

# ADVANCES IN IBS

Current Developments in the Treatment of Irritable Bowel Syndrome

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## Medical Therapies in the Pipeline for Irritable Bowel Syndrome



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### **G&H** Which medical therapies are currently available to treat irritable bowel syndrome?

**MC** Most of the currently available treatment options for irritable bowel syndrome (IBS) focus on relieving individual symptoms. Patients with constipation-predominant IBS (IBS-C) may be administered osmotic laxatives, including polyethylene glycol substances; guanylate cyclase-C agonists, such as linaclotide (Linzess, Ironwood Pharmaceuticals/Allergan) and plecanatide (Trulance, Synergy Pharmaceuticals); or a chloride channel activator, such as lubiprostone (Amitiza, Takeda Pharmaceuticals America, Inc.).

Patients with diarrhea-predominant IBS (IBS-D) are treated with opioids; loperamide is the standard over-the-counter medication. Eluxadoline (Viberzi, Allergan Holdings) recently received approval from the US Food and Drug Administration (FDA), and alosetron, a 5-HT<sub>3</sub> antagonist, is an older drug that was approved for IBS-D. Importantly, both eluxadoline and alosetron are associated with warnings from the FDA regarding risks of pancreatitis, especially in patients with prior cholecystectomy or ischemic colitis, respectively.

Medications used to treat pain associated with IBS-D (ie, antidepressants and pain modulators) are centrally acting, meaning they work in the central nervous system. This analgesic approach works on the brain to try to reduce the pain arising in the gut. Of note, these medications are not approved to treat the pain of IBS and, thus, are used off-label.

Symptoms revolving around bloating and distention may be treated with diets, including the low-fermentable oligo-, di-, and monosaccharide and polyol diet, as well as antibiotics and probiotics. However, the evidence supporting the use of these approaches is relatively limited given the small clinical trials in which they have been tested, compared to the large trials that have tested the other pharmacologic agents previously mentioned.

### **G&H** Why are new therapies needed for IBS?

**MC** New therapy is needed particularly in the area of pain relief, as the medications that are currently in use target the pain's sensory mechanisms in the brain as opposed to the pain arising within the gastrointestinal tract. Antidepressants and centrally acting analgesics may affect the functions of the central nervous system, leading to changes in cognition, level of awareness, and somnolence, among other potential adverse effects. Pain modulators or analgesics that target predominantly, if not exclusively, the gastrointestinal tract (ie, visceral analgesics) rather than the central nervous system would be beneficial.

### **G&H** What therapeutic agents are in the pipeline for IBS?

**MC** At least 4 therapeutic agents are now in the pipeline for the treatment of IBS. The first is a sodium/hydrogen exchanger inhibitor (tenapanor, Ardelyx) indicated for patients with IBS-C; tenapanor works by inhibiting

sodium uptake in the colonic mucosa to alter the fluidity of content in the bowel. Another agent in the pipeline is a neurokinin-2 receptor antagonist (ibodutant, The Menarini Group) and employs a visceral analgesic approach for use in patients with IBS-D. Phase 2B trials have been completed with this medication. A third agent that is being explored presently in single-center studies in Europe is the histamine H1-receptor antagonist ebastine, which works as a visceral analgesic based on proof-of-concept studies in animals and humans. There are other nonsedating antihistaminics available as over-the-counter medications in the United States. If this agent demonstrates success, it has the potential to reduce pain sensation arising in the gastrointestinal tract without causing central side effects such as sedation. The last agent is a biomarker-therapeutic combination that includes a screening blood test (eg, serum C4 or serum FGF19) and offers a diagnostic approach to identify bile acid diarrhea among patients presenting with IBS-D. There is now fairly good evidence that 1 in 4 patients with IBS-D has abnormalities in bile acid metabolism or absorption, and screening blood tests could be used to identify patients who have an abnormality in bile acid homeostasis or synthesis. The positive diagnosis would then be combined with a bile acid sequestrant (eg, cholestyramine, colestipol, colesevelam [Welchol, Daiichi Sankyo]) or a farnesoid X receptor agonist such as obeticholic acid (Ocaliva, Intercept), a drug currently approved for the treatment of primary biliary cholangitis. This combined diagnostic and therapeutic approach will indicate the optimal treatment for the individual patient who has bile acid malabsorption rather than empirically treating all patients and hoping for the best.

#### **G&H** What do trial data show regarding the safety of these drugs and their adverse effects?

**MC** The risk of ischemic colitis in patients treated with alosetron is estimated to be about 1 in 800 patients. Through the FDA Adverse Event Reporting System, a surveillance program set up by the FDA, it appears that patients treated with eluxadoline are at risk of developing pancreatitis, although the prevalence is not completely clear. As a result, the FDA issued a warning earlier this year stating that this medication should not be used to treat patients with IBS-D who have had their gallbladder removed. However, it is possible that the medication may induce pancreatitis even in patients who still have their gallbladder in place; indeed, pancreatitis is a known adverse effect of  $\mu$ -opioid receptor agonists caused by inducing spasm of the sphincter of Oddi. In general, it is important to keep in mind that IBS typically does not result in loss of life or significant adverse consequences or morbidity. The clinical trials that have been conducted

have occasionally identified adverse effects with a frequency of only 1 in 500 or 1 in 1000 patients. Thus, there is a distinct possibility, when conducting a phase 3 trial program with 1500 to 2000 patients, that a relatively rare adverse effect may not be identified during the trial.

