REVIEW

Intestinal Permeability, Irritable Bowel Syndrome with Constipation, and the Role of Sodium-Hydrogen Exchanger Isoform 3 (NHE3)

Brian E Lacy[1], David Rosenbaum[2], Susan Edelstein[2], Kenji Kozuka[2], Laura A Williams[2], David C Kunkel[3]

[1]Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, FL, USA; [2]Ardelyx, Inc, Waltham, MA, USA; [3]Division of Gastroenterology, University of California San Diego, La Jolla, CA, USA

Correspondence: Brian E Lacy, Division of Gastroenterology and Hepatology, Mayo Clinic, Davis Building, 4500 San Pablo Road, Jacksonville, FL, 32224, USA, Tel +1 904-953-6319, Fax +1 904-953-7366, Email lacy.brian@mayo.edu

Abstract: Increased intestinal permeability has been identified as one of the many pathophysiological factors associated with the development of irritable bowel syndrome (IBS), a common disorder of gut–brain interaction. The layer of epithelial cells that lines the intestine is permeable to a limited degree, and the amount of paracellular permeability is tightly controlled to enable the absorption of ions, nutrients, and water from the lumen. Increased intestinal permeability to macromolecules can be triggered by a variety of insults, including infections, toxins from food poisoning, or allergens, which in turn cause an inflammatory response and are associated with abdominal pain in patients with IBS. This review article discusses increased intestinal permeability in IBS, focusing on IBS with constipation (IBS-C) through the lens of a patient case with a reported prior diagnosis of "leaky gut syndrome" upon initial contact with a gastrointestinal specialist. We review advantages and disadvantages of several methods of measuring intestinal permeability in patients and discuss when measuring intestinal permeability is appropriate in the therapeutic journey of patients with IBS-C. Furthermore, we discuss a possible mechanism of restoring the intestinal barrier to its healthy state through altering intracellular pH by inhibiting sodium-hydrogen exchanger isoform 3 (NHE3). Tenapanor is a minimally absorbed, small-molecule inhibitor of NHE3 that has been approved by the US Food and Drug Administration for the treatment of IBS-C in adults. Preclinical studies showed that tenapanor may restore the intestinal barrier in IBS-C by affecting the conformation of tight junction proteins via NHE3 inhibition to block the paracellular transport of macromolecules from the intestinal lumen. Testing for increased permeability in patients with IBS-C who experience abdominal pain may help inform the choice of therapeutics and alter patients' misconceptions about "leaky gut syndrome".

Keywords: tenapanor, abdominal pain, leaky gut, gut permeability, IBS-C, tight junction protein, transepithelial resistance

Introduction

Irritable bowel syndrome (IBS) is a disorder of gut–brain interaction defined by recurrent abdominal pain at least once a week associated with two of the following: defecation, changes in stool frequency or changes in stool form, occurring for at least 6 months, according to Rome IV criteria.[1] The gut–brain interaction refers to the bidirectional communication between the central nervous system and the enteric nervous system that links the cognitive and emotional centers of the brain with peripheral intestinal functions.[2] Based on the Rome IV criteria, the global prevalence of IBS is an estimated 4%, with a higher prevalence in women and individuals younger than 65 years.[3] Although not life-threatening, the disease burden significantly negatively affects patients' daily functioning, health-related quality of life (QoL), and health care resource utilization and costs.[4–6]

There are four distinct subtypes of IBS based on the prominent stool consistency: IBS with predominant constipation (IBS-C), IBS with predominant diarrhea (IBS-D), IBS with mixed bowel habits, and IBS unclassified (ie, without a significant pattern of abnormal stool).[1] According to the Rome IV criteria, IBS-C and IBS-D account for 31.5% and 29.3% of patients with IBS, respectively.[7] Patients with IBS-C report greater symptom burden and impaired functioning than other subtypes.[8] Abdominal pain has been reported as the most troublesome abdominal symptom,[9] with lack of

improvement in abdominal pain being reported as a common reason for treatment discontinuation by 29–49% of patients in the CONTOR study.[10] In this review, we discuss a patient case of IBS-C, review intestinal permeability (ie, how it is measured and how it may contribute to abdominal pain in patients with IBS-C) and discuss how restoring intestinal barrier function with tenapanor, a locally acting inhibitor of sodium-hydrogen exchanger isoform 3 (NHE3), may improve abdominal pain.

Patient Case

A 31-year-old male, referred to a gastroenterologist for a second opinion, reported an 18-month history of lower abdominal pain, bloating, and infrequent, hard to evacuate stools. Symptoms began after an apparent episode of food poisoning. While initially troubled with loose, watery, non-bloody bowel movements, for the past year the patient's bowel movements were hard, difficult to evacuate, and only occurred every 2 to 3 days. His spouse had similar symptoms but recovered completely. Laboratory tests, including a complete blood count, metabolic profile, liver chemistries, thyroid tests, celiac serologies, and C-reactive protein were normal on two separate occasions. Because of persistent symptoms, his gastroenterologist performed a colonoscopy, which was normal. A lactulose breath test ruled out both small intestinal bacterial overgrowth and intestinal methanogen overgrowth. Over-the-counter products, including docusate sodium, bisacodyl, and polyethylene glycol, did not relieve constipation symptoms and some caused abdominal cramps. He recently saw a naturopath who told him that he had "leaky gut syndrome" and suggested a trial of several different dietary supplements. The patient has since requested another opinion regarding "leaky gut".

