

# Rifaximin (Xifaxan)

Drug Regimen Review Center  
University of Utah College of Pharmacy

Joanita Lake B.Pharm, MSc (Oxon), RPh.

Scott Nelson Pharm.D. student

Gary M. Oderda, Pharm D, M.P.H

Carin S. Steinvoort, Pharm D

Bryan S. Larson, Pharm D, BCPS

May 2013

## Contents

Introduction.....	3
A. Hepatic encephalopathy (HE).....	4
Treatment of hepatic encephalopathy .....	4
<i>Guidelines</i> .....	6
B. Travelers’ Diarrhea (TD).....	7
Treatment of TD.....	7
<i>Guidelines</i> .....	7
C. Clostridium difficile Infection (CDI).....	11
Treatment of CDI.....	11
<i>Guidelines</i> .....	11
D. Irritable Bowel Syndrome (IBS).....	13
Treatment of Irritable Bowel Syndrome .....	13
<i>Guidelines</i> .....	13
Supplemental New Drug Application: Non-constipation IBS.....	16
Clinical Efficacy – Systematic review(s) .....	16
Safety and adverse effects .....	16
Pipeline products for HE .....	17
Utah Medicaid Utilization Data .....	18
Conclusion .....	20
Appendix 1 –Summary of reviews.....	21
References.....	24

## Introduction

Rifaximin (Xifaxan) is an enteric, non-systemically absorbed rifamycin that is only available as an oral preparation. Rifaximin is indicated for the treatment of travelers' diarrhea caused by noninvasive strains of *Escherichia coli* (in adults and adolescents  $\geq 12$  years of age); and adjunctive treatment of hepatic encephalopathy (reduction of risk of overt hepatic encephalopathy recurrence in patients  $\geq 18$  years of age).<sup>1</sup> Rifaximin received orphan drug status from the U.S. Food and Drug Administration in 1998 for hepatic encephalopathy.<sup>2</sup> However, it appears that rifaximin is being increasingly used off-label for indications such as Clostridium difficile infections (CDIs), prevention of travelers' diarrhea, Crohn's disease, recurrent acute diverticulitis (with mesalamine), and irritable bowel syndrome.

Rifaximin is a very expensive antibiotic that acts by inhibiting bacterial RNA synthesis in susceptible bacteria by binding to the  $\beta$  subunit of bacterial DNA-dependent RNA polymerase.<sup>2,3</sup> It is not suitable for treating systemic infections because it is not systemically absorbed and the drug remains in the gastrointestinal tract.

The mechanism of action of rifaximin in the treatment of travelers' diarrhea and bacterial overgrowth is local antibiotic activity. In hepatic encephalopathy, rifaximin decreases bacterial production of ammonia in the gut. Enterocyte metabolism of glutamine and colonic bacterial catabolism of nitrogenous sources (such as protein digestion and urea secretion) results in ammonia production in the gastrointestinal tract. When the ammonia is not removed (as in the case of liver impairment), excess ammonia accumulates, and ultimately crosses into the brain via the blood stream and causes neurotoxicity. Non-absorbable, broad spectrum antibiotics (like rifaximin) decrease bacterial digestive activity and thereby decrease the production of ammonia.

According to the Salix Drug Information Call Center, the earliest patent expiry date for the 200 mg and 550 mg tablets is 2024.<sup>4-6</sup>

## A. Hepatic encephalopathy (HE)

Hepatic encephalopathy is observed in patients with advanced liver disease and it is a serious and progressive complication. It is a neuropsychiatric syndrome caused by the body's inability to remove gut-derived toxins (particularly ammonia) from the blood stream. The accumulation of neurotoxins in the blood that then pass through the blood brain barrier cause deleterious brain signs and symptoms such as personality changes, intellectual impairment, reduced level of consciousness and altered neuromuscular activity.<sup>7</sup>

HE can be classified by causes:

- Type A - acute liver failure
- Type B - the presence of a portosystemic 'shunt' which allows blood to bypass the liver, without intrinsic liver disease
- Type C - cirrhosis of the liver. Approximately 70% of people with cirrhosis present with subclinical or mild hepatic encephalopathy and 23-40% progress to a more severe form of the disease.

Hepatic encephalopathy can be classified as 'overt' or 'minimal'. Overt HE episodes can be episodic (also called 'acute') or persistent (also called 'chronic').<sup>8</sup> These episodes are debilitating and can present without warning. It frequently results in hospitalization, and can result in coma and even death.<sup>7</sup> Patients with minimal hepatic encephalopathy may appear to have normal mental and neurological status, but specific psychometric tests have abnormal results.<sup>8</sup>

HE can also be classified by severity through the Conn score/West Haven classification:

Grade 0: No personality or behavioral abnormality detected.

Grade 1: lack of awareness, euphoria or anxiety, shortened attention span, impaired performance of addition.

Grade 2: lethargy or apathy, minimal disorientation for time or place, subtle personality change, inappropriate behavior, impaired performance of subtraction

Grade 3: somnolence to semi stupor but responsive to verbal stimuli, confusion, gross disorientation

Grade 4: coma (unresponsive to verbal or noxious stimuli)

It has been estimated that there are up to one million patients with cirrhosis in the United States, and approximately 150,000 hospitalizations occur annually due to complications of encephalopathy. It has a significant impact on the healthcare system, costing approximately \$7 billion every year.<sup>9</sup> The NICE final scope document (Rifaximin for maintaining remission from episodes of hepatic encephalopathy) states that the one and three year survival rates after experiencing an episode of hepatic encephalopathy are 42% and 23% respectively.<sup>8</sup>

### Treatment of hepatic encephalopathy

There are two components to treatment of hepatic encephalopathy; managing acute episodes, and maintenance treatment in order to reduce the recurrence of episodes. Treatment acts by reducing the production and absorption of ammonia in the gut, and include lactulose (a disaccharide to convert soluble ammonia to insoluble ammonium) which can be combined with antibiotics such as neomycin (to inhibit ammonia-generating bacteria).<sup>8</sup> Long-term antibiotics for preventing recurrence are not recommended due to the associated toxicities. Neomycin is associated with increased risk of nephrotoxicity and ototoxicity.<sup>7</sup> Treatment options for preventing recurrence include lactulose and rifaximin. Lactulose is associated with side effects such as diarrhea, which can lead to worsening of HE symptoms.<sup>10</sup> However, in the trials of rifaximin for HE, it was not possible to assess the differences in treatment of those patients not using lactulose concomitantly as 91% of patients were also using lactulose.<sup>11</sup> According to two trials (performed outside the US) rifaximin 400 mg three times daily is as effective as lactitol or lactulose, but a recent systematic review showed that rifaximin is not superior to non-absorbable disaccharides in the treatment of episodic or persistent HE, but it may be better tolerated.<sup>12-14</sup> Efficacy of rifaximin for prevention of encephalopathy has not been established in patients with a Model for End-Stage Liver Disease (MELD) score >25.<sup>11</sup>

