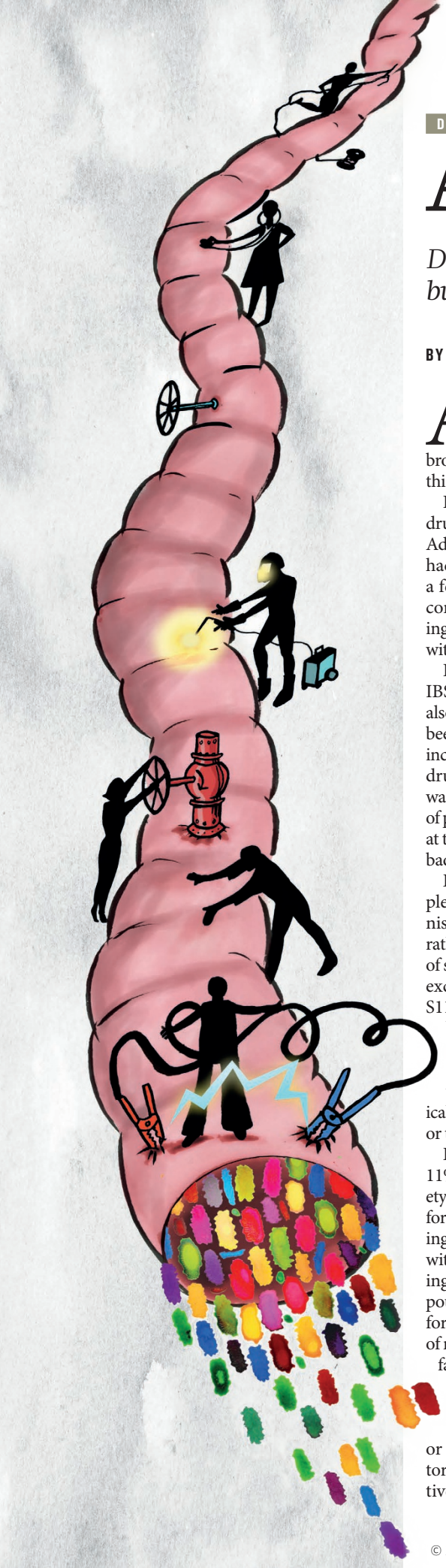


SARAH J. COLEMAN

DRUG DEVELOPMENT

A healthy pipeline

Drugs for irritable bowel syndrome have so far been limited, but a promising stream of options could soon enter the market.

BY BRANWEN MORGAN

After decades without any specific drugs for irritable bowel syndrome (IBS), the first few years of the millennium brought hope in the form of two approvals. But this new era turned out to be a false dawn.

In February 2000, alosetron became the first drug to be approved by the US Food and Drug Administration (FDA) for use in women who had IBS with diarrhoea (IBS-D). But within a few months there were reports of serious complications among people who were taking the drug and several deaths. Alosetron was withdrawn that November.

In 2002, the FDA approved tegaserod for IBS with constipation (IBS-C). But this drug also encountered problems. By 2007, it too had been withdrawn, this time over concerns of an increase in risk of cardiovascular problems. IBS drug development was not going well. "There was a general waning of enthusiasm on the part of pharma," says Alex Ford, a gastroenterologist at the University of Leeds, UK, "because of the bad experience with alosetron and tegaserod".

Enthusiasm was also dampened by an incomplete understanding of the multiple mechanisms that drive IBS. It is not one disease, but rather a condition comprised of a constellation of symptoms, and its diagnosis depends on the exclusion of other possible causes (see page S110). Localized gut problems include altered bowel function, bloating and abdominal pain, and for many people, anxiety and stress can cause these symptoms to wax and wane. It is difficult to stratify patients for clinical trials, to develop appropriate animal models or to identify genuine drug targets.

But hundreds of millions of people — around 11% of the global population (see 'Global variety') — have IBS, so there is a considerable need for treatments. And slowly the hurdles are falling. The FDA has approved three drugs for IBS within the past four years, and there is a bulging drug pipeline ahead with numerous compounds — some of which are already approved for other conditions — that target all manner of mechanisms from gut neurotransmission to faecal composition.

THE SEROTONIN STORY

Because people often have either IBS-D or IBS-C, the treatment mainstays have historically been antidiarrhoeal agents and laxatives, which can ease some of the functional issues, but do nothing to target the underlying mechanisms. In the 1970s, physicians began reporting that certain serotonin-targeting antidepressants were effective at slowing down bowel movement, even at low doses. And, as the evidence mounted, drug developers started to look to the serotonin system for ideas.

