effects on abdominal pain and uncertain tolerability; effects on stool consistency, frequency, and urgency were not adequately assessed. Nonabsorbable antibiotics show positive effects on global symptoms, abdominal pain, bloating, and stool consistency but may be most efficacious in patients with altered intestinal microbiota. Alosetron improves global symptoms and abdominal pain and normalizes bowel irregularities, including stool frequency, consistency, and fecal urgency. Both the nonabsorbable antibiotic rifaximin and the 5-HT_3 receptor antagonist alosetron improve quality of life. Targeted therapies provide more complete relief of IBS symptoms than conventional agents. Familiarization with the quantity and quality of evidence of effectiveness can facilitate more individualized treatment plans for patients with this heterogeneous disorder.

Keywords: antidepressant therapy, antibiotic therapy, alosetron, evidence, targeted review

Introduction

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal (GI) disorder characterized by episodes of abdominal pain and/or discomfort and altered bowel habits. A previous systematic review of the literature showed that the prevalence of IBS ranged from 3% to 20% in North America, with most estimates falling between 10% and 15%.[1] A more recent community-based survey supports these earlier estimates, finding a prevalence of IBS in the US of approximately 14.1%.[2] More than 80% of the surveyed patients were 18–54 years of age, and 64% were women. Further, among US patients with symptoms of IBS, more than three-quarters had not received a definitive diagnosis.[2] IBS diagnoses are now often classified according to three symptom patterns: diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C), and an

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alternating pattern of these two (IBS-A). The true prevalence of each IBS subtype is not established, but IBS-A and IBS-D are thought to be more common.[2–4]

The negative impact of IBS symptoms on daily functioning and quality of life can be substantial. The IBS in the Real World Survey,[5] conducted by the International Foundation of Functional Gastrointestinal Disorders, found that nearly half of patients diagnosed with IBS experience daily symptoms. Among survey respondents, 26% reported missing at least 1 day of work or school during the preceding 3 months (average 7.9 days), and 68% reported missing at least 1 day of personal activities (average 10.5 days) because of their illness.[5] Nearly 90% of patients with IBS-D report experiencing abdominal pain, gas, and sudden urgency[5] and, as symptom severity increases, so too does the level of impairment in daily functioning and quality of life. Patients with severe IBS symptoms may experience quality of life impairments that are comparable with, or even greater than, those associated with diabetes or depression.[6,7]

In 2009, the American College of Gastroenterology (ACG) IBS Task Force updated its evidence-based position statement on the management of IBS.[3] In the update, the Task Force determined that the strongest evidence for efficacy in IBS-D existed for three classes of medications: tricyclic antidepressants (TCAs), antibiotics (ie, rifaximin), and the 5-HT_3 antagonist alosetron.[3] Each class received a strong recommendation for clinical use in IBS (Grade 1B), indicating that the evidence is of moderate to high quality and that the benefits clearly outweigh any risk or burden of therapy.[3] To provide further detail regarding the ACG recommendations, a comprehensive search of the literature was carried out for published clinical studies involving these agents in the treatment of IBS, with special attention to the IBS-D subtype, with a goal of highlighting the underlying pathophysiologic mechanisms and delineating the breadth of their respective treatment effects.

Methods

A literature search using PubMed was conducted for randomized placebo-controlled trials in IBS reported in English over the past 25 years and used the search terms "irritable bowel syndrome," "colonic diseases," "functional disease," "IBS," "spastic colon," and/or "irritable colon." Trials evaluating IBS-C, those conducted in children, clinical case studies, open-label studies, and studies with an active comparator alone (ie, studies with no placebo arm) were excluded. Articles that evaluated TCAs, antibiotics, or alosetron in IBS were included for this review. To capture any other relevant clinical trials meeting our inclusion criteria that had not been published in full, similar searches were carried out to find congress abstracts in EMBASE, Biosis, Inside Conferences on Dialog, and Conference Papers Index from the past 5 years; relevant information from these searches was included.

Results

Pathophysiology

The pathophysiology of IBS is traditionally linked to a complex interaction between altered gut motility, visceral hypersensitivity, and environmental stress. Although IBS-D is generally thought to be associated with increased motility patterns and IBS-C with decreased motility, no consensus definition exists on the pattern of motility responsible for either bowel pattern abnormality.[8] The key role of serotonin in intestinal motor and secretory function has given rise to the hypothesis that altered serotonin signaling leads to either constipation or diarrhea in IBS.[9,10] Specifically, increased serotonin activity may be associated with IBS-D, and decreased serotonin activity may be associated with IBS-C.[11,12] In addition to these well-recognized abnormalities, a dysfunctional brain-gut axis involving the central, autonomic, and enteric nervous systems has also been implicated in IBS pathophysiology. Other theories proposed in IBS include various causes such as inflammation, disturbances in immune function, and alterations in the gut microbiota.[13–15]

Conventional therapies

The management of IBS often includes the use of conventional therapies, which are those that are directed toward specific symptoms of IBS (eg, loperamide for diarrhea, laxatives for constipation, antispasmodics for abdominal pain).[15,16] Because of the heterogeneous nature of their symptoms, patients with IBS are often treated with medications from more than one drug class in an effort to achieve relief. However, use of multiple conventional therapies has not provided sufficient benefit, and IBS patients have expressed dissatisfaction with these treatment regimens. In the IBS in the Real World Survey,[5] 40% of respondents rated their over-the-counter drug as "not effective" in relieving IBS symptoms. Few controlled trials have demonstrated efficacy for these conventional agents in IBS, despite their frequent use. Furthermore, greater drug exposure from use of multiple therapies may lead to higher safety risks.

Targeted therapies

In contrast with conventional therapies, which treat only one specific symptom of IBS, targeted treatment strategies are directed at addressing the underlying pathophysiologic

mechanisms that are believed to cause IBS. These targeted treatments have the potential to relieve multiple rather than single symptoms of IBS. For example, the TCA imipramine has been shown to prolong both orocecal and whole gut transit times in patients with IBS-D,[17] which is likely the result of its cholinergic and histaminergic antagonism. Additionally, inhibition of the reuptake of norepinephrine and/or serotonin (depending on the TCA) both centrally and peripherally can reduce nociception.[9,10,18,19] In view of the controversial hypothesis that small intestinal bacterial overgrowth (SIBO) may play a role in the pathogenesis of IBS,[20] nonabsorbable antibiotics have been investigated for the treatment of IBS,[21,22] where benefits are presumably due to effects on gut microflora. Alosetron, a selective 5-HT_3 antagonist, has also been shown to provide multisymptom relief in IBS. 5-HT_3 receptors are extensively distributed on enteric neurons in the human GI tract. Antagonism by alosetron at 5-HT_3 receptors leads to reduction in visceral pain,[23] slowed colonic transit,[24] and decreased GI secretions,[25] actions that address the underlying pathophysiological mechanisms that are operant in IBS. Of these agents, alosetron is currently the only Food and Drug Administration (FDA)-approved agent for the treatment of women with severe IBS-D.[26] In this article we review the current evidence for each of these agents as it pertains to IBS-D.

Antidepressants

In its updated position statement, the ACG IBS Task Force asserted that TCAs are more effective than placebo at relieving global IBS symptoms, noting that these agents also appear to reduce abdominal pain.[3] A recent meta-analysis including 579 IBS patients treated with TCAs across nine studies showed short-term (≤12 weeks) benefits.[27] In this review, symptoms of IBS were less likely to persist with TCA therapy than with placebo (relative risk 0.68; 95% confidence interval [CI] 0.56–0.83); the number needed to treat to prevent IBS symptoms from persisting in one patient was four (95% CI 3–8).[27] Unfortunately, no long-term studies have evaluated the use of TCAs in the treatment of IBS, and therefore the efficacy (and safety) of extended treatment with TCAs remains uncertain.[3]

TCAs may be effective in IBS, particularly in IBS-D, by both central and peripheral mechanisms that include increasing pain thresholds, altering visceral sensation, relieving concomitant depression, and altering gut transit times.[3,27] The anticholinergic effects of the TCAs and their ability to prolong intestinal transit times are the reasons these agents are preferred over the selective serotonin-reuptake inhibitors (SSRIs) in IBS-D.[3,17,27]

Although TCAs were first used in the treatment of functional bowel disorders more than 30 years ago,[16] only a limited number of controlled trials have evaluated their efficacy in IBS, and even fewer have been carried out in patients with IBS-D (Table 1).[28–33] Amitriptyline,[28,29] desipramine,[30,31] and imipramine[32,33] have each been evaluated in two randomized controlled trials in patients with IBS. Four of these trials were small, including 51 or fewer patients,[28–30,33] one included 107 patients,[32] and the largest TCA trial to date included 431 patients, who were divided into two treatment groups: pharmacotherapy and psychoeducation.[31] In five of the six trials, IBS was diagnosed using Rome I[28,31] or Rome II[29,32,33] diagnostic criteria, while in one, the diagnosis was made by a comprehensive history and physical exam with laboratory and imaging studies ruling out organic disease.[30] Only one trial limited enrollment specifically to IBS-D patients,[29] and of the two trials that characterized randomized patients by predominant bowel disturbance (ie, diarrhea or constipation),[30,33] only one reported treatment results by IBS subtype.[30]

Amitriptyline

Rajagopalan et al[28] evaluated the effects of amitriptyline (25–75 mg at bedtime) compared with placebo over 12 weeks in 40 adults with IBS. Amitriptyline was significantly superior to placebo in terms of the percentage of patients showing global improvement (63.6% vs 25.9%; $P < 0.01$), number of days per week with abdominal pain (1.45 days vs 4.00 days; $P < 0.01$), number of days per week that patients felt well (5.18 days vs 1.91 days; $P < 0.001$), and number of days per week with satisfactory bowel movements (5.27 days vs 3.09 days; $P < 0.05$). In a study limited to IBS-D patients (N = 50), Vahedi et al[29] reported that amitriptyline 10 mg given every night for 2 months produced significant improvement in IBS symptoms ($P = 0.005$), reduction in the frequency of patients with loose stools each day (12% vs 28%; $P < 0.05$), and a higher percentage of patients with a complete response (63% vs 26%; $P = 0.01$) compared with placebo. Abdominal pain relief did not differ between the two treatment groups.

