

Advances in Gastrointestinal Pharmacotherapy— Who Would Have Thought?

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When I was a pharmacy student at The Ohio State University in the early 1960s, there were very few medications available to treat gastrointestinal (GI) diseases compared with other medical conditions. In the mid-1970s, when I delivered my first therapeutics lecture at the University of Michigan College of Pharmacy on the treatment of peptic ulcer disease, the only medications available were antacids and anticholinergics, neither of which were very effective in standard recommended dosages. I recall that, in 1977, the Food and Drug Administration (FDA) approved the prototypical histamine-receptor antagonist (H_2RA) cimetidine, from which other drugs in the class were developed. In 1989, the proton pump inhibitor (PPI) revolution began with the introduction of the first PPI, omeprazole. The H_2RAs and the PPIs represent landmark advances in the pharmacologic treatment of acid-related disorders and have dramatically improved the lives of ambulatory and critically ill patients. During the 1990s, as a member of the FDA Gastrointestinal Advisory Panel, I participated in the approval of infliximab for the treatment of Crohn's disease and alosetron for the treatment of diarrhea-related irritable bowel syndrome, 2 GI disorders for which, until that time, there was a paucity of effective medications.

In the past 40 years, there has been a relatively slow but steady increase in the development of pharmacologic agents that have significantly advanced the treatment of GI diseases and improved the quality of life of affected patients. The status of several of these drugs also changed from prescription to over-the-counter (OTC). Among the most controversial switches was in the H_2RAs , first in one-half of their prescription dosages, and later in the full prescription dose. Omeprazole was initially labeled by the FDA with a black box warning that restricted its indications and use. In 2003, it became the first PPI to become available OTC, with more to come. Who would have thought that we

would see the day when a PPI would go from a black box warning to OTC status? Recently, polyethylene glycol 3350 became the first laxative in more than 30 years to be switched from prescription to OTC status.

As is the case with many prescription-to-OTC switches, the availability of these agents expands treatment options for patients, helps reduce costs for society, and provides a greater platform for pharmacists to participate in the self-care arena. Unfortunately, during that same period, cisapride, alosetron, and tegaserod were withdrawn from the US market because of their associations with significant adverse effects. Currently, the use of alosetron is restricted to patients with severe diarrhea-related irritable bowel syndrome (IBS), tegaserod is not available, and cisapride is an investigational drug. Although the cyclooxygenase-2 inhibitors reduced gastropathy caused by nonsteroidal antiinflammatory drugs (NSAIDs) and were a much anticipated and welcome alternative to the traditional NSAIDs, rofecoxib and valdecoxib are no longer available in the US because of concerns regarding cardi thrombotic events and safety in patients with underlying cardiac disease.

In the early days, with so few medications available to treat GI diseases, no group within pharmacy existed that focused on GI pharmacotherapy. It really was not until the 1980s that pharmacists actually developed an interest in GI medications. This appears to have coincided with the FDA approvals of the H_2RAs and the PPIs. It is my belief that 2 individuals were largely responsible for influencing the profession with regard to GI pharmacotherapy and the effects of the GI tract on drug therapy. John Siepler, who at the time was a clinical pharmacist in surgery at the University of Illinois, did more than any one clinical pharmacist to focus on GI pharmacotherapy. Most would consider John to be the "father" of GI clinical pharmacy, as he was the first to teach, practice, and publish in this specialty and served as an important mentor to many of us who followed in his footsteps. I also believe that John Wagner, a colleague of mine at the University of Michigan College of Pharmacy, was instrumental in enabling pharmacists to better understand the effects of the GI system on the

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bioavailability of drugs. These 2 remarkable individuals, in vastly different ways, brought about an intense interest among pharmacists in the GI system and changed the way in which we think about and practice pharmacy. Most importantly, the converging of these 2 aspects of pharmacy that focused on the GI system served as a model for applying basic pharmaceutical sciences to clinical pharmacy practice.

It has remained a little surprising to me that a medical specialty directed at the treatment of so many GI diseases (ie, acid-related, intestinal, pancreatic, biliary, liver) had so few pharmacists who specialized in their treatment. Most likely it was related to the small number of effective medications. In 2000, however, the American College of Clinical Pharmacy recognized the increasing number of pharmacists interested in this area of practice and founded the GI/Liver/Nutrition Practice-Related Network, which is the first, if not the only, group of pharmacists in the US focused specifically on GI pharmacotherapy. I have come to realize, however, that there is actually widespread interest among pharmacists in the treatment of GI diseases and that this interest crosses a number of disciplines ranging from community practice to the intensive care unit and includes other specialties such as nutrition, liver transplant, infectious diseases, internal medicine, and family practice.

One of the most important advancements in GI pharmacotherapy was the news that peptic ulcers are caused by a bacterium and could be cured with antibiotics. This notion was tantamount to heresy among gastroenterologists whose thinking, for many years, was that gastric acid caused ulcers. Although the medical community was slow to accept the findings of Barry Marshall and Robin Warren, the National Institutes of Health Consensus Development Conference concluded in 1994 that there was a strong association between *Helicobacter pylori* and peptic ulcer disease and recommended that *H. pylori*-positive ulcers be treated with antibiotics.¹ We now know that most ulcers are caused by *H. pylori* and not by stress, spicy foods, or hypersecretion of gastric acid and that recommended antibiotic eradication regimens can cure ulcers in the majority of patients.

