SPECIAL SUPPLEMENT

CANADIAN PRIMARY CARE TODAY

Clinical Insights, Perspectives and Disease Management

PANEL DISCUSSION:

A NEW ERA IN THE MANAGEMENT OF IRRITABLE BOWEL SYNDROME WITH CONSTIPATION (IBS-C)

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ABOUT
THE PANELISTS

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In Canada, there is significant Irritable bowel syndrome (IBS) burden which negatively impacts health care utilization, economic productivity, and most importantly patients' quality of life and psychosocial wellbeing. In this panel discussion, experts in the diagnosis and treatment of IBS discuss new strategies for diagnosing IBS-C, clinical trial data for novel therapies in IBS-C and appropriate choices of therapies according to individual patient characteristics. Methods for achieving treatment success and patient satisfaction are also discussed.

John Marshall: Could you provide some insight into the burden of IBS in Canada?

Louis Liu: Canada has a higher prevalence of IBS, compared to other countries. Approximately one in six Canadians has IBS. While most patients with IBS are cared for by their primary physicians, IBS referrals still account for 40% of new referrals to gastroenterology outpatient clinics. About 75% of IBS patients see a doctor once per year for the condition and 6% see a doctor for IBS six to ten times per year. In one survey of 3,000 Canadian patients with IBS, 12% of the respondents said they had been hospitalized for symptoms of IBS and 46% reported missing days of work or school because of the disorder.

On average, Canadians who have IBS miss 13 days of work per year accounting for $8 billion of lost productivity. This impact is comparable to other chronic illnesses, including diabetes, arthritis, and cancer. Among Canadians who are permanently unable to work due to a chronic condition, IBS is the cause approximately 6% of the time.

J.M.: These are concerning statistics. Of course, patients most notice the impact on their day to day life. Can you elaborate on how IBS affects patients' quality of life?

L.L: Patients with IBS often suffer concurrently from anxiety and depression due to the pain and lifestyle limitations of this condition. IBS impacts quality of life similar to other chronic medical conditions like asthma, migraines, panic disorder and rheumatoid arthritis (**Figure 1**). In clinical studies, patients identify the greatest impacts on their vitality, bodily pain, and general health. When we ask patients who have previously taken or are currently taking IBS medications, including newer options like lubiprostone and linaclotide, only one-third of patients are satisfied with their treatment. Patients cite side effects and low efficacy as reasons for their dissatisfaction.

J.M.: Dr. Brenner, what are your thoughts on the burden of IBS and the unmet medical needs?

Darren Brenner: Dr. Liu's comparisons to other chronic medical conditions are correct, but I would further stress the point that recent studies have shown that individuals with IBS are willing to accept a mortality risk for a potential chance at cure. Recently, Dr. Brian Lacy at the Mayo Clinic, published data from a survey querying patients with irritable bowel syndrome with diarrhea (IBS-D) about the levels of risk they would be willing to accept for an IBS cure. Patients responded that they would be willing to accept a 10% risk of death for an instantaneous cure, which is quite shocking. An older survey by Dr. Douglas Drossman, revealed that patients would be willing to give up ¼ or 15 years of their remaining life if it meant they could be cured of IBS. These studies define the seriousness of the IBS patient experience which in many instances contrasts with the practitioner perspective that IBS is a nuisance disorder and that patients should just "live with it."

