Diagnosis and Management of Diarrhea-Predominant Irritable Bowel Syndrome: Clinical Overview of Alosetron

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Abstract

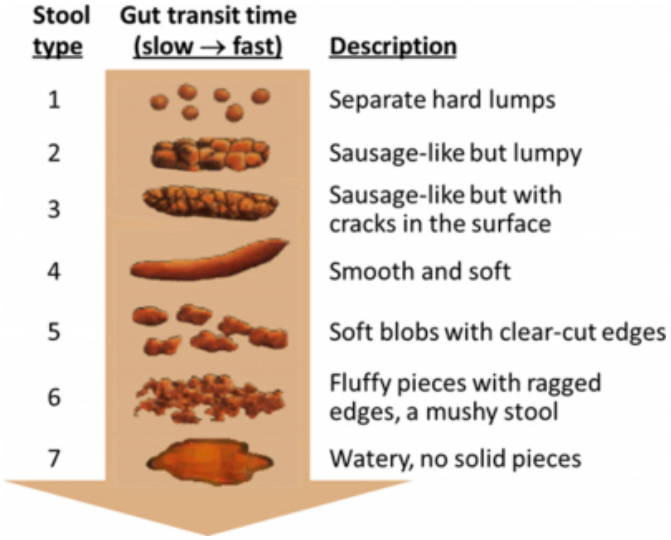
Background:Irritable bowel syndrome (IBS) is a functional bowel disorder associated with considerable impairment in quality of life and utilization of healthcare resources. Owing to the high incidence and chronicity of the disorder, nurse practitioners (NPs) and physician assistants (PAs) likely encounter IBS patients in their practices. Recent updates in the Risk Evaluation and Mitigation Strategy (REMS) for alosetronhave allowed NPs and PAs to enroll in the program to prescribe this selective 5-HT_3 receptor antagonist used to treat IBSfor patients with severe diarrhea-predominant IBS (IBS-D).Aim: To provide an overview of the diagnostic process and current treatment options for IBS, with specific focus on the efficacy, safety, tolerability, and prescribing requirements for alosetron. Methods: The supporting evidence for the labeled efficacy and safety of alosetron in the management of IBS-D was assessed.Results:Whereas conventional therapies provide benefit for a specific symptom of IBS, alosetronhas been shown to provide multisymptom relief in IBS-D, including improvements in abdominal pain, stool consistency, stool frequency, bowel urgency, and IBS-related quality of life. Analysis of postmarketing safety data captured since the alosetronrisk management program was initiated in 2002 suggests that serious outcomes associated with ischemic colitis and serious complications of constipation have been mitigated.Conclusions:Alosetronprovides a favorable risk-to-benefit profile for women with severe IBS-D who have not responded to treatment with conventional agents. By acquiring evidence-based treatment knowledge related to IBS, NPs and PAs may ultimately improve the overall management of this complicated, and relatively common, condition.

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic functional bowel disorder characterized by episodes of abdominal pain or discomfort associated with defecation or change in bowel habit, as well as features of disordered defecation.[1,2]Patients are typically classified into subtypes based on their primary symptoms.[1]Patients with IBS with constipation (IBS-C) have 25% or more bowel movements occurring as hard or lumpy stools (i.e., Bristol Stool Form Scale 1–2; separate hard lumps like nuts [difficult to pass] or sausage-shaped but lumpy stools) or 25% or fewer bowel movements occurring as watery stools (i.e., Bristol Stool Form Scale 6–7; fluffy pieces with ragged edges, a mushy stool or water, no solid pieces, entirely liquid) in the absence of use of antidiarrheals or laxatives(Figure 1).[1] In contrast, patients with IBS with diarrhea (IBS-D) have 25% or more bowel movements occurring as loose (mushy) or watery stools (Bristol Stool Form Scale 6–7) and fewer than 25% bowel movements occurring as hard or lumpy stools (Bristol Stool Form Scale 1–2) in the absence of antidiarrheals or laxatives. Patients who cannot be classified as having IBS-C or IBS-D are said to have either mixed-IBS or an alternating pattern of IBS.[1]