**Table 1. HE treatment options – preparations and dosages<sup>2,15-18</sup>**

Drug	Generic	Dosage Form(s)	Usual Dose from Product Labeling	Maximal Recommended Dose per Product Labeling
<b>Drug class</b>				
Rifaximin (Xifaxan)	No	<b>Oral tablet:</b> 200 mg 550 mg	Reduction of hepatic encephalopathy <u>recurrence</u> Oral: 550 mg 2 times/day (with or without food) Note: Supporting clinical trial evaluated efficacy over 6-month treatment period.  <u>Treatment</u> of hepatic encephalopathy ( <u>unlabeled</u> ) Oral: 600–1200 mg daily (usually in 3 divided doses) for 7–21 days	1200 mg/day
<b>Hepatic encephalopathy alternative</b>				
Lactulose (Generlac, Kristalose)	Yes	<b>Oral solution:</b> 10 g/15 mL  <b>Crystals for solution:</b> 10 g/packet	Prevention of portal systemic encephalopathy: Oral: 20-30 g (30-45 mL) 3-4 times/day; adjust dose every 1-2 days to produce 2-3 soft stools/day  Treatment of acute hepatic encephalopathy: Oral: 20-30 g (30-45 mL) every 1 hour to induce rapid laxation; reduce to 20-30 g (30-45 mL) 3-4 times/day after laxation is achieved titrate to produce 2-3 soft stools/day  Rectal administration (retention enema): 200 g (300 mL) diluted with 700 mL of water or NS via rectal balloon catheter; retain for 30-60 minutes; may repeat every 4-6 hours; transition to oral treatment prior to discontinuing rectal administration	Not established
Metronidazole (Flagyl)	Yes	<b>Oral tablet:</b> 250 mg 500 mg	Hepatic encephalopathy: Oral: 200 mg 4 times/day (may be associated with peripheral neuropathy)	2000 mg/day
Neomycin	Yes	<b>Oral tablet:</b> 500 mg	Hepatic encephalopathy: Oral: 500-2000 mg every 6-8 hours or 4000-12000 mg/day divided every 4-6 hours for 5-6 days  Note: long-term use has been associated with nephrotoxicity and ototoxicity	12000 mg/day

## Guidelines

Lactulose is the treatment of choice for hepatic encephalopathy in the 2001 treatment guidelines from the American College of Gastroenterology<sup>19</sup>, given its established safety and effectiveness. Rifaximin was not included in these guidelines since it was not released until 2004 (for travelers' diarrhea). FDA approval for hepatic encephalopathy was not received until 2010. Since the release of the 2001 ACG guidelines, a significant amount of new data regarding treatment interventions, therapies, and outcomes is available, making the 2001 guidelines outdated.<sup>20</sup> A recent review<sup>21</sup> of treatments suggests that lactulose remains the first-line agent for both acute episodic and persistent hepatic encephalopathy with rifaximin as the second-line agent used alone or in combination with lactulose. These conclusions are supported by the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program recommendations,<sup>22</sup> which suggest that rifaximin be used in patients intolerant to lactulose therapy.

**Table 2. Management strategies for HE treatment** (Recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program; from table 9 and 10)<sup>22</sup>

Management strategy of <u>episodic</u> HE		Management strategy of <u>persistent</u> HE	
<i>General management</i>	<i>Specific treatment</i>	<i>General management</i>	<i>Specific treatment</i>
Identify and treat precipitating factor (GI hemorrhage, infection, pre-renal azotemia, constipation, sedatives) Short-term (< 72 h) protein restriction may be considered in severe HE	Lactulose enemas (300 ml in 1L of water) in patients who are unable to take oral medications <i>or</i> Lactulose 30 ml orally every 1 – 2h until bowel evacuation, then adjust to a dosage that will result in 2 – 3 formed bowel movements per day (usually 15 – 30 ml orally twice daily.) Lactulose can be discontinued once the precipitating factor has resolved	No long-term protein restriction Protein from dairy or vegetable sources is preferable to animal protein Avoid sedatives and tranquilizers Avoid constipation	Lactulose dosage that produces 2 – 3 soft, formed bowel movements per day, starting at 15 – 30 ml orally twice daily <u>Alternative treatment</u> Rifaximin 400 mg orally three times daily in patients who cannot tolerate lactulose

## National Institute for Health and Care Excellence (NICE) Guidance

A NICE technology appraisal on Rifaximin as maintenance treatment for hepatic encephalopathy due in October 2013.<sup>8</sup> The first appraisal meeting was scheduled for 30 May 2013.

## B. Travelers' Diarrhea (TD)

Traveler's diarrhea affects 20-50% of international travelers. It is caused by eating contaminated food or drinking contaminated water. Most TD cases begin abruptly and result in increased frequency, volume, and weight of stool (typically four to five loose or watery bowel movements each day). Other commonly associated symptoms are nausea, vomiting, diarrhea, abdominal cramping, bloating, fever, urgency, and malaise. TD is rarely life-threatening and most cases are benign and resolve in 1-2 days without treatment (90% of cases resolve within 1 week, and 98% resolve within 1 month). Bacterial enteropathogens cause approximately 80% of TD cases and enterotoxigenic *Escherichia coli* (ETEC) has been isolated as the most common causative agent in countries surveyed. Other causative agents include other bacterial pathogens, a variety of viral and parasitic enteric pathogens. **The CDC does not recommend antimicrobial drugs to prevent TD.** Routine antimicrobial prophylaxis increases the traveler's risk for adverse reactions and for infections with resistant organisms and provides no protection against either viral or parasitic pathogens. Preventive measures are encouraged (foods and drinks to avoid vs. safer alternatives), and bismuth subsalicylate should be used as an adjunct if prophylaxis is needed. However, bismuth subsalicylate should be avoided by persons who are allergic to aspirin, during pregnancy, and by persons taking certain other medications (e.g., anticoagulants, probenecid, or methotrexate). It also has potential side effects (e.g. temporary blackening of the tongue and stool, and rarely ringing in the ears) and should not be used for more than 3 weeks.<sup>23,24</sup> If anti-infective prophylaxis is used (e.g., in immunocompromised individuals such as those with HIV infection), a fluoroquinolone (ciprofloxacin, levofloxacin, ofloxacin, norfloxacin) is recommended (if not pregnant). However, increasing resistance (e.g., *Campylobacter*) should be considered.<sup>25</sup>

Countries' risk of travelers' diarrhea <sup>26</sup>		
Low risk	Intermediate risk	High risk
US, Canada, Australia, New Zealand, Japan, and countries in Northern and Western Europe	Eastern Europe, South Africa, and some of the Caribbean islands	Asia, the Middle East, Africa, and Central and South America.