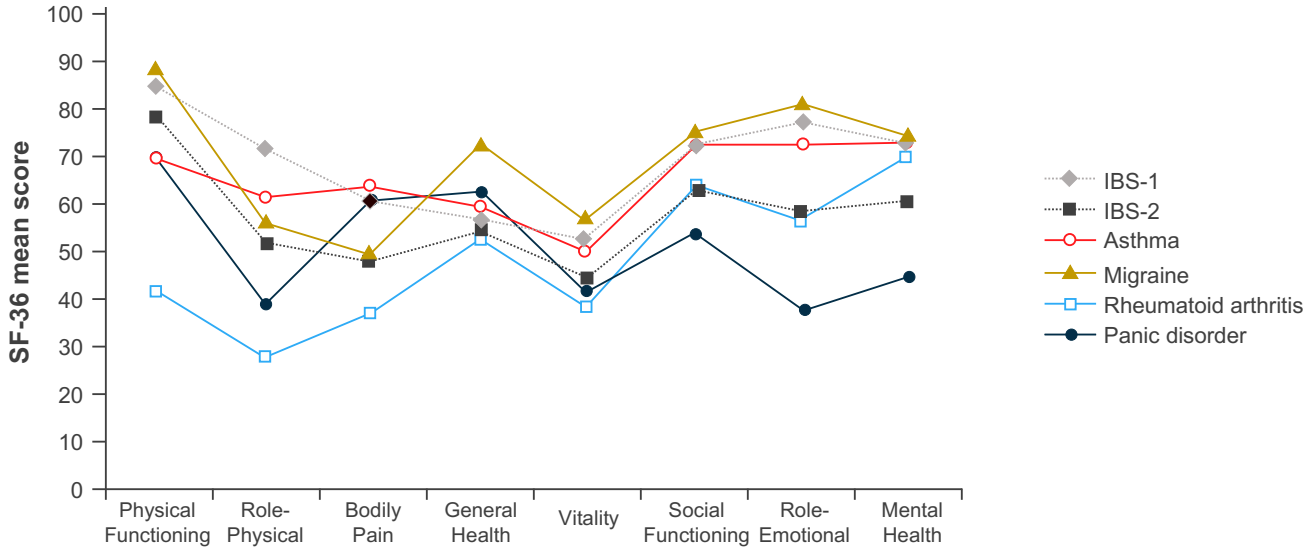
When asked about how they feel about the disease, patients say they feel stressed, frustrated, not in control, and embarrassed. They ask, 'How do I go out with my friends and have dinner, knowing that within a few minutes, I may have to run to the bathroom?' Despite this significant burden, patients have been conditioned by the medical system to have low expectations – 40% of people with IBS say they accept that their symptoms won't get better.

J.M.: Is IBS still considered a diagnosis of exclusion? What are the specific tests we should consider for IBS-C?

L.L: It takes on average four to five years before patients receive a diagnosis of IBS, and 75% of patients with IBS have yet been diagnosed. In the past, we considered IBS a diagnosis of exclusion, but this creates unnecessary anxiety for the patient and physician. This is impractical and it takes too long to rule out all possible causes of abdominal pain before making this diagnosis.

To shorten the illness journey that can prevent patients from developing depression and anxiety as they wait for a diagnosis, we need to convert the paradigm from a diagnosis of exclusion to one utilizing a positive diagnostic strategy. A positive diagnosis of IBS relies on use of the Rome IV Diagnostic criteria (**Figure 2**). Patients need to have had regular abdominal pain that is associated with at least two of the following: defecation; a change in the frequency of stool; or a change in the appearance of stool. Those with IBS-C have hard or lumpy stools at least 25% of the time and loose or watery stools less than 25% of the time without the use of laxatives. After ruling in these three criteria, five other criteria that could indicate cancer, inflammatory or malabsorptive conditions must be ruled out (**Figure 3**). If all 8 criteria are met, the positive predictive value for IBS approaches 97-98%.

Once we see that patients fit the Rome IV criteria, and we have ruled out the warning symptoms and signs with a history and physical exam, we can make a positive diagnosis and subclassify the patient using the Bristol scale. At that time, I would encourage clinicians to initiate IBS therapy while they do other tests such as complete blood count and celiac serology.



GI, gastrointestinal; HRQoL, health-related quality of life; IBS-1, a largely untreated community sample of health maintenance organization members with IBS; IBS-2, a sample of patients with IBS recruited through clinics and in the community with constipation predominant; SF-36, 36-Item Short Form Survey.
Frank L et al. Clin Ther 2002 Apr;24(4):675-89; discussion 674.

Figure 1. *Comparison of HRQoL (SF-36) in patients with IBS and with other GI and non-GI chronic disorders; adapted from Frank L et al, 2016*

JM: What has been the biggest challenge in treating IBS?