The gastrointestinal tract produces about 95% of the body's serotonin; this neurotransmitter is involved in gut motility, intestinal secretion and visceral sensitivity — all crucial elements of IBS symptoms. "Selective serotonin re-uptake inhibitors and tricyclic antidepressants have been effective in treating global IBS symptoms," says Baharak Moshiree, a gastroenterologist at the University of Miami in Florida.

There are seven main classes of serotonin receptors, some of which also have subtypes or variants, making for a complicated picture. The two classes most relevant to the gastrointestinal tract are 5-HT_3 and 5-HT_4. Alosetron is an antagonist of 5-HT_3 — it blocks the receptor's action and so slows the passage of stool through the gut. But in many ways it works too well. "Alosetron was a case of classical receptor pharmacology where you make a drug that binds to the one receptor you want to target — and it binds really tightly and really well," says neuroscientist Paul Bertrand at RMIT University in Melbourne, Australia. It binds so tightly that long-term use will block the receptor indefinitely. "This was obviously its downfall because it stayed there and many people became overly constipated," Bertrand says. Alosetron was made available again in 2002, but only for women with severe, uncontrollable IBS-D, and with tight restrictions — which were eased earlier this year.

Tegaserod is a 5-HT_4 receptor agonist — rather than blocking the receptor, the drug activates it and increases the signals sent to the circular muscles that wrap around the colon, speeding transit. Bertrand says that tegaserod was meant to be safer than alosetron because it is a partial agonist, so it doesn't elicit a full response from the receptor. "Its effect on the heart was unexpected," he says. "We now know it has some affinity to other serotonin receptors."

Serotonin receptors are found throughout the central and peripheral nervous system, and so there is a risk of adverse events from systemic exposure to serotonergic drugs.

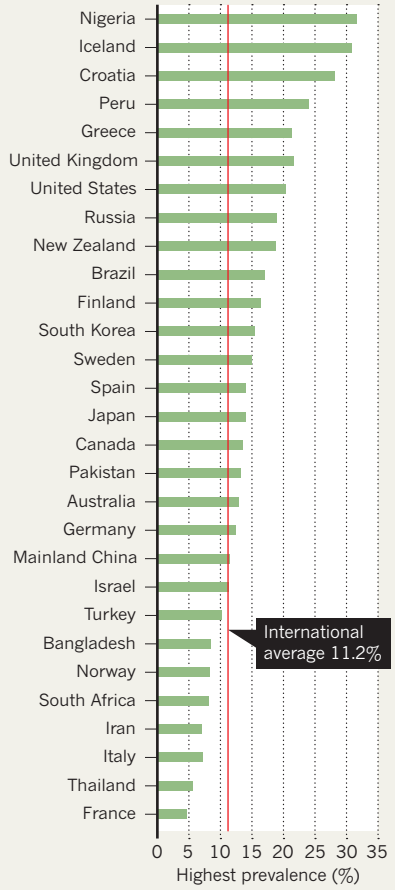
Women seem to have more of some types of serotonin receptor than men, so men may have a different clinical response. Despite the early setbacks, serotonin remains one of the most attractive targets for IBS drug development. "The overactivity or underactivity of the enteric nervous system is really the basis of IBS as far as we understand it," explains Bertrand.

The current IBS drug pipeline includes several 5-HT_4 agonists for use in patients with IBS-C, but with one crucial difference from tegaserod. "The greater specificity of the newer drugs suggest they'll be much safer," says gastroenterologist Michael Camilleri at the Mayo Clinic in Rochester, Minnesota, and president of the American Gastroenterological Association. One such agent is prucalopride, which is highly specific for the 5-HT_4 receptor and has so far not been associated with any heart issues. It was first approved in Europe in 2009 for chronic constipation in women, and extended to use in men in 2015. It is available in Canada, but it is not yet approved in the United States. Clinical trials to extend its use to IBS are ongoing.

Alternatives to alosetron are also in the pipeline. The anti-nausea drug ramosetron, which was originally approved in East Asia in the 1990s for use in people with cancer, is also a 5-HT_3 antagonist, but it is much more potent than alosetron and so can be given at lower doses. In 2008, its use in Japan was extended to men with IBS-D, and so far there have been no reports of severe side effects. Although not currently approved for women, ramosetron has been shown to also improve their IBS symptoms (S. Fukudo *et al. Gastroenterology* **150,** 358–366; 2016).