This is a familiar story for internists and gastroenterologists, as this case is representative of many patients with IBS. This syndrome commonly affects individuals less than 50 years old,[11] with more than 50% of patients with IBS exhibiting a change in predominant subtype over a 1-year period,[12–14] and the use of over-the-counter products typically fails to provide relief.[15] Infectious gastroenteritis is a known cause of IBS;[16] however, the exact mechanisms that led to this patient developing IBS-C, while his spouse recovered completely, remain unknown. Current evidence indicates that multifactorial pathophysiological disturbances may lead to the development of IBS-C, including motility disturbances, visceral hypersensitivity, an increase in intestinal permeability, and disruptions to the gastrointestinal (GI) microbiome.
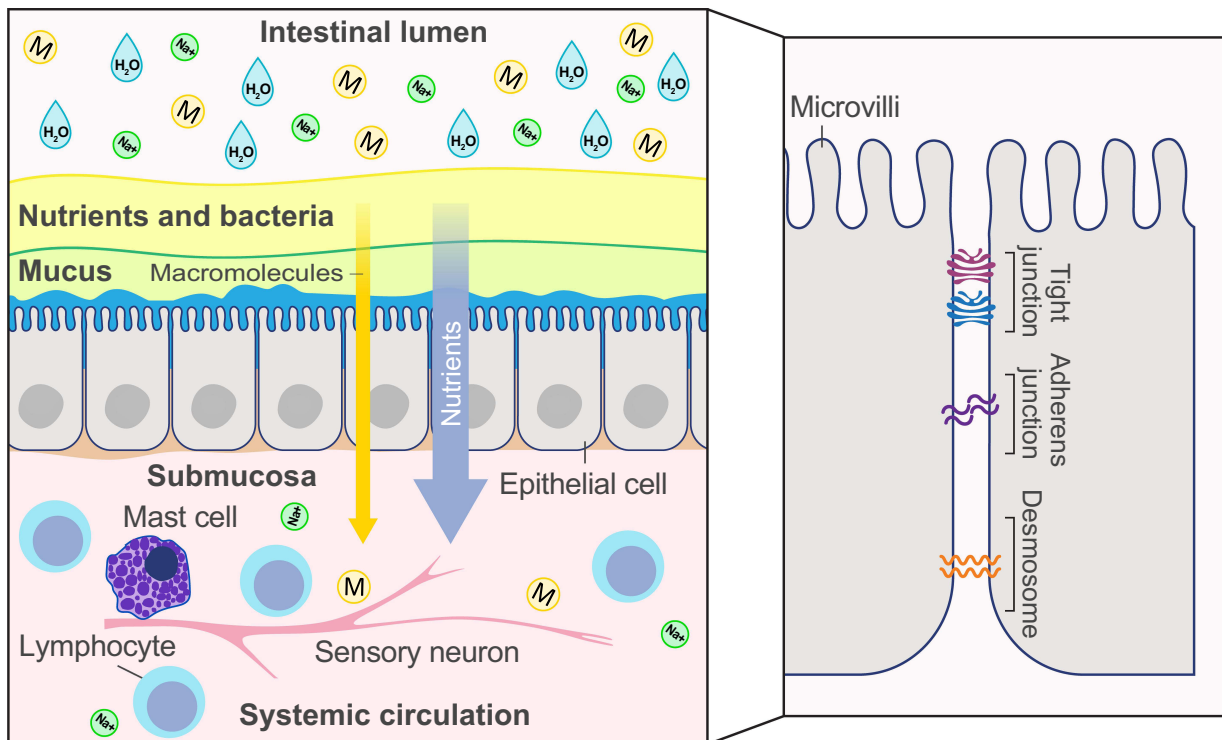
What is Intestinal Permeability?