Imipramine

In an evaluation of 51 patients with IBS, 73% of whom had IBS-D, Talley et al[33] compared the effects of imipramine (25–50 mg/d) and citalopram (20–40 mg/d) with those of placebo over 12 weeks of treatment. Neither active treatment was superior to placebo on the primary outcome of adequate relief of IBS symptoms. Likewise, abdominal pain scores did not significantly differ between the active treatment and placebo groups. However, imipramine was associated

Table 1 Characteristics of randomized controlled trials of tricyclic antidepressants in irritable bowel syndrome ± diarrhea and efficacy outcomes

Study	Treatment	Study duration	N	Population	Relief of abdominal pain	Relief of bloating	Global/overall IBS improvement	Stool frequency	Stool consistency	Urgency	Other efficacy assessments
Amitriptyline vs placebo											
Rajagopalan et al[28]	25–75 mg (titrated)	12 wk	40	Adults with IBS (Rome criteria)	++	NA/NR	++	0	NA/NR	NA/NR	+++ for days felt well + for days with satisfactory bowel movements
Vahedi et al[29]	10 mg qhs	2 mo	50	Adults with IBS-D (Rome II)	0	NA/NR	++ for complete response	NA/NR	+	NA/NR	++ for degree of symptom improvement 0 for passage of mucus + for feeling of incomplete defecation 0 for diarrhea
Desipramine vs placebo											
Greenbaum et al[30]	50–150 mg qhs vs placebo	Three 6 wk periods	41	Adults with IBS*		NA/NR	15/26 patients improved on desipramine	+		NA/NR	0 for diarrhea ++ for reduction in slow contractions
				Overall completers	++				0		
				IBS-D	+		87% of patients who improved on desipramine had IBS-D	+	0	NA/NR	++ for diarrhea + for slow contractions
Drossman et al[31]	50–150 mg (titrated)†	12 wk	431	Women with functional bowel disorder	0	NA/NR	0 for responder analysis ++ for patients with detectable desipramine	NA/NR	NA/NR	NA/NR	+ for post-treatment satisfaction 0 for IBS-QOL
Imipramine vs placebo											
Talley et al[33]	25–50 mg/d‡	12 wk	34	Adults with IBS (Rome II)	0	NA/NR	0 for IBS symptom relief at last wk, for adequate relief at ≥50% of wk, and for CGI	NA/NR	NA/NR	NA/NR	0 for anxiety and 0 for depression on HADS 0 for mental score and 0 for physical score on SF-36
Abdul-Baki et al[32]	25 mg qhs	12 wk	107	Women with IBS (Rome II)	NA/NR	NA/NR	0	NA/NR	NA/NR	NA/NR	0 for QOL score on SF-36

Notes: *IBS defined as ≥3 months of abdominal pain or distress, occurring at least biweekly for which no organic cause is evident. †Study included 12-week treatment with cognitive behavioral therapy vs education and desipramine vs placebo comparisons; however, only desipramine vs placebo results are presented in this table. ‡Treatment in this study included a citalopram 20–40 mg/d arm as well; only the imipramine vs placebo results, including number of patients, are presented in this table. Positive signs indicate significant improvement over placebo: + for $P \leq 0.05$; ++ for $P \leq 0.01$; +++ for $P \leq 0.001$; ++++ for $P \leq 0.0001$; 0 represents no statistically significant difference between active treatment and placebo.

Abbreviations: CGI, Clinical Global Impression scale; HADS, Hospital Anxiety and Depression Scale; IBS, irritable bowel syndrome; IBS-D, diarrhea-predominant IBS; IBS-QOL, Irritable Bowel Syndrome Quality of Life Questionnaire; NA/NR, not assessed or not reported; QOL, quality of life; SF-36, Medical Outcomes Study Short Form.

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with significant reductions in the Bowel Symptom Severity Rating Scale scores for both disability ($P = 0.03$) and distress ($P = 0.05$) compared with placebo. More patients receiving imipramine than citalopram or placebo reported side effects, but these differences were not significant.[33] In a second study, reported by Abdul-Baki et al,[32] 107 female patients with IBS who had failed antispasmodics were randomized to receive imipramine (25–50 mg at bedtime) or placebo. Patient-reported global symptom relief, the primary outcome measure, did not differ significantly between those patients treated with imipramine and those treated with placebo (42.4% vs 25.0%; $P = 0.06$).[32]

Desipramine

In a double-blind crossover study comparing desipramine, atropine, and placebo, Greenbaum et al[30] examined 28 patients with IBS (nine constipation-predominant and 19 diarrhea-predominant by self-report) and found that the mean pain index score decreased during all test periods, with desipramine providing statistically significant pain reduction compared with both atropine ($P < 0.025$) and placebo ($P < 0.0025$). The improvement found in patients with diarrhea predominance accounted for these differences ($P < 0.01$). Of the 15 desipramine-treated patients reporting global improvement while taking desipramine, 87% (n = 13) had diarrhea predominance.[30]

In the largest trial evaluating a TCA, Drossman et al[31] compared desipramine and placebo in a subset of 431 patients with functional bowel disorders, more than 80% of whom had IBS. Patients were randomized to receive pharmacotherapy (n = 216) with either desipramine (50–150 mg/d) or placebo for 12 weeks or psychoeducation (n = 215) with either twelve 1-hour sessions of cognitive behavioral therapy or twelve educational sessions for review of symptom diaries and educational material on functional bowel disorders. Using a composite endpoint consisting of four ratings (treatment satisfaction, global well-being, pain on the McGill Pain Questionnaire, and quality of life on the IBS Quality of Life Questionnaire) as the primary outcome measure, investigators found no significant difference between desipramine and placebo in the intent-to-treat population; however, desipramine was statistically superior to placebo in the per-protocol assessment, consisting of all patients who completed at least eight visits during the study (desipramine n = 97, placebo n = 56; $P = 0.03$).[31]

Adverse events in IBS patients treated with TCAs

Adverse events of dizziness, drowsiness, constipation, and dry mouth occurred with greater frequency during TCA treatment compared with placebo.[30–33] In the trial by Drossman et al,[31] adverse effects were cited as the primary reason for dropout (n = 26, 19.3%) in the desipramine group compared with those receiving placebo (n = 3, 5.5%). Although anticholinergic effects often develop with increasing TCA dosages,[16] the secondary amines (eg, desipramine, nortriptyline) are generally better tolerated than the tertiary amines (eg, amitriptyline, imipramine) because of their lower affinity for cholinergic, histaminergic, and α-adrenergic receptors.[16] Other safety concerns with TCAs include the risk of cardiac arrhythmias and the potential for fatal overdose, which is of particular concern in IBS patients because of a higher prevalence of suicidal ideation in this population.[16,34]

Selective serotonin-reuptake inhibitors

Five small randomized placebo-controlled studies assessed the capacity of SSRIs to improve IBS symptoms.[33,35–38] Relevant studies are summarized in Table 2. Only one study[38] reported a significant improvement in the number of days per week with abdominal pain in patients taking citalopram compared with those taking placebo, and one[36] reported that paroxetine produced a significant improvement in overall well-being compared with placebo. Limited information is available regarding tolerability, with dropout rates related as similar in two studies[33,38] and overall adverse events described as comparable in three studies;[33,35,37] one study reported no adverse event data.[36] However, given the propensity of SSRIs to commonly cause GI adverse events of nausea, vomiting, and diarrhea, TCAs may have more utility in IBS-D than SSRIs appear to have.

Nonabsorbable antibiotics

With the growing body of evidence implicating a potential role of intestinal bacteria in IBS pathophysiology,[39–42] the use of antibiotics to normalize gut flora has been investigated as a treatment for IBS. Several reports suggest a link between IBS and SIBO;[20,21,43,44] however, the association remains controversial.[45,46] The presence of SIBO may be associated with the IBS symptoms of gas, bloating, and altered bowel function through the fermentation of ingested lactulose or other carbohydrates by gut bacteria and stimulation of a gut immune response.[20,21] Lactulose hydrogen breath test (LHBT) results have varied widely, with the presence of SIBO being diagnosed in 10%[47] to 84%[21] of IBS patients. A recent systematic review and meta-analysis of studies examining SIBO in IBS noted a pooled prevalence of 54% (95% CI 32%–76%) with a positive LHBT result.[40] The use of

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Table 2 Characteristics of randomized controlled trials of selective serotonin-reuptake inhibitors in irritable bowel syndrome ± diarrhea and efficacy outcomes

Study	Treatment	Study duration	N	Population	Relief of abdominal pain	Relief of bloating	Global/overall IBS improvement	Stool frequency	Stool consistency	Urgency	Other efficacy assessments
Fluoxetine vs placebo											
Kuiken et al[35]	20 mg qhs	6 wk	40	Adults with IBS (Rome I)	0	0	0	NA/NR	NA/NR	0	0 for flatulence 0 for incomplete evacuation
Paroxetine vs placebo											
Tabas et al[36]	HFD ± 10 mg qd; titration at wk 4, 8, and 11 prn; 40 mg qd maximum dose	12 wk	81	Adults with IBS (Rome I)	0	0	++*	NA/NR	NA/NR	NA/NR	+ improvement in stool passage
Masand et al[37]	12.5 mg qd of the controlled release form; titrated biweekly to response and tolerability; 50 mg qd maximum dose	12 wk	72	Adults with IBS (Rome II)	0	0	++	NA/NR	NA/NR	NA/NR	++ for CGI-Severity improvement 0 for constipation, diarrhea, and distress
Citalopram vs placebo											
Tack et al[38]	20 mg qd for first 3 wk then 40 mg qd for wk 4-6	6 wk	23	Adults with IBS (Rome II)	+ for number of days per wk with abdominal pain	+	NA/NR	NA/NR	NA/NR	NA/NR	+ for number of days with loose stools, straining, and incomplete evacuation
Talley et al[33]	40 mg qd†	12 wk	33	Adults with IBS (Rome II)	0	NA/NR	0 for adequate IBS symptom relief at last wk, adequate relief for ≥50% of wk, and for CGI	NA/NR	NA/NR	NA/NR	0 for anxiety and 0 for depression on HADS 0 for mental score and 0 for physical score on SF-36

Notes: *Endpoint measured was "improvement in overall well-being". †Treatment in this study included an imipramine 25–50 mg/d arm as well; only the citalopram vs placebo results, including number of patients, are presented in this table. Positive signs indicate significant improvement over placebo: + for $P \leq 0.05$; ++ for $P \leq 0.01$; +++ for $P \leq 0.001$; ++++ for $P \leq 0.0001$; 0 represents no statistically significant difference between active treatment and placebo.
Abbreviations: CGI, Clinical Global Impression scale; HADS, Hospital Anxiety and Depression Scale; HFD, high fiber diet; IBS, irritable bowel syndrome; NA/NR, not assessed or not reported; SF-36, Medical Outcomes Study Short Form.