D.B.: Historically, medications either targeted abdominal symptoms like pain, or bowel symptoms including frequency, texture, straining and sensations of incomplete evacuation. Thankfully, we now have therapies which improve global symptoms. These include tenapanor, linaclotide, and plecanatide.

Treatments for IBS-C in 2023 include:

- Plecanatide (Trulance®)
- Linaclotide (Constella®)
- Tenapanor (Ibsrela®)
- Cognitive behavioral therapy / hypnotherapy
- Diet modification (low FODMAPs)
- Selective serotonin reuptake inhibitors (SSRIs)/Tricyclic antidepressants (TCAS)
- Soluble fibre (psyllium)

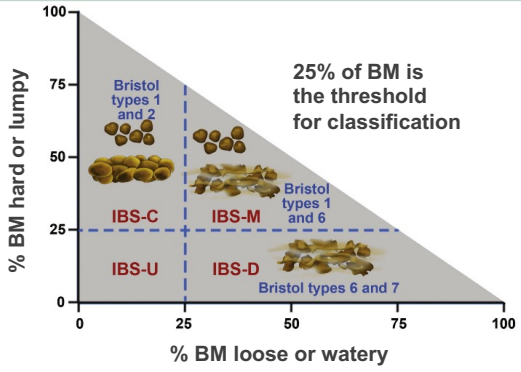
Tenapanor is a sodium/hydrogen exchanger 3 channel inhibitor. This medication blocks the reuptake of sodium and water from both the small and large intestine leading to softer stool and increased peristalsis. Based on animal models, researchers believe the molecule also reduces intercellular tight junction permeability and antagonizes the TRPV 1 receptor, producing analgesic effects. This is a drug that's taken twice daily with meals, and the most common adverse events include diarrhea, abdominal pain, and nausea.

Another treatment option is linaclotide. It activates a receptor in the intestinal epithelium called the guanylate cyclase C (GC-C) receptor. This activation leads to an increase in intracellular cyclic guanosine monophosphate (GMP), which causes secretion of chloride ions into the intestinal lumen. That creates a negative electrical charge in the lumen, leading to cellular secretion of sodium. The sodium and chloride in the lumen form sodium chloride, or salt, creating an

Recurrent ***abdominal pain*** at least ***1 day/week*** in the last ***3 months*** associated with more than 2 of the following:

1. Related to defecation
2. Associated with a change in frequency of stool
3. Associated with a change in form (appearance) of stool

with symptom ***onset at least 6 months*** *prior to diagnosis*



Subtypes of IBS by predominant stool pattern:

a. IBS-C: hard or lumpy stools ≥25% and loose or watery stools <25% of bowel movements

b. IBS-D: loose or watery stools ≥25% and hard or lumpy stools <25% of bowel movements

c. IBS-M: hard or lumpy stools ≥25% and loose or watery stools ≥25% of bowel movements

ROME Foundation.
Mearin F, Lacy BE, Chang L, et al. Gastroenterology 2016;150:1393-407.

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Figure 2. *ROME IV diagnostic criteria; adapted from Mearin et al, 2016*