The GI tract serves as a functional barrier between the body and the surrounding environment that is essential for maintaining human health. Consisting of a complex system of physical and chemical layers (epithelial cells, immune cells, commensal microbiota, mucus, and digestive secretions), the intestinal tract protects the internal milieu from exposure to pathogens and toxins while facilitating the uptake of nutrients and water. Perhaps, the most important physical barrier in the intestine is the epithelium, which consists of a single layer of epithelial cells interconnected by tight junctions, adherens junctions, and desmosomes (Figure 1A).[17] Movement of solutes and fluid across the intestinal epithelium is regulated by tight junctions between epithelial cells as well as across the apical membrane of epithelial cells and is essential for normal health.[17]

Infections in the GI tract can change intestinal permeability, both acutely and chronically, disrupting ionic gradients and osmotic pressure and allowing systemic infiltration of macromolecules (eg, toxins, bacteria, food allergens).[17,18] A recent study showed that acute *Clostridioides difficile* infection in mice can cause significant intestinal epithelial damage and increase intestinal permeability through tight junction-dependent mechanisms.[19] Increased intestinal permeability can, in turn, activate epithelial immune cells, followed by cytokine release and inflammation, which can modify neural control of GI sensory-motor and secretory functions and increase visceral hypersensitivity (Figure 1B).[20,21] Patients with IBS without an infectious etiology have also displayed aberrant long-term increases in intestinal permeability associated with alterations in tight junction proteins and adhesion molecules, similar to postinfection IBS (PI-IBS).[20] Factors positively associated with the development of IBS and increased intestinal permeability include psychological distress, depression, anxiety, and food intolerance (Table 1).[22,23]

Why is Intestinal Permeability Important, but Not "Leaky Gut"?

"Leaky gut syndrome" is the theory that toxins and bacteria freely permeate, or pass through, the intestinal epithelial barrier into the body, causing symptoms of chronic GI distress. While this theory makes a great visual to help explain increased intestinal permeability in plain language, it is not an accurate description of what truly happens. "Leaky gut" is not a definitive

A. Intestinal Epithelium With Normal Permeability
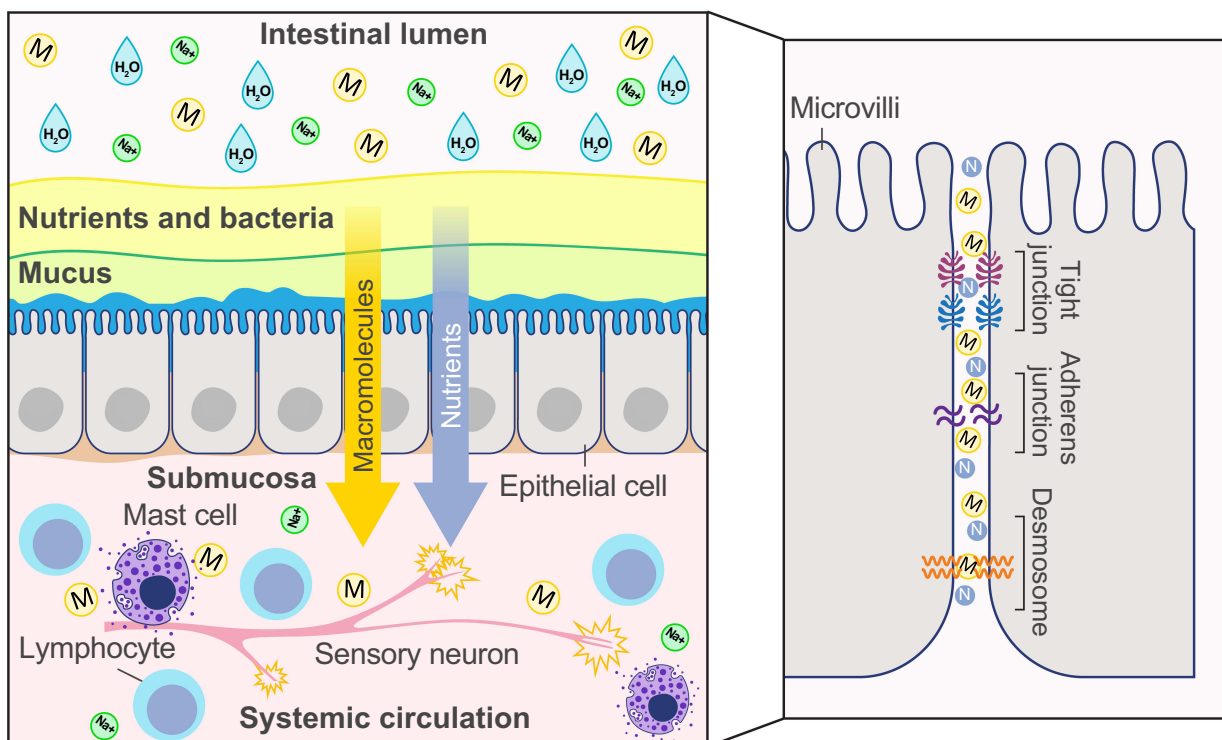

B. Increased Intestinal Permeability

Figure 1 Schematic diagram of the intestinal epithelium with (**A**) normal permeability, and (**B**) increased permeability. (**A**) In normal intestinal epithelium, nutrients are absorbed from the lumen of the intestine into systemic circulation by passive, or paracellular, transport between the intercellular spaces. Tight junction proteins interconnecting the epithelial cells stop the transport of macromolecules from the lumen into systemic circulation. (**B**) In intestinal epithelium with increased permeability, the tight junction complex is disrupted and allow paracellular transport of macromolecules. They may activate mucosal mast cells to produce an inflammatory response, which can excite TRPV1-expressing sensory neurons, leading to increased visceral hypersensitivity and abdominal pain.
Abbreviations: H_2O, water; M, macromolecule; N, nutrients; Na^+, sodium ion; TRPV1, transient receptor potential cation channel subfamily V member 1.

