AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 11: Peptic Ulcer Disease and Dyspepsia

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290-2010-00006-C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the National Academy of Medicine (formerly the Institute of Medicine) and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 21,000 leads about potential topics has resulted in identification and tracking of about 2,250 topics across the 14 AHRQ priority areas and 1 cross-cutting area; more than 600 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated semi-annually. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 170 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the five to eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts' rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of "lower," "moderate," or "higher" within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ's Effective Health Care Web site.

Results

The table below lists the three topics for which (1) preliminary phase III data for drugs were available; (2) information was compiled and sent for expert comment before May 8, 2015, in this priority area; and (3) we received five to seven sets of comments from experts between July 1, 2014, and May 18, 2015. (Nine topics in this priority area were being tracked in the system as of May 8, 2015.) We present one summary on one topic (indicated below by an asterisk) that emerged as having potential for high impact on the basis of experts' comments.

Priority Area 11: Peptic Ulcer Disease and Dyspepsia

Topic	High-Impact Potential
1. Eluxadoline (Viberzi) for treatment of diarrhea-predominant irritable bowel syndrome	No high-impact potential at this time; archived in horizon scanning system on basis of experts' comments
2. * Rifaximin (Xifaxan) for treatment of diarrhea-predominant irritable bowel syndrome	Lower end of the high-impact-potential range
3. Vedolizumab (Entyvio) for treatment of moderate to severe ulcerative colitis and Crohn's disease	No high-impact potential at this time; archived in horizon scanning system on basis of experts' comments

Discussion

Compared with other priority areas, we have identified relatively few leads and topics that meet inclusion criteria for new developments related to peptic ulcer and intestinal tract diseases in the horizon scanning system, despite extensive searches. Most research activity in this field focuses on drugs and biologics for irritable bowel syndrome and inflammatory bowel diseases (e.g., Crohn's disease, ulcerative colitis), and we continue tracking novel drugs and interventions such as fecal microbiota therapy for irritable bowel disease that are in clinical trials but have not yet reported phase III data.

Prior Potential High Impact Topic Archived

- **Teduglutide (Gattex) for treatment of short bowel syndrome:** In the December 2014 Potential High-Impact Interventions report (and earlier reports), commenters were generally optimistic that this intervention had potential to improve patient health outcomes by

reducing the frequency of and dependence on parenteral nutrition in patients with severe short bowel syndrome. Some commenters surmised that the drug's high cost, over time, could reduce or eliminate any potential savings from reducing the dependence on parenteral nutrition. In December 2012, the U.S. Food and Drug Administration (FDA) approved teduglutide for treating adults with short bowel syndrome who require additional nutrition from parenteral nutrition. This intervention has been diffusing for more than 2 years and, therefore, no longer meets criteria for tracking and was archived in January 2015 in the horizon scanning system.

Eligible Topics Deemed Not High-Impact

- **Eluxadoline (Viberzi) for treatment of diarrhea-predominant irritable bowel syndrome:** Eluxadoline is an orally administered compound that reportedly reduces gastrointestinal motility while decreasing pain and constipation through mixed opioid receptor activity as an agonist to the mu and kappa receptors and an antagonist to the delta receptor. In May 2015, FDA approved eluxadoline under the tradename Viberzi™ for treating diarrhea-predominant irritable bowel syndrome in adults. FDA has recommended classifying eluxadoline as a controlled substance, thus prompting final scheduling designation from the U.S. Drug Enforcement Administration. According to FDA, eluxadoline may increase the risk of pancreatitis caused by spasms in the common bile and pancreatic ducts. Thus, FDA advises that the drug should be avoided in patients with a history of bile duct obstruction, pancreatitis, severe liver impairment, or severe constipation, and in patients who drink more than three alcoholic beverages per day. Experts commenting on this topic thought available data suggested the drug provided symptomatic relief in only a small proportion of patients and provided little more than a modest benefit compared with placebo in patients who responded to treatment. Several experts also noted that the estimated cost of about $3,000 per year, combined with the modest potential benefit, would likely limit use of eluxadoline, thus reducing its potential to fulfill an unmet need for more effective treatments for irritable bowel syndrome. Based on experts' comments, this topic was archived in May 2015 in the horizon scanning system.
- **Vedolizumab (Entyvio) for treatment of moderate to severe ulcerative colitis and Crohn's disease:** Vedolizumab is an intravenously infused humanized monoclonal antibody that inhibits the integrin receptor with the goal of reducing gastrointestinal inflammation. Vedolizumab is thought to have greater target specificity than other monoclonal antibodies, thereby lowering the risk of systemic immunosuppression that can occur with other monoclonal antibodies. FDA approved vedolizumab in May 2014 for treating adults with moderately to severely active ulcerative colitis and Crohn's disease who have not achieved adequate response to treatment with one or more standard therapies, including corticosteroids, immunomodulators, or tumor necrosis factor inhibitors. FDA required the manufacturer to conduct a postmarketing study to evaluate vedolizumab's risk of causing progressive multifocal leukoencephalopathy (PML), a rare but often fatal viral infection of the central nervous system. Although no PML was reported in vedolizumab trials, use of another integrin receptor antagonist, natalizumab, has been linked to increased PML risk. Experts commenting on this intervention noted the modest remission rates for vedolizumab compared with placebo, as reported in clinical trials. Some experts also cited adverse event rates up to 24% reported in some vedolizumab trials and the unknown risk of PML outside of well-controlled clinical trial populations as limiting the drug's potential to fulfill an unmet need for more efficacious treatments for ulcerative colitis and Crohn's disease. Several