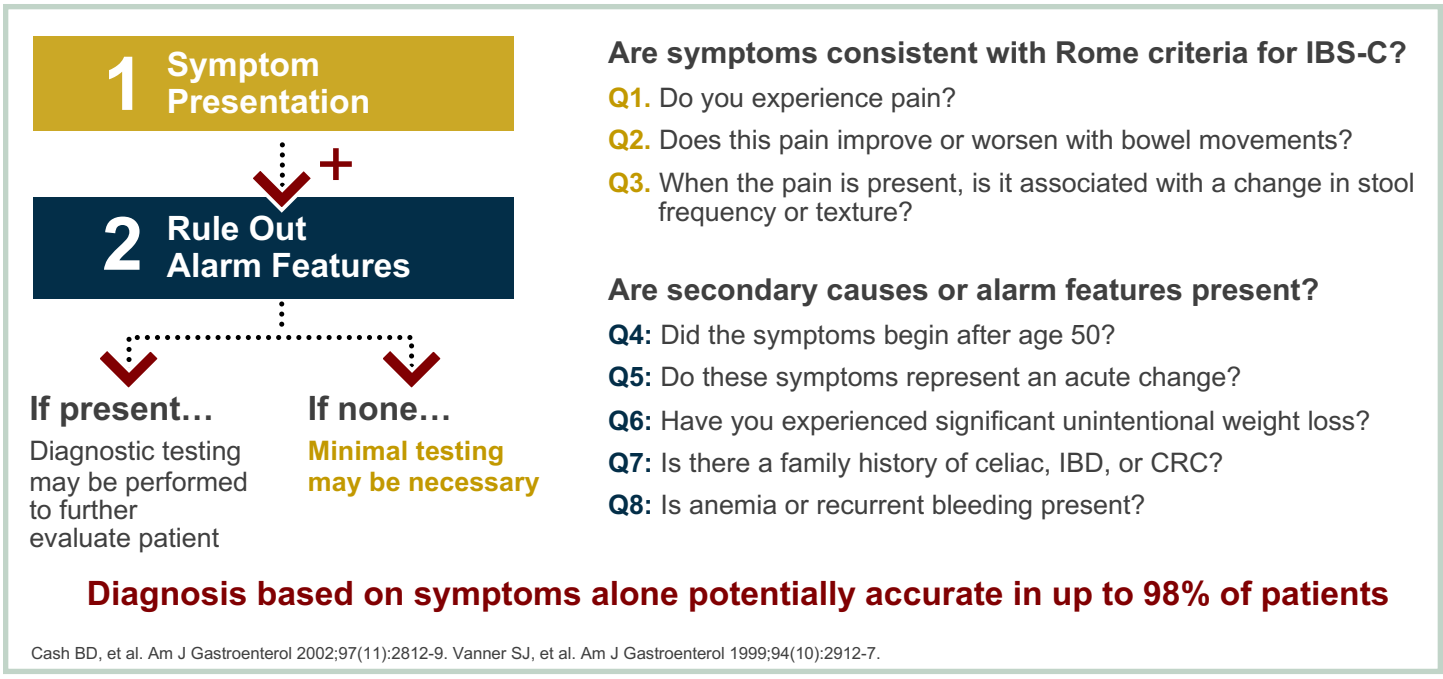


***Figure 3**. Algorithm for the diagnosis of IBS-C; adapted from Cash BD, et al, 2002*

osmotic gradient that draws water into the lumen, thus increasing stool weight and increasing peristalsis. In addition, the cyclic GMP generated inside the cell may cross (based on pre-clinical studies) the basolateral membrane and reduce firing of the pain neurons in the intestinal submucosa. Linaclotide is a once-daily drug, recommended to be taken 30 minutes before the first meal of the day. Common adverse events include diarrhea.

Plecanatide is also a once-daily option but can be taken any time of day with or without meals. Similar to linaclotide, it also activates GC-C receptors, but is pH-dependent and works more effectively in the small intestine than the colon. This may explain why plecanatide led to fewer adverse effects, such as diarrhea, which is the most common adverse event and which occurred at lower rates to tenapanor and linaclotide in non-head-to-head clinical trials.

A recent systematic review of these three therapeutic agents found that none dominated nor was inferior to the others. Overall, linaclotide appeared to be numerically most effective, but it was also associated with the highest rates of adverse events. Importantly, clinical trials of the three used a double-blinded, randomized controlled approach with the same FDA responder endpoint: a 30% reduction in pain and an increase of at least one additional complete bowel movement per week during the same week for six of twelve weeks. Across the studies, 10% to 12% more subjects in the treatment arm met this primary endpoint, compared to individuals receiving placebo.

J.M.: Plecanatide is new in Canada, but prescribers in the U.S. have more experience with it. From a clinical perspective, what has this therapy meant to your patients?