### Treatment of TD

TD usually is a self-limited disorder and often resolves without specific treatment, but oral rehydration is often needed to replace lost fluids and electrolytes. Some patients may benefit from antimicrobial treatment (usually for 3-5 days) and the Centers for Disease Control (CDC) use examples such as those who develop three or more loose stools in an 8-hour period especially if associated with nausea, vomiting, abdominal cramps, fever, or blood in stools.<sup>23</sup> "Currently, fluoroquinolones are the drugs of choice. Commonly prescribed regimens are 500 mg of ciprofloxacin twice a day or 400 mg of norfloxacin twice a day for 3-5 days. Trimethoprim-sulfamethoxazole and doxycycline are no longer recommended because of the high level of resistance to these agents. Bismuth subsalicylate may be used as treatment: one fluid ounce or two 262 mg tablets every 30 minutes for up to eight doses in a 24-hour period, which can be repeated on a second day. If diarrhea persists despite therapy, travelers should be evaluated by a doctor and treated for possible parasitic infection."<sup>23</sup>

Rifaximin is unlikely to provide benefit to the patient and increases the risk of drug-resistant bacteria in the absence of a proven or strongly suspected bacterial infection when it is used for traveler's diarrhea.<sup>11</sup> Rifaximin may be ineffective in and should *not* be used for treatment of diarrhea known or suspected to be caused by pathogens other than *E. coli* (e.g., *Campylobacter jejuni*, *Shigella*, *Salmonella*) or if complicated by fever or bloody stools. If diarrhea symptoms get worse or persist more than 24-48 hours, Xifaxan should be discontinued and alternative antibiotics should be considered.<sup>11</sup>

### Guidelines

The Infectious Diseases Society of America (IDSA) guidelines<sup>27</sup> for travel medicine recommend fluoroquinolones (FQs) as first-line treatment unless contraindications exist. Rifaximin is recommended as an alternative to fluoroquinolones in the treatment of persons with afebrile, nondysenteric traveler's diarrhea. Rifaximin is not approved for the treatment of persons with diarrhea associated with fever or passage of bloody stools or when

Shigella, Salmonella, or Campylobacter species are suspected pathogens (very low systemically absorption). Attributes that make it attractive for use in diarrhea include limited absorption, a good safety record, activity against a wide range of enteropathogens, and no other uses other than for enteric diseases (lower risk of resistance in other countries). Azithromycin is also recommended as an alternative to fluoroquinolones in areas that have high rates of fluoroquinolone resistance (e.g., fluoroquinolone-resistant *Campylobacter* in Thailand and India). Some patients should not receive fluoroquinolones (e.g., children, pregnant women) or may need an alternative if they have not responded to fluoroquinolone treatment after 48 hours.<sup>28</sup>

**Diagnosis codes submitted**

No diagnosis codes were submitted for any patients for treatment of Traveler's diarrhea (ICD-9 009.2) during 2010-2012 in the Utah Medicaid system.

**Table 2. TD treatment options – preparations and dosages<sup>2,16,25,28-33</sup>**

Drug	Generic	Dosage Form(s)	Usual Dose from Product Labeling	Maximal Recommended Dose per Product Labeling
<b>Drug class</b>				
Rifaximin (Xifaxan)	No	<b>Oral tablet:</b> 200 mg 550 mg  Xifaxan 200MG Tablets (SALIX PHARMACEUTICALS): 30/\$359.99 or 90/\$1,060.02 Xifaxan 550MG Tablets (SALIX PHARMACEUTICALS): 60/\$1,352.03 or 180/\$3,801.18 <sup>2</sup>	Treatment of Travelers' Diarrhea Oral: 200 mg 3 times/day for 3 days	1200 mg/day
<b>Traveler's diarrhea alternatives</b>				
Azithromycin (Zithromax, Z-PAK, Zmax)	Yes	<b>Oral tablet:</b> 250 mg 500 mg 600 mg  <b>Powder for oral suspension:</b> 100 mg/5 mL 200 mg/5 mL 1000 mg/packet  <b>Microspheres for oral suspension, extended release:</b> 2000 mg/60 mL  <b>IV powder for reconstitution:</b> 500 mg vial	Treatment of Travelers' Diarrhea Oral: 1000 mg as a single dose Alternatively, 500 mg once daily for 3 days	2000 mg/day
Ciprofloxacin (Cipro)	Yes	<b>Oral tablet:</b> 100 mg 250 mg 500 mg 750 mg  <b>Oral extended release tablet:</b> 500 mg 1000 mg	Treatment of Travelers' Diarrhea Oral: 500 mg every 12 hours for 1–3 days. Duration of 3–7 days recommended for empiric treatment in HIV-infected adults.  Prevention of Travelers' Diarrhea Oral: 500 mg once daily Note: Although anti-infective prophylaxis generally is discouraged, some clinicians state that it can be given during the period of risk	Oral: 1500 mg/day IV: 1200 mg/day

		<p><b>Microcapsules for oral suspension:</b> 250 mg/5 mL 500 mg/5 mL</p> <p><b>IV premixed in D5W:</b> 200 mg/100 mL 400 mg/200 mL</p> <p><b>Injection solution:</b> 10 mg/mL</p>	(for ≤3 weeks) beginning the day of travel and continuing for 1 or 2 days after leaving the area of risk.	
<b>Norfloxacin</b> (Noroxin)	No	<b>Oral tablet:</b> 400 mg	Dysenteric enterocolitis ( <i>Shigella</i> ) ( <b>unlabeled use</b> ): 400 mg twice daily for 3 days (IDSA, 2001) Traveler's diarrhea ( <b>unlabeled use</b> ): Oral: 400 mg twice daily for 3 days (Mattila, 1993), single dose may also be effective	Maximum 400 mg twice daily because of the risk of crystalluria
<b>Ofloxacin</b>	Yes	<b>Oral tablet:</b> 200 mg, 300 mg, 400 mg	Treatment of Travelers' Diarrhea ( <b>unlabeled use</b> ): Oral: 300 mg twice daily for 1–3 days	General: 400 mg twice daily (800 mg) TD: 600 mg
<b>Levofloxacin</b> (Levaquin)	Yes	<p><b>Oral tablet:</b> 250 mg, 500 mg, 750 mg</p> <p><b>Oral solution:</b> 25 mg/mL</p> <p><b>IV solution:</b> 250 mg/50 mL; 500 mg/100 mL; 750 mg/150 mL; 25 mg/mL</p>	Traveler's diarrhea ( <b>unlabeled use</b> ): Oral: 500 mg for one dose (Sanders, 2007)	

## C. Clostridium difficile Infection (CDI)

Patients, especially older adults, who take antibiotics and also get medical care, are most at risk for *Clostridium difficile* infections (*C. difficile*). It causes diarrhea linked to 14,000 American deaths each year.<sup>34</sup> More severe cases are now being caused by a more virulent strain of *C. difficile* and data has been published on decreased effectiveness of metronidazole in the treatment of severe disease.<sup>35</sup>

### Treatment of CDI

#### Guidelines

The Society for Healthcare Epidemiology of America (SHEA)/Infectious Diseases Society of America (IDSA) recommend using oral metronidazole for mild to moderate CDI and oral vancomycin for severe CDI.<sup>35</sup> For initial, severe, complicated cases vancomycin (oral or NG) plus metronidazole (IV) is recommended. Recurrences can occur as a result of either relapse of infection of the original strain or re-infection of patients who remained susceptible and are exposed to new strains. IDSA/SHEA guidelines recommend the same treatment as the initial treatment for the first recurrence, but vancomycin is recommended in patients with a white blood cell count of 15,000 cells/mL or higher or a rising serum creatinine level as they are at higher risk of developing complications. For a second recurrence, vancomycin is recommended and metronidazole should not be used beyond the first recurrence or for long-term therapy because of the potential for cumulative neurotoxicity. The guidelines state that management of patients who do not respond to this course of treatment or experience a further relapse is challenging.