experts expected that the modest demonstrated efficacy and requirement for repeated IV infusions would likely continue to limit vedolizumab's role to a second- or third-line therapy, used after other treatments have been attempted. Based on experts' comments, this topic was archived in May 2015 in the horizon scanning system.

Topic Deemed High-Impact

We present one intervention that experts who commented thought has potential for high impact: rifaximin, an antibiotic that acts in the gut, for treating diarrhea-predominant irritable bowel syndrome.

Rifaximin (Xifaxan) for Treatment of Diarrhea-Predominant Irritable Bowel Syndrome

- **Key Facts:** Some researchers have hypothesized that the development of irritable bowel syndrome (IBS) symptoms, such as increased gas production, diarrhea, and weight loss, could be related to the microbiotic environment and bacterial overgrowth in the small intestine. Rifaximin is a nonsystemic, oral antibiotic derived from the antibiotic rifamycin that acts locally in the gut, and it has been previously approved by FDA for treating travelers' diarrhea caused by *E. coli* in adults and children who are at least 12 years old and for treating hepatic encephalopathy in adults with liver failure. The drug was subsequently studied for its potential to reduce IBS symptoms, such as diarrhea. In May 2015, FDA approved rifaximin (Xifaxan®) 550 mg tablets for treating IBS with diarrhea in adults. For this indication, rifaximin's FDA-approved, labeling recommends one 550 mg tablet, taken 3 times per day, for 14 days. According to labeling, patients who experience IBS recurrence can repeat the same treatment regimen up to two more times.

  In 2014, the manufacturer reported results from its TARGET-3 study of 2,579 patients who received rifaximin to treat diarrhea-predominant IBS. After the initial 2-week rifaximin regimen, 42% of patients (1,074 of 2,579) were deemed treatment responders, defined as having reductions of at least 30% in pain and at least 50% in number of days experiencing loose or watery stools (the primary endpoint). Among initial treatment responders, 36% did not have recurrent diarrhea-predominant IBS symptoms. However, 64% (692 of 1,074) of initial responders had recurrent IBS symptoms. Investigators randomly assigned 636 initial responders with recurrent IBS to receive a repeat course of rifaximin or placebo. Repeat treatment achieved the primary endpoint in 33% of the rifaximin group and 25% of the placebo group ($p=0.02$). Adverse events rates were similar between groups.

  Pricing for rifaximin is reported on the online pharmacy-pricing aggregator GoodRx at about $1,270 to $1,300 for 42 tablets at a dosage of 550 mg each, which is enough for a recommended treatment course over 14 days. The drug is already widely available on third-party payer formularies, having been approved more than 5 years ago for other indications.
- **Key Expert Comments:** Experts generally thought that most physicians and patients would welcome the availability of a new oral drug to treat IBS, although some clinicians might be concerned about the potential for overprescribing antibiotics and an increase in microbial resistance. Although the drug may not provide effective relief of IBS in a large share of patients, it appears safe and effective for those patients in whom it is effective. Most experts thought that the generally limited effectiveness of current IBS treatments created an unmet need for new therapeutic options for patients with IBS. Some experts though the drug might reduce some disparities because it is indicated in use in men and women, unlike alosetron, which is approved to treat diarrhea-predominant IBS only in women.