Table 1 Factors Associated with Abnormal Intestinal Permeability

Nutritional factors	Tight junction downregulation
	Histone deacetylase inhibitors
	ENS modulators
Infections and toxins	Viral, bacterial, and protozoal intestinal infections
	Environmental toxins
	Food poisoning (eg, preformed toxins, *Bacillus cereus*)
Hygiene hypothesis	Sterile environment
	Lack of farming
Lifestyle factors	Anxiety, depression, and/or trauma (psychological distress)
	Impaired function and diversity of the intestinal microbiota
	Medications (eg, aspirin, NSAIDs)
Endogenous factors	Hypoperfusion of the intestine
	Chronic inflammation / autoimmunity
	Bile acid malabsorption
	Genetics
	Ischemia

Notes: Adapted from Bischoff SC, Barbara G, Buurman W, et al. Intestinal permeability–a new target for disease prevention and therapy. *BMC Gastroenterol*. 2014;14:189, adapted with permission from SNCSC.[17]
Abbreviations: ENS, enteric nervous system; NSAID, nonsteroidal anti-inflammatory.

medical diagnosis according to most medical professionals, and despite lay claims to the contrary, tests of blood, stool, hair, and nail cannot accurately diagnose "leaky gut". Importantly, a normal, healthy gut always "leaks" to some degree; epithelial cells contain transmembrane pores and transporters that regulate passive or active transport of molecules and ions, tight junctions open selectively to allow passage of nutrients, and temporary gaps regularly form when epithelial cells are renewed every 5 days in humans (ie, cell shedding[17]). Furthermore, small exogenous or endogenous agents (eg, antigens) can cause immune cells in the mucosa and lamina propria (the thin layer of connective tissue lining the intestines) to produce an inflammatory response, independent of macromolecule (eg, bacteria, toxins) permeation.[24]

Intestinal permeability can be accurately measured, as discussed below, and changes in intestinal permeability are associated with a number of different disease states.[17] Intestinal permeability more accurately accounts for the dynamic function of the GI tract as a complex system of multiple defensive layers that are normally selectively permeable. A systematic review of IBS studies published through 2020 showed that 37–62% of patients with IBS-D and 16–50% of patients with PI-IBS had measurable increases in intestinal permeability versus healthy controls.[25] In IBS-C studies, increased intestinal permeability was found in 4–25% of patients.[25] Importantly, these data highlight that many, but not all, patients with IBS may have a pathologically "leaky gut" as the main pathophysiological feature.

How is Intestinal Permeability Measured?

Methods for measuring intestinal permeability have not evolved much in the past decade, and in vivo permeability assays such as the lactulose/mannitol test, measures of sucralose, sucrose, PEG4000/400, and ^{51}Cr-EDTA are still the most widely used (Table 2). Other methodologies are available, such as ex vivo measurement using an Ussing chamber, which evaluates short-circuit current as a marker for the transportation of ions across the epithelium. However, this approach is somewhat limited due to the requirement for fresh intestinal biopsy tissue. The measurement of bacteria-related markers within blood, feces, or biopsy material is another alternative to in vivo permeability assays. While this approach holds promise for the future, it is currently not well established due to limited data, unclear/low assay specificity, and the need for some assays to be carried out within specialist laboratories (Table 2).

In vivo permeability assays typically employ noninvasive oral administration of large oligosaccharides (eg, lactulose) and small sugars (eg, mannitol).[17] While the small sugars can freely permeate a healthy intestinal epithelium, the large

Table 2 Methods for Measuring Intestinal Permeability

Means	Hu	An	Test Molecules	Test Site	Material Needed	Disadvantages
Ex vivo						
Ussing chamber	x	x	H_2O, ions, sugars, etc.	Site specific	Biopsies	Invasive
In vivo—permeability assays						
Lactulose/mannitol	x	x	Oligosaccharides of different MW	Small intestine	Urine	Time consuming
Sucralose	x	(x)	Sucralose (comb)*	Colon	Urine	Time consuming
Sucrose	x	(x)	Sucrose (comb)*	Stomach	Urine	Time consuming
PEG4000/400	x	(x)	Polyethylene glycols	Whole intestine	Urine	Time consuming
^{51}Cr-EDTA	x	x	^{51}Cr-EDTA	Whole intestine	Urine	Radioactivity
In vivo—bacteria-related						
LAL assay	x	x	Endotoxin (LPS)	Whole intestine	Plasma	Assay limitation
EndoCAb	x	x	Anti-LPS antibodies	Whole intestine	Serum	Only in acute phase
D-lactate	x	x	Bacterial lactate	Whole intestine	Plasma	Low specificity
Butyrate production	x	x	BPB (PCR)	Colon	Feces	Special labs, limited data
Hemolysin test	x	x	Pathogens (cell culture)	Colon	Feces	Special labs, limited data
Inner colon mucus	x	x	Quantification of bacteria	Colon	Biopsies	Invasive, limited standardization
Liver steatosis	x	x	Fat content in liver	Whole intestine	MRT, US	Expensive, unspecific
Breath tests	x	x	Fat content in liver	Whole intestine	GC/MS	Unclear specificity