In an uncontrolled case series<sup>36</sup> (patients with multiple recurrences of CDI), off-label oral rifaximin therapy (400 mg 2 times per day for 2 weeks) cured 7 of 8 patients when it was started immediately following the last course of vancomycin and before symptom recurrence, but caution is recommended with use of rifaximin in the IDSA/SHEA guideline because of the potential for isolates to develop an increased MIC during treatment.<sup>35,37</sup>

Other potential treatment options discussed in the IDSA/SHEA guidelines include “fecal transplant” (high degree of success in several uncontrolled case series; the availability of treatment is limited), administration of the probiotic *Saccharomyces boulardii* with high dose vancomycin, alternative antimicrobials such as nitazoxanide (Alinia)(FDA-approved for Diarrhea caused by *Cryptosporidium parvum* or *Giardia lamblia* and CDI is an unlabeled use), and intravenous immunoglobulins. Fidaxomicin (Dificid) was approved by the FDA in May 2011 for the treatment of diarrhea due to *Clostridium difficile* (CDAD) and was therefore not included in the SHEA/IDSA 2010 guidelines update.<sup>38</sup> Fidaxomicin is a macrolide antibiotic with a narrow spectrum of antibacterial activity and after oral administration, only minimal systemic absorption occurs and the drug remains mainly confined to and acts locally in the GI tract.<sup>39</sup> Nitazoxanide is an antiprotozoal (nitrothiazolyl-salicylamide derivative).<sup>40</sup>

Table adapted from table 3 of the IDSA/SHEA guidelines<sup>35</sup>

CDI occurrence	Recommended treatment
Initial episode, Mild or moderate	Metronidazole, 500 mg 3 times per day by mouth for 10–14 days
Initial episode, Severe	Vancomycin, 125 mg 4 times per day by mouth for 10–14 days
Initial episode, Severe, Complicated	Vancomycin, 500 mg 4 times per day by mouth or by nasogastric tube, plus metronidazole, 500 mg every 8 hours intravenously. If complete ileus, consider adding rectal instillation of vancomycin
First recurrence	Same as initial
Second recurrence	Vancomycin in a tapered and/or pulsed regimen

Definitions can be found in table 3 of the guidelines.

**Table 3. CDI treatment options – preparations and dosages**<sup>2,17,38-41</sup>

Active Ingredient	Generic	Strengths	FDA Approval Date	Usual Dose from Product Labeling
Rifaximin (Xifaxan)	No	<b>Oral tablet:</b> 200mg 550mg	200 mg May 25, 2004 550 mg - March 24, 2010	<i>Clostridium difficile</i> -associated diarrhea ( <u>unlabeled use</u> ): Oral: 200-400 mg 2-3 times/day for 14 days <sup>36</sup>
Metronidazole (Flagyl and Flagyl ER)	Yes (excludes capsule, extended release tablet)	<b>Oral capsule:</b> 375mg  <b>Oral tablet:</b> 250mg 500mg 750mg ER  <b>Infusion:</b> Premixed iso-osmotic NaCl solution: 500 mg (100 mL)	July 18, 1963	Antibiotic-associated pseudomembranous colitis: IDSA Guidelines (Cohen, 2010): Mild-to-moderate infection: Oral: 500 mg 3 times/day for 10-14 days Severe complicated infection: I.V.: 500 mg 3 times/day with oral vancomycin (recommended agent) for 10-14 days <b>Note:</b> Due to the emergence of a new strain of <i>C. difficile</i> , some clinicians recommend converting to oral vancomycin therapy if the patient does not show a clear clinical response after 2 days of metronidazole therapy.
Vancomycin (Vancocin)	Yes	<b>Oral capsules:</b> 125mg 250mg  <b>IV solution</b>	April 15, 1986	<i>C. difficile</i> -associated diarrhea (CDAD): Oral: Manufacturer recommendations: 125 mg 4 times/day for 10 days IDSA guideline recommendations: Severe infection: 125 mg every 6 hours for 10-14 days; Severe, complicated infection: 500 mg every 6 hours with or without concurrent I.V. metronidazole. May consider vancomycin retention enema (in patients with complete ileus) <sup>35</sup> Rectal ( <u>unlabeled route</u> ): Retention enema (in patients with complete ileus): SHEA/IDSA guideline recommendations: Severe, complicated infection in patients with ileus: 500 mg every 6 hours (in 100 mL 0.9% sodium chloride) with oral vancomycin with or without concurrent I.V. metronidazole <sup>35</sup>
Fidaxomicin (Dificid)	No	200mg	May 27, 2011	Treatment of diarrhea due to <i>Clostridium difficile</i> (CDAD): Oral: 200 mg twice daily for 10 days in adults ≥18 years of age. Safety and efficacy not established in patients <18 years of age. Designated an orphan drug by FDA for treatment of <i>C. difficile</i> infection (CDI) in pediatric patients.
Nitazoxanide (Alinia)	No	500mg, 100mg/5mL	July 21, 2004	<i>Clostridium difficile</i> -associated diarrhea ( <u>unlabeled use</u> ): Oral suspension or tablets: 500 mg every 12 hours for 10 days <sup>42</sup>

## D. Irritable Bowel Syndrome (IBS)

Irritable bowel syndrome (IBS) is a common functional gastrointestinal (GI) disorder with several symptoms, including abdominal pain or discomfort, diarrhea or constipation (or both), abdominal bloating, passing mucous, or a feeling that a bowel movement is incomplete. The pain may improve with a bowel movement. It has both physical and mental causes, but is a syndrome not a disease (no underlying disease process or structural abnormality and the GI tract does not become damaged). It is associated with various factors including brain-gut signal problems, GI motor problems, hypersensitivity (lower pain threshold), mental health problems, bacterial gastroenteritis, small intestinal bacterial overgrowth (SIBO), neurotransmitters and hormones, genetics, and food sensitivities. It has also been called colitis, mucous colitis, spastic colon, nervous colon, and spastic bowel.<sup>43,44</sup> IBS is the most commonly diagnosed gastrointestinal disorder and it affects between 3 and 20 percent of the population (twice as many women than men; and most often people younger than 45 years), but less than one-third of people consult a healthcare provider.<sup>43,45,46</sup> IBS is defined by the American College of Gastroenterology (ACG) guidelines (2009 update) as “abdominal pain or discomfort that occurs in association with altered bowel habits over a period of at least three months.”

There are four subtypes (based on stool consistency)<sup>43</sup>:

1. IBS with constipation (IBS-C)
  - hard or lumpy stools at least 25% of the time
  - loose or watery stools <25% of the time
2. IBS with diarrhea (IBS-D)
  - loose or watery stools at least 25% of the time
  - hard or lumpy stools <25% of the time
3. Mixed IBS (IBS-M)
  - hard or lumpy stools at least 25% of the time
  - loose or watery stools at least 25% of the time
4. Unsubtyped IBS (IBS-U)
  - hard or lumpy stools <25% of the time
  - loose or watery stools <25% of the time

## Treatment of Irritable Bowel Syndrome

There is no cure for IBS, but the symptoms can be managed through a combination of changes in eating, diet, and nutrition; probiotics; therapies for mental health problems; and medications.<sup>43</sup> The subtypes (based on usual stool consistency) determine the types of treatment that are most likely to improve the person’s symptoms. Medication options discussed in the guidelines<sup>47</sup> include fiber supplements, laxatives, antidiarrheals, antispasmodics, antidepressants, alosetron (Lotronex), tegaserod (Zelnorm), lubiprostone (Amitiza), Linaclotide (Linzess), probiotics, and rifaximin (Xifaxan).