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LHBT for determining SIBO has been controversial because of suboptimal specificity, leading to a high false-positive rate.[40] However, other lines of evidence that implicate a role for altered bacteria in IBS pathophysiology include the strong temporal association between acute enteric infection and subsequent IBS symptoms,[39,48] qualitative changes observed in the intestinal microbiota of IBS patients,[41,49] evidence of low-grade inflammation in IBS patients (perhaps triggered by luminal bacteria[50]), and accumulating evidence of a therapeutic benefit of antibiotics and probiotics in IBS.[44,51,52]

Neomycin

Pimentel et al[21] investigated the effect of a 10-day course of neomycin or placebo on IBS symptoms in 111 patients meeting Rome I criteria for IBS. IBS-D was present in 41% of patients at baseline, while 34% of patients had IBS-C. The primary outcome was a composite symptom score that included scores for abdominal pain, diarrhea, and constipation. In the intention-to-treat analysis, neomycin achieved a greater reduction in the composite score than placebo (35.0% ± 5.0% vs 11.4% ± 9.3% reduction, respectively; $P < 0.05$); the reduction was also significant for neomycin in the subgroup of patients with abnormal baseline LHBT results ($P < 0.01$).[21] Further, more patients treated with neomycin than with placebo achieved a ≥ 50% reduction in composite score (43% vs 23%, respectively; $P < 0.05$). Among the 41 neomycin-treated patients who had an abnormal LHBT finding at baseline, eight (20%) had a normal LHBT result after treatment; this group experienced a greater improvement in symptoms than those whose LHBT result remained abnormal. Adverse events during the study were not adequately detailed to compare the two groups.[21]

Rifaximin

Rifaximin, a nonabsorbable antibiotic with activity against gram-negative and gram-positive bacteria, as well as aerobic and anaerobic bacteria,[53] is the most extensively studied medication in its class for IBS (Table 3).[21,44,51,54–58] Studies published to date have randomized patients who met Rome I,[44] Rome II,[54–60] or a combination of Rome II IBS criteria and presentation with intestinal gas-related symptoms (bloating or excessive flatulence).[51] One study limited enrollment to patients with IBS-D,[54–57] while the largest two trials evaluated patients with nonconstipated IBS.[59,60] Overall, patients were to receive rifaximin or placebo for 10–14 days and be followed for 10–12 weeks thereafter.

Pimentel et al[44] treated 87 patients with either rifaximin 400 mg three times daily or placebo for 10 days with subsequent follow-up for 10 weeks. Results showed significant improvements in global symptoms of IBS ($P = 0.02$ vs placebo) and bloating ($P = 0.01$ vs placebo) throughout the 10-week follow-up, although differences in relief of abdominal pain, diarrhea, and constipation between the two groups were not significant.

In a more recent, larger phase II study (N = 388) reported only in abstracts to date,[54–57] rifaximin 550 mg twice daily or placebo was administered for 14 days to adults with IBS-D, defined by Rome II criteria, who were followed for 12 weeks. The rifaximin treatment group had a significantly higher percentage of patients than the placebo group with sustained global symptom improvement (52% vs 44%, respectively; $P = 0.03$) and bloating (46% vs 40%; $P = 0.04$) throughout the 12 weeks.[54] These improvements were more evident in patients with mild to moderate symptoms at baseline[55] and, notably, rifaximin did not significantly improve global IBS symptoms or bloating versus placebo in patients with severe IBS symptoms.[56] At 4 weeks, rifaximin significantly improved overall quality of life from baseline ($P = 0.02$);[57] improvements in the individual domains of dysphoria, body image, health worry, social reaction, and relationship improvements were significant ($P < 0.05$ for each) compared with placebo. Quality of life measures at the trial endpoint were not reported.[57]

Most recently, Pimentel et al[22] reported results from two identically designed, multicenter, phase III, placebo-controlled trials (TARGET 1 N = 623; TARGET 2 N = 637; total N = 1260) in patients with nonconstipated IBS (defined by Rome II criteria) who were treated with rifaximin 550 mg or placebo three times daily for 2 weeks and followed for an additional 10 weeks. Adequate relief of global IBS symptoms for at least 2 weeks of the first 4 weeks after treatment (the primary endpoint) was significant for rifaximin compared with placebo in both studies (TARGET 1 40.8% vs 31.2%, respectively, $P = 0.01$; TARGET 2 40.6% vs 32.2%, respectively, $P = 0.03$). Likewise, rifaximin treatment yielded a significantly greater rate of adequate relief of IBS-associated bloating over this same time period compared with placebo (TARGET 1 39.5% vs 28.7%, $P = 0.005$; TARGET 2 41.0% vs 31.9%, $P = 0.02$). Global symptom relief was also observed in both trials during follow-up, with the exception of relief of bloating in TARGET 1, where differences were significant between rifaximin- and placebo-treated patients for only the first 2 months.[22]

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Table 3 Characteristics of randomized controlled trials of nonabsorbable antibiotics in IBS and efficacy outcomes

Study	Treatment	Study duration	N	Population	Relief of abdominal pain	Relief of bloating	Global/overall IBS improvement	Stool frequency	Stool consistency	Urgency	Other efficacy assessments
Neomycin vs placebo											
Pimentel et al[21]	500 mg bid	10 d treatment, 7 d follow-up	111	Adults with IBS (Rome I)	NA/NR	NA/NR	NA/NR	NA/NR	NA/NR	NA/NR	CS:† + for reduction of CS and ≥50% improvement in CS
Rifaximin vs placebo											
Pimentel et al[44]	400 mg tid	10 d treatment, 10 wk follow-up	87	Adults with IBS without underlying predisposition to SIBO (Rome I)	0	++	+	NA/NR	NA/NR	NA/NR	0 for diarrhea
Sharara et al[51]	400 mg bid	10 d treatment, 10 d follow-up	124	Men with bloating/ flatulence *and* abdominal discomfort or bowel disturbance or abnormal stool consistency							
				All patients	NA/NR	+	+ for symptom relief at end of treatment; + at end of follow-up	NA/NR	NA/NR	NA/NR	+ for mean symptom score at end of treatment; 0 for mean symptom score at end of follow-up
				70 with IBS-D, -A, or -C (Rome II)	NA/NR	NA/NR	+ for symptom relief at end of treatment; + at end of follow-up	NA/NR	NA/NR	NA/NR	
				54 who did not meet Rome II criteria	NA/NR	NA/NR	0 for symptom relief at end of treatment	NA/NR	NA/NR	NA/NR	NA/NR
IBS-D phase II study:* Lembo et al[54]	550 mg bid	14 d treatment, 12 wk follow-up	388	Adults with IBS-D (Rome II)	NA/NR	+ at end of treatment; + at end of follow-up	+ at end of treatment; + at end of follow-up	NA/NR	NA/NR	NA/NR	NA/NR

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IBS-D phase II study:* Ringel et al[55]	550 mg bid	14 d treatment, 12 wk follow-up	388	Adults with IBS-D (Rome II)	NA/NR	0 in patients with mild–moderate pain at baseline; 0 in patients with severe pain; + in patients with mild–moderate bloating at baseline; 0 in patients with severe bloating	+ in patients with mild–moderate pain at baseline; 0 in patients with severe pain; ++ in patients with mild–moderate bloating at baseline; 0 in patients with severe bloating	NA/NR	NA/NR	NA/NR	Most substantial confounders of clinical response: daily bloating, abdominal pain, and use of rescue medications
IBS-D phase II study:* Pimentel et al[56]	550 mg bid	14 d treatment, 12 wk follow-up	388	Adults with IBS-D (Rome II)	NA/NR	0 in patients with mild–moderate pain at baseline; 0 in patients with severe pain; + in patients with mild–moderate bloating at baseline; 0 in patients with severe bloating	+ in patients with mild–moderate pain at baseline; 0 in patients with severe pain; ++ in patients with mild–moderate bloating at baseline; 0 in patients with severe bloating	NA/NR	NA/NR	NA/NR	Most substantial confounders of clinical response: daily bloating, abdominal pain, and use of rescue medications
IBS-D phase II study:* Chey et al[57]	550 mg bid	14 d treatment, 12 wk follow-up	388	Adults with IBS-D (Rome II)	NA/NR	NA/NR	NA/NR	NA/NR	NA/NR	NA/NR	+ for IBS-QOL total score; + for dysphoria, body image, health worry, social reaction, and relationship improvements

(*Continued*)

Table 3 (*Continued*)

Study	Treatment	Study duration	N	Population	Relief of abdominal pain	Relief of bloating	Global/overall IBS improvement	Stool frequency	Stool consistency	Urgency	Other efficacy assessments
TARGET 1 and 2 studies; Pimentel et al[58]	550 mg tid	2 wk	1260	Adults with nonconstipated IBS							
				623 in TARGET 1	+	++	++	NA/NR	++	NA/NR	+ for relief during all 3 mo;
				637 in TARGET 2	+	+	+	NA/NR	++	NA/NR	++ for relief during all 3 mo;
				1260 in total	++	+++	+++	NA/NR	+++	NA/NR	+++ for relief during all 3 mo

Notes: *Reanalysis of the data from one phase II study. †Composite score based on abdominal pain, diarrhea, and constipation (0–5 scale for each); higher scores denote more severity. Positive signs indicate significant improvement over placebo: + for $P \leq 0.05$; ++ for $P \leq 0.01$; +++ for $P \leq 0.001$; 0 represents no statistically significant difference between active treatment and placebo.