Figure 1

Figure 1. Bristol Stool Form Scale



The exact pathophysiology of IBS is uncertain, but it is likely of multifactorial etiology with traditional links to abnormalities such as altered gut motility, visceral hypersensitivity, and psychological distress.[3,4]Gut hypersensitivity with enhanced visceral perception may result in the abdominal pain or discomfort that characterizes IBS. Additionally, IBS is increasingly being recognized as a disorder arising from a dysregulated brain-gut axis, the bidirectional interaction between the central, autonomic, and enteric nervous systems believed to control the motor, sensory, and secretory functions of the gastrointestinal (GI) tract.[3-5]Brain-gut axis dysfunction may be associated with the abnormal perception and/or modulation of visceral input. Neuronal dysfunction as exemplified by abnormalities in visceral autonomic innervation may also contribute to IBS pathophysiology.[6,7]

IBS has an estimated prevalence of 3% to 20% in the United States[8]; the incidence is slightly higher among women.[2] IBS causes substantial negative effects on quality of life (QOL), with studies finding impairments in QOL in patients with IBS that are similar to those in patients with other chronic diseases, including diabetes, depression, and even end-stage renal disease.[9,10] Additionally, IBS is associated with significant socioeconomic burden, often leading to decreasedproductivity,greater time lost from work,[11,12] and increased healthcare resource utilization.[2]

Because of both the high prevalence of IBS and the chronic nature of the disorder, nurse practitioners (NPs) and physician assistants (PAs) are likely toencounter patients with this condition in their practice. Therefore, these clinicians need to beknowledgeable ofcurrent developments and practices in the diagnosis of IBS, particularly IBS-D, and the evidence base that directs treatment. As a result of recent updates to the Risk Evaluation and Mitigation Strategy (REMS)for alosetron (Lotronex®, Prometheus Laboratories, Inc., San Diego, CA), NPs and PAscan now enroll in a program to prescribe this selective serotonin type 3 (5-HT_3) receptorantagonist, which has shown benefit in IBS-D patients.[13] This article presents an overview of the diagnostic process for IBS, discusses the supporting evidence for current treatment options, and provides a detailed review of the efficacy, safety, and tolerability of alosetron given the allowance by the US Food and Drug Administration (FDA) for these healthcare professionalsto prescribe this medication.

CLINICAL PRESENTATION/DIAGNOSIS

Although the defining symptom of IBS is abdominal pain or discomfort,[1] the clinical presentation can vary substantially, with predominating symptoms such as bloating, urgency, constipation, and/or diarrhea.[4] Importantly, none of the symptoms of IBS are pathognomonic for the disorder, and many of them overlap with those of other GI motility disorders (e.g., chronic constipation, gastroesophageal reflux disease, dyspepsia) as well as nonmotility disorders (e.g., celiac disease, lactose intolerance, Inflammatory bowel disease).[14]The potential symptom overlap and broad differential diagnosis associated with IBS require clinicians to rule out underlying organic pathology before proceeding with treatment.[2]The most common conditions that must be eliminated from the diagnosis include colorectal cancer, systemic hormonal disturbances, enteric infections, and diseases associated with malabsorption, such as inflammatory bowel disease or celiac disease.[2] As a result, patients who present with “alarm features”that may be associated with these diseases should undergo further investigation to rule out suspected underlying pathology.[2] Such alarm features include rectal bleeding, weight loss, iron deficiency anemia, nocturnal symptoms, and a family history of certain organic diseases including colorectal cancer, inflammatory bowel disease, and celiac disease. However, in patients exhibiting Rome diagnostic criteria for IBS without the presence of alarm features, routine diagnostic testing (e.g., complete blood count, serum chemistries, thyroid function testing) is not recommended as laboratory tests areunlikely to uncover any underlying organic pathology in this group of patients.[2]

IBS is a functional disorder that is not associated with any objective physical, radiographic, or laboratory markers.[4]According to the American College of Gastroenterology,[2,7]clinicians should feel confident in making a diagnosis of IBS in patients that meet symptom-based criteria and have an absence of alarm features. Although there are several symptom-based diagnostic criteria, those developed by an international working group—the Rome III criteria—are the most recent and wellestablished (Table 1).[1,2]

Figure 2

Table 1. Rome III Diagnostic Criteria* for Irritable Bowel Syndrome[Reprinted with permission from Longstreth et al.]

Recurrent abdominal pain or discomfort† at least 3 days in each of the last 3 months
associated with ≥2 of the following:
1. Improvement with defecation
2. Onset associated with a change in frequency of stool
3. Onset associated with a change in form (appearance) of stool

*Criteria fulfilled for the last 3 months with symptom onset ≥6 months prior to diagnosis.

