REVIEW ARTICLE

Drug Saf 2011; 34 (7): 545-565
0114-5916/11/0007-0545/$49.95/0

The Risk of Ischaemic Colitis in Irritable Bowel Syndrome Patients Treated with Serotonergic Therapies

James H. Lewis

Division of Gastroenterology, Georgetown University Medical Center, Washington, DC, USA

Contents

Abstract

Ischaemic colitis (IC) is the most common form of ischaemic injury to the gastrointestinal (GI) tract. IC typically presents with the sudden onset of lower abdominal pain, cramping and rectal bleeding, and is usually self-limited with low morbidity, although it may cause gangrenous or fulminant colitis, especially when the right colon is involved. Multiple medical conditions, as well as several pharmacological agents, are associated with IC, including irritable bowel syndrome (IBS) and drugs used for its treatment that act on gut serotonin 5-HT receptors. These include the selective 5-HT_3 receptor antagonist alosetron, currently approved for the treatment of severe diarrhoea-predominant IBS in women who fail to respond to conventional treatment, and cilansetron, another 5-HT_3 receptor antagonist that is no longer in clinical development. In addition, the 5-HT_4 receptor partial agonist tegaserod, which was approved for the treatment of constipation-predominant IBS in women, was associated with IC in the postmarketing setting, as was renzapride, a 5-HT_4 agonist/5-HT_3 antagonist.

Although several hypotheses have been proposed, the pathophysiological basis for development of IC with 5-HT_3 receptor antagonists or 5-HT_4 receptor agonists remains unknown. Of interest, several population-based studies demonstrated that a diagnosis of IBS (independent of serotonergic therapies) increases the risk of developing IC 2- to 4-fold. As a result, IBS patients with the acute onset of abdominal pain, tenderness, diarrhoea or lower intestinal bleeding, especially those with predisposing conditions or medications, should be evaluated promptly for IC. The management of IC remains supportive; most cases of non-gangrenous IC, as seen in the alosetron

and tegaserod databases, have been transient and have resolved spontaneously without complications or death.

Despite the small number of deaths associated with alosetron in patients with complications of constipation and because of the ongoing requirement to prescribe alosetron under a risk management plan, misconceptions persist regarding the definition, incidence, severity and outcome of IC in clinical trials and the postmarketing setting. In this article, the frequency and clinical characteristics of IC associated with the use of alosetron and other serotonergic agents are examined, evidence of an association between IC and IBS is reviewed, and a scoring system to aid in the diagnosis of IC in any clinical situation is proposed.

Ischaemic colitis (IC) is the most common form of ischaemic injury of the gastrointestinal (GI) tract,[1] occurring in the general population with an incidence of 4.5–44 cases per 100 000 person-years.[2,3] The actual incidence is likely higher, however, as many patients with mild or transient disease do not seek medical attention,[4] and the diagnosis in others may be missed or attributed to other causes of acute colitis.[1,5]

IC encompasses a wide clinical spectrum of large bowel injury, including reversible, transient segmental colitis, acute transmural necrosis (gangrenous colitis), chronic colitis with stricture formation and fulminant colitis.[1] The most characteristic clinical presentation of IC includes the acute onset of lower abdominal pain, cramping, and bloody diarrhoea or haematochezia.[6,7] Severe lower GI bleeding that requires transfusion is atypical in IC patients and points to a need to consider other diagnoses.

The term IC has been part of the medical lexicon for decades, although it is recognized as being quite non-specific, and some authors use other terms such as 'colon ischaemia'[1] or 'acute large bowel ischaemia' (ALBI).[8,9] However, the term IC is preferred when searching the literature or clinical databases using *International Classification of Diseases (9th edition)* [ICD-9] codes,

Table I. Characteristics of acute mesenteric ischaemia, chronic mesenteric ischaemia and ischaemic colitis

Acute mesenteric ischaemia	Chronic mesenteric ischaemia	Ischaemic colitis
Clinical presentation		
Abdominal pain severe enough to elicit physician attention and persists >2–3 h[4,7] Clinical picture not suggestive of other abdominal problems (e.g. cholecystitis, diverticulitis)[7]	Generalized abdominal pain that begins shortly after meals and persists for 1–3 h; increases in severity over wk to mo[4,7] Marked weight loss[4,7]	Typically transient and self-limited, without sequelae[4] Mild to moderate abdominal pain, diarrhoea or lower intestinal bleeding with minimal to moderate abdominal tenderness[4,7] Abdominal pain (87%), rectal bleeding (84%), diarrhoea (56%) and vomiting (30%)[9] 87% left-sided, 9.4% right-sided, 2.4% bilateral and 1.2% transverse only[9]
Prognosis		
Mortality 59–93% (average 71%)[4]	Substantial risk of incapacitation or acute thrombosis of an involved vessel[4] Few patients require surgery; surgical revascularization has a success rate of 59–100% and a recurrence rate of 0–26.5%, and percutaneous transluminal mesenteric angioplasty has success rates of 63–100% and a recurrence rate of 10–67%[4] 5-y survival rates for patients who survive surgical revascularization: 81–86%[4]	Most patients improve and recover over 1–2 wks[1] and do not require medical attention[4] Among the minority of patients requiring hospitalization, 88% of episodes that preceded admission did not require surgery, were not fatal and patients were hospitalized for 2 d[9] 50% with bilateral, 36% with right-sided and 3% with left-sided ALBI required surgery[9] Mortality higher in ALBI beginning after hospitalization (33%) vs those with ALBI before hospitalization (2%)[9]

ALBI = acute large bowel ischaemia.

and IC is the term used by the US FDA.[10,11] Some physicians equate IC with conditions such as acute mesenteric ischaemia (AMI) or chronic mesenteric ischaemia (CMI);[12] however, AMI and CMI are frequently associated with serious morbidity (e.g. need for surgical resection), and AMI is associated with high mortality rates.[4,7,12] In contrast, the majority of cases of IC resolve spontaneously without specific medical intervention.[4] Both IC and AMI risk is increased in patients with generalized atherosclerosis and heart failure.[13,14] The serotonergic therapies used to treat IBS have been associated with IC but have not been shown to cause AMI or CMI. Table I describes the clinicopathological characteristics that distinguish AMI, CMI and IC.

IC can be classified as either non-gangrenous or gangrenous.[6,15,16] Non-gangrenous IC involves the mucosa and submucosa of the left colon (typically the splenic flexure or sigmoid colon) and accounts for 80–90% of all cases.[1,6,8,9,16,17] Non-gangrenous IC can be further classified into a reversible or non-reversible form. The reversible, transient form of IC is associated with less severe injury than the non-reversible form, which is less common and is characterized by more extensive injury that may result in a chronic segmental colitis with stricture formation, often with damage penetrating the muscularis propia.[6] This gangrenous form of the disease accounts for the remaining 10–20% of cases of IC and usually arises in the right colon or bilateral colonic segments from vascular occlusion or co-morbid illnesses while the patient is already hospitalized.[6,8,18] These patients often present with sepsis and shock related to the more severe nature of the abdominal pathology.[6]

Many factors have been associated with an increased risk for developing IC. Genetic factors have been proposed to play a role in its development in patients aged <55 years who have no other serious illnesses. Theodoropoulou and colleagues[19] found that the 506 Q allele of the factor V R506 Q (Leiden) mutation and the mutant 4G allele of plasminogen-activating inhibitor-1 were significantly associated with IC compared with wild-type genes in healthy controls ($p = 0.005$ for both comparisons), perhaps by leading to a hypercoagulable state. Strenuous physical exercise, such as running a marathon[20,21] or long-distance cycling, has also been implicated in the development of IC,[22] as has the use of both therapeutic pharmacological agents and illicit drugs (table II). Whereas several pharmacological agents have been associated with IC,[1,4,8,23,24] Longstreth and Yao[8] found that the drugs dispensed most commonly to 379 patients with ALBI were antihypertensives (75%), opioids (33%), statins (30%), female hormones (29.4%) and potentially constipating non-opioids (26.4%), all of which were taken by a statistically significantly greater number of IC

Table II. Pharmacological agents associated with ischaemic colitis[8,23,24]

Class	Examples of specific agents[a]
Analgesics	NSAIDs
Antihypertensives	ACE inhibitors, angiotensin-receptor blockers, β-blockers, calcium channel blockers
Antibacterials	Amoxicillin, ampicillin, macrolides, cephalosporins, chloramphenicol, fluoroquinolones, tetracycline, doxycycline
Appetite suppressants	Phentermine
Chemotherapeutics	Vinca alkaloids, taxanes
Constipation-inducing medications	Opioids, anticholinergics, loperamide, many others possible
Decongestants	Pseudoephedrine
Cardiac glycosides	Digitalis
Diuretics	Etacrynic acid, furosemide
Ergot alkaloids	Ergotamine, methysergide
Hormonal therapies	Estrogens with progesterone, danazol, flutamide
Illicit drugs	Cocaine, amphetamine
Immunosuppressive agents	Interferon-α, cyclosporine, prednisone, azathioprine, mercaptopurine
Laxatives	Sodium polystyrene (kayexalate) in sorbitol, magnesium citrate/sodium phosphate, bisacodyl, glycerin enemas
Psychotropic medications	Barbiturates, tricyclic antidepressants, chlorpromazine
Serotonin agonists/antagonists	Alosetron, tegaserod, sumatriptan
Statins	Simvastatin
Vasopressors	Dopamine, adrenaline (epinephrine), noradrenaline (norepinephrine), vasopressin

a A more complete listing of individual agents is contained in the source references.[8,23,24]

patients than non-IC controls. Drugs that appeared to have an independent association with IC in men and women were antibiotics, opioids and non-opioid agents that can cause constipation.[8] Drugs that were independently associated with IC among women only were antibiotics, female hormones, opioid analgesics and potentially constipating non-opioid drugs.[8]

Numerous medical and surgical conditions, including irritable bowel syndrome (IBS), can increase the risk of developing IC (table III).[4-6,8,13,22,24-27] Factors that were independently associated with IC among women in the series reviewed by Longstreth and Yao[8] included hypertension, rheumatoid arthritis, chronic obstructive pulmonary disease, congestive heart failure, atrial fibrillation, diabetes mellitus and IBS.