The success of eradicating *H. pylori* and healing peptic ulcers has been accompanied by other important advances in the treatment of acid-related disorders, including the dramatic decrease in NSAID-associated gastropathy and improvement in the treatment of gastroesophageal reflux disease (GERD). The advent of the PPI class of drugs revolutionized the treatment of these diseases and is reflected in the reduction of NSAID-related upper GI complications and hospitalizations and the fact that most patients with GERD are able to manage reflux symptoms with continued PPI therapy rather than undergoing surgery. Who would have thought that we would be recommending antibiotics to heal a peptic ulcer, using PPIs to reduce the risk

of NSAID-related ulcers, and managing reflux symptoms with once-daily regimens?

The treatment of other GI diseases has also changed over the past 40 years as a result of pharmacologic and technologic advances; however, a number of challenges and unmet needs remain. The medical treatment of the global symptoms associated with diarrhea- and constipation-related IBS with alosetron or tegaserod, respectively, constituted an important advance in management of this troublesome disorder. Now, with the restricted use of alosetron and the withdrawal of tegaserod, each symptom must be treated separately as in the past and, in many cases, with unproven medications. Who would have thought that the treatment of IBS would have been set back in this way after more effective medications had become available?

There is no known medical cure for ulcerative colitis or Crohn's disease. The current standard of care for mild-to-moderate disease is the use of drugs that deliver 5-aminosalicylic acid to the ileal and colonic mucosa. Technologic advances over the years have led to the development of novel drug delivery systems that protect orally administered 5-aminosalicylic acid from absorption and include the use of prodrugs, delayed-release formulations, controlled-release formulations, and most recently, formulations that combine both delayed-release and sustained-release technology. Immunosuppressive treatment is the mainstay of severe ulcerative colitis and Crohn's disease. The knowledge that the metabolism of azothoprine and mercaptopurine is mediated by specific enzymes whose biologic activity is genetically determined has led to the monitoring of thiopurine *S*-methyltransferase in an attempt to avoid toxicity or explain inefficacy. The chimeric antitumor necrosis factor, infliximab, has changed the treatment paradigm of severe ulcerative colitis and Crohn's disease, but unmet needs remain, including the secondary loss of response to infliximab, long-term fistula healing in Crohn's disease, and the induction and maintenance of remission in refractory inflammatory bowel disease (IBD). Alternatively, newer biologic agents such as adalimumab and natalizumab have yielded promising results in clinical trials. Effective medical management of IBD will most likely require greater emphasis on individualizing therapy with a combination of drugs.

Recent progress has been made in the pharmacologic management of chronic hepatitis B and C in patients at risk of developing cirrhosis and hepatocellular cancer. Antiviral treatment offers the only way to interrupt the progression of the disease. Recombinant interferon alfa, lamivudine, and adefovir dipivoxil are available for treating chronic hepatitis B, while recombinant or pegylated interferons in combination with ribavirin are the only medications available for chronic hepatitis C infection. Although these medications have had an important impact on the treatment of chronic viral hepatitis, they are not without limitations.

Advances in the pharmacology and therapeutics of GI diseases also include the development of drugs such as octreotide, which improves the capacity to control active variceal bleeding in cirrhosis; the prokinetic agent metoclopramide; lubiprostone, a locally acting chloride channel activator that enhances intestinal fluid secretion and is indicated for the treatment of chronic idiopathic constipation in adults; and rifaximin, a nonsystemic antibiotic that is FDA-approved for the treatment of traveler's diarrhea caused by noninvasive enterotoxigenic *Escherichia coli*, but looks promising for the treatment of other causes of diarrhea, including that associated with *Clostridium difficile* colitis.

Despite the progress in GI pharmacotherapy over the past 40 years, the medical treatment of GI diseases is characterized by a number of challenges and unmet needs. The pharmacologic struggle continues to identify drugs with marked clinical efficacy to treat functional disorders such as nonulcer dyspepsia and IBS. The search is ongoing for agents that will directly inhibit intestinal secretory mechanisms in patients with acute high-volume watery diarrhea. The need is great for more effective and safer prokinetic agents that are not associated with tachyphylaxis to treat gastroparesis. The necessity to develop drug therapies that will restore or more effectively interfere with inflammatory pathways in patients with acute pancreatitis, chronic viral hepatitis, and IBD, and the ability to reverse fibrosis in cirrhosis rank among the most important challenges in GI pharmacotherapy.

Future therapeutic options for GI diseases will focus on improved treatment strategies as well as the development of new drugs. These include optimal regimens for eradicating *H. pylori* using drugs that rarely promote resistance and sequential regimens that reduce preexisting resistant

organisms, novel PPIs and PPI formulations with a quicker onset and longer duration of antisecretory action, and the optimal prevention and treatment of NSAID-related gastropathy and nonvariceal upper GI bleeding. In addition, more effective drugs to treat functional GI disorders, IBD, chronic viral hepatitis, pancreatitis, and gastroparesis will become available. Exploration of the underlying mechanisms of hepatic fibrosis will lead to antifibrotic therapy. Exciting pharmacologic approaches to treating and preventing GI diseases will incorporate new knowledge of pharmacogenomics and the use of nonpathogenic microorganisms, including those that are genetically modified. Although important advances in GI pharmacotherapy were introduced into clinical practice during the past 4 decades, ongoing research will provide the clinician with more effective and safer drugs to medically treat and possibly cure many GI diseases. Pharmacists will continue to expand their roles and responsibilities as integral members of the medical team. Who would have thought?

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Reference

1. NIH Consensus Conference. *Helicobacter pylori* in peptic ulcer disease. NIH Consensus Development Panel on *Helicobacter pylori* in peptic ulcer disease. JAMA 1994;272:65-9.