### Guidelines

The American College of Gastroenterology (ACG) panel reviewed 300 studies on the natural course, diagnosis, and treatment of IBS and developed a series of recommendations. These were graded as strong (1) or weak (2) and the evidence were rated as strong (A), moderate (B), or weak (C). The update to the guidelines was published as a supplement to the *The American Journal of Gastroenterology* January 2009 issue.<sup>44,47,48</sup>

According to the guidelines, short-term use of rifaximin helps reduce overall symptoms, especially bloating (grade 1B). Its long-term safety and effectiveness are uncertain, and it is not approved for IBS. Symptom recurrence is common and cost can be a prohibitive factor. The National Digestive Diseases Information Clearinghouse (NDDIC) state that rifaximin can reduce abdominal bloating by treating Small intestinal bacterial overgrowth (SIBO), but the use of antibiotics to treat IBS is still being debated, and more research is needed.<sup>43</sup>

**Table 4. Treatment of IBS – Evidence-Based Position Statement (*The American Journal of Gastroenterology* January 2009)<sup>44,47,48</sup> and information<sup>49-52</sup>**

Treatment	Highlights of recommendations & FDA information
Antibiotics: Rifaximin (Xifaxan)	Short-term use of rifaximin helps reduce overall symptoms, especially bloating (grade 1B). Its long-term safety and effectiveness are uncertain, and it is not approved for IBS. Symptom recurrence is common. Cost can be a prohibitive factor. The National Digestive Diseases Information Clearinghouse (NDDIC) state that rifaximin can reduce abdominal bloating by treating Small intestinal bacterial overgrowth (SIBO), but the use of antibiotics to treat IBS is still being debated, and more research is needed. <sup>43</sup>
Laxatives, bulking agents & fiber that contain psyllium (ispaghula husk) e.g. Metamucil, Fiberall, Hydrocil, Konsyl	Bulking agents that contain psyllium (ispaghula husk) is moderately effective (grade 2C), but neither wheat bran nor corn bran is better than a placebo in managing IBS (grade 2C). Polyethylene glycol improve stool frequency (not abdominal pain) in adolescents with IBS-C (one small study; grade 2C)
Anti-diarrheals: Loperamide (Imodium)	Anti-diarrheals: Loperamide (Imodium) reduces stool frequency and improves consistency but is no better than placebo in treating pain or bloating (grade 2C)
Antispasmodics: Hyoscine, cimetropium, pinaverium	Antispasmodics (Hyoscine, cimetropium, and pinaverium as well as peppermint oil) may provide short-term relief of abdominal pain (grade 2C), but data on long-term efficacy and safety are lacking.
Probiotics	There are many strains of probiotics, and preparations and doses vary. It appears that Lactobacilli alone don't relieve IBS symptoms, but <i>bifidobacteria</i> certain combination products improve symptoms (grade 2C).
Bicyclic fatty acid/selective C-2 chloride channel activator: Lubiprostone (Amitiza)	Lubiprostone (Amitiza) (newest IBS drug), is effective in relieving overall symptoms of women with constipation-predominant IBS (IBS-C) (grade 1B). <u>Labeled Indications:</u> Treatment of chronic idiopathic constipation; treatment of irritable bowel syndrome with constipation in adult women Not approved for use in males with irritable bowel syndrome with constipation.
Selective 5-HT <sub>3</sub> Receptor Antagonist: Alosetron (Lotronex)	Alosetron (Lotronex) is effective in relieving symptoms of men (grade 2B) and women with diarrhea-predominant IBS (IBS-D)(grade 2A), but its availability and use are limited because it's been linked to severe constipation and ischemic colitis (grade 2A) The benefit vs harm is most favorable in women with severe IBS that did not respond to conventional therapies (grade 1B). <u>Labeled Indications:</u> Treatment of <u>women</u> with severe diarrhea-predominant irritable bowel syndrome (IBS) who have failed to respond to conventional therapy <u>Prescribing and Access Restrictions:</u> As a requirement of the REMS program, access to the medication is restricted. Physicians must enroll in the Prometheus Prescribing Program for Lotronex® ( <a href="http://www.lotronexppi.com">www.lotronexppi.com</a> or 1-888-423-5227) in order to prescribe this medication. Program stickers must be affixed to all prescriptions; no phone, fax, or computerized prescriptions are permitted with this program.

<p>Partial neuronal 5-HT<sub>4</sub> receptor agonist: Tegaserod (Zelnorm)</p>	<p>Tegaserod (Zelnorm) helps relieve overall symptoms of women with constipation-predominant IBS (IBS-C) (grade 1A) and in both men and women with mixed IBS (grade 1B). Most common side-effect is diarrhea (grade 1A). <u>Labeled Indications:</u> Emergency treatment of irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) in women (&lt;55 years of age) in which no alternative therapy exists <u>Prescribing and Access Restrictions:</u> Available in U.S. under an emergency investigational new drug (IND) process. Emergency situations are defined as immediately life-threatening or requiring hospitalization. Physicians with patients who may qualify can contact the FDA's Division of Drug Information via email (druginfo@fda.hhs.gov). The FDA may either deny the request or authorize shipment of Zelnorm® by Novartis. Additional information can be found at <a href="http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103223.htm">http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103223.htm</a>.</p>
<p>Antidepressants: Tricyclic antidepressants (TCAs) Selective Serotonin Reuptake Inhibitors (SSRIs)</p>	<p>TCAs &amp; SSRIs are effective reducing abdominal pain and in relieving overall symptoms, but limited safety data exist in people with IBS (grade 1B).</p>
<p>Psychological therapies</p>	<p>Trials (20 RCTs) have shown that psychological therapies, including cognitive therapy, dynamic psychotherapy, and hypnotherapy (but <i>not</i> relaxation therapy) are more effective than usual care in relieving overall symptoms (grade 1B).</p>
<p><b>FDA-approved after the Position Statement was published</b></p>	
<p>Gastrointestinal Agent, Miscellaneous: Linaclotide (Linzess)</p>	<p>FDA approved Aug 2012 - <u>Labeled Indications:</u> Treatment of chronic idiopathic constipation (CIC); treatment of IBS with constipation (IBS-C) in adults Medication Guide and <b>[U.S. Boxed Warning]: Use is contraindicated in pediatric patients ≤6 years of age. Avoid use in pediatric patients 6-17 years of age. Deaths observed in young juvenile animals during nonclinical studies;</b> deaths not observed in older juvenile animals. Sufficient safety and efficacy data does not exist to support use in pediatric patients.</p>

## Supplemental New Drug Application: Non-constipation IBS

A supplemental New Drug Application (sNDA) for Xifaxan 550 mg sNDA for non-constipation IBS was submitted to the FDA, but the response letter (March 7, 2011) stated that the FDA does not consider it ready for approval due to a newly expressed need for retreatment information.<sup>53</sup>

## Clinical Efficacy – Systematic review(s)

Appendix 1 contains a summary of reviews.