- **High-Impact Potential:** Lower end of the high-impact-potential range

Peptic Ulcer Disease and Dyspepsia Intervention

Rifaximin (Xifaxan) for Treatment of Diarrhea-Predominant Irritable Bowel Syndrome

Unmet need: Approximately 5% to 7% of U.S. adults have received a diagnosis of irritable bowel syndrome (IBS); however, some studies have estimated that up to one in five adults may be affected by the condition.[1] As many as 40% of these patients experience diarrhea-predominant IBS, characterized by symptoms including abdominal pain; loose, watery stools; and urgency.[2] No cure exists for IBS. Treatments are aimed at symptomatic relief, but questions of safety and efficacy remain. Only one medication, alosetron, has been approved by the U.S. Food and Drug Administration (FDA) for treating diarrhea-predominant IBS. However, alosetron has a labeled indication for use only in women. Further, alosetron is available only from physicians participating in a special manufacturer prescribing program and is associated with rare but serious side effects, including ischemic colitis and serious complications of constipation (mechanical or neuromuscular obstruction, impaction, toxic megacolon, secondary bowel ischemia, and perforation), that have resulted in hospitalization and, rarely, blood transfusion, surgery, and death.[3]

Intervention: Rifaximin is a nonsystemic, oral antibiotic that acts locally in the gut.[4] Researchers have hypothesized a relationship between gut microbiota and symptom development in patients with IBS. Bacterial overgrowth in the small intestine may lead to increased gas production, diarrhea, and weight loss.[1,5] Rifaximin is a semi-synthetic antibacterial agent derived from the antibiotic rifamycin SV, which purportedly inhibits bacterial RNA synthesis by binding to the beta subunit of bacterial DNA-dependent RNA polymerase. Rifaximin's antibacterial activity has the potential to reduce IBS symptoms, such as diarrhea.[4] When rifaximin is ingested, most of the antibiotic passes through the stomach and intestines and does not enter the bloodstream, thus limiting systemic antibiotic-associated side effects.[5] For treating IBS, rifaximin's labeled, recommended dosage is one 550 mg tablet, taken 3 times per day, for 14 days. Patients who experience IBS recurrence can repeat the same treatment regimen up to two more times.[6]

Clinical trials: In October 2014, Salix reported treatment-response results from its TARGET-3 study of 2,579 patients who received rifaximin to treat diarrhea-predominant IBS. After the initial two-week rifaximin regimen, 42% of patients (1,074 of 2,579) were deemed treatment responders, defined as having reductions of at least 30% in pain and at least 50% in number of days experiencing loose or watery stools (the primary endpoint). Among initial treatment responders, 36% did not have recurrent diarrhea-predominant IBS symptoms; however, the remainder (64% [692 of 1,074]) of initial responders had relapsed disease at up to 18 weeks of followup. Investigators randomly assigned 636 initial responders with recurrent IBS to receive a repeat course of rifaximin or placebo. Repeat treatment achieved the primary endpoint in 33% of the rifaximin group and 25% of the placebo group ($p=0.02$). An additional repeat course of rifaximin or placebo achieved the primary endpoint in 37% of the rifaximin group and 29% of the placebo group ($p=0.04$). Adverse events rates were similar, with adverse events reported in 43% of rifaximin patients and 46% of placebo patients.[5]

In January 2011, Pimentel and colleagues reported treatment response in a combined 1,260 patients in the TARGET 1 and TARGET 2 trials, who were randomly assigned to receive rifaximin or placebo for diarrhea-predominant IBS. During the first 4 weeks after treatment, 40.8% of the rifaximin group and 31.2% of the placebo group in TARGET 1 had adequate symptom relief ($p=0.01$). In the TARGET 2 study, 40.6% of rifaximin patients and 32.2% of placebo patients had adequate symptom relief ($p=0.03$). The combined rate of responders in the two trials was 40.7% in the rifaximin group and 31.7% in the placebo group ($p<0.001$). Similarly, adequate bloating relief was significantly higher in the rifaximin group than in the placebo group (39.5% vs. 28.7%,

p=0.005, in TARGET 1; 41.0% vs. 31.9%, p=0.02, in TARGET 2; 40.2% vs. 30.3%, p<0.001, in the combined studies). The incidence of adverse events was similar in the two groups.[7]

Manufacturer and regulatory status: Salix Pharmaceuticals, Inc. (Morrisville, NC), a subsidiary of Valeant Pharmaceuticals International, Inc. (Laval, Quebec, Canada), developed rifaximin for treating diarrhea-predominant IBS. Rifaximin had been previously approved by FDA for treating travelers' diarrhea caused by *E. coli* in adults and children who are at least 12 years old and for treating hepatic encephalopathy in adults with liver failure.