Table III. Medical/surgical conditions predisposing patients to ischaemic colitis[6,8,11,13,22,25,26]

Risk factors	Specific conditions or states
Shock	Cardiac failure, sepsis, anaphylaxis
Hypovolaemia	Diuretics, haemodialysis
Cardiovascular	Diabetes mellitus, amyloidosis, rheumatoid arthritis, hypertension, hyperlipidaemia, congestive heart failure, atrial fibrillation
Vasculitis, collagen vascular disorders	System lupus erythematosus, polyarteritis nodosa, rheumatoid arthritis, scleroderma, Takayasu's arteritis, allergic granulomatosis, *Thromboangiitis obliterans*, Buerger's disease
Colon obstruction	Colon cancer, stricture, diverticular disease, impaction, constipation, volvulus
Malignancy	Colon carcinoma
Gastrointestinal conditions	Irritable bowel syndrome
Haematological disorders	Sickle cell disease, protein C and protein S deficiencies
Thrombosis	Arterial embolus, cholesterol embolus, colectomy with inferior mesenteric artery ligation, post-abdominal aortic reconstruction
Mesenteric venous thrombosis	Hypercoagulable states, portal hypertension, pancreatitis
Surgery	Abdominal, aortic or cardiovascular surgery
Other causes	Abdominal trauma, long-distance running/cycling, chronic obstructive pulmonary disease

Interest in IC has increased over the past decade, in part as a result of the attention the disorder received after the approval, subsequent withdrawal and reintroduction of the serotonin 5-HT_3 receptor antagonist alosetron for the treatment of diarrhoea-predominant IBS.[28,29] Indeed, prior to November 1997, the FDA Adverse Event Reporting System (AERS) database did not even include the search term 'ischaemic colitis'.[30] Despite safety precautions instituted to allow the reintroduction of alosetron, a number of misconceptions persist with respect to the IC associated with this agent and IBS in general. In addition, recent evidence has established a link between IBS and IC[2,3,27,28,31,32] that suggests that IC may be part of the natural history of IBS itself.[29]

In this article, evidence of the association between IC, IBS and the serotonergic drugs used to manage IBS is reviewed, clinical characteristics of and risk factors in patients developing IC while receiving these specific agents are examined, and a scoring system to aid in the clinical diagnosis of IC is proposed.

1. Epidemiological Evidence of an Association Between Ischaemic Colitis (IC) and Irritable Bowel Syndrome (IBS)

Questions were raised initially about the quality of the studies used to establish an association between IBS and IC, arising from methodological issues (e.g. the use of relatively non-specific ICD codes to identify both IBS and IC cases) or the potential for the misdiagnosis of IC as IBS (where mild IC and IBS symptoms may overlap);[10,33,34] however, the link has become more widely appreciated as epidemiological evidence has mounted (tables IV and V).[3,8,11,18,27,28,31,32,35,36] In particular, Cole and colleagues[32] analyzed medical claims data from a large US health maintenance organization and compared the rate of IC in patients with IBS with the rate in the general population. The analysis included 87 449 persons with a diagnosis of IBS (based on ICD-9 coding) from January 1995 to December 1999. The diagnosis of IC in these cases was substantiated after a review of medical records in which diagnostic studies confirmed the diagnosis. Overall,

Table IV. Incidence of ischaemic colitis (IC) and association with irritable bowel syndrome (IBS)

Reference, y	Population or data source	IBS diagnostic criteria and exclusions	IC diagnostic criteria and exclusions	Chart review (yes/no)	Incidence of IC
Singh et al., 2004[35]	Medi-Cal 1995–2002	Patient claims data Excluded patients on alosetron or tegaserod	Patient claims data	Not stated	1.79 per 1000 patient-y vs 0.47 per 1000 patient-y among non-IBS patients
Cole et al., 2004[32]	Medical claims data from UnitedHealthcare® database between January 1995 and December 1999	ICD-9 code 564.1 of ''irritable colon'' excluding patients with Crohn's disease, ulcerative colitis, colorectal cancer, chronic pancreatitis or pancreatic cancer, liver cirrhosis, celiac disease, other intestinal malabsorption syndromes or ovarian cancer	IC patients identified by ICD-9 code 557 for ''vascular insufficiency of the intestine'' with diagnostic studies including endoscopic, radiographic, surgical and/or histopathological observations being necessary for confirmation of IC Exclusions were Crohn's disease, ulcerative colitis (or routine dispensing of a 5-aminosalicylate drug), a small bowel resection or *Clostridium difficile* diarrhoea or colitis within 14 d before or after the 557 code diagnosis was submitted	No	42.8 per 100 000 patient-y
Walker et al., 2004[28]	UnitedHealthcare® 1995–1999	IBS diagnosis based on insurance diagnostic codes	IC case identification based on insurance diagnosis and procedure codes	No	0.4 per 1000 patient-y for IBS patient vs 0.01 per 1000 patient-y among non-IBS patients
Sotiriadis et al., 2007[18]	Hospitalized patients with colon ischaemia between 1998 and 2005	NA	ICD-9 codes 557.0, 557.1 or 557.9 identified patients with diagnoses of mesenteric ischaemia or infarction, bowel ischaemia or infarction, or IC, respectively Only biopsy-proven cases of IC were included Excluded patients aged <20 y or with a prior history of colonic resection, bowel obstruction, recent or concurrent colonic or pelvic cancer, Crohn's disease, ulcerative colitis or mesenteric ischaemia without colon involvement	Yes, retrospective review of computerized records	3 per 1000 hospital admissions
Hervé et al., 2009[31]	Hospitalized patients with first episode of IC vs peptic ulcer disease (January 1999– December 2003) matched for sex and 10-y age class	Rome II criteria and based on file exam Standardized self-questionnaire	Potential cases derived from ICD-10 codes K55.0 ''acute disorders of intestine'' and K55.8 Definite diagnosis based on clinical, endoscopic and, when possible, histological criteria; otherwise patients were excluded Exclusion criteria also included prior IC episode, recent vascular surgery, infectious colitis, antibiotic treatment or intensive care unit stay	Yes	16.9% of 113 IC patients (vs 1.8% of controls) had IBS
Zou et al., 2009[36]	85 consecutive patients diagnosed at a medical school-affiliated hospital endoscopy centre between March 2005 and April 2008	NA	IC diagnosed from clinical, colonoscopic and pathological findings, partly combined with abdominal computed tomography, plain abdominal radiography and angiography Patients with IBD and *C. difficile* colitis were excluded	No, retrospective review	7.1% of 85 patients had IBS

Continued next page

Table IV. Contd

Reference, y	Population or data source	IBS diagnostic criteria and exclusions	IC diagnostic criteria and exclusions	Chart review (yes/no)	Incidence of IC
Longstreth and Yao, 2010[8]	Consecutive hospitalized patients aged ≥20 y with acute large bowel ischaemia and controls matched for y of birth and sex from the San Diego area Kaiser Permanente Medical Care Plan from 2000 to 2006	NA	Potential cases derived from ICD-9-CM codes 557.0, 557.1 and 557.9 for "acute, chronic and unspecified vascular insufficiency of intestine", respectively Definite cases determined by medical record review. Cases of small bowel ischaemia, mechanical large bowel obstruction or pseudo-obstruction were excluded	Yes	3.2% of 379 patients (vs 1.1% of controls) had IBS
Chang et al., 2010[11]	Postmarketing surveillance of alosetron safety database containing both clinical trial and postmarketing adverse event reports	NA	MedDRA® keyword search including colitis ischaemic or intestinal ischaemia, colitis as a serious adverse event, abdominal pain or discomfort, gastrointestinal pain or discomfort, haematochezia, or diarrhoea haemorrhagic adjudicated to three categories: insufficient to support diagnosis, possible IC or probable IC	No	0.95 per 1000 patient-y

IBD = inflammatory bowel disease; **ICD-9** = International Classification of Diseases (9th edition); **ICD-9-CM** = ICD-9, Clinical Modification; **MedDRA**® = Medical Dictionary for Regulatory Activities; **NA** = not applicable.

740 cases of IC were identified among 5.4 million people observed for 8.5 million person-years. The crude incidence of IC was 42.8 cases per 100 000 person-years in patients with IBS compared with 7.2 cases per 100 000 person-years in the general population. After adjusting for age, sex and calendar year, the incidence of IC was found to be 3.4-fold greater among patients with IBS than among those without the diagnosis (95% CI 2.6, 4.5).[32]

In a later analysis, Suh and colleagues[3] estimated the relative risk for IC among patients with and without IBS or constipation in a review of data from the MarketScan® research databases, which include medical services and prescription data from approximately 100 insurance companies. In this analysis, data extraction was carried out from 1 January 1999 to 31 December 2002 for patients with diagnoses of IBS or constipation, or diagnoses of IC based on ICD-9 codes. Patients were excluded from the IBS cohort if they had a constipation co-morbidity during this study period, and were excluded from the analysis if they had IC and received a serotonergic agent at any time during the study period. The two case cohorts – patients with IBS (n = 11 492) and patients with constipation (n = 9996) – were each matched 1 : 1 to a control group consisting of patients who did not have the relevant disease and who had at least one physician visit and at least one prescription filled during the index period (1 January 2000 to 31 December 2001). These patients were followed from the index date (date of doctor visit) until the end of the study period (31 December 2002). The relative risk for IC was found to be 3.17-fold (95% CI 1.27, 7.93) higher for patients with IBS.[3]

Singh and colleagues[35] performed a population-based study on 37 271 persons aged >18 years with IBS enrolled in Medi-Cal (the Medicaid programme for California) between 1995 and 2002 to determine the incidence rate of IC. These patients, representing >146 000 patient-years of observation, were compared with 1 264 503 non-IBS individuals serving as controls, representing nearly 3.7 million person-years of observation. IBS and IC were identified using diagnosis codes from patient claims data, and any patient who

Table V. Odds ratios for the increased association of irritable bowel syndrome with ischaemic colitis

Reference, y	Patient population	OR (95% CI)
Cole et al., 2004[32]	Medical claims data	3.39 (2.57, 4.48)
Walker et al., 2004[28]	UnitedHealthcare® claims database	2.75 (1.94, 3.90)
Singh et al., 2004[35]	Medi-Cal population	3.15 (2.5, 3.9)
Suh et al., 2007[3]	MarketScan database	3.17 (1.27, 7.93)
Chang et al., 2008[27]	HealthCore database	2.01 (1.62, 2.48)
Hervé et al., 2009[31]	Hospitalized patients	7.5[a] (1.72, 32.80)–11.05[b] (2.45, 49.74)
Longstreth and Yao, 2010[8]	Hospitalized patients	2.72 (1.04, 7.14) [in women only]

a OR excluding patients with missing data.

b OR based on 87 paired cases and controls with full data availability.