Abbreviations: CS, composite score; IBS, irritable bowel syndrome; IBS-A, irritable bowel syndrome with alternating diarrhea and constipation symptom predominance; IBS-C, constipation-predominant IBS; IBS-D, diarrhea-predominant IBS; IBS-QOL, Irritable Bowel Syndrome Quality of Life Questionnaire; SIBO, small intestinal bowel overgrowth.

Overall, the safety profile of rifaximin appears similar to that of placebo.[22,44] However, given the high prevalence of IBS in the general population, the chronic and recurrent nature of the disorder, and the potential for repeated use of antibiotics to treat this condition, induction of antibiotic resistance has been raised as a clinical issue that warrants further examination.[61,62] Indeed, the new drug application for rifaximin submitted to the FDA for the indication of nonconstipated IBS was recently addressed in a complete response letter and was not approved with the data submitted; the FDA has requested additional data on retreatment with rifaximin in view of the hypothetical risk of antibiotic resistance with repeated courses.[63]

Alosetron

Alosetron is a selective 5-HT_3 antagonist that is currently the only FDA-approved agent for IBS-D, specifically in women with severe IBS-D who have an inadequate response to conventional therapy.[26] The efficacy of this medication in IBS is thought to result from selective antagonism of the 5-HT_3 receptor, leading to normalization of several key abnormalities implicated in the pathophysiology of IBS-D: GI motility, intestinal secretion, and pain perception or visceral hypersensitivity.[9,10,18,19] Alosetron affects motor activity by slowing intestinal tract transit time[24,64] and enhancing fluid reabsorption. Alosetron reduces sensation of IBS-related visceral pain by decreasing blood flow to the brain's emotional motor center[23] by relaxing colonic tissue and altering the perception of distention in the abdomen.[65]

Numerous randomized controlled trials investigated the effect of alosetron on IBS (Table 4).[66–75] Each of these studies enrolled at least 300 patients with IBS, with most enrolling more than 600 patients. Women made up approximately 84% of the overall clinical trial population.[66–78] The diagnosis of IBS in these investigations was based on Rome I[66–69,71,72,74,76] or Rome II[70,73,75,77,78] criteria. Three of the more recent studies included women with nonconstipated IBS, IBS-D, or severe IBS-D,[73,75,77,78] reflecting patient populations that are more consistent with the use of alosetron in the clinical practice setting.[79]

Review of the clinical data shows that alosetron has consistently demonstrated efficacy in producing significant relief of abdominal pain and discomfort compared with placebo.[66–69,74,76,77] Camilleri et al[66] found that alosetron 1 mg and 2 mg twice daily provided adequate relief of pain and discomfort in female patients with IBS significantly more often than placebo ($P < 0.05$).[66] Likewise, Bardhan et al[67] found that alosetron 2 mg twice daily significantly increased the proportion of pain-free days in the total population ($P \leq 0.05$),

specifically in women ($P \leq 0.05$). A later dose-ranging trial performed in men with IBS-D revealed that alosetron 1 mg twice daily provided significantly more relief from IBS pain than placebo ($P = 0.012$), whereas no significant effect was seen with the dosages of 0.5 mg, 2 mg, or 4 mg twice daily.[76] The most consistent and statistically significant effect of alosetron was on adequate relief of abdominal pain[68,69,74,76,77] when given at a dosage of 1 mg twice daily. This significant abdominal pain relief was observed in clinical trials typically of 12 weeks' duration, but benefits have also been demonstrated over the long term. Chey et al[74] found that patients receiving alosetron had significantly greater 48-week average adequate relief of pain than patients receiving placebo.

Alosetron has been shown to improve multiple other IBS symptom domains, and significant global symptom improvements on the Global Improvement Scale or by overall satisfaction ratings ($P < 0.05$ for all)[70,73,75,77] have been noted. Additionally, significant improvements in stool frequency[66–70,74,75,77] and stool consistency[66–70,74–77] were reported in several studies ($P < 0.05$ for all). One of the most bothersome IBS symptoms, fecal urgency, has been shown to be significantly improved with alosetron.[66,68–70,74,75,77] In particular, when patients with severe bowel urgency symptoms (defined as lack of satisfactory control of urgency for at least 10 of 14 days during the trial screening phase) were assessed over 12 weeks of treatment, alosetron elicited significant improvement of urgency, as evidenced by the proportion of patients who achieved satisfactory control of urgency for a median 66% of days, compared with a median 43% of days in those receiving placebo ($P < 0.001$).[75] Moreover, alosetron has been shown to improve the quality of life of IBS patients.[71] Watson et al[71] reported statistically significant improvements from baseline in IBS-D in all nine domains of the IBS Quality of Life Questionnaire (emotional health, mental health, sleep, energy, physical functioning, food/diet, social functioning, role-physical, and sexual relations) compared with placebo in one study (n = 626; $P \leq 0.05$ for all nine) and in eight of nine domains in another study (n = 647; $P \leq 0.05$ for all eight).

Alosetron was generally well tolerated in clinical trials; however, it was associated with a greater incidence of constipation than placebo, which appeared to be dose related.[66–70,72,74–77] Ischemic colitis (IC) and complications of constipation are known serious adverse events that have been associated with alosetron in clinical trials and postmarketing experience.[76,77,80,81] In IBS clinical trials, the cumulative incidence of IC in women receiving alosetron was 0.2% through 3 months and 0.3% through 6 months. The incidence of serious complications of constipation was approximately 0.1% in women who were treated with either alosetron or placebo.[26] A recent review of alosetron postmarketing safety data gathered over the past 5–6 years has shown that the incidence of IC and complications of constipation has been stable over time, and occurrences have remained rare since its reintroduction to the market in 2002 (0.36 and 0.95 cases per 1000 patient-years, respectively).[81] Moreover, serious outcomes of these adverse events have been mitigated effectively with the alosetron prescribing program, with no cases of transfusions, surgeries, or deaths reported since the institution of the risk management program (now a Risk Evaluation and Mitigation Strategies [REMS] program).[81]

Despite several hypotheses that have been proposed to explain the association of alosetron and other serotonergic drugs with IC, the underlying pathophysiologic mechanism or mechanisms by which IC develops remain unknown. It is interesting to note that numerous epidemiologic studies using various methodologies have described an increased risk for the development of IC in patients with IBS.[82–87] Across these studies, a diagnosis of IBS was associated with a 2–3.4 times increase in the odds of developing IC, bringing into question whether IC is part of the natural history of IBS.[88]

The ACG IBS Task Force classified the quality of evidence supporting the use of alosetron in IBS as high and has determined that alosetron is more effective than placebo at relieving global IBS symptoms in men and women with IBS-D.[3] Given the risk of potentially serious side effects of IC and complications of constipation, the benefit:risk ratio for alosetron is most favorable in women who have not responded to conventional therapies, and indeed this is the population for which alosetron is indicated.

Discussion

Evidence for the use of the TCAs, antibiotics, and the 5-HT_3 antagonist alosetron in patients with IBS and IBS-D indicates that these agents are effective for the treatment of multiple symptoms operant in the IBS patient. The 2009 ACG IBS Task Force has recognized these options as the treatment strategies with the strongest evidence supporting their use in this population.[3] Rather than being one-dimensional treatments, each of the highlighted classes or agents described has the potential to modulate an underlying pathophysiologic mechanism believed to cause IBS, in contrast to conventional agents that are often prescribed but not FDA approved specifically for IBS-D.

The TCAs are thought to act on visceral hypersensitivity by increasing pain thresholds and may act peripherally as well to slow gut transit times.[3,27] TCA studies in IBS are few in number and include small patient populations, but

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Table 4 Characteristics of randomized controlled trials of alosetron in irritable bowel syndrome and efficacy outcomes

Study	Treatment	Study duration	N	Population	Relief of abdominal pain	Relief of bloating	Global/overall IBS improvement	Stool frequency	Stool consistency	Urgency	Other efficacy assessments
Alosetron vs placebo											
Camilleri et al[66]	1, 2, 4, or 8 mg bid	12 wk	370	Adults with IBS-D or -A (Rome I)							
				Women	1 mg: + 2 mg: + 4 mg: 0 8 mg: 0	NA/NR	NA/NR	All doses: +	All doses: +	All doses: +	NA/NR
				Men	All doses: 0	NA/NR	NA/NR	All doses: 0	All doses: 0	All doses: 0	NA/NR
Bardhan et al[67]	0.1, 0.5, or 2 mg bid	12 wk	462	Adults with IBS-D, -A, -C, or other IBS (Rome I)							
				All patients	0.1 mg: 0 0.5 mg: 0 2 mg: + in wk 5–8, 9–12	NA/NR	NA/NR	0.1 mg: 0 0.5 mg: + in wk 1–2, 9–12 2 mg: + 1 in wk 1–2, 9–12	NA/NR	NA/NR	2 mg: + for diarrhea
				Women	0.1 mg: 0 0.5 mg: 0 2 mg: + in wk 9–12	NA/NR	NA/NR	0.1 mg: 0 0.5 mg: + in wk 1–2 2 mg: + in wk 1–2	0.1 mg: ++ 0.5 mg: ++ 2 mg: ++; all at wk 1–2, 9–12	NA/NR	2 mg: + for diarrhea
				Men	All doses: 0	NA/NR	NA/NR	0.1 mg: 0 0.5 mg: 0 2 mg: + in wk 1–2	0.1 mg: 0 0.5 mg: ++ in wk 1–2, 9–12 2 mg: ++ in wk 1–2, 9–12	NA/NR	All doses: 0 for diarrhea
Camilleri et al[68]	1 mg bid	12 wk	647	Women with IBS-D or -A (Rome I)							
				All patients	+ overall and weekly in wk 2–12	NA/NR	NA/NR	+++ weekly in wk 1–12	+++ weekly in wk 1–12	+++ weekly in wk 1–12	NA/NR
				IBS-D	+ overall	NA/NR	NA/NR	NA/NR	NA/NR	NA/NR	NA/NR
				IBS-A	0	NA/NR	NA/NR	NA/NR	NA/NR	NA/NR	NA/NR
Camilleri et al[69]	1 mg bid	12 wk	626	Nonconstipated womenwith IBS-D or -A (Rome I)							
				All patients	+++ overall	NA/NR	NA/NR	NA/NR	NA/NR	NA/NR	NA/NR