†Discomfort means an uncomfortable sensation not described as pain, defined in pathophysiology research and clinical trials as a pain/discomfort frequency of ≥2 days per week during screening evaluation.

The number of patients suffering from severe IBS may be larger than once thought, because symptom severity is not currently included as part of the diagnostic assessment for IBS. This is important, because severity affects treatment choices; certain treatments are indicated only in patients with mild to moderate disease, whereas others are relegated to use only in patients with severe disease. Although no consensus definition of severe IBS exists, an inadequate response to conventional therapy has been suggested as a practical and clinically meaningful criterion.Asin most chronic disorders, symptom severity in IBS correlates with lower QOL and higher healthcare resource use as well.[15,16]Accordingly, the diagnosis of IBS should incorporate an assessment of disease severity that takes into account not only specific symptoms, but also patients' perceptions of their symptoms and the effect of those symptoms on QOL, functional ability, and psychological status.[17,18]While no consensus definition of severe IBSexists, an inadequate response to conventional therapy has been suggested as a practical and clinically meaningful criterion.[19]

MANAGEMENT OF IBS

The treatment goals for patients with IBS include improvingindividual symptomssuch as abdominal pain, bloating, constipation, and diarrhea,; addressingglobal IBS symptoms, as well as reducing the negative effects of the disease on health outcomes, specifically QOL, work/social activities, and healthcare resource use.[20] Effective symptomatic relief will preventunnecessary repetition of diagnostic procedures. An effective patient-provider relationship is also considered essential in meeting these goals. Healthcare professionalsare encouraged to listen actively with empathy to assessand interpret patients' perceptions of their illness, to determine symptom severity and impact on QOL, and to set realistic and consistent treatment goals.[7,18]

IBS subtype and severity of symptoms are key determinants for consideration in formulating an effective treatmentstrategy.Conventional pharmacologic therapies are typically directed at one or two specific IBS symptoms[7], rather than the entire symptom complex. Conventional, gut-specific approaches to managing constipation in IBS patients include dietary fiber, bulking agents, or osmotic laxatives (polyethylene glycolor lactulose) to regulate bowel function, although only limited evidence supports the efficacy of these therapies.[2]Antispasmodic agents, such as dicyclomine and hyoscyamine, may provide short-term relief of abdominal pain or discomfort, particularly in those with symptoms induced by meals and who complain of tenesmus, although no evidence existsthat these agents provide long-term benefit.[2,20] Alternatively, lubiprostone, a selective ClC-2 chloride channel activator that is indicated for IBS-C in women age 18 years or older,[21] has demonstrated statistically significant efficacy over placebo in overall response and across multiple symptoms including abdominal pain/discomfort and bloating.[22]Additionally, severity of constipation, bowel movement frequency, and stool consistency have also been shown to improve significantly with lubiprostone.[22] Therapies used in the treatment of IBS are listed in Table 2.[18]

Figure 3

Table 2. Summary of Pharmacotherapy for Diarrhea-Predominant Irritable Bowel Syndrome [Reprinted with permission from Harris and Heitkemper.]

		Treatment Effect
Therapy/Medication	**GI Indication**	**Level of Evidence†**
Tricyclic antidepressants	Abdominal pain, diarrhea	1B
Selective serotonin reuptake inhibitors	Abdominal pain, bloating, constipation	1B
Serotonin-norepinephrine reuptake inhibitors	Abdominal pain	Not rated
Alosetron‡	IBS-D (women only)	1B for women with IBS-D with an inadequate responsive to conventional agents; otherwise, 2A for women with IBS, 2B for men with IBS
Probiotics (*B infantis*)	Bloating, all types of IBS	2C
Rifaximin	Nonconstipation IBS	1B
Hypnotherapy	All IBS	1C

*Includes only IBS therapies discussed in detail in this article.

†American College of Gastroenterology levels of evidence.

‡Approved by the US Food and Drug Administration (FDA) for female patients with severe IBS-D only.

§Withdrawn by FDA in March 2006.

¶ FDA approved for female patients with IBS.

GI, gastrointestinal; IBS-D, diarrhea-predominant irritable bowel syndrome; IBS-C, constipation-predominant irritable bowel syndrome.