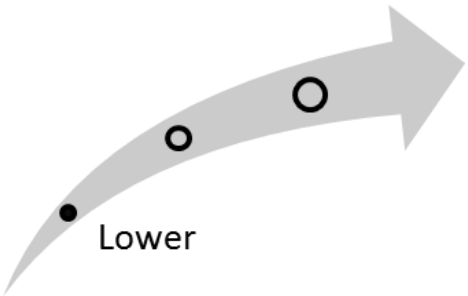
In May 2015, FDA approved rifaximin 550 mg tablets with the trade name Xifaxan® under a supplemental new drug application for treating IBS with diarrhea in adults.[2,8] Per approved labeling, rifaximin dosage for treating IBS is 550 mg, three times per day, for 14 days. In patients with recurrent IBS with diarrhea, a course of rifaximin can be repeated up to twice at the same dosage.[6] In May 2004, FDA approved rifaximin tablets for treating traveler's diarrhea in adults and children aged 12 years or older, at a dosage of 200 mg, 3 times per day, for 3 days. The drug is also FDA-approved to reduce the "risk of overt hepatic encephalopathy recurrence in adults" at a dosage of 550 mg tablets twice per day.[6]

Diffusion: As of June 2015, the manufacturer had not released sales projections for rifaximin for treating IBS, given the recent FDA approval in late May 2015. Rifaximin 550 mg tablets have been commercially available in the United States since March 2010, indicated for reducing the risk of overt hepatic encephalopathy recurrence in adults. According to GoodRx, a U.S.-based, online aggregator of prescription-drug prices, rifaximin's retail price for 42 pills (i.e., 550 mg taken 3 times per day for 14 days) is about $1,200 to $1,300.[9] The drug is widely available on third-party payer formularies, having been approved more than 5 years ago for the other indications.

Clinical Pathway at Point of This Intervention

Treatment for IBS focuses on responding to symptoms through changes in diet and lifestyle, improvement of gastrointestinal health (e.g., using laxatives or antidiarrheals as appropriate), and use of stress-relief techniques and psychotherapy.[1,10-13] Before rifaximin's May 2015 approval, only one drug, alosetron, had an FDA-approved, labeled indication for treating diarrhea-predominant IBS, and it is approved for use only in women. Rifaximin will be used as a primary pharmacotherapy for patients with diarrhea-predominant IBS who have not obtained adequate relief from conservative measures, such as diet and stress relief techniques.

Figure 1. Overall high-impact potential: rifaximin (Xifaxan) for treatment of diarrhea-predominant irritable bowel syndrome



Most experts who commented on this intervention noted the need for more effective treatments for diarrhea-predominant IBS, with clinical reviewers rating the unmet need as higher than other reviewers. Experts noted that although the treatment may not provide adequate relief in about half of patients who initially try it, patients who do respond generally appear to do well, and up to two repeat treatments may ultimately provide relief. Several experts thought many clinicians and

patients would welcome another drug approved to treat IBS, given the limited availability of other drugs with labeled indications for treating diarrhea-predominant IBS. Some experts believe that concerns about overuse of antibiotics might limit the use of the drug. However, other experts thought the availability of a new IBS therapy with a seemingly good safety profile would be appealing to many clinicians and their patients. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered comments on this intervention.[14-19] We have organized the following discussion of expert comments by the parameters on which they commented. The experts made their comments before rifaximin's May 2015 approval as an IBS treatment.