D.B.: Plecanatide is a molecule which is almost identical to human uroguanylin. The only difference between the two molecules is a single amino acid substitution, allowing plecanatide to hypothetically bind to GC-C receptors more robustly (**Figure 4**). Uroguanylin is a small peptide naturally secreted into the small intestine in response to a meal. It binds to GC-C receptors with the effects previously described. My patients appreciate that plecanatide offers them a therapy which mimics a naturally occurring process . This is messaging that can help reassure those patients who do not want to take pharmaceutical interventions.

Plecanatide also has a rapid onset of action. This is important for patients; they want to know the medication they're taking will work quickly and efficiently. Studies with plecanatide have revealed significant improvements in abdominal bloating by week one and in abdominal pain and cramping by week two (**Figure 5**). The effect is maintained throughout the entire treatment period (12 weeks). In addition, there is no evidence of rebound effect if patients decide to discontinue therapy.

With plecanatide, there is very minimal systemic absorption, which means no drug interactions, no concern for patients with hepatic or renal impairment, and no clinical data demonstrating the development of drug tolerance.

What's most important at the end of the day is the patient's experience with the therapy. Often my patients find medications increase stool frequency and improve stool texture, but they still feel like they have not completely emptied the bowel. With plecanatide, the complete spontaneous bowel movement frequency endpoint is more robust, compared to other medications. Patients also appreciate the flexibility of using plecanatide--they choose when to take the medication as it does not need to be consumed with or before meals. These caveats plus once-a-day dosing improves compliance.

JM: What's your approach for choosing among therapies, and matching the right drug for the right patient?

LL: This is a challenging question to answer, as we don't have head-to-head comparisons between agents that demonstrate superiority in a specific patient sub-group. I discuss the treatment options with patients and develop a tailored program in alignment with the patient's beliefs and past experiences, because research shows that when patients are involved in treatment decisions, it enhances treatment satisfaction.

For patients with mild IBS-C, non-pharmaceutical interventions are often adequate. However, patients with moderate IBS-C require pharmacotherapy, and more severe IBS-C patients often require psychological therapy and more regular follow ups, in addition to pharmacotherapy.