Note: Tricyclic antidepressants include amitriptyline, imipramine, nortriptyline, and desipramine); selective-serotonin reuptake inhibitors include fluoxetine, sertraline, paroxetine, citalopram, and escitalopram; serotonin-norepinephrine reuptake inhibitors include duloxetine and venlafaxine).

Conventional symptom-targeted approaches for patients with IBS-D include antidiarrheal agents such as loperamide, which has been found to improve stool frequency in IBS patients but not abdominal pain or global IBS symptoms.[2] The combination of diphenoxylate and atropine, which is used to treat various types of chronic diarrhea, has not been studied in controlled trials in IBS patients.[20] An evolving approach to managing IBS-D is to manipulate the gut flora with probiotics and antibiotics, a strategy based on the idea that altered intestinal bacteria contribute to the development of IBS symptoms.[20,23]Indeed, promising results have been achieved with certain probiotics[2] and with the minimally absorbable antibiotic rifaximin[23] in patients with IBS.

A recent systematic review of 19 randomized controlled trials in 1650 IBS patients examined the effects of probiotics and found that these agents significantly reduced IBS symptoms.[24] The relative risk of symptoms persisting in the probiotic group was 0.71 (95% confidence interval [CI] 0.57, 0.88), with a number needed to treat of 4 (95% CI 3, 12.5) when the outcome was examined as a dichotomous variable (10 studies) or continuous variable (15 trials) (standardized mean difference [SMD] –0.34; 95% CI –0.60, –0.07). Additionally, this review found a statistically significant effect of probiotics on improving abdominal pain (SMD –0.51; 95% CI –0.91, –0.09; P=0.016) and flatulence (SMD –0.22; 95% CI –0.42, –0.01; P=0.04).[24] While probiotics appear to be effective in IBS, the degree of benefit and the most effective species and strains remain unclear.

In 2011, Pimentel and colleagues[23] reported results from two large-scale, identically designed, multicenter, placebo-controlled trials of rifaximin (TARGET 1, n=623; TARGET 2, n=637; total, n=1260) in patients with nonconstipated IBS (Rome II criteria). In both studies, rifaximin was administered three times daily for 2 weeks, and patients were followed for another 10 weeks. For at least 2 of the first 4 weeks, rifaximinwas associated with a statistically significant relief of global IBS symptoms (primary end point) compared with placebo (TARGET 1 40.8% vs 31.2%, respectively, P=0.01; TARGET 2 40.6% vs 32.2%, respectively,P=0.03) and provided significant reliefof bloating from IBS (TARGET 1 39.5% vs 28.7%,P=0.005; TARGET 2 41.0% vs 31.9%,P=0.02).[23]The FDA requested more safety and efficacy data relative to repeated rifaximin courses of therapy before it can consider approving this agent for nonconstipated IBS.[25]

Patients who do not respond to peripherally acting agentsare often treated with antidepressants.[2] Tricyclic antidepressants (TCAs) appear to be effective at relieving global IBS symptoms and may be beneficial in patients with IBS-D owing in part to their anticholinergic effects.[2]The selective 5-HT_3 receptor antagonist alosetron improves a wide variety of symptoms in IBS-D because of its targeted action onserotonergic processes, which directly addresses key pathophysiologic abnormalities present in patients with IBS-D, thereby normalizing GI motility, intestinal secretion, and pain perception or visceral hypersensitivity.[2,13]

OVERVIEW OF ALOSETRON HYDROCHLORIDE

Alosetronis a selective 5-HT_3 receptor antagonist used in IBS-D. After oral administration, alosetron achieves peak plasma concentrations at 1 hour. It can be given without regard to food.[13,26]Alosetron is extensively metabolized by the liver, predominantly by the cytochorme P450 1A2 isoenzyme, and is eliminated with its metabolites through the kidneys. Plasma concentrations are dose proportional after single doses up to 8 mg but are more than proportional after single doses of 16 mg.[13] Healthy volunteers show no accumulation of drug in the plasma from repeated dosing, which is a finding consistent with the short terminal elimination half-life of this agent (~1.5 hr).[13,26,27]