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				IBS-D	+++ overall	0	NA/NR	+++ in wk 1–12	+++ in wk 1–12	++ in wk 1–2; +++ in wk 3–12	+ for reduction of days with sensation of incomplete evacuation in mo 2, ++ at mo 3
Watson et al[71,*]	1 mg bid	12 wk	1273	Women with IBS-D or -A (Rome I)	NA/NR	NA/NR	NA/NR	NA/NR	NA/NR	NA/NR	+ in IBS-D on all QOL subscales[†] in both studies* (except mental health subscale in Camilleri[69])
Lembo et al[70]	1 mg bid	12 wk	801	Nonconstipated women without satisfactory control of bowel urgency (Rome II)	NA/NR	NA/NR	+++ in wk 4, 8, and 12	+++	+++	+++	+++ for reduction of days with sensation of incomplete evacuation
Olden et al[73] (Same cohort as Lembo et al[70])	1 mg bid	12 wk	801	Nonconstipated women without satisfactory control of bowel urgency (Rome II)	NA/NR	NA/NR	NA/NR	NA/NR	NA/NR	NA/NR	+++ for overall satisfaction with treatment at 12 wk
Chey et al[74]	1 mg bid	48 wk	714	Women with IBS-D or -A (Rome I)							
				IBS-D	++ for 48 wk average	0	NA/NR	++	+	+++	NA/NR
				IBS-D with greater urgency	++ for 48 wk average		NA/NR	++	+	+++	NA/NR
Lembo et al[75,‡]	1 mg bid	12 wk	492	Women with severe IBS-D (Rome II)	NA/NR	NA/NR	+++ at wk 4, 8, 12	+++	+++	+++	+ for reduction of days with sensation of incomplete evacuation for 11 of 12 wk
			711	Women with IBS-D without satisfactory control of bowel urgency (Rome II)	NA/NR	NA/NR	+++ at wk 4, 8, 12	+++	+++	+++	++ for the % of subjects with ≤1 d of uncontrolled urgency at wk 1–2; +++ for wk 3–12

(*Continued*)

Table 4 (*Continued*)

Study	Treatment	Study duration	N	Population	Relief of abdominal pain	Relief of bloating	Global/overall IBS improvement	Stool frequency	Stool consistency	Urgency	Other efficacy assessments
Chang et al[76]	0.5, 1, 2, or 4 mg bid	12 wk	662	Men with IBS-D (Rome I)	0.5 mg: 0 1 mg: + at wk 5–12 2 mg: 0 4 mg: 0	All doses: 0	NA/NR	All doses: 0	All doses: +++	All doses: 0	0 for reduction of days with sensation of incomplete evacuation
Krause et al (efficacy and safety)[77]	0.5 mg qd, 1 mg qd, or 1 mg bid	12 wk	705	Women with severe IBS-D who had failed conventional therapy (Rome II)	All doses: + at each 4 wk interval (1–4, 5–8, 9–12)	NA/NR	All doses: + at wk 12	All doses: ++ at each 4 wk interval (1–4, 5–8, 9–12)	All doses: +++ at each 4 wk interval (1–4, 5–8, 9–12)	0.5 mg: + at wk 9–12 1 mg qd: + at wk 9–12 1 mg bid: 0	All doses: ++ at each 4 wk interval (1–4, 5–8, 9–12) for normalization of bowel patterns
Nicandro et al (QOL)[78] (same cohort as Krause et al[77])	0.5 mg qd, 1 mg qd, or 1 mg bid	12 wk	705	Women with severe IBS-D who had failed conventional therapy (Rome II)	NA/NR	NA/NR	++ all alosetron-treated subjects on overall treatment satisfaction	NA/NR	NA/NR	NA/NR	IBS-QOL 0.5 mg qd: + in 8/9 domains 1 mg qd: + in 5/9 domains 1 mg bid: + in 7/9 domains Reduction in lost work productivity 0.5 mg qd: + 1 mg qd: 0 1 mg bid: ++++

Notes: *Primary efficacy reported in Camilleri et al,[68,69] respectively. †QOL subscales: emotional health, sleep, energy, physical and social functioning, food/diet, role-physical, sexual relations, and mental health. ‡Counted as a reanalysis of Lembo et al.[70] Positive signs indicate significant improvement over placebo: + for $P \leq 0.05$; ++ for $P \leq 0.01$; +++ for $P \leq 0.001$; ++++ for $P \leq 0.0001$; 0 represents no statistically significant difference between active treatment and placebo.
Abbreviations: IBS, irritable bowel syndrome; IBS-A, irritable bowel syndrome with alternating diarrhea and constipation symptom predominance; IBS-C, constipation-predominant IBS; IBS-D, diarrhea-predominant IBS; NA/NR, not assessed or not reported; IBS-QOL, Irritable Bowel Syndrome Quality of Life Questionnaire; QOL, quality of life.

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amitriptyline[28,29] and desipramine[30,31] appear to be effective for global IBS symptom relief. The capacity of these agents to reduce abdominal pain is less clear. The largest study of any of the TCAs is an investigation of desipramine.[31] However, in this study, interpretation of the efficacy of desipramine was compromised by high patient withdrawals and noncompliance, although results showed it was effective in those patients who were able to tolerate it. The other TCA reviewed here, imipramine 25–50 mg/day, did not show efficacy in IBS but was evaluated in only two small-scale studies.[32,33] This agent may be effective in larger patient populations and perhaps at higher doses. Overall, the reported efficacy of the TCAs in the control of stool frequency and consistency has varied.[28–30] The tolerability of the TCAs depends largely on the propensity of these agents to exert cholinergic, histaminergic, and adrenergic side effects,[16] which indeed may affect adherence. Additionally, the prescriber must also be cognizant that the TCAs can be associated with death in overdose,[34] especially in light of suicidal ideation findings that were related purely to IBS symptoms in secondary and tertiary care patients observed by Miller et al.[34]

Evidence that antibiotics show a therapeutic benefit in IBS has been evaluated and scrutinized for many years; however, the role of antibiotics in the management of IBS remains undefined, owing in part to uncertainty about the association between altered intestinal flora and IBS pathogenesis. Study findings suggesting differences in the gut microbiota between IBS sufferers and healthy controls[41,49] have been inconsistent, and the relative contributions of the various altered bacterial populations to IBS physiology and symptom development have not been determined.[89] Likewise, the link between SIBO and IBS symptoms remains controversial, particularly because of the wide variability in reported prevalence rates of SIBO in IBS patients (most studies report a 10% prevalence, whereas Pimentel et al[21] have a reported prevalence as high as 84%), and the lack of sensitivity and specificity of breath testing methods (ie, lactulose, glucose, sucrose) for diagnosing SIBO.[40,45,90,91] Indeed, in the single study that used direct aspiration and culture of jejunal secretions to assess SIBO, no difference in the prevalence of SIBO (defined as $\geq 10^5$ cfu/mL) was found between IBS patients and controls.[92] Additionally, a retrospective cohort study by Chan et al[93] found that only 32% of those receiving an antibiotic course for SIBO realized a complete symptomatic response. Interestingly, the IBS condition was found to be an independent risk factor for an incomplete response to antibiotics using multivariate regression analysis. Most recently, Yu et al[45] found that the abnormal rise in H_2 measured by the LHBT appears to be explained by variations in orocecal transit time in patients with IBS and not by the presence of SIBO.

Acute clinical trials of rifaximin in nonconstipated IBS have provided evidence of global symptom improvements and bloating relief.[44,51,54–60] At present, it is not clear if rifaximin can provide durable effects beyond 3 months, if it provides relief in patients with severe symptoms, or if repetitive treatment would lead to antibiotic resistance. Longer-term studies of rifaximin are necessary to support its use in IBS.

Alosetron is the only FDA-approved agent for use in women with severe IBS-D. Its proposed mechanism of action involves targeting the 5-HT_3 serotonin receptor subtype known to play a role in influencing GI motility, intestinal secretion, and pain perception or visceral hypersensitivity.[9,10,18,19] Alosetron is effective for relieving global IBS symptoms[70,73,75,77] and abdominal pain/discomfort,[66–69,74,76,77] as well as multiple other symptom domains, including stool frequency,[66–70,74,75,77] stool consistency,[66–70,74–77] and fecal urgency,[66,68–70,74,75,77] for up to 1 year of treatment. Likewise, alosetron improves quality of life in IBS patients.[71,78] Institution of the REMS program upon the market reintroduction of alosetron has provided health care providers and patients with a valuable tool allowing proper patient selection. The potential for side effects of constipation and IC are predictable and well understood such that complications from either of these adverse events have been mitigated to the point of being virtually nonexistent since the REMS program was initiated.[81] Alosetron represents a viable and highly effective therapeutic option in women with severe IBS-D, providing multisymptom relief, a well-characterized tolerability profile, and improvements in quality of life.

Conclusion

High-quality placebo-controlled clinical evidence of efficacy in IBS is available for TCAs, antibiotics, and alosetron. Depending on the nature of the symptoms in the individual patient with IBS, each of these targeted therapies is able to provide benefit that goes beyond the monosymptomatic relief conferred by conventional therapies. Knowledge of the differential treatment effects of each of these agents may facilitate development of a more personalized treatment approach in IBS. Despite current and emerging evidence, alosetron remains the only therapeutic option that is FDA approved for the treatment of IBS-D. As new therapies are investigated, the effects of specific agents on multitiered patient-reported outcome measures (as are now recommended by the FDA)[94] will be informative to the field and

will help shape future evidence-based practice guidelines for the treatment of IBS.