OR = odds ratio.

had received alosetron or tegaserod was excluded. The investigators identified 262 cases of IC among the IBS patients for a calculated IR of 1.79 per 1000 patient-years. In contrast, the incidence rate of IC for non-IBS controls was 0.47 per 1000 person-years. Adjusted for age and sex, the IBS group was noted to have a 3.15 increased risk of developing IC compared with the control population (95% CI 2.5, 3.9). A correlation was present between age and IC. The IR was 0.77 among those aged 20–25 years and 2.76 among those aged ≥80 years. In comparison, the respective incidence rates based on age in the control population were 0.15 and 1.49; however, the relative risk of IC was found to decrease with age, from 5.3 at age 20–25 years to 1.84 at age ≥80 years.

A retrospective case-control study was carried out to assess risk factors associated with IC by analyzing medical managed care claims data from the HealthCore Managed Care Database from 1 January 2000 to 31 May 2005.[27] Patients with IC were identified using ICD-9 codes and were matched in a 1 : 4 ratio with control patients who had at least one physician visit during this time; patients who filled a prescription for alosetron or tegaserod at any time during the study were excluded. Overall, 1754 patients with IC were matched with 6970 controls. Multivariate conditional logistical regression modelling identified IBS as an independent predictor of IC. Patients with IC were twice as likely as those without IC to have had a diagnosis of IBS (odds ratio [OR] 2.01; 95% CI 1.62, 2.48) and were 1.62-fold more likely to have had a diagnosis of constipation (95% CI 1.34, 1.96). A statistically significant interaction emerged between age and prior IBS on risk for IC. Among patients aged <43 years, those with IC were >6-fold as likely to have been diagnosed with IBS as patients without IC. The authors suggested that age-related cardiovascular morbidity and antidiarrhoeal use may have masked the relationship between IC and IBS in older patients.[27] These findings are in agreement with those of other case series that identified a similarly increased risk of IBS in patients with IC.[8,27]

A multicentre, retrospective, case-control study compared the frequency of IBS in 113 patients hospitalized at five university hospitals in France for a first episode of IC with that in a control group of 113 patients matched for sex and 10-year age class and hospitalized for a first episode of peptic ulcer bleeding.[31] The diagnosis of IBS was based on a thorough review of medical records and a standard questionnaire, not simply on ICD coding. Missing data prompted the exclusion of 26 patients (24 IC patients and 2 controls), leaving 87 case-control pairs. Their analysis showed that the prevalence of IBS was 16.9% in patients with IC versus 1.8% in controls, and the risk of IBS was 11.05-fold greater among patients with IC than among controls ($p < 0.001$; 95% CI 2.45, 49.74). When only the 87 case-control pairs without missing data were considered, the risk of IBS was 7.5-fold greater among patients with IC than among controls ($p = 0.002$; 95% CI 1.72, 32.80).[31] A secondary, conservative analysis in all 113 pairs (that assumed all IC patients with missing data

did not have IBS and that all controls with missing data had IBS) found a significantly greater risk of IBS in patients with IC (prevalence 13.3% in IC patients vs 3.5% in controls; OR 4.17; $p < 0.02$; 95% CI 1.34, 12.99).[31] This represented the first multicentre study that established a reliable link between IBS and IC based on complete analysis of medical records, as opposed to case analysis by examination of ICD coding alone,[31] and confirmed data from earlier studies that showed an increased risk of IBS in patients with IC.

The increased risk of IC in patients with IBS in the studies cited previously was independent of serotonergic therapies since it was observed in studies that excluded patients being treated with these agents, or where similar studies were conducted before these agents became available. The role of serotonergic therapies in any alteration of colonic blood flow that may lead to IC remains unclear. However, numerous studies using real-world, clinical practice data have demonstrated that IBS itself is an independent risk factor for IC. This is reflected in population-based, case-control studies suggesting that patients with IBS are approximately 2- to 4-fold more likely to develop IC than those without IBS. While the strength of these retrospective population-based studies can be challenged, it must be noted that the increased risk of IC was observed even when the diagnoses of IC and IBS were based on a thorough review of individual medical files rather than reliance on ICD-9 coding alone, suggesting that the relationship between IC and IBS is not merely an artifact of inaccurate diagnosis and coding.[31] In a study of 700 IC patients diagnosed between 1995 and 1999 (compared with 6440 controls), the adjusted OR for IBS as a cause of IC was 2.75. If the diagnosis of IBS was made within the preceding 6 months of IC, the incidence of IC in this population was 7.9% versus 1.1% among controls, IBS being second only to congestive heart failure/ischaemic heart disease as a recent risk factor.[28]

2. Association of IBS-Targeted Treatments With IC

Many commonly used pharmacological agents have been implicated in the development of IC, including triptans, NSAIDs, antibiotics, diuretics, amphetamines and barbiturates among others (table II).[8,23,24] IBS-targeted medications, including alosetron and tegaserod, have also been associated with IC. Alosetron is a potent and selective 5-HT_3 receptor antagonist used in the treatment of diarrhoea-predominant IBS in women.[37-39] After the introduction of alosetron in early 2000, 80 reports of IC and 100 cases of serious complications of constipation (including two deaths in the latter subgroup) were reported, prompting the voluntary withdrawal of alosetron from the US market in late 2000.[10] Of interest, the FDA's AERS listed alosetron as the leading drug suspected as causing IC in the fall of 2000, despite its having been on the market for <1 year. Alosetron was responsible for 27% of all reports of IC reported between November 1997 (when IC was introduced as a search term in the database) and October 2000. Sumatriptan accounted for 7% of cases, Premarin® (conjugated estrogens) accounted for 4% and all other drugs (78 in total) accounted for 62%.[30] At the request of IBS sufferers and advocacy groups, alosetron was reintroduced in November 2002 in conjunction with a comprehensive alosetron risk minimization action plan (RiskMAP) and a more restrictive indication (treatment of women with severe diarrhoea-predominant IBS who have failed to respond to conventional treatment).[10,12,29]

Subsequently, Chang and colleagues[12] used prespecified diagnostic criteria to perform a blinded assessment of possible IC cases that occurred during the alosetron clinical trial programme, as well as in the postmarketing period after the initial introduction and again after reintroduction. Pooled data from clinical trials revealed an association of alosetron with a significantly increased rate of IC compared with placebo (0.14% vs 0.0%; $p = 0.03$). All 19 cases of alosetron-related IC seen in the clinical trial programme were the transient, reversible type, without long-term consequences. Nine of these patients were hospitalized, but none required surgical intervention or died; likewise, no cases of AMI or CMI were found.[12] In postmarketing surveillance evaluated through February 2004, 89 possible cases of IC were reported in AERS. Because of inadequate

documentation of a medical evaluation or failure to meet IC diagnostic criteria in the absence of further diagnostic testing, such as imaging or endoscopy, 35 of these cases were eliminated. One additional case determined to have no possible association with alosetron was also eliminated, leaving 53 total cases associated with alosetron and an estimate of one case per 1000 patient-years.[12] Overall, 52 of 53 patients (98.1%) had reversible colitis, and one patient each had colonic stricture and gangrene. Hospitalization occurred in 36 of the 53 patients, 3 had surgery, 1 was transfused and no deaths occurred. In addition, 12 cases of AMI or CMI were reported during postmarketing surveillance; 7 of these cases were excluded as they did not meet the diagnostic criteria (n = 4) or because no possible association with alosetron use was found by the reviewers (n = 3).[12] In the five remaining cases, all were remarkable for vascular disease risk factors complicating their medical histories, making the potential association with alosetron unclear.[12] At the time of an FDA meeting of its Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Subcommittee to discuss the reintroduction of alosetron in April 2002, a total of 13 deaths had occurred. Three of these deaths were considered probably related and two possibly related to alosetron (three associated with AMI and two with complications of constipation); two were related to alternative causes and six were deemed unrelated.[30] No death was associated with IC. The details of these five cases resulting in death were considered by the FDA to be probably or possibly related to alosetron and most involved the use of alosetron for off-label indications (table VI).