Notes: *In combination with lactulose/mannitol test. Reprinted from Bischoff SC, Barbara G, Buurman W, et al. Intestinal permeability–a new target for disease prevention and therapy. *BMC Gastroenterol.* 2014;14:189, reprinted with permission from SNCSC.[17]
Abbreviations: ^{51}Cr-EDTA, chromium-labeled EDTA; An, suitable for animal models; BPB, butyrate-producing bacteria; EndoCAb, circulating endotoxin core antibias; GC, gas chromatography; Hu, suitable for the human system; LAL, limulus amebocyte lysate assay; LPS, lipopolysaccharide; MRT, magnetic resonance tomography; MS, mass spectroscopy; MW, molecular weight; PCR, polymerase chain reaction; PEG, polyethylene glycols; US, ultrasound.

oligosaccharides can only traverse an intestinal barrier that is compromised. Thus, lactulose is not absorbed to any significant degree in a healthy individual, while mannitol is readily absorbed, which can then be measured after being filtered by the kidneys. The ratio of these molecules (lactulose:mannitol) is measured in the urine after a specified time and reflects the status of the GI epithelium. A diagnostic benefit of using lactulose and mannitol is that neither molecule is metabolized extensively, and both are excreted largely unchanged in the urine in proportion to the quantities absorbed into the circulation.[26] Another advantage of these molecules is that they are relatively inert, enabling widespread clinical use. Nonetheless, measures of intestinal permeability in vivo are relatively rare in clinical trials.

Zhou et al[27] used the lactulose/mannitol test with 24-hour urine collection to assess intestinal permeability changes after dietary glutamine supplementation for treatment of PI-IBS. This clinical trial not only indicated that increased intestinal permeability may be an underlying etiological factor for patients with PI-IBS, it also demonstrated the utility and safety of lactulose/mannitol testing in conjunction with other agents.[27] However, the lactulose/mannitol test has its limitations, one being that it can only assess the small intestine.[17] In fact, all currently available intestinal permeability tests are site-specific,[17] which is a possible confounding factor, among others, for studies attempting to discern the prevalence of increased intestinal permeability in vivo.

Can Increased Intestinal Permeability Lead to Pain in IBS?

The confluence of increased intestinal permeability, inflammation, and visceral pain in IBS has been extensively reviewed by Camilleri et al.[28] A study by Zhou et al[23] showed that patients with IBS-D and increased intestinal permeability had greater hypersensitivity to both somatic and visceral stimuli than patients with IBS-D with normal intestinal permeability and healthy controls.[29] Although similar studies have not been performed in patients with IBS-C, the mechanisms are likely similar. Increased intestinal permeability allows macromolecules to infiltrate the bloodstream and activate mast cells, initiating an inflammatory cascade;[17] the degree of intestinal permeability has been directly associated with the inflammatory response and IBS symptom severity.[22,25,30] Greater numbers of activated mast cells close to nerve endings correlate with the severity and frequency of abdominal pain in patients with IBS-C and IBS-D.[31–33] In addition to the intestinal upsurge in activated mast cells and other immune cells in the intestinal submucosa,[34,35] a study reported that a three-fold increase in intestinal transient receptor potential vanilloid type-1 (TRPV1) immunoreactive sensory nerve fibers can be a predictor of pain in patients with IBS, regardless of subtype.[33] These observations highlight the relationship between increased intestinal permeability and the development and severity of abdominal pain in patients with IBS-C.

Why is It Important to Treat Increased Intestinal Permeability in IBS?

IBS is associated with considerable disease burden that markedly disrupts a patient's daily life.[5,6,8,25,36] Chronic visceral pain of varied severity is a key disease characteristic that constitutes part of the ROME IV diagnostic criteria for IBS.[1] Patients with IBS experience abdominal pain at least once a week on average,[1,37] and those with IBS-C more frequently experience diffuse abdominal pain of greater severity than those with other subtypes.[8] Patients with IBS report having worse health-related QoL than patients with diabetes or end-stage renal disease[36] and would give up an average of 15 years of life to be symptom-free.[5] Consequently, patients are willing to take considerable medication risks to alleviate their IBS symptoms, including an average 10% risk of sudden death, for a hypothetical cure.[38,39] Considering the worldwide prevalence of IBS is estimated at between 4% (Rome IV criteria) and 10% (Rome III criteria),[3] a thorough investigation into the root causes of related abdominal pain and effective treatment methods is warranted.