#### **G&H** How do these therapies compare in terms of efficacy?

**MC** From an efficacy standpoint, it is my perception that the more recently approved drugs appear to have relatively similar efficacy, especially when comparing them using the same clinical trial endpoints. For example, loperamide is very efficacious for diarrhea but has not been proven to be effective for the pain component of IBS-D. However, eluxadoline, which is efficacious for treatment of diarrhea, has not demonstrated a significant effect on pain alone, although there is an effect on the composite endpoint of pain and diarrhea in comparison to placebo. Whereas this efficacy on the composite endpoint may suggest greater benefit compared to loperamide, it is important to note that the older studies conducted with loperamide never appraised the combined endpoint, and, in fact, one trial did show benefit with loperamide on pain relief. Thus, for treating diarrhea alone, eluxadoline and loperamide appear to be similar.

Relative efficacy of drugs for chronic idiopathic constipation (rather than IBS-C) was assessed using network meta-analysis. This suggested that the approved drugs lubiprostone, linaclotide, tegaserod, bisacodyl, and sodium picosulphate and the experimental drugs prucalopride, velusetrag, and elobixibat have similar efficacy for primary endpoints, which were at least 3 complete spontaneous bowel movements (CSBMs) per week and an increase over baseline by at least 1 CSBM per week. Regarding the guanylate cyclase-C agonists or chloride channel activators for IBS-C (ie, plecanatide, linaclotide, lubiprostone), there is similar efficacy for the relief of constipation and possibly lower pain relief with lubiprostone. However, it is important to note that there are no head-to-head comparisons of these medications. Thus, treatment choice is often determined by what the patient can tolerate and the adverse effects associated with each medication. Some studies have claimed that linaclotide causes more diarrhea compared with plecanatide, but the methods for assessing this adverse effect were different in the trials with these 2 drugs, and a strict comparison cannot be made. In addition, linaclotide dose can be titrated lower if the patient experiences diarrhea because there are 3 approved doses that have a beneficial effect on the constipation. A number of patients who receive lubiprostone experience nausea, which can be a factor in determining which medicine to administer to patients with IBS-C.

### G&H What do you believe are the most exciting targets in the emerging treatment landscape?

**MC** I believe that the major unmet need is the pain component of IBS; therefore, the targets that have been most interesting to me are the neurokinin-2 receptor antagonist (ie, ibodutant) and the histamine H1-receptor antagonist (ie, ebastine), which appear to be more specific for peripheral targets of visceral pain. These emerging areas will hopefully transpire into beneficial options for treatment of patients with pain in association with IBS.

### G&H What is the role of bile acids in patients with IBS, and how do they compare to the use of biomarkers?

**MC** A systematic review of the literature—based on studies from many countries—shows that, on average, 25% to 33% of patients with IBS-D have evidence of either increased bile acid synthesis or bile acid malabsorption. In the past, patients who showed a poor response to loperamide for the management of diarrhea would be given a trial with a sequestrant for bile acids. The challenge was that bile acid sequestrants are nonspecific and have other effects that may not be related to binding bile acids; therefore, in a patient with symptomatic benefit, it was not certain whether the medicine was treating bile acid malabsorption. The availability of the screening blood tests as biomarkers for bile acid malabsorption (eg, fasting morning serum C4 or serum FGF19) could play a major role in terms of selecting patients for bile acid sequestrant therapy. There is also evidence from studies performed at the Mayo Clinic that there is a subgroup of patients with IBS-C who have a deficiency of bile acids in their colon. It is conceivable that in the future, this might be a patient population in whom clinicians could supplement bile acids in order to normalize colonic function through the action of these natural laxatives. An alternative would be an experimental medication that inhibits the ileal bile acid transporter (eg, elobixibat).

### G&H How soon will these drugs be available for clinical use?

**MC** The medications that are currently in the pipeline are at least 2 or 3 years away from being available because phase 3 trials need to be completed. However, laboratories are now offering measurement of serum C4 and other bile acid biomarkers, and bile acid binders that are approved for other indications are available.

### G&H What are the challenges impacting the development of IBS drugs?

**MC** The biggest challenge throughout the last several decades has been the difficulty in developing a proof-of-concept model for visceral pain in humans that predicts whether a drug will be efficacious in phase 2B and phase 3 clinical trials. The field currently lacks an effective, simple model whereby clinicians can test new drug entities in carefully performed studies in the laboratory to see whether the drugs have an effect on visceral pain. It is likely that this has been a deterrent to quickly screen for the efficacy of visceral analgesics, and, consequently, many drugs have come in and out of development. For example, talnetant and pexacerfont were targeting pain mechanisms through neurokinin- and corticotropin-releasing hormone receptors, and went through large phase 2B or phase 3 trials and eventually were proven not to be efficacious.

### G&H What are the priorities of research in this area?

**MC** One of the main areas needing continued focus is in the relief of visceral pain and the use of peripherally active analgesics. The development of a proof-of-concept model that can be tested in humans would also be a way to advance this field.

*Dr Camilleri conducts industry-supported research studies with alosetron, tegaserod, talnetant, pexacerfont, elobixibat, prucalopride, velusetrag, linaclotide, and lubiprostone. However, he has no personal financial conflicts.*

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