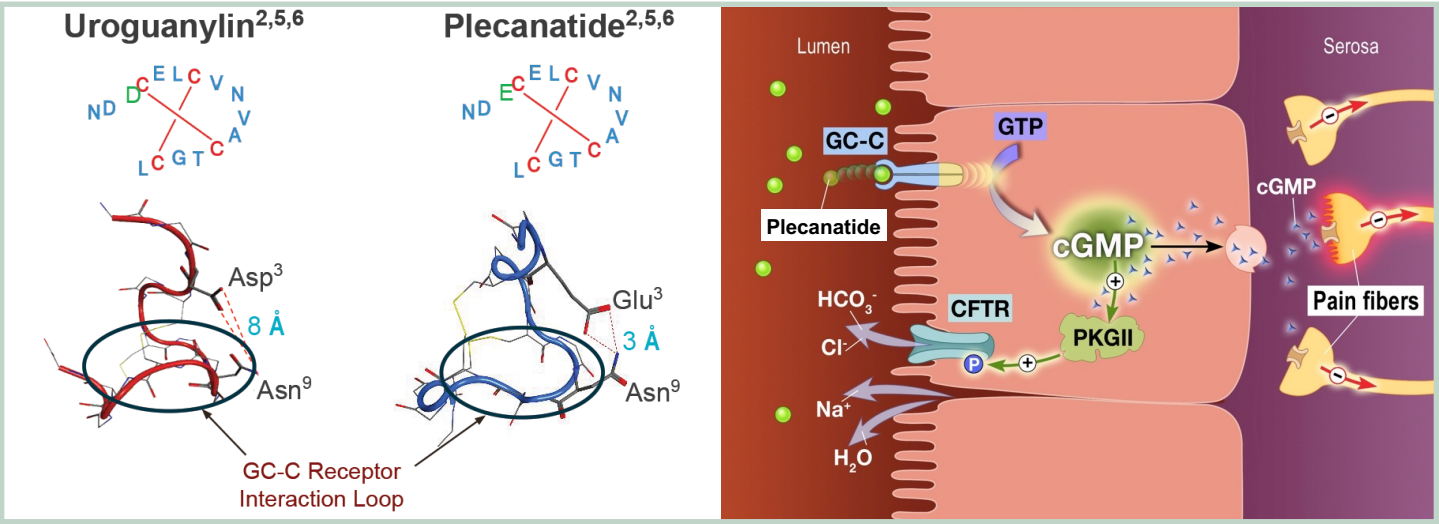


Figure 4. *Basic structure of uroguanylin vs plecanatide (LEFT PANEL) and Mechanism of Action of plecanatide (RIGHT PANEL); Adapted from Camilleri, 2015; Shailubhai et al, 2013; Shailubhai et al, 2016*

D.B.: I agree with Dr Liu. There are many treatment options, but the ones with the best outcomes will be those chosen by the patients. You want to consider what other day-to-day factors are playing a role in exacerbating symptoms, and what factors lead to improved symptoms. I think cost, coverage, and comfort of both the patient and practitioner ultimately drive treatment decisions. If physicians don't try some of the newer medications, they won't become comfortable prescribing them. I recommend everyone try plecanatide, because it's easy to prescribe, given it is a once-a-day medication, it has minimal side effects, no drug-drug interactions and physicians and patients should see a quick response.

JM: How do you define patient success in treatment?

D.B.: First and foremost, the diagnosis of IBS must be concrete. We can no longer say, "I think it's IBS" because the other tests have come back negative. That doesn't work for patients anymore, and if they don't trust the diagnosis, they will do their own research online. It's also important to emphasize to patients that there is no cure for this disorder. I ask patients about a percentage of improvement and I consider a 70-80% improvement from baseline effective.

The majority of the time, success is based not upon what I want, but what a patient wants. For example, a patient may find bloating to be the symptom that frustrates them the most, rather than bowel movement frequency, so if the medication addresses bloating, they're satisfied and I'm satisfied too.

J.M.: If you're switching from one pharmacologic therapy for IBS-C to another, do you do a washout between treatments?

L.L.: As the drugs don't have systemic absorption, I don't do a wash out between them.

J.M.: Are there any commonly used treatment options that you would discourage?

L.L.: I would encourage my colleagues to reconsider recommending the use of probiotics. A recent survey of practitioners in the US, who collectively treated 2,600 patients, found that one-third recommend probiotics. The reality is that the data is just not robust enough to support probiotic use in the treatment of IBS-C. It is reasonable to give probiotics a trial, as many patients want them; however, if they do not provide satisfactory relief, clinicians should stop and move to different treatment options.

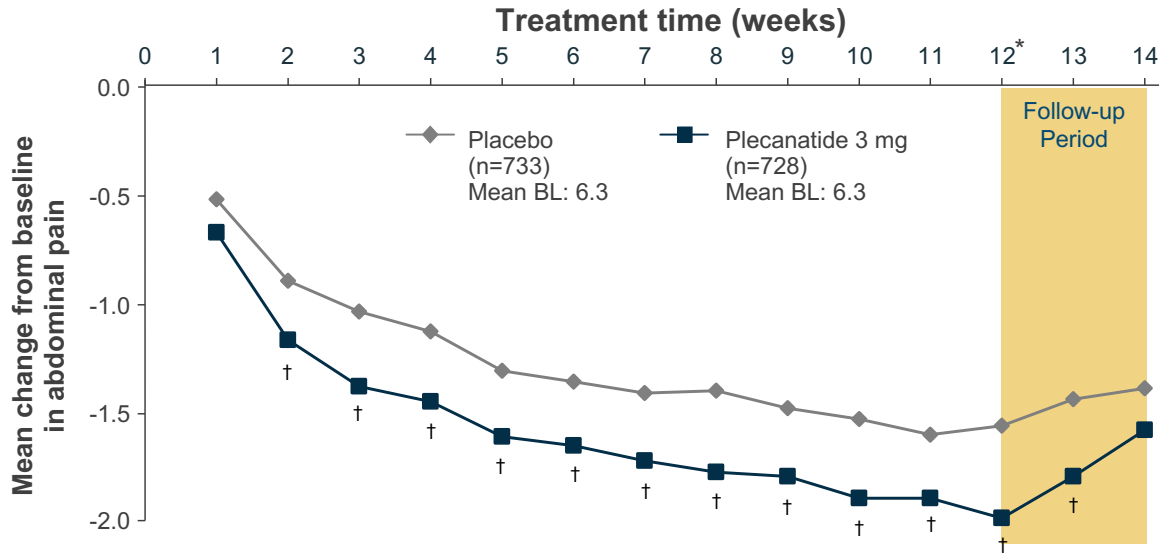
In addition, almost 20% of practitioners start a new over-the-counter medication or encourage patients to continue with over-the-counter medications that have proven ineffective. These medications may temporarily improve bowel function but not abdominal symptoms, so they don't improve global symptoms that patients need for meaningful relief.