The findings of a review on the effectiveness of preventing traveler's diarrhea showed that rifaximin and fluoroquinolones were effective in **preventing travelers' diarrhea**.<sup>54</sup> The authors of the study stated that clinicians should be aware of the geographical patterns, itineraries, traveler behaviors and areas where the risk of travelers' diarrhea was high (high-risk areas) and that routine chemoprophylaxis with rifaximin may be a reasonable choice for a short-term trip (less than 14 days) where the area was high-risk, predominantly with diarrheogenic E. coli pathogens (if not contraindicated). However, the CDC does not recommend prophylaxis of TD as discussed earlier.

Eltawil et al<sup>55</sup> stated that due to its safety profile, rifaximin should be considered as a second option for **hepatic encephalopathy** in patients who failed to respond to disaccharide therapy, and as a first treatment for patients who were intolerant to disaccharides. Jiang et al<sup>14</sup> concluded that rifaximin was not superior to non-absorbable disaccharides for acute or chronic hepatic encephalopathy in the long-term or short-term treatment, except that it may be better tolerated.

Rifaximin proved more effective than placebo for global symptoms and bloating in **IBS** patients, but the Centre for reviews and dissemination stated that the modest therapeutic gain was similar to that yielded by other currently available therapies for IBS.<sup>56</sup>

Rifaximin plus fiber supplementation appears to provide symptom relief and could prevent more complications in patients with symptomatic uncomplicated **diverticular disease**, but more studies are needed.<sup>57</sup>

## Safety and adverse effects

The most common adverse reactions in travelers' diarrhea ( $\geq 5\%$ ) include flatulence, headache, abdominal pain, rectal tenesmus, defecation urgency and nausea; and the most common adverse reactions in HE ( $\geq 10\%$ ) include peripheral edema, nausea, dizziness, fatigue, ascites, flatulence, and headache.<sup>11</sup>

Postmarketing experience include reports of C.dif-associated colitis and hypersensitivity reactions (exfoliative dermatitis, angioneurotic edema, and anaphylaxis).<sup>11</sup>

### Contraindications

- Hypersensitivity to rifaximin or rifamycin antibiotics

### Special populations

- Pregnancy: It may cause fetal harm (based on animal studies) and has been classified as category C (should be used only if the potential benefit justifies the potential risk to the fetus).
- Nursing: Unknown whether excreted in human milk (benefit vs risk – discontinue nursing vs discontinue drug)
- Pediatric: 200mg for Travelers' diarrhea - Safety and efficacy has not been established < 12 years  
550 mg for HE – safety and efficacy have not been established <18 years

- Geriatric: Insufficient patients >65 years were included in the rifaximin 200 mg studies. The rifaximin 500 mg studies included 19.4% >65 years and 2.3% > 75 years with no overall differences compared to younger patients, but the product label states that greater sensitivity of some older patients cannot be ruled out.
- Renal: It is poorly absorbed from the GI tract and is almost entirely excreted in feces as unchanged so clinically important changes in the elimination of rifaximin are not expected (it has not been studied in this population).
- Hepatic: dosage adjustment is not required because it acts locally, but it should be used with caution in patients with severe hepatic impairment as the clinical trials were limited to patients with MELD scores <25 and systemic exposure was higher in patients with hepatic impairment compared to healthy subjects. The Model for End-Stage Liver Disease (MELD) is a disease severity index which is a reliable measure of mortality risk in patients with end-stage liver disease.<sup>58</sup>
- Gender, race, or ethnicity: There is no information regarding treatment differences based on gender, race, or ethnicity

### Warnings and precautions

- Travelers' Diarrhea not caused by E.Coli (as discussed earlier)
- Clostridium difficile-associated diarrhea (CDAD) has been reported and it can occur over two months after the administration of antibacterial agents. It can range from mild diarrhea to fatal colitis and should therefore be considered in all patients to ensure appropriate management and treatment.<sup>11</sup>
- Development of drug resistant bacteria (as discussed earlier)
- It should be used with caution in patients with severe hepatic impairment due to increased exposure in these patients

### Interactions

- ❖ Please refer to the product labeling for complete prescribing information.<sup>2,11</sup>

### Pipeline products for HE

**OCR-002 (Ornithine phenylacetate)** is currently in Phase 2 development and it has received Orphan Drug designation in the United States and Europe and has been granted fast track status by the U.S. Food and Drug Administration. It directly lowers circulating blood levels of ammonia by enabling alternate metabolic pathways in the muscle and kidney in patients with hepatic encephalopathy (those with liver cirrhosis, acute liver failure and acute liver injury). The injectable formulation is being developed for hospitalized patients; and an oral formulation to treat and prevent recurrences of hepatic encephalopathy.<sup>9,59</sup>

## Utah Medicaid Utilization Data

### 2010

GENERIC	DESCRIPTION	CLAIMS	UNITS	DAYS	PATIENTS
Rifaximin	XIFAXAN TAB 200MG	188	14,274	3,531	59
Rifaximin	XIFAXAN TAB 550MG	61	2,758	1,534	29
<b>Total</b>		<b>249</b>	<b>17,032</b>	<b>5,065</b>	<b>88</b>

### 2011

GENERIC	DESCRIPTION	CLAIMS	UNITS	DAYS	PATIENTS
Rifaximin	XIFAXAN TAB 200MG	118	10,149	2,642	39
Rifaximin	XIFAXAN TAB 550MG	320	16,176	8,316	110
<b>Total</b>		<b>438</b>	<b>26,325</b>	<b>10,958</b>	<b>149</b>

### 2012

GENERIC	DESCRIPTION	CLAIMS	UNITS	DAYS	PATIENTS
Rifaximin	XIFAXAN TAB 200MG	72	4,794	1,585	30
Rifaximin	XIFAXAN TAB 550MG	555	32,008	15,508	112
<b>Total</b>		<b>627</b>	<b>36,802</b>	<b>17,093</b>	<b>142</b>

The number of patients and claims for rifaximin 200 mg has decreased over the last 3 years, but the number of patients and claims for rifaximin 550 mg has increased considerably in the last 3 years. Since 2010 the total number of claims for rifaximin increased by 152% and the total number of patients increased by 61%, since 2010.

DIAGNOSIS	ICD	2010		2011		2012	
		Claims	%	Claims	%	Claims	%
Hepatic Encephalopathy	572.2	43	49%	61	41%	65	46%
Traveler's Diarrhea	009.2	0	0%	0	0%	0	0%
Irritable Bowel Syndrome	564.1	16	18%	23	15%	19	13%
Other		29	33%	65	44%	58	41%
<b>TOTAL PATIENTS TAKING RIFAXIMIN</b>		<b>88</b>	100%	<b>149</b>	100%	<b>142</b>	100%

Depending on the year, 33-41% of patients did not have a diagnosis code submitted for any of the above conditions. The reason could be either that no diagnosis code was submitted, or that a diagnosis for another off-label use was submitted. At least 15% of patients had diagnosis codes submitted for IBS which is an off-label indication.