One area of contention raised by the FDA regarding the expert review of IC cases associated with alosetron sponsored by the manufacturer (GlaxoSmithKline, Research Triangle Park, NC, USA)[12] was that reports were excluded from the analysis if they lacked sufficient clinical information to confirm IC by prespecified stringent criteria. In contrast, FDA representatives argued that the absence or delay in obtaining such information should not have led to the exclusion of these patient reports when the reported event was serious and/or when the reporting physician believed that IC was present.[10] FDA reviewers also questioned the accuracy and relevance of combining true incidence data from randomized controlled clinical trials with voluntarily submitted postmarketing adverse events (yielding reporting rates rather than incidence data).[10]

In an updated review of these safety reports from November 2002 through June 2008, Chang and colleagues[11] sought to overcome any questions concerning their methodology by following adjudication criteria recommended by the FDA. Since the reintroduction of alosetron into the US market in November 2002 and through June 2008, a total of 29 072 patients received 203 939 alosetron prescriptions, yielding data from 16 762 patient-years of use. In their review of the alosetron safety database since reintroduction, Chang and colleagues[11] identified 26 potential cases of IC, 21 of which were adjudicated as probable or possible IC, including 5 patients in clinical trials (4 treated with alosetron and 1 with placebo) and 16 from postmarketing data. Table VII compares the characteristics of the 58 patients adjudicated as having possible or probable IC before withdrawal of alosetron to the 16 adjudicated IC cases since reintroduction. Of the 16 patients with IC, 69% had one or more pre-existing conditions (e.g. hypertension, constipation, diverticulitis) or concurrent medication use (e.g. estrogens, NSAIDs, triptans) that have been associated with IC.[8,9,11] Symptoms resolved or improved in all 16 patients without the need for surgery and no deaths have been recorded.[11]

Constipation was recorded as a presenting symptom in a minority (19–24%) of these patients diagnosed with IC.[11] Of the total 74 patients with possible or probable IC from the two combined postmarketing periods through June 2008, 48 (65%) were hospitalized and 3 (4%; all from the initial period) went on to have intestinal surgery but no deaths occurred. Most were aged <65 years and all but one were women. Overall, IC was resolved or improved in 77.5% of the initial 58 patients in the period prior to reintroduction (through June 2002) and in all 16 patients reported after November 2002. Among those for whom IC was

reported as unresolved at the time of the initial reporting period (7% [4/58]) or the status was reported as unknown (15.5% [9/58]), long-term follow-up data remain unavailable.[11,30]

To my knowledge, other than the cases collectively reported in US clinical trial and postmarketing surveillance studies,[11] there remains only a single published report of IC associated with alosetron.[41] In this report, a male patient with IBS developed IC within the first week of use and recovered with conservative management. In the large series of 379 IC patients reported by Longstreth and Yao[8] from the San Diego area Kaiser Permanente database from the year 2000 through 2006, no instances of IC were associated with alosetron use.

The investigational 5-HT_3 antagonist cilansetron was also associated with possible development of IC. In a review of two large, randomized, double-blind, placebo-controlled, parallel-group, phase III studies of cilansetron, Chey and Cash[42] reported eight suspected cases of IC among 4000 clinical trial patients receiving cilansetron, yielding an event rate of 3.77 per 1000 person-years of exposure. With the receipt of a 'non-approvable' letter from the FDA in 2005, indicating the need for additional clinical trial data, development of this agent has been suspended in the US.[43]

Tegaserod is a potent partial agonist of the 5-HT_4 receptor[44] that was approved by the FDA in 2002 for the treatment of IBS with constipation in women.[45] While IC was not seen in clinical trials

Table VI. Postmarketing reports of death associated with patients receiving alosetron (March–December 2000)[30,40]

Patient	Case description
82-y-old woman with diarrhoea-predominant IBS	Patient developed constipation, sudden nausea and diffuse abdominal pain without rectal bleeding 10 d after receiving alosetron. Past history included multiple colonic diverticula and a 'spastic colon' on colonoscopy 18 mo earlier, with a prior admission for diverticulitis. In the ED, the patient was found to be dehydrated, oliguric and septic, and abdominal CT revealed extensive sigmoid diverticulosis with fluid in the pelvis. Exploratory laparotomy showed a ruptured diverticulum and faecal soilage. No IC changes were described in the resected colonic specimen. The patient died on the fourth post-operative day from cardiac arrest. No autopsy was performed. US FDA reviewers considered alosetron to be probably related to the event
67-y-old woman with Alzheimer's disease residing in a nursing home	Patient received alosetron for chronic diarrhoea. She had no past history of IBS but did have a history of depression and constipation. After about 2 mo on alosetron, the patient suffered an unspecified head injury and was taken to the ED for difficulty eating and breathing; alosetron was discontinued. The patient required endotracheal intubation. She became transiently hypoxaemic during insertion of a nasogastric tube and was diagnosed as having a bowel obstruction evident on abdominal radiograph. A total colectomy was performed about 10 h later for sigmoid necrosis, with the surgeon noting a diagnosis of Ogilvie's syndrome. The patient died 4 d post-operatively of acute respiratory distress syndrome. No autopsy was performed
A 59-y-old woman hospitalized with a 9-mo history of 25 lb weight loss with worsening abdominal pain, chronic constipation, hypertension, nausea, vomiting and post-prandial urgency	Patient was treated with a single-capsule of chlordiazepoxide and clidinium for what was thought to be IBS and was discharged. The patient was readmitted 2 wk later for pain, diarrhoea, haematochezia, nausea, vomiting and uncontrolled hypertension, and was treated with empiric antibiotics for fever and leukocytosis and started on alosetron for 'IBS symptoms'. The patient was again discharged with persistent abdominal symptoms and readmitted 1 wk later for abdominal pain that had become constant, diarrhoea, rectal bleeding and ongoing weight loss. Angiography revealed total occlusion of the superior mesenteric and celiac arteries. Exploratory laparotomy found severe ischaemia and necrosis of the entire GI tract and two vascular grafts were placed. However, re-exploration 24 h later revealed complete infarction of the small bowel and colon, and the patient died shortly thereafter
46-y-old woman with severe coronary artery disease receiving warfarin and other medications	Patient was treated with alosetron for 5 d for diarrhoea associated with 'stomach flu'. Approximately 2 wk after stopping alosetron, the patient presented with GI bleeding with hypoprothrombinaemia. Her warfarin was discontinued, and a colonoscopy showed no evidence of IC. One wk later (3 wk after stopping alosetron), the patient developed abdominal pain and haemodynamic instability and underwent an exploratory laparotomy. Small bowel necrosis was found and attributed to superior mesenteric vein occlusion. A jejunal resection was performed, and the patient died of unspecified causes 8 mo later
92-y-old woman with peripheral vascular disease, pseudo-obstruction and IBS	Patient was started on alosetron and after approximately 3 mo experienced upper body pain and collapsed in a chair. The patient was found to have abdominal distention, and a head CT scan revealed an acute parietal infarction. The patient died, and the death certificate listed ''intestinal infarction (ischaemia)'' as the cause of death. No corroborating information was provided to support the diagnosis

CT = computed tomography; **ED** = emergency department; **GI** = gastrointestinal; **IBS** = irritable bowel syndrome; **IC** = ischaemic colitis.

Table VII. Characteristics of patients with possible or probable ischaemic colitis (IC). Data from postmarketing experience before alosetron withdrawal and after reintroduction are compared[11,30]

Characteristic	Before June 2002 (before withdrawal; 58 cases)	November 2002–June 2008 (after reintroduction; 16 cases)
Demographics		
Prescribing time span [mo]	10	68
Patient-y exposure[a]	48 829	16 762
Sex [male/female]	1/57	0/16
Median age [y (range)]	55 (25–80)	56 (31–81)
Age ≥65 y [n (%)]	13 (22)	5 (31)
Median time to onset [d (range)]	14 (0.5–136)	90 (3–1825)
Clinical presentation [n (%)]		
Abdominal pain	46 (79)	14 (88)
Abdominal pain and haematochezia/bloody diarrhoea	39 (67)	12 (75)
Concurrent constipation	14 (24)	3 (19)
Use of hormone replacement therapy or oral contraceptives	18 (31)	6 (38)[b]
Outcomes [n (%)]		
Resolved or improved	45 (77.5)	16 (100)
Required hospitalization	39 (67)	9 (56)
Required surgery	3 (5.2)	0 (0)
Required transfusion	1 (1.7)	0 (0)
Death	0 (0)	0 (0)

a Assumes all prescriptions were for 1 mo duration.

b Reported as estrogens.

involving >11 600 patients,[46] including 451 patients who completed a 13-month uncontrolled extension study,[47] several adverse events, including IC, were reported after approval of tegaserod.[48-50] By 15 April 2004, the FDA had received 20 reports of IC and 4 reports of intestinal ischaemia with tegaserod, which included cases of intestinal ischaemia (n = 1), intestinal gangrene (n = 1), mesenteric ischaemia (n = 1) and abdominal compartment syndrome with intestinal ischaemia (n = 1).[50] Overall, 17 of the 20 reports of IC were adjudicated as probable IC, 1 was adjudicated as indeterminant and the remaining 2 were not adjudicated.[50] Table VIII describes characteristics and outcomes of the 17 tegaserod cases adjudicated as probable IC.[50] All 17 patients presented with co-morbid medical conditions or medication usage that may have contributed to the development of IC. In particular, almost half of these patients (8/17 [47%]) were receiving either oral hormone therapy or a hormone patch. None of the patients required surgery secondary to IC; however, one patient was placed on total parenteral nutrition and subsequently died because of line sepsis. Between 15 April 2004 and 1 June 2004, the Office of Drug Safety received reports of an additional seven cases of IC, one case of bowel infarction and one case of IC secondary to small vessel ischaemia associated with the use of tegaserod.[50] These nine cases had not been adjudicated at the time of publication of the 2004 FDA briefing document.[50] It should be noted that the manufacturer of tegaserod offered a rebuttal to the FDA analysis, arguing that the incidence of IC in their postmarketing database was likely no different from the background rate of IC occurring in the general population,[46] a view also offered by others.[51] Only a single report of IC associated with tegaserod has been published outside of an FDA review,[49] although it has also been questioned.[52] As with alosetron, no cases involving tegaserod were recorded in the Kaiser Permanente series.[8]

In March 2007, tegaserod was withdrawn from the market at the request of the FDA after a pooled analysis demonstrated an increased risk of cardiovascular events with tegaserod versus placebo (0.11% vs 0.01%).[53] Tegaserod is currently available from the FDA only through an emergency investigational drug protocol.[54]

Renzapride is a novel combined 5-HT_4 agonist and 5-HT_3 antagonist that was being developed for constipation-predominant IBS. In a long-term study involving 971 patients, three instances of IC were reported.[55] A lack of sufficient efficacy compared with placebo led to the discontinuation of renzapride development in 2008.[56]

3. Pathophysiology of IC

Alterations in the systemic circulation and anatomic or functional changes in local mesenteric vasculature, and reduced resistance of the tissue to hypoxic injury may all contribute to