Ninety-five percent of all serotonin in the human body resides in enterochromaffin cells of the GI tract.[28,29]These cells release serotonin in response to chemical stimuli or increased intraluminal pressure, activating peristaltic and secretory reflexes.[29-31]Enteric neurons contain extensive distributions of 5-HT_3 receptors, which are ligand-gated

cation channels. Upon activation of these receptors, neuronal depolarization affects the regulation of visceral pain, colonic transit, and GI secretions.[13]By blocking 5-HT_3 receptor activation,alosetron is thought to provide its clinical benefits of reducing the perception of pain [32,33] and decreasing exaggerated motor responses.[29,34]

Alosetron is indicated for women with severe IBS-D whose symptoms are chronic (generally lasting 6 months or longer), who have noanatomic or biochemical abnormalities of the GI tract, and who have not responded adequately to conventional therapy.[13]According to the alosetron prescribing information, severe IBS-D is defined as diarrhea occurring in conjunction with one or more of the following: frequent and severe abdominal pain/discomfort, frequent bowel urgency or fecal incontinence,or disability or restriction of daily activities due to IBS.[13]

According to an evidence-based systematic review conducted by the American College of Gastroenterology (ACG) Task Force on IBS, the efficacy of alosetron is supported by high-quality evidence.[2]The Task Force concluded that the benefit-to-risk ratio for alosetron is most favorable for women with IBS-D who have not responded adequately to conventional therapies (Grade 1B recommendation).[2]Additionally, in the broader population of female patients with IBS-D, the Task Force reported that alosetron is more effective than placebo at relieving global IBS symptoms and gave the medication a Grade 2A recommendation in this population.[2]These conclusions were based on a number of published clinical studies of up to 48 weeks' duration that demonstrated the benefits of alosetron for relieving both global and individual symptoms in women with IBS-D.[2]Clinical studies have not been performed to adequately confirm the benefits of alosetron in men.

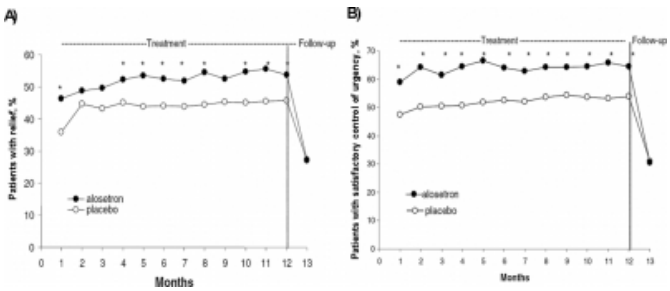
EFFICACY

The efficacy of alosetron in IBS has been welldocumented and is supported by five 12-week, multicenter, randomized, double-blind, placebo-controlled studies that evaluated the use of alosetron in doses ranging from 0.5 mg once daily to 1 mg twice daily in female patients with nonconstipatedIBS or IBS-D.[35-39] In general, these trials showed that alosetron provides significant relief of IBS pain and discomfort,[35-37,39] control of bowel urgency,[35-39] reduction in frequency of bowel movements,[35-39] improvement in stool consistency,[35-39]while also improving global IBS symptoms[37]and reducing the interference of IBS symptoms ondaily activities (e.g., work productivity, social/leisure time) compared with placebo.[13]Additionally, in health-related QOL assessments from two of the randomized, placebo-controlled trials involving nearly 1,300 patients, alosetron-treated patients showed significant improvements in quality of life (including appetite and dietary limitations), reductions in IBS symptominterference with social activities, and an increased ability to carry out work or other primary activity.[40]In another randomized, double-blind, placebo-controlled trial in705 women with severe IBS-D, 12 weeks of treatment with alosetron significantly improved IBS-related quality of life, workplace productivity, social/leisure activity, and treatment satisfaction.[41]

In a 48-week, multinational, double-blind, placebo-controlled study,alosetron 1 mg twice daily demonstrated long-term benefits.[13,42]Over 48 weeks, significantly higher proportions of patientsreceivingalosetron (n=279), compared with those receiving placebo (n=290), experienced adequate relief of IBS pain and discomfort (52% vs 44%, respectively;P=0.01) andsatisfactory control of bowel urgency (64% vs52%, respectively;P=0.001) (Figure 2).[13,42]A subset of 417 IBS-D patients (alosetron n=198, placebo n=219) who experienced frequent bowel urgency at baseline (≥10 days of the 14-day screening period)had greater rates of adequate relief of IBS pain and discomfort with alosetron (52%) than with placebo (41%;P=0.005). The 48-week average rate of satisfactory control of bowel urgency in this population with more severe urgency symptoms was also significantlyhigher withalosetron(60%) than with placebo(48%;P=0.001). Significant improvement of these symptoms occurred for most of the 48-week treatment period with no evidence of tachyphylaxis.