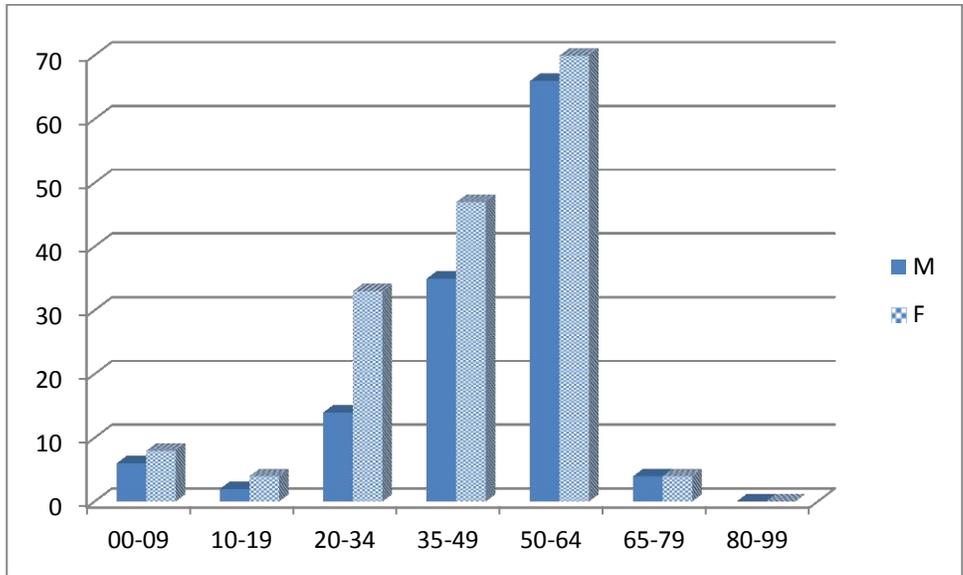


Figure 1 - Age and gender characteristics of patients that filled prescriptions for rifaximin (2010-2012)

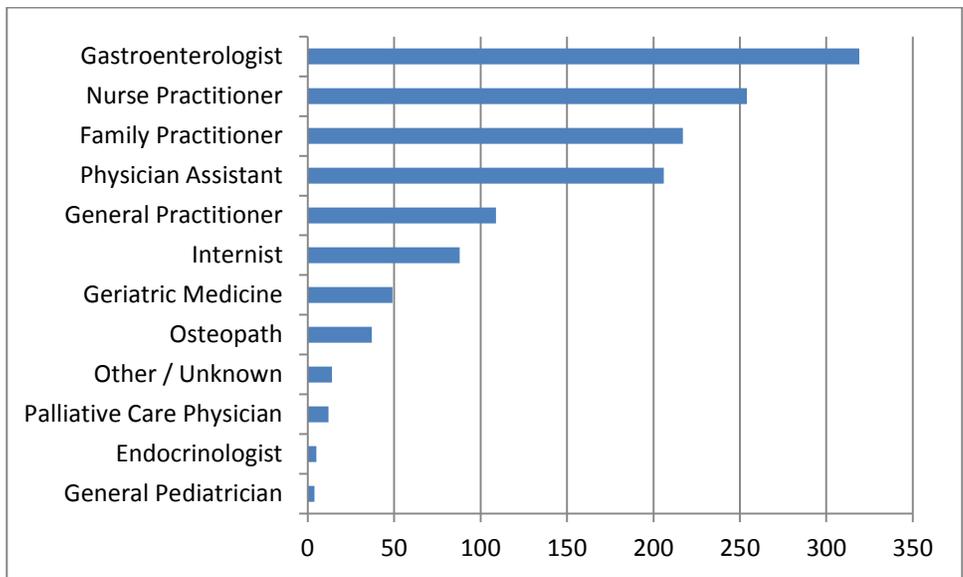


Figure 2 – Prescribers of rifaximin prescriptions (2010-2012)

## Conclusion

Rifaximin appears to be as effective as lactulose for hepatic encephalopathy, but there is a lack of robust clinical trials for HE without combination lactulose therapy and there is a big difference in cost. Also, no studies have been conducted in the treatment of overt HE, or in patients with severe liver impairment (rifaximin was studied in patients with mild to moderate symptoms). Rifaximin 550 mg is FDA-approved for reduction of hepatic encephalopathy recurrence. A recent review<sup>21</sup> of treatments suggests that lactulose remains the first-line agent for both acute episodic and persistent hepatic encephalopathy with rifaximin as the second-line agent used alone or in combination with lactulose. These conclusions are supported by the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program recommendations,<sup>22</sup> which suggest that rifaximin be used in patients not tolerant of lactulose therapy.

The CDC does not recommend antimicrobial drugs to prevent TD. Rifaximin has been used for *prevention* of travelers' diarrhea, but safety and efficacy for such *prophylaxis* has *not been* established. The IDSA guidelines<sup>27</sup> for travel medicine recommend fluoroquinolones (FQs) as 1<sup>st</sup>-line treatment of TD unless contraindications exist. Rifaximin is recommended as an alternative to fluoroquinolones in the treatment of persons with afebrile, nondysenteric traveler's diarrhea. Rifaximin 200 mg is FDA-approved for the treatment of E. coli traveler's diarrhea with a treatment regimen of 200 mg three times per day for three days (quantity limit of 9 tablets would therefore be appropriate). Rifaximin is not approved for the treatment of persons with diarrhea associated with fever or passage of bloody stools or when Shigella, Salmonella, or Campylobacter species are suspected pathogens (very low systemically absorption). Azithromycin is also recommended as an alternative to fluoroquinolones in areas that have high rates of fluoroquinolone resistance or in patients that cannot take fluoroquinolones.

Rifaximin is not FDA-approved for treatment of Clostridium difficile infections (CDIs), prevention of travelers' diarrhea, Crohn's disease, recurrent acute diverticulitis (with mesalamine), and irritable bowel syndrome. A supplemental New Drug Application (sNDA) for Xifaxan 550 mg sNDA for non-constipation IBS was submitted to the FDA, but the response letter (March 7, 2011) stated that the FDA does not consider it ready for approval due to a newly expressed need for retreatment information.<sup>53</sup> The ACG position statement recommends that short-term use of rifaximin helps reduce overall symptoms, especially bloating (grade 1B), but its long-term safety and effectiveness are uncertain.<sup>48</sup> The National Digestive Diseases Information Clearinghouse (NDDIC) state that rifaximin can reduce abdominal bloating by treating small intestinal bacterial overgrowth (SIBO), but the use of antibiotics to treat IBS is still being debated, and more research is needed.<sup>43</sup> Insufficient evidence exists for other off-label uses.

Generic treatment alternatives are available and rifaximin is significantly more expensive than generically available alternatives. Rifaximin has a different safety profile than alternative medication options, but there is no direct evidence that it is safer or better tolerated than alternatives. Since 2010 the total number of claims for rifaximin increased by 152% and the total number of patients increased by 61%. Diagnosis codes submitted indicate off-label use and potential lack of diagnosis code submission.