Table VIII. Characteristics of postmarketing cases of ischaemic colitis reported among tegaserod-treated patients (as of 15 April 2004)[50]

Characteristic	Postmarketing cases (n = 20)
Demographics	
Sex [n (%)]	
female	19 (95)
male	1 (5)
Mean age [y (range)]	55.1 (26–82)
18–40 [n (%)]	3 (15)
>40 to <65 [n (%)]	10 (50)
≥65 [n (%)]	6 (30)
Unknown [n (%)]	1 (5)
Median time to onset [n (%)]	
≤1 d	3 (15)
2–20 d	6 (30)
21–122 d	7 (35)
230–398 d	3 (15)
Unknown	1 (5)
Clinical presentation [n (%)]	
Abdominal pain	15 (75)
alone	1 (5)
with nausea	5 (25)
with non-bloody diarrhoea	5 (25)
with abdominal bloating	1 (5)
with haematochezia, bloody diarrhoea or rectal bleeding	11 (55)
Haematochezia, bloody diarrhoea or rectal bleeding without presence of abdominal pain	3 (15)
Abdominal bloating without pain	1 (5)
Nausea or vomiting	5 (25)
Hypotension	4 (20)
Worsening of sepsis	1 (5)
No available information	1 (5)
Evaluation [n (%)]	
Colonoscopy	12 (60)
alone	2 (10)
with biopsy	10 (50)
Sigmoidoscopy	6 (30)
alone	1 (5)
with biopsy	5 (25)
Emergency laparotomy	1 (5)
Unknown/lack of information	1 (5)
Documented risk factors [n (%)]	
Any condition or medication use	15 (75)
hormonal therapy	8 (40)
tobacco use	1 (5)
other	6 (30)
Venue of evaluation [n (%)]	
Inpatient hospitalization	13 (65)
Emergency department	2 (10)
Outpatient/office	3 (15)
Not specified	2 (10)
Outcome [n (%)]	
Improvement or resolution/discharge	11 (55)
Surgery	1 (5)
Not specified	8 (40)
Death	1 (5)

insufficient blood supply for mucosal requirements, leading to the development of IC.[6] Diverse hypotheses have been proposed to describe a unifying mechanism for spontaneous IC, including an infectious aetiology, degenerative alterations in the vascular tree and accentuation of local vasospastic responses to systemic hypotension.[6,8]

Longstreth and Yao[8] found that the pre-existing co-morbidities most closely associated with IC among men and women in the Kaiser Permanente health plan were hypertension (OR 3.21), chronic obstructive pulmonary disease (OR 3.13), diarrhoea (OR 2.36), atrial fibrillation (OR 2.21), congestive heart failure (OR 1.94) and diabetes (OR 1.82). Among drugs, antibiotics (OR 3.3), opioids (OR 1.96) and potentially constipating non-opioid agents (OR 1.75) led the list of independently-associated factors.

It has been suggested that tegaserod-associated development of IC is mediated by effects on serotonin signalling, possibly at the 5-HT_1 and 5-HT_4 receptors.[49] In addition to being a partial agonist of the 5-HT_4 receptor, tegaserod has moderate affinity for the 5-HT_1 receptor and may share vascular effects with other 5-HT_1 receptor agonists (e.g. sumatriptan) that have been associated with IC.[49,57] However, according to the manufacturer, no apparent mechanism explains IC as no visceral vasoconstrictor action of tegaserod has been demonstrated in pharmacological studies, including high-dose exposures in animal models.[46]

Table IX. Criteria used by Longstreth and Yao[9] for the diagnosis of acute large bowel ischaemia (ALBI)

Level	Criteria
1	Colonoscopic *and* biopsy findings 'typical' of ALBI; surgical specimen findings 'typical' of ALBI, or passage of a large bowel 'cast' associated with ALBI[78]
2	Colonoscopy findings typical of ALBI
3	Computed tomographical findings typical for ALBI
4	Clinical features resembling a previous episode for which there was level 1 evidence of ALBI

FDA reviewers hypothesized that patients with congenital or acquired thrombophilia who receive alosetron might be predisposed to IC, as might individuals with a hypercoagulable state be at risk for some alosetron drug interactions mediated by certain cytochrome P450 system phenotypes, although no specific mechanism could be identified.[30]

Citing data from human and animal studies, Camilleri[58] re-evaluated several mechanisms involving treatment with a 5-HT_3 antagonist that might lead to the development of IC. As noted by others, Camilleri[58] found that potential causes of IC included coagulopathy, thromboembolism, vasospasm and effects on mucosal blood flow. Genetic predisposition to the development of IC has been proposed as a sequelae of a hypercoagulable state induced by mutations in the coagulation cascade,[19] and has been suggested as a possible explanation for IC developing in alosetron and tegaserod patients taking estrogens or other hormonal replacement therapies;[59] however, only a minority of patients have taken oral contraceptives (OCs) or related agents (table VII). Moreover, no evidence of coagulopathy, thrombophilia or small-vessel vasculitis has been shown on histological specimens from IBS patients receiving alosetron.[58] Furthermore, no evidence of alteration of coagulation factors or endothelial or platelet function in the presence of 5-HT_3 antagonists can be found in the literature.[58] In women receiving OCs, alosetron did not further increase the concentration and activity of biochemical markers of thrombosis risk, suggesting that thromboembolic risk is not increased when alosetron is co-administered with an OC,[60] which occurred in approximately 40% of patients.[11]

Although 5-HT_3 receptor antagonists inhibit the intradermal serotonin-induced flare response in human skin, it is unclear whether 5-HT_3 receptors mediate such effects on vascular beds in the GI mucosa.[58,61] A recently published study in rats found that both alosetron and cilansetron caused a small and transient constriction of the mesenteric vascular bed without altering colonic blood flow.[62] An earlier preclinical study with alosetron, also conducted in rats, showed no evidence of an alosetron effect on baseline colon haemodynamic parameters with either acute or chronic administration, nor did alosetron have any effect on the haemodynamic response to either superior mesenteric artery occlusion or reactive hyperaemia.[63] With regard to the potential role of serotonin in modulation of vasomotor responses in the mucosa, it is relevant that submucosal vasomotor reflexes are modulated by 5-HT_4 or 5-HT_1 receptors but not by 5-HT_3 receptors.[58] Evidence to suggest that 5-HT_3 or 5-HT_4 antagonists cause vascular dysfunction is lacking. Preconstricted arterioles exhibit a normal dilatory response to balloon distension in the presence or absence of 5-HT_3/5-HT_4 antagonists, suggesting that these receptors do not change the ability of normal vessels to undergo reflex vasodilation.[64]

Table X. Criteria for diagnosis of ischaemic colitis (IC) as approved by the US FDA (2002)[79] and described by Chang et al. (2010)[11]

Diagnosis	Criteria
1: no IC	Insufficient evidence to support the diagnosis, i.e. medical history positive for an alternative diagnosis or is inconclusive or inadequate, or no data on any imaging studies or histology
2: possible IC	Diagnosis supported primarily by clinical evidence Medical history consistent with IC Some cases include radiographic and/or endoscopic findings that were compatible with but not diagnostic of IC
3: probable IC	Diagnosis supported by clinical evidence together with endoscopic and/or biopsy findings Medical history consistent with IC Endoscopy (colonoscopy) OR radiographic AND/OR biopsy consistent with IC No evidence for any more likely diagnosis Clinical evidence was assumed in those cases with good documentation of biopsy and/or endoscopy findings but poor documentation of clinical evidence

Table XI. Criteria used by Chang et al.[12] to identify and confirm ischaemic colitis (IC) among alosetron users

Causality assessment	Screening criteria
Probable IC	Medical history consistent (e.g. abdominal discomfort, haematochezia, diarrhoea) and supported by colonoscopic or other imaging modalities and/or biopsy evidence of IC, and no other diagnosis more likely
Undetermined/pending	Positive medical history but results of colonoscopy or other diagnostic studies are pending
Insufficient data	Medical history positive, inconclusive or inadequate but no supporting medical information is available
Probably not IC	Results of diagnostic studies are negative or support a different, more probable diagnosis

Adjudication criteria for IC caused by alosetron

Criteria	Assessment				
	Definite	*Probable*	*Possible*	*Probably not*	*Definitely not*
Correct exposure and sequence of events	Yes	Yes	Yes	Partly	No
Objective supportive evidence	Yes	Yes	Yes	Ambiguous or conflicting	Ambiguous or conflicting
Positive dechallenge	Yes	Yes	Ambiguous or negative	Ambiguous or negative	Ambiguous or negative
Positive rechallenge	Yes	Not done	Not done	Not done	Not done
Other causes excluded	Yes	Yes	Yes	No	No

Mucosal mast cell mediators are thought to play a role in the nociceptive visceral pain response in IBS,[65,66] and mast cell infiltration has been associated with colonic ischaemia *in vitro*.[67] The role of mast cell infiltration with release of histamine or other cytokines is unknown in the pathophysiology of IC from alosetron, although evidence of this effect has been shown in an animal study of acute colon ischaemia.[68]

IC may result from constipation, possibly as an adverse effect of a medication[2,8,27] and, in a patient receiving alosetron, possibly from slowed colonic transit induced by 5-HT_3 antagonism.[58] Whereas constipation is a dose-related pharmacological effect of alosetron, occurring at a rate of 4–39% in phase III acute trials,[29] most patients with IC associated with alosetron did not report constipation as an antecedent event. Indeed, constipation was cited by only 24% (14/58) of patients in the initial postmarketing period (i.e. before June 2002) and in 19% (3/16) in the second postmarketing period from November 2002 through June 2008.[11] Among 401 patients hospitalized for IC in the series examined by Longstreth and Yao[9] from the Kaiser Permanente database from January 2000 through December 2006, only 7% of 424 episodes of all-cause IC had constipation recorded as immediately preceding the presenting symptoms. In a comparison of 379 of these original 401 patients with controls, constipation was not found to be an independent risk factor for IC but, oddly enough, diarrhoea was a risk factor (OR 2.36; 95% CI 1.33, 4.89; $p = 0.0218$).[8]