JM: What final advice would you give to clinicians about optimizing the management of IBS-C?

LL: I want to emphasize the importance of establishing a good patient-physician relationship and an early positive diagnosis in the disease course. Initiating therapy early on can prevent patients from developing associated anxiety and depression, which only add to the challenge in managing patients with IBS.

Managing patient expectations is equally important. Patients need to appreciate that treatment will not lead to a complete resolution of their abdominal symptoms, and that they will continue to experience day-to-day variation in symptoms. Developing a management strategy with patients will enhance their overall satisfaction.

DB: Engage in shared decision making – explain what's out there and let patients make their own choices. Don't minimize the symptoms, as they are very serious for the patient. Be sure to make an efficient and accurate diagnosis. Half of the referrals I receive for IBS are patients who have been diagnosed with IBS but don't have IBS. Finally, use your guidelines. When patients hear a medication is strongly recommended in expert guidelines, patients feel more comfortable.



*End of study drug administration.
†P≤0.05.
Pooled intention-to-treat (ITT) population; values are least squares (LS) mean.
The severity of abdominal pain was assessed on an 11-point numeric rating scale from 0 (none) to 10 (worst possible).
Trulance (Plecanatide) Product Monograph. Laval, QC: Bausch Health, Canada Inc.; 2021. Data on file.

Figure 5. *Mean change from baseline in abdominal pain; Adapted from Trulance (Plecanatide) Product Monograph. Laval, QC: Bausch Health, Canada Inc.; 2021*

KEY TAKEAWAYS

✓ Irritable bowel syndrome with constipation, or IBS-C, is a common yet frequently mis- or underdiagnosed condition.

✓ It affects approximately 3-5% of the world population.

✓ A diagnosis can be quickly and accurately established via a few simple questions.

✓ First and foremost, an individual must meet Rome IV Criteria for IBS and experience the passage of hard/lumpy stools with at least 25% of bowel movements whilst not concurrently passing loose, mushy, or water stools more than 25% of the time.

✓ If these criteria are met and an individual is less than 50 years of age, denies acute symptom changes or weight loss, is not experiencing recurrent bleeding or has evidence of anemia or a family history of celiac, colon cancer, or inflammatory bowel disease, then the accuracy of the diagnosis based on these questions alone approaches 97%.

✓ Importantly multiple societies including the American College of Gastroenterology (ACG) and American Gastroenterological Association (AGA) both agree that most individuals meeting criteria for IBS-C require no diagnostic testing to confirm or refute the diagnosis.

✓ Once established, treatment should be initiated. Despite multiple treatment options, many (especially over the counter) prove ineffective as these improve bowel symptoms but not the other abdominal symptoms.

✓ Newer therapeutics like linaclotide, tenapanor, and plecanatide have proven effective for both global and individual IBS symptoms, are safe, and have high tolerability.

✓ Ultimately, a strong practitioner-patient relationship and shared decision making will improve outcomes and patient satisfaction.

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