Figure 4

Figure 2. (A) Average monthly adequate relief of IBS pain and discomfort in patients with IBS-D. (B) Average monthly satisfactory control of bowel urgency in patients with IBS-D. *



SAFETY

Constipation is the most commonly reported adverse event observed with alosetron in clinical trials[13]and in clinical use. This effect is dose-related and has been observed in approximately 29% of patients receiving alosetron 1 mg twice daily (n=9316) and in 11% of those receiving alosetron 0.5 mg twice daily (n=243).[13]Adverse events that occurred in patients with IBS who were receiving alosetron 1 mg twice daily for 8 to 24 weeks in 22 repeat-dose clinical studies included constipation (29% and 6% for alosetron and placebo, respectively), abdominal pain or discomfort (7% and 4%), nausea (6% and 5%), and GI discomfort and pain (5% and 3%).[13] In these studies, the incidence of constipation differed significantly between alosetron- and placebo-treated patients (P<0.0001).[13]Table 3 summarizes the GI adverse events that occurred in a 12-week clinical trial conducted inwomen with severe IBS-D, the treatment population for which alosetron is indicated.

Figure 5

Table 3.Gastrointestinal Adverse Events Reported in ≥3% of Women with Severe Diarrhea-Predominant Irritable Bowel Syndrome and More Frequently on Alosetron than Placebo

		Alosetron		
Adverse Event	Placebo (n=176) %	0.5 mg once daily (n=175) %	1 mg once daily (n=172) %	1 mg twice daily (n=176) %
Constipation	5	9	16	19
Abdominal pain	3	5	6	7
Diarrhea	2	3	2	2
Hemorrhoidal hemorrhage	2	3	2	2
Flatulence	2	2	1	3
Hemorrhoids	2	1	1	3
Abdominal pain upper	1	3	1	1

Clinicians need to be familiar with the boxed warning in the alosetronprescribing information describingthe risk of infrequent but serious GI adverse effects that have been associated with the use of the drug.[13] Serious complications of constipation (CoC), including obstruction, ileus, impaction, toxic megacolon, and secondary bowel ischemia, have been reported with alosetron use during clinical trials, with some cases requiring intestinal surgery.[13] The incidence of serious CoC was approximately 0.1% (1 per 1000 patients) among women receiving alosetron. Rare cases of perforation and death have been reported from postmarketing clinical practice.[13,43] Additionally, ischemic colitis (IC) has been reported in patients receiving alosetron during clinical trials and during marketed use of the agent.[13]The incidence of IC in clinical trials was 0.2% through 3 months (2 per 1000 patients, 95% CI 1–3) and 0.3% through 6 months (3 per 1000 patients, 95% CI 1-4).The majority of these cases were reversiblewith conservative treatment including bowel rest and antibiotics.

Reports of these complications prompted a voluntary withdrawal of alosetron from the market November 2000,[44,45] approximately 8 months after its introduction in the United States. Following withdrawal, many patients and physicians sent communications to the FDA requesting the drug be put back on the market.[45] After an FDA Advisory Committee was convened, alosetron was approved for reintroduction and returned to the market in November of 2002 with a more restricted indication and the institution of a risk management plan to mitigate these potential complications.[46]

A subsequent review of postmarketing safety data gatheredsince the 2002 reintroduction of alosetron (16,762 patient-years of use) indicated that the absolute number of possible cases of IC and CoChas been much lower than that reported before the drug was withdrawn.[47] The incidence rates show that these complications continue to be rare (0.95 and 0.36 cases per 1,000 patient-years for IC and CoC, respectively) and have remained stable or havedecreased over time. Serious outcomes associated with these complications appear to be mitigated since alosetron was reintroduced under the risk management program, as there were no surgeries or deaths among patients with possible or probable IC or CoC associated with alosetron during the review period.[47]