In rats, restraint stress induced an increase in luminal serotonin, which in turn accelerated colonic transit and stimulated colonic motility.[69] Intraluminal administration of the 5-HT_3 antagonist ondansetron inhibits the stress-associated acceleration of colonic transit, suggesting that this effect is mediated by 5-HT_3 receptors.[69] Although small changes in mucosal blood flow are evident on Doppler images from constipated patients with normal or slow colonic transit, it is unclear whether these subtle changes can affect the autoregulatory processes that control colonic mucosal blood flow.[58,70,71] It is also unclear whether increased intraluminal pressures in constipation or in response to 5-HT_3 antagonists compromise mucosal blood, leading to ischaemia. Increases in luminal pressure or straining may temporarily decrease mucosal blood flow but such changes are usually transient.[58,72] Additionally, the effects of 5-HT_3 antagonists on colonic tone and phasic pressure activity are generally not consistent with an increase in luminal pressure.[58,73-75] Finally, although acute bowel distension in dogs has been shown to compromise intestinal blood flow when intraluminal pressures exceed 30 mmHg, this effect would be expected to occur only if pressure changes are sustained over time. Human

Table XII. Ischaemic colitis (IC) clinical diagnosis assessment instrument[80]

Parameter evaluated	Point value
I. Clinical presentation	
A. Classic	+3
B. Symptoms consistent (not classic)	+2
C. Non-specific symptoms	+1
D. Symptoms or history suggests another diagnosis	–1
II. Colonoscopic (flexible sigmoidoscopy) findings	
A. Typical appearance/distribution	
(1) splenic flexure, descending, sigmoid	+4
(2) transverse, hepatic flexure	+3
(3) rectum, cecum	+2
B. Non-specific appearance	+1
C. Normal or findings suggest another diagnosis	–1
D. Not performed or done >2 wk after symptom onset and found to be normal	0
III. Computed tomography scan or abdominal film findings	
A. Thumbprinting or wall thickening	+2
B. Non-specific features	+1
C. Normal or not suggestive of IC	–1
D. Not performed or obtained >2 wk after symptom onset and found to be normal	0
IV. Other abdominal imaging (if performed)	
A. Barium enema or angiography findings suggestive of IC	+2
B. Non-specific findings	+1
C. Not compatible with IC	–1
D. Not performed or obtained >2 wk after symptom onset and found to be normal	0
V. Histopathology	
A. Biopsy 'diagnostic' of IC	+3
B. Consistent with IC	+2
C. Non-specific	+1
D. Suggests another diagnosis	–1
E. Not performed or obtained >2 wk after symptom onset and found to be normal	0
VI. Clinical course	
A. Self-limited, reversible with symptoms resolved within 2 wk	+3
B. Symptoms resolve over 2–8 wk	+2
C. Symptoms resolve after >8 wk	+1
D. Symptoms resolve, time not stated	+1
E. Symptoms not resolved because of stricture, chronic ulceration, etc., attributed to IC	+2
F. Outcome not stated	0
G. Course inconsistent with IC	–1

Scoring

Assessment (minimum points needed per criterion)	**I**	**II**	**III**	**IV**	**V**	**VI**
Very likely IC (≥11)	3	3	0	0	2	3
Probable IC (7–10)	2	2	0	0	0	3
Possible IC (4–6)	1	1	0	0	0	2
Unlikely IC (≤3)	0	0	0	0	0	0

Table XIII. Proposed causality assessment method of alosetron causing ischaemic colitis (IC)[80]

Criteria	Point value
I. Temporal compatibility	
A. IC develops on alosetron	+3
B. IC develops within 2 wk off alosetron	+1
C. IC develops >2 wk but <12 wk after stopping alosetron	0
D. IC develops prior to alosetron or >12 wk after alosetron stopped	–1
II. Pre-existing colonic pathology	
A. Normal findings on barium enema, colonoscopy or flexible sigmoidoscopy pretreatment	+2
B. No diagnostic testing performed or not stated	0
C. Pre-existing pathology	
diverticular disease	–1
inflammatory bowel disease or other colitis	–2
III. Risk factors for IC[a]	
A. None present (no. stated)	+1 to +3
B. Not stated	0
C. One or more present (no. stated)	–1 to –3
prior history of IC	
vasculitis (e.g. systemic lupus erythematosus, polyarteritis nodosa)	
hypercoagulable state	
infectious colitis	
long-distance running, cycling	
medications (e.g. digoxin, oral contraceptives, triptans, cocaine)	
abdominal aortic aneurysm repair, etc.	
IV. IC confounders	
A. None	+2
B. Secondary causes of IC (e.g. distal obstructing carcinoma, volvulus, radiation)	–2
C. Severe constipation/faecal impaction due to alosetron	+1
D. Diverticulitis	–1
E. None stated	0
V. Clinical course (if alosetron discontinued)	
A. Prompt resolution within 14 d	+2
B. Slow resolution (>2 wk)	+1
C. Not stated	0
D. Fails to resolve and not suggestive of IC	–1
E. Fails to resolve because of stricture, chronic colitis attributed to IC	+1
F. Resolves despite continued alosetron	–3
VI. Response to rechallenge	
A. Positive (IC recurs on alosetron)	+3
B. Negative (IC fails to recur on alosetron)	–1
C. Indeterminant	+1
D. Not performed	0

Scoring						
Assessment (minimum points needed per criterion)	**I**	**II**	**III**	**IV**	**V**	**VI**
Definitely related to alosetron (≥11 points)	3	2	1	2	2	0–1
Probably related to alosetron (7–10 points)	2	2	0	2	1	0
Possibly related to alosetron (4–6 points)	1	0	0	2	1	0
Unlikely to be related (≤3 points)						

a Score 1 point per risk factor up to 3.

manography studies, however, have not demonstrated such high baseline, sustained pressures (e.g. >10 mmHg).[58,76]

Taken together, the studies cited in this review suggest that slowed colonic transit, occurring either spontaneously or after the use of antidiarrhoeals, or through other agents such as alosetron that affect colonic motility, is unlikely to be a significant risk factor in the pathogenesis of IC.

4. Diagnosis of IC

The diagnosis of IC depends on a high index of clinical suspicion (e.g. in patients after aortic or cardiac bypass surgery), with pre-existing systemic conditions (e.g. vasculitides, coagulopathies, infections), in association with concomitantly administered drugs (e.g. antibiotics, opioids, cocaine), after strenuous or prolonged physical exertion such as running a marathon, after a major cardiovascular episode accompanied by hypotension, and in patients with obstructing or potentially obstructing colon lesions (e.g. carcinoma, diverticulitis).[4,9,77] The sudden onset of mild-to-moderate abdominal pain, diarrhoea or lower intestinal bleeding with mild-to-moderate abdominal tenderness should prompt an evaluation for IC, especially in patients with any of the predisposing conditions described in this review.[4,7]

Although the presence of IBS appears to increase a patient's risk of developing IC over time, the mechanism remains unclear. While some individuals with IC may be misdiagnosed as having IBS,[34] this seems unlikely given the acute nature of IC and the chronic nature of IBS.

4.1 Proposed Scoring System for Diagnosing IC

Although an indepth discussion of the clinical features, differential diagnosis and management of IC is beyond the scope of this review, the interested reader is referred to a number of technical reviews and other sources.[4-7] Nevertheless, it is useful to describe the methodologies that have been proposed to assist in making the diagnosis of IC associated with various drugs and other causes. While all use similar clinical criteria, differences remain. Longstreth and Yao[9] relied on several clinical features and diagnostic tests to categorize the level of evidence used to confirm the presence of IC (ALBI) in their series of hospitalized patients. A suspicion of IC was based initially on the presence of abdominal pain, rectal bleeding or diarrhoea that occurred within 10 days of hospitalization. The authors then applied the findings of several diagnostic tests to confirm the diagnosis (table IX).

Diagnostic criteria for IC proposed by GlaxoSmithKline were approved by the FDA in 2002[79] and used by Chang and colleagues[11] in a 2010 review of data from the RiskMAP for alosetron (table X). In an earlier analysis of IC cases, Chang and colleagues[12] developed alternative criteria designed to screen for and adjudicate cases of IC associated with alosetron (table XI).

To assist in the standardization of the case reporting definition for IC among cases reported to the sponsor, a separate expert panel comprising three clinical gastroenterologists and a statistician were asked to independently develop a more objective ischaemic colitis clinical diagnosis assessment instrument.[80] The evaluation criteria used in this instrument were developed after an extensive review of the literature on IC as it relates to epidemiology, symptom presentation, natural history and clinical guidelines for diagnosis, and was validated using the 80 cases in the GlaxoSmithKline safety database available for review at the time (table XII).[80] In an effort to provide a more objective assessment, a numerical value was applied to each of six clinical or diagnostic criteria and a cumulative point score was calculated to determine if the diagnosis of IC was very likely, probable, possible or unlikely. Use of the instrument increased agreement between the investigators on the likelihood of the diagnosis by 34%.[80] This panel also developed a causality assessment IC scoring system to determine whether alosetron or an alternative cause was most likely responsible for the IC using the same database of IC cases (table XIII).

5. Conclusions

IC is the most common form of GI ischaemia, accounting for approximately half of all cases.

The majority of IC cases are self-limited and resolve spontaneously. In contrast, mesenteric ischaemia, which some have erroneously equated with IC, is typically associated with poorer outcomes. Many medical conditions and drugs have been associated with IC, including the serotonergic agents used in the management of constipation- and diarrhoea-predominant IBS. Epidemiological studies also suggest that the diagnosis of IBS is a significant but underappreciated risk factor associated with the development of IC, raising the possibility that IC may be part of the natural history of IBS itself. It can be argued that there are several important differences in the epidemiological studies used to support the association between IBS itself and IC (including the fact that they were geographically distinct, included patients who were hospitalized or diagnosed in an endoscopic centre, and used ICD-9 codes followed by a medical record review or reported consecutive patients using clinical criteria). Furthermore, these methodological differences likely account for the differences in the rates of IBS in these IC patients. However, comparisons using a case-control analysis are persuasive and control for potential confounders. Collectively, these epidemiological studies provide persuasive evidence that patients with IBS have an increased risk for IC.