Evidence indicates that modulating intestinal permeability may improve GI symptoms, especially abdominal pain, in some patients with IBS. Although no guidelines recommend testing for intestinal permeability in patients meeting criteria for IBS, it may be useful for gastroenterologists to consider intestinal permeability testing (eg, lactulose/mannitol) with patients with IBS-C upon diagnosis to determine whether increased intestinal permeability could be contributing to their symptoms (Figure 2). Routine measuring of intestinal permeability both in clinical practice and for research studies may be helpful to guide patient therapy (discussed below). This positive diagnostic strategy may better inform health care practitioners on the optimal treatment option for each patient with IBS-C. The challenge is that diagnostic testing is not always readily available to the large number of patients with IBS who might benefit from this approach. Moreover, large studies would be needed to specify standards for a positive or negative test.

How Can Increased Intestinal Permeability in IBS-C Be Treated?

Current guidelines recommend the use of secretagogues (eg, lubiprostone, linaclotide, and plecanatide) and the NHE3 inhibitor, tenapanor, for patients with IBS-C.[37,40] Of note, the 5-hydroxytryptamine receptor 4 agonist tegaserod is US Food and Drug Administration (FDA)-approved and recommended for women younger than age 65 years with one or fewer cardiovascular risk factors who have not adequately responded to secretagogues,[37,40] although this agent has been removed from the US market for commercial reasons and will not be discussed further in this review.[41] While all of the recommended drugs have evidence to support their use, only lubiprostone and tenapanor are reported to modulate intestinal permeability.[43,44] In the absence of head-to-head studies and with the lack of treatment options for patients who are refractory to secretagogues, this review will focus on how tenapanor could improve abdominal pain in patients with IBS-C by aiding in the restoration of normal intestinal permeability.

Tenapanor is a first-in-class, minimally absorbed, small-molecule inhibitor of NHE3 approved by the FDA for the treatment of IBS-C in adults.[45] It is also FDA approved as an add-on therapy for hyperphosphatemia in adults with chronic kidney disease on dialysis who have an inadequate response to phosphate binders or who are intolerant of
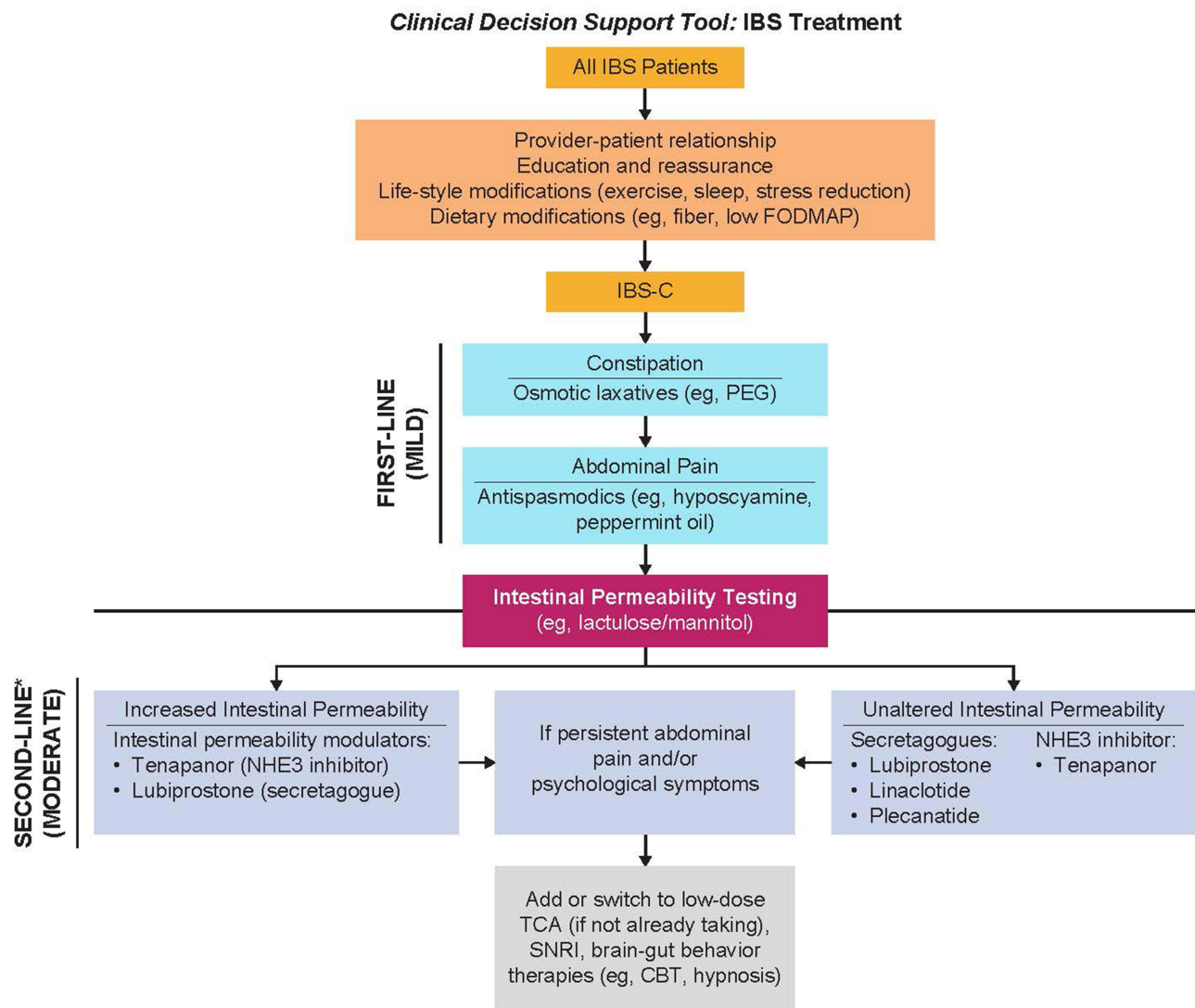
Figure 2 Clinical treatment decision guide for IBS-C.