Studies have not yet shown the exact cause for or risk factors associated with the development of IC in patients treated with alosetron or other 5-HT_3 receptor antagonists. However, IBS itself has been suggested as a risk factor for IC, with population-based studies demonstrating a 3-4-fold higher rate of IC among IBS patients than the general population.[47]Given the risks of IC and CoC associated with its use,alosetron should not be initiated in a patient with constipation. Likewise, alosetron is contraindicated in patients with (1) a history of chronic or severe constipation or sequelae from constipation; (2) intestinal obstruction, stricture, toxic megacolon, GI perforation, and or adhesions; (3) ischemic colitis, impaired intestinal circulation, thrombophlebitis, or hypercoagulable state; (4) Crohn's disease or ulcerative colitis;(5) diverticulitis; or (6) severe

hepatic impairment.[13]

LOTRONEX PRESCRIBING PROGRAM

Alosetron is prescribed under the Prescribing Program for Lotronex(PPL), which emphasizes the importance of appropriate patient selection, education, and follow-up forthe successful use ofalosetronfor IBS-D. To prescribe alosetron, healthcare professionals must enroll in the PPL, which was recently expanded to include NPs and PAs as prescribers.[13]This program, which provides the education and tools needed for the safe use of alosetron, requires prescribers, patients, and pharmacists to adhere to a set of actions and responsibilities.[13] An overview of the program is depicted in Figure 3.[48]After enrolling in the program, prescribers must review and provide a Medication Guide to patients and have them complete a Patient Acknowledgement Form that discusses the risk and benefits of alosetron.[49-51]Prescribers agree to monitor and counsel patients, as well as to report all serious adverse events.[49] Patients agree to discontinue the drug and inform their physicians immediately if they experience constipation or signs of IC (e.g., worsening of abdominal pain, blood in stool).[51]

Figure 6

Figure 3.Enrollment Process for the Prescribing Program for Lotronex.

The success of the PPLin achieving proper patient selection was underscored in a survey of 4803 patients enrolled in the program and followed through December 2004. Results demonstrated that 90% of women enrolled fulfilled clinical criteria for severe IBS and more than 90% were in compliance with the key elements of the program (e.g., signing a Patient Acknowledgment Form, discussing risks of the medication with a provider, discussing reasons to stop taking the drug).[51,53]

ALOSETRON DOSING AND ADMINISTRATION

Alosetron therapy recommended starting dose is 0.5 mg twice daily; it may be given, with or without food, and can be maintained at this dosage in patients whose symptoms are well controlled.[13]In patients whose symptoms are not controlled after 4 weeks of therapy, the dosage can be increased to 1 mg twice daily. However, the drug should be discontinued in patients who do not have adequate symptom control after 4 weeks of treatment with the higher dosage. For those who develop constipation,for example if they have not had a bowel movement for more than 2 days, the medication should be withheld until bowel movements resume, after which alosetron can be restarted either using the original dose or a reduced dose of 0.5 mg once daily. Alosetron should be discontinued immediately in patients who develop signs of IC, such as rectal bleeding, bloody diarrhea, or new or worsening abdominal pain, and evaluated.[13]If ischemic colitis is confirmed alosetron should not be restarted.

CONCLUSIONS

Irritablebowel syndrome occurs in up to 20% of individuals in North America. While its diagnosis can be challenging, symptom-based criteria in the absence of alarm features should lead to confidence in making the diagnosis. The subtype of IBS and the severity of symptoms present are key drivers ofIBS management strategies. Conventional therapies (e.g., loperamide, anti-spasmodics) may provide benefit for a specific symptom, but have not been shown to provide the more global relief of symptoms that many patients with IBS require. While the probiotic Bifidobacteriuminfantis 35624 and theminimally absorbable antibiotic rifaximin have demonstrated efficacy against several IBS symptoms,[2,23,54] neither have been FDA-approved for the IBS indication to date. TCAsappear to primarilyprovide global symptom relief, but these agentsalso have not been FDA-approved for use in patients with IBS. In clinical trials, the selective 5-HT_3 antagonist

alosetronprovidedmultisymptom relief in IBS-D including improvements in abdominal pain, control of bowel urgency, even when severe, improvements in stool consistency and frequency, while also improving IBS-related QOL.[2,13]Serious outcomes associated with IC and CoC have been mitigated under the alosetron prescribing program.[47]Alosetron represents an important therapeutic option that provides a favorable risk-to-benefit profile for women with severe IBS-D who are often inadequately treated. By acquiring evidence-based treatment knowledge related to IBS, NPs and PAs may ultimately improve the overall management of this complicated condition.

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