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Supplementary Tables

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Table 1 Randomized controlled trials of tricyclic and selective serotonin-reuptake inhibitor antidepressants in irritable bowel syndrome: study characteristics and efficacy outcomes

Study	Diagnostic criteria	Sample size, type of IBS,* dosage, analysis population	Study type and duration	Relief of abdominal pain with or without discomfort	Relief of bloating and/or distension	Effect on stool frequency	Effect on stool consistency	Effect on urgency	Global or overall IBS improvement	Other efficacy assessments
Tricyclic antidepressant: amitriptyline										
Rajagopalan et al[1]	Rome	*Patients*: 40, age 21–65 yr, with IBS and symptoms for ≥1 yr *Treatment*: amitriptyline 25–75 mg (titrated) vs placebo	Randomized, DB, PC design; 12 wk treatment	Reduction in days per wk with abdominal pain: +, $P < 0.01$	NA/NR	0	NA/NR	NA/NR	+, 63.6% with amitriptyline vs 25.9% with placebo, $P < 0.01$	Days felt well: +, $P < 0.001$ Days with satisfactory bowel movements: +, $P < 0.05$
Vahedi et al[2]	Rome II	*Patients*: 50, mean age 36 yr, with IBS-D and symptoms for ≥12 wk during the preceding yr, 42% women *Treatment*: amitriptyline 10 mg qhs vs placebo	Randomized, DB, PC design; 2 mo treatment	0	NA/NR	NA/NR	Number of loose stools per day: +, $P < 0.05$	NA/NR	Complete response: ITT +, $P = 0.01$	Degree of symptom improvement: +, $P = 0.01$; Passage of mucus: 0; Feeling of incomplete defecation: +, $P < 0.05$; Diarrhea: 0

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Tricyclic antidepressant: desipramine

Greenbaum et al[3]	Clinical diagnosis (history, PE, labs, stool studies, procto-sigmoidoscopy, and barium enema at screening or within previous yr)	*Patients:* 41 (27 women) with IBS defined as ≥3 mo of abdominal pain or distress not attributed to menstruation, with diarrhea, constipation, or alternating symptoms occurring at least biweekly with no organic cause; concomitant meds allowed, including analgesics and antibiotics *Treatment:* desipramine 50–150 mg qhs, atropine 0.4–1.2 mg qhs, or placebo *Analysis population:* 1. Overall completers (n = 28) 2. IBS-D (n = 19) 3. IBS-C (n = 9) 4. IBS-D vs IBD-C	DB, PC, crossover design; 3 6 wk test periods	Pain index: NA/NR 1. +, $P < 0.0025$ 2. +, $P < 0.025$ 3. N too small for meaningful comparison 4. Significant differences favoring IBS-D ($P < 0.01$) over IBS-C	Mean frequency of stools: 1. +, $P < 0.025$ 2. +, $P < 0.025$ 3. N too small for meaningful comparison 4. No significant differences between IBS-D and IBS-C	Mean frequency of loose stools: 1. 0 2. 0 3. N too small for meaningful comparison 4. No significant differences between IBS-D and IBS-C	NA/NR	1. 15 of 26 patients with improvement while receiving desipramine 2. 87% of patients who reported global improvement had IBS-D	Reduction in diarrhea: 1. 0 2. +, $P < 0.005$ 3. 0 4. Significant differences between IBS-D; ($P < 0.025$) and IBS-C; Reduction in slow contractions: 1. +, $P < 0.01$ 2. +, $P < 0.05$ 3. N too small 4. 0 No significant differences for number of fast contractions or motility indices; Other assessments included Brief Psychiatric Rating Scale and HAM-D

(*Continued*)

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Table 1 (*Continued*)

Study	Diagnostic criteria	Sample size, type of IBS, * dosage, analysis population	Study type and duration	Relief of abdominal pain with or without discomfort	Relief of bloating and/or distension	Effect on stool frequency	Effect on stool consistency	Effect on urgency	Global or overall IBS improvement	Other efficacy assessments
Drossman et al[4]	Rome I and physicians' clinical diagnosis	*Patients:* 431 women aged >18 yr with functional bowel disorder with moderate to severe abdominal pain with or without altered bowel habit; 78% of whom had IBS on Rome I criteria; 87% had IBS diagnosis by physician *Treatment:* desipramine 50–150 mg (titrated) vs placebo	Randomized (variable-sized blocks of 6 and 12), comparator-controlled design; 12 wk treatment with CBT vs education and desipramine vs placebo (only desipramine vs placebo results presented here)	McGill average daily pain: ITT: 0	NA/NR	NA/NR	NA/NR	NA/NR	Responder analysis: ITT: 0 PPP: +, $P = 0.02$; Patients with detectable desipramine: +, $P = 0.006$; Global well-being: ITT: 0	Post-treatment satisfaction: ITT: +, $P = 0.011$; IBS-QOL: ITT: 0; Composite score: ITT: 0 PPP: +, $P = 0.03$; Patients with detectable desipramine: +, $P = 0.01$
Tricyclic antidepressant: imipramine										
Talley et al[5]	Rome II	*Patients:* 34 with IBS (IBS-D 73%) *Treatment:* imipramine 25–50 mg/d, citalopram 20–40 mg/d, vs placebo ("n" represents imipramine vs placebo results presented here)	Randomized, DB, PC, PG, pilot study; 12 wk treatment	0	NA/NR	0	NA/NR	NA/NR	Adequate relief of IBS symptoms at last wk: 0; Adequate relief of IBS symptoms ≥ 50% of wk: 0; CGI: 0; BSSRS: Disability +, $P = 0.05$ Distress: +, $P = 0.02$	HADS: anxiety 0 and depression 0; SF-36: menta 0 and physical 0

Abdul-Baki et al[6]	Rome II	*Patients:* 107 patients with IBS (42% female) *Treatment:* imipramine 25 mg qhs vs placebo	Randomized, DB, PC study; 12 wk treatment	NA/NR	NA/NR	NA/NR	NA/NR	NA/NR	Global symptom relief: ITT: 0 PPP: +, $P < 0.05$	QOL using SF-36: 0
SSRI: fluoxetine										
Kuiken et al[7]	Rome I	*Patients:* 40 adults with IBS (IBS-D 40%) *Treatment:* fluoxetine 20 mg qhs vs placebo	Randomized, DB, PC study; 6 wk treatment	0	0	NA/NR	NA/NR	0	0	Flatulence: 0 Incomplete evacuation: 0
SSRI: paroxetine										
Tabas et al[8]	Rome I	*Patients:* 81 adults with IBS *Treatment:* HFD ± paroxetine 10 mg qd vs placebo; titration at wk 4, 8, and 11 prn; maximum dose 40 mg qd	Randomized, DB, PC study; 12 wk treatment	0	0	NA/NR	NA/NR	NA/NR	++[†], $P = 0.01$	Stool passage: +
Masand et al[9]	Rome II	*Patients:* 72 adults with IBS (women 87.5%) *Treatment:* paroxetine CR 12.5 mg qd titrated biweekly to response and tolerability; maximum dose 50 mg qd	Randomized, DB, PC study; 12 wk treatment	0	0	NA/NR	NA/NR	NA/NR	NA/NR	CGI-Severity improvement: ++, $P < 0.01$; Constipation, diarrhea, distress: 0

(*Continued*)

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Table 1 (*Continued*)

Study	Diagnostic criteria	Sample size, type of IBS, * dosage, analysis population	Study type and duration	Relief of abdominal pain with or without discomfort	Relief of bloating and/or distension	Effect on stool frequency	Effect on stool consistency	Effect on urgency	Global or overall IBS improvement	Other efficacy assessments
SSRI: citalopram										
Tack et al[10]	Rome II	*Patients:* 23 adults with IBS (women 78.3%) *Treatment:* citalopram 20 mg qd for 3 wk then 40 mg qd for 3 wk	Crossover study; 6 wk treatment	No. days per wk with abdominal pain: +, $P < 0.05$	+; $P < 0.05$	NA/NR	NA/NR	NA/NR	NA/NR	No. days with loose stools, straining, and incomplete evacuation: +, $P < 0.05$
Talley et al[5]	Rome II	*Patients:* 33 adults with IBS (IBS-D 76%) *Treatment:* citalopram 20–40 mg/d, imipramine 25–50 mg/d, vs placebo ("n" represents citalopram vs placebo results presented here)	Randomized, DB, PC, PG, pilot study; 12 wk treatment	0	NA/NR	0	NA/NR	NA/NR	Adequate IBS symptom relief at last wk: 0; CGI: 0; BSSRS: Disability: 0 Distress: 0	Adequate symptom relief for ≥50% of wk: 0

Notes: *According to predominant stool pattern, if available; †Endpoint was "improvement in overall well-being." + Indicates significant improvement over placebo; 0 represents no statistically significant difference between active treatment and placebo. If a study did not report on a particular assessment, it was noted as "not assessed." If more than one population is assessed for a particular parameter, the populations are numbered (see sample size, type of IBS, dosage, analysis population column); subsequent efficacy values are presented to correspond to the population so designated.

Abbreviations: BSSRS, bowel syndrome severity rating scale; CBT, cognitive behavioral therapy; CGI, Clinical Global Impression scale; CR, controlled release; DB, double-blind; HADS, Hospital Anxiety and Depression Scale; HAM-D, Hamilton Rating Scale for Depression; HFD, high-fiber diet; IBS, irritable bowel syndrome; IBS-C, constipation-predominant IBS; IBS-D, diarrhea-predominant IBS; IBS-QOL, Irritable Bowel Syndrome Quality of Life Questionnaire; ITT, intent-to-treat population; NA/NR, not assessed or not reported; PC, placebo-controlled; PE, physical exam; PG, parallel group; PPP, per-protocol population; QOL, quality of life; SF-36, Medical Outcomes Study Short Form; SSRI, selective serotonin-reuptake inhibitor.