Based on the apparent background incidence rate of IC among IBS sufferers, just how much the use of alosetron or related agents further increases the frequency of IC is not known with any certainty. The overall risk of alosetron-associated IC based on postmarketing data is approximately 1 per 1000 person-years. A somewhat higher frequency was seen in the cilansetron trials,[42] but a much lower frequency was estimated for tegaserod and, in contrast with reports of IC occurring with other agents during clinical trials, reports of IC with tegaserod did not appear until after approval.[81] Moreover, although the FDA mandated that a warning about the risk of IC be added to the labelling for tegaserod,[50,82] the causality of these reported cases has been challenged[46,52] although the relative risk of IC between any of these drugs cannot be determined as no direct head-to-head comparisons have been made. In addition, voluntarily submitted reports obtained in the postmarketing setting cannot be used to determine true incidence rates.

A review of the alosetron- and tegaserod-associated cases reported in postmarketing surveillance programmes shows that many of the patients who developed IC had co-morbid medical conditions or were taking additional medications that have also been identified as potential risk factors for IC. These confounding variables make it more difficult to determine the exact causal factor(s), although the estimated risk appears to have been lower with tegaserod. Whether this apparent difference is related to the underlying type of IBS being treated (i.e. diarrhoea vs constipation predominant) or the pharmacodynamic differences between 5-HT_3 antagonists and 5-HT_4 agonists, the precise pathophysiological basis for the development of IC with serotonergic agents remains unknown.[58]

The requirement of a prescribing programme for alosetron, the only approved therapy for the treatment of diarrhoea-predominant IBS,[83] has helped educate both patients and physicians in the early identification of signs and symptoms of possible IC. The objective of the RiskMAP – to minimize the risk of serious GI adverse events in patients taking alosetron – has been attained. The incidence of possible or probable IC since reintroduction is rare and has remained stable since the initial postmarketing period. No significant differences in the apparent incidence of IC during these two respective periods have occurred among alosetron users, which is not surprising given the infrequent, idiosyncratic nature of the event. Nevertheless, the RiskMAP for alosetron has reduced serious clinical outcomes[11] by alerting the patient and physician alike to the possibility of IC (along with complications of constipation). Having a defined set of diagnostic criteria or an agreed-upon clinical scoring system for the diagnosis of IC would be a welcome advance in the field, especially as we continue to investigate the mechanisms under which IC occurs and given the diverse number of drugs and medical conditions associated with its development. Whether the IC risk of serotonergic therapies will be discovered to be additive to that of IBS (in and of itself) will require additional study.

Acknowledgements

The author reports being a member of the speaker's bureau and a consultant for Prometheus Laboratories Inc., San Diego, CA, USA. The author would like to thank Dr John Simmons, an employee of Peloton Advantage, Parsippany, NJ, USA, for his assistance with literature searching, fact checking, manuscript review, and preparation of the tables. Editorial services from Peloton Advantage were made available to the author and were funded by Prometheus Laboratories. The author himself received no remuneration for authoring this paper, retained full control of the content and takes responsibility for the integrity and accuracy of this review.

References

1. Brandt LJ, Boley SJ. Colonic ischemia. Surg Clin North Am 1992 Feb; 72 (1): 203-29
2. Higgins PD, Davis KJ, Laine L. Systematic review: the epidemiology of ischaemic colitis. Aliment Pharmacol Ther 2004 Apr 1; 19 (7): 729-38
3. Suh DC, Kahler KH, Choi IS, et al. Patients with irritable bowel syndrome or constipation have an increased risk for ischaemic colitis. Aliment Pharmacol Ther 2007 Mar 15; 25 (6): 681-92
4. Brandt LJ, Boley SJ. AGA technical review on intestinal ischemia. American Gastrointestinal Association. Gastroenterology 2000 May; 118 (5): 954-68
5. Brandt LJ, Feuerstadt P, Blaszka MC. Anatomic patterns, patient characteristics, and clinical outcomes in ischemic colitis: a study of 313 cases supported by histology. Am J Gastroenterol 2010 Oct; 105 (10): 2245-52
6. Gandhi SK, Hanson MM, Vernava AM, et al. Ischemic colitis. Dis Colon Rectum 1996 Jan; 39 (1): 88-100
7. American Gastroenterological Association medical position statement: guidelines on intestinal ischemia. Gastroenterology 2000 May; 118 (5): 951-3
8. Longstreth GF, Yao JF. Diseases and drugs that increase risk of acute large bowel ischemia. Clin Gastroenterol Hepatol 2010 Jan; 8 (1): 49-54
9. Longstreth GF, Yao JF. Epidemiology, clinical features, high-risk factors, and outcome of acute large bowel ischemia. Clin Gastroenterol Hepatol 2009 Oct; 7 (10): 1075-80
10. Gallo-Torres H, Brinker A, Avigan M. Alosetron: ischemic colitis and serious complications of constipation. Am J Gastroenterol 2006 May; 101 (5): 1080-3
11. Chang L, Tong K, Ameen V. Ischemic colitis and complications of constipation associated with the use of alosetron under a risk management plan: clinical characteristics, outcomes, and incidences. Am J Gastroenterol 2010 Apr; 105 (4): 866-75
12. Chang L, Chey WD, Harris L, et al. Incidence of ischemic colitis and serious complications of constipation among patients using alosetron: systematic review of clinical trials and post-marketing surveillance data. Am J Gastroenterol 2006 May; 101 (5): 1069-79
13. Elder K, Lashner BA, Al SF. Clinical approach to colonic ischemia. Cleve Clin J Med 2009 July; 76 (7): 401-9
14. Stamatakos M, Douzinas E, Stefanaki C, et al. Ischemic colitis: surging waves of update. Tohoku J Exp Med 2009; 218 (2): 83-92
15. Boley SJ, Schwartz S, Lash J, et al. Reversible vascular occlusion of the colon. Surg Gynecol Obstet 1963 Jan; 116: 53-60
16. Marston A, Pheils MT, Thomas ML, et al. Ischaemic colitis. Gut 1966 Feb; 7 (1): 1-15
17. Boley SJ. 1989 David H. Sun lecture. Colonic ischemia: 25 years later. Am J Gastroenterol 1990 Aug; 85 (8): 931-4
18. Sotiriadis J, Brandt LJ, Behin DS, et al. Ischemic colitis has a worse prognosis when isolated to the right side of the colon. Am J Gastroenterol 2007 Oct; 102 (10): 2247-52
19. Theodoropoulou A, Sfiridaki A, Oustamanolakis P, et al. Genetic risk factors in young patients with ischemic colitis. Clin Gastroenterol Hepatol 2008 Aug; 6 (8): 907-11
20. Cohen DC, Winstanley A, Engledow A, et al. Marathon-induced ischemic colitis: why running is not always good for you. Am J Emerg Med 2009 Feb; 27 (2): 255-7
21. Sanchez LD, Tracy JA, Berkoff D, et al. Ischemic colitis in marathon runners: a case-based review. J Emerg Med 2006 Apr; 30 (3): 321-6
22. Lucas W, Schroy III PC. Reversible ischemic colitis in a high endurance athlete. Am J Gastroenterol 1998 Nov; 93 (11): 2231-4
23. Cappell MS. Colonic toxicity of administered drugs and chemicals. Am J Gastroenterol 2004 Jun; 99 (6): 1175-90
24. Hass DJ, Kozuch P, Brandt LJ. Pharmacologically mediated colon ischemia. Am J Gastroenterol 2007 Aug; 102 (8): 1765-80
25. Green BT, Tendler DA. Ischemic colitis: a clinical review. South Med J 2005 Feb; 98 (2): 217-22
26. Heer M, Repond F, Hany A, et al. Acute ischaemic colitis in a female long distance runner. Gut 1987 July; 28 (7): 896-9
27. Chang L, Kahler KH, Sarawate C, et al. Assessment of potential risk factors associated with ischaemic colitis. Neurogastroenterol Motil 2008 Jan; 20 (1): 36-42
28. Walker AM, Bohn RL, Cali C, et al. Risk factors for colon ischemia. Am J Gastroenterol 2004 July; 99 (7): 1333-7
29. Lewis JH. Alosetron for severe diarrhea-predominant irritable bowel syndrome: safety and efficacy in perspective. Expert Rev Gastroenterol Hepatol 2010 Feb; 4 (1): 13-29
30. Briefing document for the Joint Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Subcommittee. Lotronex® (alosetron hydrochloride tablets) [online]. Available from URL: http://www.fda.gov/ohrms/dockets/AC/02/briefing/3848B1_01_GSK%20Briefing%20Pkg.pdf [Accessed 2010 Nov 23]
31. Hervé S, Beaugerie L, Bouhnik Y, et al. Irritable bowel syndrome is more frequent in patients hospitalized for ischaemic colitis: results of a case-control study. Neurogastroenterol Motil 2009 Nov; 21 (11): 1170-6
32. Cole JA, Cook SF, Sands BE, et al. Occurrence of colon ischemia in relation to irritable bowel syndrome. Am J Gastroenterol 2004 Mar; 99 (3): 486-91
33. Brinker A, Avigan M. Epidemiology of ischaemic colitis. Aliment Pharmacol Ther 2004 Sept. 15; 20 (6): 697-8
34. Brinker A, Senior J, Beitz J. Misdiagnosis of ischemic colitis as irritable bowel syndrome [abstract no. PII-16]. Clin Pharmacol Ther 2003; 73 (2): 33
35. Singh G, Mithal A, Triadafilopoulos G. Patients with irritable bowel syndrome have a high-risk of developing ischemic colitis [abstract no. 349]. Gastroenterology 2004; 126 (4 Suppl. 2): A41