Notes: *Selection of medication should be based on the clinical features and needs of the patient. Tegaserod (5-HT$_4$ agonist) is FDA-approved and recommended for women younger than age 65 years with one or more cardiovascular risk factors who have not adequately responded to secretagogues[37,40]; however, tegaserod has been removed from the US market for commercial reasons[41] and, therefore, is not included in this chart. Reprinted from *Gastroenterology*. 163(1), AGA Institute, Clinical Decision Support Tool: IBS Treatment. Page No. 152, Copyright 2022, with permission from Elsevier.[42.]

Abbreviations: 5-HT$_4$, 5-hydroxytryptamine receptor 4; FDA, Food and Drug Administration; IBS-C, irritable bowel syndrome with constipation; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; NHE3, sodium-hydrogen antiporter 3; TCA, tricyclic antidepressant; SNRI, serotonin-norepinephrine reuptake inhibitor; PEG, polyethylene glycol; CBT cognitive behavioral therapy.

phosphate binders.[44,46] NHE3 is located on the apical surface of epithelial cells in the small intestine and proximal colon and is primarily responsible for absorbing dietary sodium and water and regulating acid-base homeostasis via proton exchange (Figure 3).[47] Inhibition of NHE3 reduces dietary sodium absorption, which in turn retains luminal water, resulting in softer stools and accelerated intestinal transit.[44,48,49]

In vivo studies in rodents and translational experiments with human small intestinal stem cell-derived enteroid monolayers showed that blocking NHE3 with tenapanor reduces sodium absorption and increases sodium excretion in the stool.[44] The reduction in sodium absorption led to intracellular proton retention,[44] which decreased the intracellular pH and increased transepithelial resistance (TEER).[44] This increase was thought to result from a conformational change in tight junction proteins that reduces intestinal permeability (Figure 3).[44] Supporting this proposed mechanism of action, a study using human colonic epithelial monolayers demonstrated that inflammatory cytokines reduced TEER and increased macromolecule permeability, and
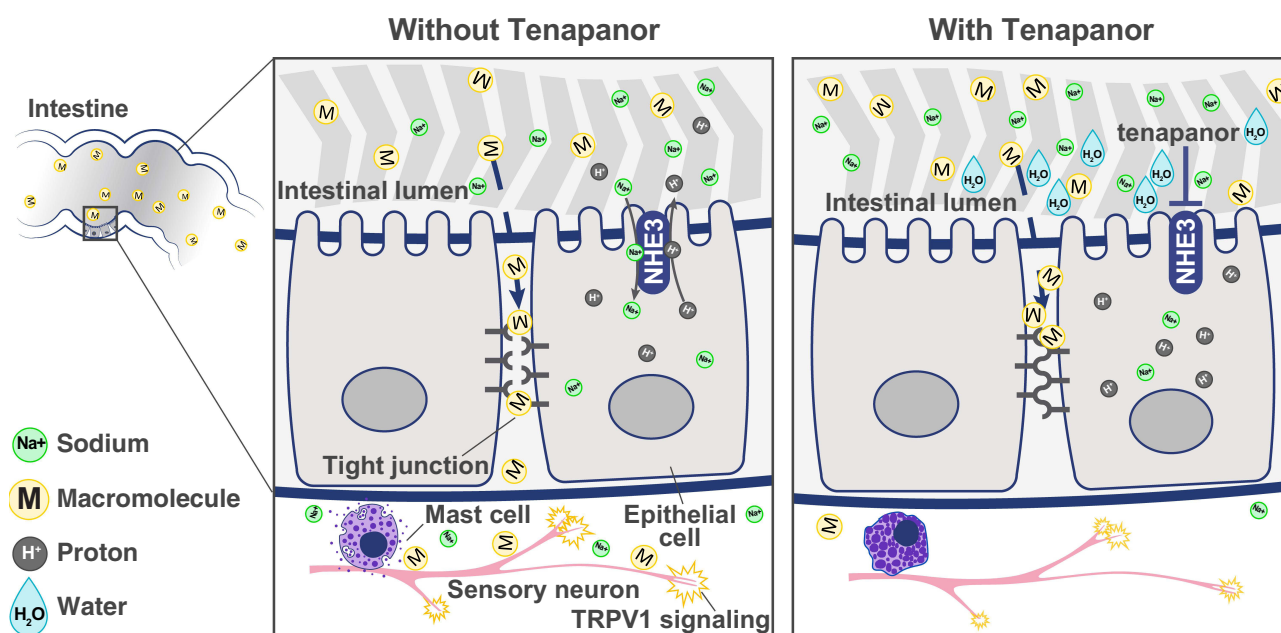
Figure 3 Mechanism of action of tenapanor. Tenapanor inhibits NHE3 located on the apical surface of the intestinal epithelial cells. NHE3 inhibition reduces sodium absorption, leading to water retention in the lumen that in turn softens stools and accelerates intestinal transit. NHE3 inhibition also causes retention of intracellular protons in the epithelial cell, which decreases the intracellular pH and increases TEER. This increase is thought to result from a conformational change in the tight junction proteins that decreases intestinal permeability to macromolecules. Tenapanor also normalizes sensory neuronal excitability and TRPV1 currents and reduces visceral hypersensitivity. This figure is published under Creative Commons license CC-BY: King AJ et al. *Am J Physiol Gastrointest Liver Physiol.* 2024. doi: 10.1152/ajpgi.00233.2023. Copyright © 2024, American Journal of Physiology-Gastrointestinal and Liver Physiology.[50]
Abbreviations: H⁺, proton; H₂O, water; M, macromolecule; Na⁺, sodium ion; NHE3, sodium-hydrogen antiporter 3; TEER, transepithelial resistance; TRPV1, transient receptor potential cation channel subfamily V member 1.