Unmet need and health outcomes: Five experts with clinical and research backgrounds rated the unmet need for effective new IBS treatments as moderate to high,[14-17,19] with clinical experts rating the unmet need highest.[14,17] One clinical expert noted, "Irritable bowel syndrome is a chronic condition that accounts for millions of health care visits and millions in dollars in health care costs annually. Symptoms can be quite burdensome to patients and thus as a result of very limited therapeutic options, alternative therapies are needed. An effective therapy has the potential to improve the associated morbidity of irritable bowel syndrome and improve the quality of life of patients."[17] A health systems expert countered, "Ultimately, irritable bowel syndrome affects a small number of individuals in the United States. While there is only said to be one medication approved by the FDA to treat irritable bowel syndrome with diarrhea, it appears as though there are multiple off-label treatment methods used to treat patients with this disorder. For this reason, treating irritable bowel syndrome appears to only have minimal importance."[18]

Experts were divided on rifaximin's potential to improve health outcomes and fulfill the unmet need for effective new treatments for diarrhea-predominant IBS. One health systems expert noted: "In general, it appears as though Xifaxan has the potential to effectively treat irritable bowel syndrome, according to the clinical studies. However, the variety of other off label options creates a competition for use. Overall, there is only a minimal potential for Xifaxan to fulfill the unmet need."[18] However, one clinical expert stated, "This is a relatively unappreciated and unused modality in family practice, internal medicine, and gastroenterology practices. It has the potential to improve the lifestyle of millions of patients (e.g., not being tethered to a bathroom, able to work, etc.). Expanded use of this intervention would have a huge impact on quality of life and productivity."[14] This clinical expert added, "The majority of patients with irritable bowel syndrome are not satisfied with their treatment efficacy. This intervention would reduce the percentage of those patients…. It does not work in everyone, but when it does work, it is impressive."[14] One research expert presented a middle ground, stating, "The treatment sounds promising, but there are still questions about how frequently a patient would need to be treated for this disabling condition. Since current treatments can be associated with significant adverse effects and rifaximin does not seem to have this concern, it could meet an unmet need."[15]

Acceptance and adoption: Most experts anticipated good acceptance for rifaximin from both physicians and patients with IBS.[14-17,19] One clinical expert noted, "Doctors would love it - an oral pill to treat irritable bowel syndrome that works with minimal or no side effects. Perfect," and that "Patients would love it - an oral pill to treat irritable bowel syndrome that works with minimal or no side effects. Almost perfect - it is not a one-shot cure. THAT would be perfect."[14] However, one health systems expert thought that "It appears as though Xifaxan has the potential to effectively improve the condition of a patient with irritable bowel syndrome. However, there are multiple other

treatment options, even if many of them are considered off label. For this reason, it is likely that clinicians will minimally accept the use of Xifaxan to treat irritable bowel syndrome."[18] One clinical expert who expected good physician acceptance also observed that some "clinicians may be apprehensive about utilizing antibiotics at increasing rates due to concerns about antibiotic resistance."[17]

Health care delivery infrastructure and patient management: Most experts believe that the availability of rifaximin as an oral drug to treat IBS would likely cause little disruption to health care infrastructure or the way physicians manage patients with IBS.[15-19] However, one clinical expert thought that rifaximin might disrupt both health care infrastructure and patient management. The clinical expert stated, "The disruption would be a good one. Fewer office visits for irritable bowel syndrome symptoms and exacerbations would be needed. There would be fewer referrals from primary care offices to specialists. There would be fewer hospitalizations."[14] This clinical expert stated that for patient management, "the disruption would be moderate, depending on the number of irritable bowel syndrome patients in the practice and the efficacy of the intervention. For example, in practices with 20% irritable bowel syndrome prevalence (not uncommon), if 30% of patients are improved on rifaximin, then that could be an effect on 6% of the practice's patient population. That is not an insignificant number."[14]

Health disparities: Two experts thought rifaximin might help alleviate gender-based disparities, since the only other FDA-approved drug for treating diarrhea-predominant IBS, alosetron, is indicated only for use in women.[17,19] One clinical expert noted, "IBS tends to impact women more than men. Given this gender disparity, this therapy has the potential to diminish gender-specific disparities in this chronic condition."[17] Other experts doubted whether the drug would substantially impact health disparities, although the potential to increase disparities exists if patients face barriers to insurance coverage for rifaximin. One clinical expert noted, "This is an expensive medication if not covered by the patient's formulary - if they have insurance at all. Since they would not have the benefit of the medication, they would be sicker and more prone to losing days at work and in caring for their families. Disability due to irritable bowel syndrome is not the norm, but it does occur in some cases. The lack of access to this intervention would make disability more likely, again in lower socioeconomic status groups."[14]

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