Table 2 Randomized controlled trials of rifaximin in irritable bowel syndrome: study characteristics and efficacy outcomes

Study	Diagnostic criteria	Sample size, type of IBS,* dosage, analysis population	Study type and duration	Relief of abdominal pain with or without discomfort	Relief of bloating and/or distension	Effect on stool frequency	Effect on stool consistency	Effect on urgency	Global or overall IBS improvement	Other efficacy assessments
Pimentel et al[11]	Rome I	Patients: 87, aged 18–65 yr, with IBS without an underlying condition predisposing to SIBO, 66% women *Treatment:* rifaximin 400 mg tid vs placebo for 10 days in 1:1 ratio in blocks of 4 patients (rifaximin = 43, placebo = 44)	Randomized, DB, PC design; 10-d treatment. 10 wk follow-up	VAS-abdominal pain: 0	VAS-bloating: +, $P = 0.010$	NA/NR	NA/NR	NA/NR	Overall improvement: +, $P = 0.020$	VAS-diarrhea: 0, diarrhea common AE
Sharara et al[12]	1. Intestinal gas-related symptoms 2. Rome II 3. Patient not meeting Rome II	*Patients:* 124, 54% men *Treatment:* rifaximin 400 mg bid vs placebo *Analysis population:* 1. History of bloating and/or excessive flatulence for >12 wk and any of the following: chronic abdominal pain or discomfort, disturbances in bowel movements including feeling of incomplete evacuation, or abnormal stool consistency 2. 70 IBS patients met Rome II criteria with 20% IBS-D, 42% IBS-A, 38% IBS-C 3. 54 patients did not meet Rome II criteria	Randomized, DB, PC design; 10 d treatment, 10 d follow-up	NA/NR	1. +, $P = 0.02$ 2. NA/NR	NA/NR	NA/NR	NA/NR	Subjective feeling of symptom relief at end of treatment: 1. +, $P = 0.03$ 2. +, $P = 0.04$ 3. 0; Subjective feeling of symptom relief at end of follow-up: 1. +, $P = 0.02$ 2. +, $P = 0.05$	1. Mean symptom score at end of treatment: +, $P = 0.03$; At follow-up: 0

(*Continued*)

Table 2 (*Continued*)

Study	Diagnostic criteria	Sample size, type of IBS,* dosage, analysis population	Study type and duration	Relief of abdominal pain with or without discomfort	Relief of bloating and/or distension	Effect on stool frequency	Effect on stool consistency	Effect on urgency	Global or overall IBS improvement	Other efficacy assessments
IBS-D phase II study 1. Lembo et al[13] 2. Ringel et al[14] 3. Pimentel et al[15] 4. Chey et al[16]	Rome II	*Patients:* 388 with IBS-D *Treatment:* rifaximin 550 mg bid for 14 d vs placebo	DB, multicenter design; 14 d DB treatment, 14 d placebo, followed by 12 wk follow-up	1. NA/NR 2. NA/NR 3. NA/NR 4. NA/NR	1. Adequate relief of IBS-related bloating symptoms: At end of treatment: +, $P = 0.04$; At end of follow-up: +, $P < 0.05$ 2. and/or 3. In patients with baseline abdominal pain mild-moderate: 0 or severe: 0; Relief of bloating symptoms in patients with baseline bloating mild to moderate: +, $P = 0.03$, or severe: 0. 4. NA/NR	1. NA/NR 2. NA/NR 3. NA/NR 4. NA/NR	1. NA/NR 2. NA/NR 3. NA/NR 4. NA/NR	1. NA/NR 2. NA/NR 3. NA/NR 4. NA/NR	1. Adequate relief of global symptoms: At end of treatment: +, $P = 0.03$; At end of follow-up: +, $P < 0.05$ 2. and/or 3. Relief of global symptoms in patients with baseline abdominal pain mild-moderate: +, $P = 0.04$, and severe: 0; Relief of global symptoms in patients with baseline bloating mild to moderate: +, $P = 0.006$, and severe: 0 4. NA/NR	1. NA/NR 2. and/or 3. The most substantial confounders of clinical response were daily bloating, abdominal pain, and use of rescue medications 4. IBS-QOL total score: +, $P = 0.02$; also +, $P < 0.05$ for dysphoria, body image, health worry, social reaction, and relationship improvements
Pimentel et al[17] TARGET 1 and TARGET 2 studies[17]	Rome II	*Patients:* 1260 with nonconstipated IBS enrolled in 2 identically designed TARGET 1 (n = 623) and TARGET 2 (n = 637) studies *Treatment:* rifaximin 550 mg tid vs placebo: 1. TARGET 1 2. TARGET 2 3. Total from both trials	Randomized, DB, PC, PG design; 2 wk treatment, 10 wk follow-up	Daily abdominal pain improvement (for at least 2 of first 4 wk after treatment): 1. +, $P = 0.02$ 2. +, $P = 0.02$ 3. +, $P < 0.001$	Defined as for at least 2 of first 4 wk after treatment (weekly assessment): 1. +, $P = 0.005$ 2. +, $P = 0.02$ 3. +, $P < 0.001$	NA/NR	Daily symptoms 1. +, $P < 0.001$ 2. +, $P = 0.01$ 3. +, $P < 0.001$	NA/NR	Defined as relief for at least 2 of first 4 wk after treatment (weekly assessment): 1. +, $P = 0.01$ 2. +, $P = 0.03$ 3. +, $P < 0.001$	Relief of IBS-related abdominal pain and loose or watery stools for at least 2 of first 4 wk after treatment based on daily assessments: 1. +, $P = 0.04$ 2. +, $P = 0.008$ 3. +, $P < 0.001$

Notes: *According to predominant stool pattern, if available. + Indicates significant improvement over placebo; 0 represents no statistically significant difference between active treatment and placebo. If a study did not report on a particular assessment, it was noted as "not assessed." If more than one population is assessed for a particular parameter, the populations are numbered (see sample size, type of IBS, dosage, analysis population column); subsequent efficacy values are presented to correspond to the population so designated.

Abbreviations: AE, adverse event; DB, double-blind; IBS, irritable bowel syndrome; IBS-A, irritable bowel syndrome with alternating diarrhea and constipation symptom predominance; IBS-C, constipation-predominant IBS; IBS-D, diarrhea-predominant IBS; IBS-QOL, Irritable Bowel Syndrome Quality of Life Questionnaire; NA/NR, not assessed or not reported; PC, placebo-controlled; PG, parallel group; SIBO, small intestinal bowel overgrowth; VAS, visual analog scale.

Table 3 Randomized controlled trials of alosetron in irritable bowel syndrome: study characteristics and efficacy outcomes

Study	Diagnostic criteria	Sample size, type of IBS,* dosage; analysis population	Study type and duration	Relief of abdominal pain with or without discomfort	Relief of bloating and/or distension	Effect on stool frequency	Effect on stool consistency	Effect on urgency	Global or overall IBS improvement	Other efficacy assessments
Camilleri et al[18]	Rome I	*Patients:* 370 adults aged ≥ 18 yr with IBS-D or IBS-A; 67% women *Treatment:* alosetron 1, 2, 4, 8 mg bid vs placebo *Analysis population:* 1. Women 2. Men	Randomized, DB, PC, dose-ranging, PG design; 12 wk treatment	Relief of pain and discomfort 1. +, for 1 mg bid ($P = 0.015$) and 2 mg bid ($P = 0.023$) in women; 0 for 4 or 8 mg bid in women 2. 0, for all dosage strengths in men	NA/NR	1. All doses: +, $P < 0.05$ 2. 0	1. All doses: +, $P < 0.05$ 2. 0	1. All doses: +, $P < 0.05$ 2. 0	NA/NR	NA/NR
Bardhan et al[19]	Rome I	*Patients:* 462 adults aged >18 yr with IBS-D (32.9%), IBS-A (32.3%), IBS-C (31.3%), or IBS other (3.5%), 73% women *Treatment:* alosetron 0.1, 0.5, 2 mg bid vs placebo *Analysis population:* 1. Total 2. Women 3. Men	Randomized, DB, PC, PG, design; 12 wk treatment	Mean % of pain-free days (diary cards): 1. 2 mg bid: +, $P < 0.05$ in wk 5–8 and 9–12 2. 2 mg bid: +, $P < 0.05$ in wk 9–12 3. 0; VAS for pain and discomfort: 1. + for 2 mg bid, $P = 0.04$ 2. 0 3. 0	NA/NR	Diary cards: 1. 0.5 and 2 mg bid: +, $P < 0.05$ in wk 1–2 and 9–12 2. 0.5 and 2 mg bid: +, $P < 0.05$ in wk 1–2 3. 2 mg bid: +, $P < 0.05$ in wk 1–2	1. and 2. 0.1, 0.5, and 2 mg bid: +, $P < 0.002$ in wk 1–2 and 9–12 3. 0.5 and 2 mg bid: +, $P < 0.002$ in wk 1–2 and 9–12	NA/NR	NA/NR	VAS for diarrhea: 1. 2 mg bid: +, $P = 0.03$ 2. 2 mg bid: +, $P = 0.033$ 3. 0
Camilleri et al[20]	Rome I for last 6 mo	*Patients:* 647 women aged ≥ 18 yr with IBS-D (71%), IBS-A (28%) for ≥ 6 mo; IBS-C (1%) although exclusionary *Treatment:* alosetron 1 mg bid vs placebo	Randomized, DB, PC, PG design; 12 wk treatment	Proportion with adequate relief of pain and discomfort: Overall: +, 41% alosetron, 29% placebo, CI 4.7–19.2; IBS-D +; IBS-A 0; Weekly results: +, $P < 0.05$ from wk 2–12; Change in pain severity scores: +, $P < 0.05$ at mo 2 and 3	NA/NR	+, $P < 0.001$ each wk, wk 1–12	+, $P < 0.001$ each wk, wk 1–12	+, $P < 0.001$ each wk, wk 1–12	NA/NR	NA/NR

(*Continued*)

Table 3 (*Continued*)