this increase could be attenuated by tenapanor.[50] Interestingly, in a rat model of IBS-like colonic hypersensitivity, tenapanor also normalized colonic sensory neuronal excitability and TRPV1 currents and reduced visceral hypersensitivity.[50]

Clinical trial data in patients with IBS-C demonstrated that oral administration of tenapanor 50 mg twice a day (BID) versus placebo significantly improved key IBS-C symptoms, including increased complete spontaneous bowel movements and decreased abdominal pain.[51,52] In fact, tenapanor was associated with improvement in abdominal pain and other abdominal symptoms, independent of changes in bowel movements in a subset of patients.[53] Tenapanor 50 mg BID had an acceptable safety profile[51,52,54] and was generally well tolerated when administered for up to 55 consecutive weeks.[54] The most common treatment-emergent adverse event (TEAE) in all tenapanor trials was mild to moderate transient diarrhea (11%), with no notable increase or change in TEAEs with long-term use.[54] The low incidence of serious TEAEs (1%)[51,52,54] and tenapanor-related TEAEs (diarrhea) leading to tenapanor discontinuation (3.5%)[54] further supports its long-term safety and tolerability in patients with IBS-C. Current American Gastroenterological Association guidelines recommend tenapanor for adult patients with IBS-C.[40]

Conclusions

There is growing evidence that suggests that increased intestinal permeability and associated inflammatory processes contribute to abdominal pain in patients with IBS-C. Tenapanor, a minimally absorbed NHE3 inhibitor, is an FDA-approved treatment for adults with IBS-C that effectively relieves constipation and abdominal pain. The beneficial clinical effect of tenapanor on abdominal pain may be mediated partly by reducing intestinal permeability, related inflammation, and visceral hypersensitivity. Based on results from non-clinical studies, following inhibition of NHE3, the intracellular proton retention decreased the intracellular pH and increased TEER, which reduced intestinal permeability to macromolecules. To guide treatment selection, it may be useful for gastroenterologists to consider intestinal permeability testing (eg, lactulose/mannitol) with patients with IBS-C upon diagnosis to determine whether increased intestinal

permeability could be contributing to the severity of their symptoms ([Figure 2](#)). Treatment targeting intestinal permeability could bring significant relief to patients with IBS-C.

Abbreviations

BID, twice a day; IBS, irritable bowel syndrome; IBS-C, IBS with constipation; IBS-D, IBS with predominant diarrhea; FDA, US Food and Drug Administration; GI, gastrointestinal; NHE3, sodium-hydrogen exchanger isoform 3; PI-IBS, postinfectious IBS; QoL, quality of life; TRPV1, transient receptor potential vanilloid type-1; TEAE, treatment-emergent adverse event; TEER, transepithelial resistance.

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Author Contributions

All authors made a significant contribution to the work reported; participated in the conception, study design, execution, and acquisition of data, analysis, and interpretation; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work. All authors read and approved the final version of the manuscript.

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