36. Zou X, Cao J, Yao Y, et al. Endoscopic findings and clinicopathologic characteristics of ischemic colitis: a report of 85 cases. Dig Dis Sci 2009 Sep; 54 (9): 2009-15
37. Delvaux M, Louvel D, Mamet JP, et al. Effect of alosetron on responses to colonic distension in patients with irritable bowel syndrome. Aliment Pharmacol Ther 1998 Sep; 12 (9): 849-55
38. Clayton NM, Sargent R, Butler A, et al. The pharmacological properties of the novel selective 5-HT3 receptor antagonist, alosetron, and its effects on normal and perturbed small intestinal transit in the fasted rat. Neurogastroenterol Motil 1999 Jun; 11 (3): 207-17
39. Lotronex® (alosetron hydrochloride) tablets [package insert]. San Diego (CA): Prometheus Laboratories Inc., 2010
40. Prometheus Laboratories, Inc., San Diego (CA). (Data on file)
41. Friedel D, Thomas R, Fisher RS. Ischemic colitis during treatment with alosetron. Gastroenterology 2001 Feb; 120 (2): 557-60
42. Chey WD, Cash BD. Cilansetron: a new serotonergic agent for the irritable bowel syndrome with diarrhoea. Expert Opin Investig Drugs 2005 Feb; 14 (2): 185-93
43. Cilansetron: Solvay Pharmaceuticals suspends registration activities in the U.S., while discussions in Europe continue [press release]. 2005 Nov 29 [online]. Available from URL: http://global.abbottgrowth.com/services/news/newsreleases/0,,36458-2-0,00.htm [Accessed 2010 Jul 28]
44. Pfannkuche JJ, Buhl T, Games R, et al. The properties of a new prokinetically-active drug, SDZ HTF 919 [abstract no.]. Neurogastroenterol Motil 1995; 7: 280
45. FDA patient safety news. New drug for women with constipation-predominant IBS [online]. Available from URL: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/transcript.cfm?show=10 [Accessed 2011 Jan 27]
46. Joelsson BE, Shetzline MA, Cunningham S. Tegaserod and ischemic colitis [letter]. N Engl J Med 2004 Sep 23; 350 (13): 1363-4
47. Muller-Lissner S, Kamm MA, Musoglu A, et al. Safety, tolerability, and efficacy of tegaserod over 13 months in patients with chronic constipation. Am J Gastroenterol 2006 Nov; 101 (11): 2558-69
48. Brinker AD, Mackey AC, Prizont R. Tegaserod and ischemic colitis. N Engl J Med 2004 Sep 23; 351 (13): 1361-4
49. DiBaise JK. Tegaserod-associated ischemic colitis. Pharmacotherapy 2005 Apr; 25 (4): 620-5
50. FDA briefing document. Gastrointestinal Drugs Advisory Committee. Zelnorm® for treatment of chronic constipation [online]. Available from URL: http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4056B1_02_A-FDA-Zelnorm.pdf [Accessed 2011 Jan 27]
51. Heading R, Bardhan K, Hollerbach S, et al. Systematic review: the safety and tolerability of pharmacological agents for treatment of irritable bowel syndrome: a European perspective. Aliment Pharmacol Ther 2006 Jul 15; 24 (2): 207-36
52. Shetzline MA, Cohard-Radice M, Joelsson B. Ischemic colitis, irritable bowel syndrome, and tegaserod: an alternative viewpoint. Pharmacotherapy 2005 Nov; 25 (11): 1684-5
53. US Food and Drug Administration. Public Health Advisory. Tegaserod maleate (marketed as Zelnorm) [online]. Available from URL: http://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm078972.htm [Accessed 2010 Mar 8]
54. US Food and Drug Administration. Zelnorm (tagaserod maleate) information [online]. Available from URL: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103223.htm [Accessed 2010 Mar 8]
55. Lembo AJ, Cremonini F, Meyers N, et al. Clinical trial: renzapride treatment of women with irritable bowel syndrome and constipation-a double-blind, randomized, placebo-controlled, study. Aliment Pharmacol Ther 2010 May; 31 (9): 979-90
56. Lotronex® risk management program [online]. Available from URL: http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4040B1_17_FDA-Tab-2.pdf [Accessed 2009 Jul 13]
57. Zelnorm® [package insert]. East Hanover (NJ): Novartis Pharmaceuticals, 2006
58. Camilleri M. Is there an experimental basis for the development of ischaemic colitis as a result of 5-HT_3 antagonist treatment? Neurogastroenterol Motil 2007 Feb; 19 (2): 77-84
59. Deana DG, Dean PJ. Reversible ischemic colitis in young women: association with oral contraceptive use. Am J Surg Pathol 1995 Apr; 19 (4): 454-62
60. Koch K, Campanella C, Baidoo CA, et al. Pharmacodynamics and pharmacokinetics of oral contraceptives coadministered with alosetron (Lotronex). Dig Dis Sci 2004 Aug; 49 (7-8): 1244-9
61. Millson D, Sohail S, Lettis S, et al. Duration of inhibition of the flare response to intradermal 5-hydroxytryptamine in man by GR68755, an novel specific 5-HT3 receptor antagonist. Br J Clin Pharmacol 1992; 33: 546-7
62. Painsipp E, Shahbazian A, Holzer P. Alosetron, cilansetron and tegaserod modify mesenteric but not colonic blood flow in rats. Br J Pharmacol 2009 Nov; 158 (5): 1210-26
63. Grundy D, McLean P, Stead R. Impact of 5-HT3 receptor blockade on colonic haemodynamic responses to ischaemia and reperfusion in the rat. Neurogastroenterol Motil 2007 July; 19 (7): 607-16
64. Reed DE, Vanner SJ. Long vasodilator reflexes projecting through the myenteric plexus in guinea-pig ileum. J Physiol (Lond) 2003 Dec 15; 553 (Pt 3): 911-24
65. Barbara G, Wang B, Stanghellini V, et al. Mast cell-dependent excitation of visceral-nociceptive sensory neurons in irritable bowel syndrome. Gastroenterology 2007 Jan; 132 (1): 26-37
66. Buhner S, Li Q, Vignali S, et al. Activation of human enteric neurons by supernatants of colonic biopsy specimens from patients with irritable bowel syndrome. Gastroenterology 2009 Oct; 137 (4): 1425-34
67. Sand E, Themner-Persson A, Ekblad E. Infiltration of mast cells in rat colon is a consequence of ischemia/reperfusion. Dig Dis Sci 2008 Dec; 53 (12): 3158-69
68. Ravnefjord A, Pettersson M, Rehnstrom E, et al. Acute colonic ischaemia in rats results in long-term structural changes without alterations of colonic sensitivity. Int J Exp Pathol 2008 Dec; 89 (6): 476-89
69. Nakade Y, Fukuda H, Iwa M, et al. Restraint stress stimulates colonic motility via central corticotropin-releasing factor and peripheral 5-HT3 receptors in conscious rats. Am J Physiol Gastrointest Liver Physiol 2007 Apr; 292 (4): G1037-44

70. Emmanuel AV, Kamm MA. Laser Doppler flowmetry as a measure of extrinsic colonic innervation in functional bowel disease. Gut 2000 Feb; 46 (2): 212-7
71. Kvietys PR, Miller T, Granger DN. Intrinsic control of colonic blood flow and oxygenation. Am J Physiol 1980 Jun; 238 (6): G478-84
72. Kvietys PR, Barrowman JA, Harper SL, et al. Relations among canine intestinal motility, blood flow, and oxygenation. Am J Physiol 1986 July; 251 (1 Pt 1): G25-33
73. von der Ohe MR, Hanson RB, Camilleri M. Serotonergic mediation of postprandial colonic tonic and phasic responses in humans. Gut 1994 Apr; 35 (4): 536-41
74. Hammer J, Phillips SF, Talley NJ, et al. Effect of a $5HT_3$-antagonist (ondansetron) on rectal sensitivity and compliance in health and the irritable bowel syndrome. Aliment Pharmacol Ther 1993 Oct; 7 (5): 543-51
75. von der Ohe MR, Camilleri M, Kvols LK. A $5HT_3$ antagonist corrects the postprandial colonic hypertonic response in carcinoid diarrhea. Gastroenterology 1994 May; 106 (5): 1184-9
76. Boley SJ, Agrawal GP, Warren AR, et al. Pathophysiologic effects of bowel distention on intestinal blood flow. Am J Surg 1969 Feb; 117 (2): 228-34
77. Theodoropoulou A, Koutroubakis IE. Ischemic colitis: clinical practice in diagnosis and treatment. World J Gastroenterol 2008 Dec 28; 14 (48): 7302-8
78. Ardigo GJ, Longstreth GF, Weston LA, et al. Passage of a large bowel cast caused by acute ischemia: report of two cases. Dis Colon Rectum 1998 Jun; 41 (6): 793-6
79. GlaxoSmithKline. Lotronex® (alosetron hydrochloride) tablets briefing document for the Joint Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Subcommittee. Vol. 1 [online]. Available from URL: http://www.fda.gov/ohrms/dockets/ac/02/briefing/3848B1_01_GSK%20Briefing%20Pkg.pdf [Accessed 2010 Jul 20]
80. Ringel Y, Wilson J, D'Agostino R, et al. Development and validation of an ischemic colitis clinical diagnostic assessment instrument [abstract no. 1152]. Gastroenterology 2005; 128 (4 Suppl. 2): A467
81. Wooltorton E. Tegaserod (Zelnorm) for irritable bowel syndrome: reports of serious diarrhea and intestinal ischemia. CMAJ 2004 June 22; 170 (13): 1908
82. Bess AL, Cunningham SR. Dear Health Care Professional letter: important drug warning and prescribing information for Zelnorm [online]. Available from URL: http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4056B1_02_C-FDA-Appendix-1.pdf [Accessed 2011 Jan 25]
83. American College of Gastroenterology Task Force on Irritable Bowel Syndrome. An evidence-based position statement on the management of irritable bowel syndrome. Am J Gastroenterol 2009 Jan; 104 Suppl. 1: S1-35

Correspondence: Professor *James H. Lewis*, Division of Gastroenterology, Georgetown University Medical Center, 3800 Reservoir Road, NW, Washington, DC 20007, USA.
E-mail: lewisjh@gunet.georgetown.edu