Study	Diagnostic criteria	Sample size, type of IBS,* dosage; analysis population	Study type and duration	Relief of abdominal pain with or without discomfort	Relief of bloating and/or distension	Effect on stool frequency	Effect on stool consistency	Effect on urgency	Global or overall IBS improvement	Other efficacy assessments
Camilleri et al[21]	Rome I for last 6 mo	*Patients:* 626 nonconstipated women aged ≥ 18 yr with IBS-D (71%), IBS-A (27%) for ≥ 6 mo; IBS-C (2%) although exclusionary *Treatment:* alosetron 1 mg bid vs placebo *Analysis population:* 1. All patients 2. IBS-D patients	Randomized, DB, PC, PG, design; 12 wk treatment	Proportion with adequate relief of pain and discomfort: 1. Overall: 41% alosetron vs 26% placebo, $P < 0.001$; CI 7.8–22.5 2. Overall: 43% alosetron vs 26% placebo, patients were responders for all 3 mo, $P < 0.001$; For each mo: +, $P < 0.05$; Weekly with significant benefit achieved by wk 4–12 +, $P < 0.01$	1. NA/NR 2. 0	Weekly from wk 1–12 1. NA/NR 2. +; $P < 0.001$	Weekly from wk 1–12 1. NA/NR 2. +, $P < 0.001$	Weekly from wk 1–12 1. NA/NR 2. +, $P < 0.01$	1. NA/NR 2. NA/NR	No significant differences in alosetron efficacy between IBS-D and IBS-A Incomplete evacuation: 1. NA/NR 2. For mo 1: 0; For mo 2: +, $P = 0.02$; For mo 3: +, $P = 0.009$
Watson et al[22]	Rome I	*Patients:* 1273 women aged ≥ 18 yr with IBS-D (71%) or IBS-A (27%) for ≥ 6 mo; IBS-C (2%) although exclusionary *Treatment:* alosetron 1 mg bid vs placebo *Primary efficacy reported in Camilleri et al, 2000 and 2001	Randomized, DB, PC, PG design; 12 wk treatment	See individual trials (Camilleri et al, 2000 and 2001) above	See individual trials (Camilleri et al, 2000 and 2001) above	See individual trials (Camilleri et al, 2000 and 2001) above	See individual trials (Camilleri et al, 2000 and 2001) above	See individual trials (Camilleri et al, 2000 and 2001) above	NA/NR	QOL: across both studies, alosetron resulted in significant improvement in IBS-D +, $P < 0.05$ on all scales (emotional health, sleep, energy, physical and social functioning, food/diet, role-physical, and sexual relations), except mental health was significantly improved for Camilleri et al, 2001 only

Lembo et al[23]	Rome II	*Patients:* 801 women aged ≥ 18 yr, nonconstipated with IBS-D (98%) or IBS-A (2%), with lack of satisfactory control of bowel urgency (required to occur on ≥ 50% of days during 2 wk screening) *Treatment:* alosetron 1 mg bid vs placebo	Randomized (2:1 ratio), DB, PC design; 12 wk treatment	NA/NR	NA/NR	Median stool frequency: +, $P < 0.001$	Median stool consistency: +, $P < 0.001$	Median proportion of days with satisfactory control of urgency: +, $P < 0.001$	Proportion of responders: +, $P < 0.001$ at wk 4, 8, 12	Percentage of days with incomplete evacuation (lower): +, $P < 0.001$
Wolfe et al[24]	Rome I for at least 6 mo	*Patients:* 859, aged ≥ 18 yr, with IBS-D or IBS-A for ≥ 6 mo, 74% women *Treatment:* alosetron 1 mg bid vs placebo	Randomized (3:1 ratio), DB, PC design; 48 wk treatment	NA/NR	NA/NR	NA/NR	NA/NR	NA/NR	NA/NR	Safety only
Olden et al[25]	Rome II	*Patients:* 801 women aged ≥ 18 yr nonconstipated with IBS-D (98%) or IBS-A (2%) with lack of satisfactory control of bowel urgency (required to occur on ≥ 50% of days during 2 wk screening) *Treatment:* alosetron 1 mg bid vs placebo	Randomized (2:1 ratio), DB, PC design; 12 wk treatment	See Lembo et al, 2001 above	See Lembo et al, 2001 above	See Lembo et al, 2001 above	See Lembo et al, 2001 above	See Lembo et al, 2001 above	See Lembo et al, 2001 above	Overall satisfaction with treatment 12 wk: 69% alosetron, 45% placebo +, $P < 0.001$; significantly more patients taking alosetron were satisfied or very satisfied across 11 distinct medication attributes +, $P < 0.001$
Chey et al[26]	Rome I	*Patients:* 714 women aged ≥ 18 yr with IBS-D (80%) or IBS-A (20%); same patients in Lembo et al, 2001 *Treatment:* alosetron 1 mg bid vs placebo *Analysis population:* 1. IBS-D subgroup (n = 569) 2. IBS-D with more frequent urgency (urgency on ≥ 10 d of 14 d screening; n = 417)	Randomized, DB, PC, PG design; 48 wk treatment	48 wk adequate pain and discomfort relief: 1. +, $P = 0.01$ 2. +, $P = 0.005$	1. 0 2. NA/NR	Rate of satisfactory control of stool frequency: 1. +, $P = 0.004$ 2. +, $P = 0.009$	Rates of satisfactory control of stool consistency: 1. +, $P < 0.014$ 2. +, $P < 0.012$	48 wk average satisfactory control of urgency: 1. +, $P < 0.001$ 2. +, $P < 0.001$	NA/NR	NA/NR

(*Continued*)

Table 3 (*Continued*)

Study	Diagnostic criteria	Sample size, type of IBS,* dosage; analysis population	Study type and duration	Relief of abdominal pain with or without discomfort	Relief of bloating and/or distension	Effect on stool frequency	Effect on stool consistency	Effect on urgency	Global or overall IBS improvement	Other efficacy assessments
Lembo et al[†27]	1. Population A: Rome II 2. Population B: Rome II	*Patients:* 1. Population A: 492 women aged >18 yr with severe IBS-D (>3 mo of IBS symptoms); 89% IBS-D and 11% IBS-A 2. Population B: 711 women aged >18 yr (257 from Population A and 454 from Lembo et al, 2001) with IBS-D who lacked satisfactory control of bowel urgency ≥ 71% of the time during screening (≥ 10 of 14 d); 95% IBS-D and 5% IBS-A *Treatment:* alosetron 1 mg bid vs placebo	1. and 2. Randomized, DB, PC design; 12 wk treatment	NA/NR	NA/NR	1. +, $P < 0.001$ 2. +, $P < 0.001$	1. +; $P < 0.001$ 2. +, $P < 0.001$	Satisfactory control of urgency: 1. +, $P < 0.001$ 2. +, $P < 0.001$	GIS responders: 1. +, $P < 0.001$ at wk 4, 8, 12 2. +, $P < 0.001$ at wk 4, 8, 12	Sense of incomplete evacuation improved: 1.At 12 wk: +, $P = 0.018$ 2. For 11 of 12 wk: +; Diarrhea: Similar between treatment groups
Chang et al[28]	Rome I	*Patients:* 662 men aged >18 yr with IBS-D (≥ 6 mo of IBS symptoms) *Treatment:* alosetron 0.5, 1, 2, or 4 mg bid vs placebo	Randomized, DB, PC, dose-ranging study; 12 wk treatment	Average adequate relief of pain and discomfort in wk 5–12: +, $P = 0.04$ for alosetron 1 mg bid; 0 for other doses	All doses: 0	All doses: 0	All doses: +, $P < 0.001$	All doses: 0	NA/NR	Incomplete evacuation: 0 Pain-free days: 0
1. Krause et al (efficacy and safety)[29] 2. Nicandro et al (QOL)[30]	Rome II	*Patients:* 705 women aged ≥ 18 yr with severe IBS-D (≥ 6 mo of symptoms of IBS) who had failed conventional therapy *Treatment:* alosetron 0.5 mg qd, 1 mg qd, and 1 mg bid vs placebo	Randomized, DB, PC design; 12 wk treatment	1. Average adequate relief of pain and discomfort: +, for all 3 alosetron doses at each 4 wk interval (1–4, 5–8, and 9–12), $P \leq 0.038$) 2. NA/NR	1. NA/NR 2. NA/NR	1. All alosetron doses: +, $P \leq 0.006$ for each dose at each 4 wk assessment 2. NA/NR	1. All alosetron doses: +, $P \leq 0.001$ for each dose at each 4 wk assessment 2. NA/NR	1. At wk 9–12: + for alosetron 0.5 and 1 mg qd, $P < 0.05$ 2. NA/NR	1. Proportion of responders for IBS-GIS + for all 3 alosetron doses at wk 12: $P \leq 0.02$; at wk 4: $P \leq 0.028$;	1. Normalization of bowel patterns: +, $P \leq 0.004$ for all alosetron doses at each 4 wk assessment 2. IBS-QOL questionnaire (9 symptom domains):

		at wk 8: $P \leq 0.009$ 2. Overall treatment satisfaction: +, $P \leq 0.003$	improvements: +, except for domains of emotional and sleep with alosetron 1 mg qd; physical functioning with alosetron 1 mg qd and 1 mg bid; and sexual relations all alosetron groups; Work productivity time reductions: +, for alosetron 0.5 mg qd ($P = 0.02$) and 1 mg bid ($P = 0.0001$)

Notes: *According to predominant stool pattern, if available. †Counted as a reanalysis of Lembo et al, 2001. + Indicates significant improvement over placebo; 0 represents no statistically significant difference between active treatment and placebo. If a study did not report on a particular assessment, it was noted as "not assessed." If more than one population is assessed for a particular parameter, the populations are numbered (see sample size, type of IBS, dosage, analysis population column); subsequent efficacy values are presented to correspond to the population so designated.

Abbreviations: CI, confidence interval; DB, double-blind; GIS, global improvement scale; IBS, irritable bowel syndrome; IBS-A, irritable bowel syndrome with alternating diarrhea and constipation symptom predominance; IBS-C, constipation-predominant IBS; IBS-D, diarrhea-predominant IBS; NA/NR, not assessed or not reported; PC, placebo-controlled; PG, parallel group; QOL, quality of life; VAS, visual analog scale.

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