GLOBAL VARIETY

The global prevalence of irritable bowel syndrome varies hugely, which may reflect access to health care or stigma surrounding the condition. The highest estimated rates are shown, but within countries the reported rates vary dramatically.



SOURCE: C. CANAVAN *ET AL. CLIN. EPIDEMIOL.* **6,** 71–80 (2014).

VARIED TARGETS

Fundamentally, IBS involves a problem with how the bowel functions. Because of this, many drugs aim to treat symptoms by changing the local environment in the gut — mainly by modifying fluid levels to affect the speed of faecal transit. Lubiprostone, which was approved by the FDA for IBS-C in 2008, activates chloride channels to increase fluid levels. Linaclotide, which was approved in the United States in 2012, targets the enzyme guanylate cyclase, and not only stimulates the release of ions and water, but also relieves pain. Diarrhoea is a common side effect, however. Plecanatide, which is still in phase III trials for IBS-C, activates the same receptor as linaclotide, but is a weaker agonist — this should reduce the chance of rebound diarrhoea.

Around one-quarter of IBS-D cases are caused by excess bile acid, which is produced by the liver to help with the digestion of fats. Bile-acid balance can be affected by changes in the gut microbiota and by immune dysregulation, which is why anti-inflammatory drugs and antibiotics, such as rifaximin (approved in 2015), may ease IBS symptoms. Problems also occur when too much bile acid is produced, or if too little is absorbed in the small intestine. Three bile-acid modulators are in early-stage clinical trials for IBS-D — colesevelam and colestipol, which absorb bile acid (and are already approved as cholesterol-lowering agents), and obeticholic acid, which reduces production of bile acid and is set to launch later this year to treat an autoimmune liver disease. Bile-acid levels can also be increased to help with IBS-C. Elobixibat has completed phase II trials for IBS-C in Europe and the United States; it partially inhibits absorption of bile acid, allowing more to pass into the colon.

> ***"The greater specificity of the newer drugs suggest they'll be much safer."***

Opioids have long been known to affect stool composition; constipation is a recognized side effect of morphine use. The μ-opioid receptor agonist loperamide is a well-established over-the-counter medication for general diarrhoea. It works by slowing down bowel contractions, which allows the intestines more time to absorb fluid, but it can also cause constipation. Eluxadoline, the second drug approved by the FDA for IBS-D last year, also stimulates the μ-opioid receptor, but at the same time dampens activity of the δ-opioid receptor. Pamela Hornby, lead scientist on the gastrointestinal discovery team at the pharmaceutical company Janssen near Philadelphia, Pennsylvania, which developed eluxadoline, explains that this contrasting action helps to "normalize gastrointestinal transit without causing rebound constipation". Adding, "it helps with pain, too".

BETTER TOOLS

One of the reasons that these locally acting drugs are popular with drug developers is that their effects are easier to see in animals. "We have quite a good model for motility and muscle physiology," says Jakub Fichna, a biochemist at the Medical University of Łódź, Poland. The symptoms that lack robust IBS models, however, are also those that have the greatest unmet medical need. For example, pain, which may or may not be associated with a change in bowel function, is not easy to quantify — and is even harder to target at a molecular level.

In an effort to meet this need, Fichna's group has adapted a mouse model of colon sensitivity to allow the team to replicate the sensation and pattern of visceral pain associated with IBS. Fichna suspects that multiple signals are involved in these sensations, involving systems found throughout the body. "We were working mostly in opioids and cannabinoids, but now we are also looking at nociception and are slowly entering into the serotonin area," he says. "Probably all of these are involved in visceral pain." The challenge will be to establish whether it is possible to isolate the actions of each of these systems in the gastrointestinal tract and, if they can be, whether activation of particular receptors relieves or exacerbates IBS symptoms.

IBS drug development has come a long way in the past few years. With so many treatments in the pipeline, now is an exciting time to be an IBS researcher, says Ford. For clinicians like Moshiree, it is a relief to finally have more treatment options available. "Patients usually know within a few weeks if a drug is going to work," she says, "and if they don't, you need something else to put them on." A better understanding of the multitude of mechanisms behind IBS will be pivotal, particularly in relation to how diet, anxiety and stress influence symptoms. Summing up the feeling within the community, Fichna says that pharmacology is not enough when you want to combat IBS because there are so many other factors involved. "There is no single target, no single magic pill." He relishes the challenges ahead. "This is part of the adventure." ■

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