In conclusion, rifaximin has no compelling advantage over current medication options and is much more costly, but may be a treatment option for some patients after alternative treatment options have been exhausted.

## Appendix 1 –Summary of reviews

Author(s)	Title	Date of publication	Number of studies that met inclusion criteria	Indication reviewed	Results	Author(s) conclusions/Center for Reviews and Dissemination (CRD) summary
<i>Systematic reviews</i>						
Menees SB, et al. <sup>56</sup>	The Efficacy and Safety of Rifaximin for the Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis	2012	5  4	IBS	<p>Meta-analysis found rifaximin to be more efficacious than placebo for global IBS symptom improvement (OR=1.57; 95% CI=1.22, 2.01; therapeutic gain=9.8%; number needed to treat (NNT)=10.2), with mild heterogeneity (<math>P=0.25</math>, <math>I^2=26\%</math>).</p> <p>Secondary outcome (bloating): Rifaximin was significantly more likely to improve bloating than placebo (OR=1.55; 95% CI=1.23–1.96; therapeutic gain=9.9%; NNT=10.1), with no significant heterogeneity (<math>P=0.27</math>, <math>I^2=23\%</math>).</p>	Rifaximin proved more effective than placebo for global symptoms and bloating in IBS patients. The modest therapeutic gain was similar to that yielded by other currently available therapies for IBS. AEs were similar between rifaximin and placebo.
Jiang Q, et al. <sup>14</sup>	Rifaximin versus nonabsorbable disaccharides in the management of hepatic encephalopathy: a meta-analysis (Structured abstract)	2008	5 (264 patients)	Hepatic encephalopathy	<p>It was noted that there was a discrepancy in the number of patients reported to be randomised for one trial. The range of trial quality was 3 to 5 points. There was no evidence of publication bias. There was no statistically significant difference between rifaximin and non-absorbable disaccharides in terms of clinical efficacy or diarrhea. There was a statistically significant association between the use of rifaximin and the decreased risk of abdominal pain (RR: 0.28, 95% CI 0.08 to 0.95), but statistically significant heterogeneity was reported (<math>I^2=62.7\%</math>). Blood ammonia concentrations were not analyzed due to large differences in baseline concentrations. Sensitivity analysis also revealed that there was no statistically significant difference between rifaximin and non-absorbable disaccharides in the treatment of hepatic encephalopathy according to ethnicity or chronic versus acute state of hepatic encephalopathy. However, no data on the presence or absence of heterogeneity was reported for the sensitivity analysis.</p>	<p>CRD summary:</p> <p>The authors concluded that rifaximin was not superior to non-absorbable disaccharides for acute or chronic hepatic encephalopathy in the long-term or short-term treatment, except that it may be better tolerated. Given the lack of reporting on methodological processes and the small number of included participants, this conclusion should be interpreted with caution.</p>

Alajbegovic S, et al. <sup>54</sup>	Effectiveness of rifaximin and fluoroquinolones in preventing travelers' diarrhea (TD): a systematic review and meta-analysis (Structured abstract)	2012	11	Travelers' diarrhea	Nine studies were included in the meta-analysis (1,310 participants; rifaximin 604, fluoroquinolone 706) and two studies were reviewed narratively. All studies had low risk of bias in allocation concealment and blinding, four studies were unclear risk of randomization. A few studies had high risk in incomplete outcome data, selective reporting and other bias. There was a statistically significant reduction of diarrhea with rifaximin RR 0.33 (95% CI 0.24 to 0.45; I <sup>2</sup> =3.1%; four RCTs) and fluoroquinolone RR 0.12 (95% CI 0.07 to 0.20; I <sup>2</sup> =0%; five RCTs). Number-needed-to-treat to prevent one episode of travelers' diarrhea was 4.5 with rifaximin and 2.8 with fluoroquinolone. Also fluoroquinolone was significantly reduced the moderate/severe travelers' diarrhea compared with placebo RR 0.51 (95% CI 0.095 to 2.71; I <sup>2</sup> =3.8%; three RCTs). Similar rates of adverse events were found between antibiotic and placebo groups. Further results were reported.	CRD summary: The findings showed that rifaximin and fluoroquinolones were effective in prevention of travelers' diarrhea. The authors acknowledged some limitations of this review but their overall conclusion presented and appear likely to be reliable.
Bianchi M, et al. <sup>57</sup>	Meta-analysis: long-term therapy with rifaximin in the management of uncomplicated diverticular disease (Structured abstract)	2011	4	Diverticular disease	Four RCTs were included in the review (n=1,660 patients, 970 in the rifaximin group and 690 in the control group). One trial was blinded. Three trials had adequate sequence generation. All trials had adequate allocation concealment. Incomplete outcome data was addressed and all included trials were considered to be free of selective reporting and other bias. The Jadad scores ranged from 2 to 4 points. A significant increase in symptom relief was found in favor of rifaximin plus fiber supplementation compared with control groups (RD 29.0%, 95% CI 24.5 to 33.6; four RCTs; NNT=3). A statistically, but not clinically, significant reduction in complication rate was found in the rifaximin group compared with the control group (RD -1.7%, 95% CI -3.2 to -1.5; four RCTs; NNT=59). No evidence of statistical heterogeneity was found (I <sup>2</sup> =0%). When only acute diverticulitis was considered, the pooled risk difference in the control group for complication rate was -1.9% (95% CI -3.4 to -0.57; four RCTs; NNT=50). Three out of four trials reported side effect data; the authors reported that no significant differences were found between treatment and control groups. No evidence of publication bias was found.	CRD summary: This review concluded that treatment with rifaximin plus fiber supplementation was effective in obtaining symptom relief and could prevent more complications at one year in patients with symptomatic uncomplicated diverticular disease. This conclusion reflects the results presented, but the small number of included trials and the potential for missed data mean that it should be interpreted with some caution.
Eltawil KM, et al. <sup>55</sup>	Rifaximin vs conventional oral therapy for hepatic encephalopathy: a meta-analysis (Structured abstract)	2012	12	Hepatic encephalopathy	Twelve trials were included in the review, with 565 patients (range 14 to 136). Five described the randomization methods; eight had clearly reported allocation concealment; most had patient blinding to treatment; and six reported observer blinding to treatment. The methods for handling missing data, the descriptions of drop-outs, and power calculations were not adequately reported in any of the	CRD summary: This review concluded that rifaximin was similar to other oral therapies in its clinical efficacy for hepatic encephalopathy and it had fewer side-effects. This was a well-conducted review,

				<p>included trials. Neurological function: Seven trials compared rifaximin with disaccharides and reported that both groups experienced either full resolution of hepatic encephalopathy or a clinically significant improvement, but there was no statistically significant difference between the groups. A similar result was seen in the five trials comparing rifaximin with antibiotics. In the combined analysis of all 12 trials, the results favored rifaximin, but were not statistically significant (OR 1.96, 95% CI 0.94 to 4.08; <math>I^2=27\%</math>). Adverse events: Patients receiving rifaximin had lower rates of diarrhea (OR 0.20, 95% CI 0.04 to 0.92; eight trials; <math>I^2=66\%</math>), but the rates of abdominal pain, nausea, anorexia and weight loss were similar between the two groups. The combined analysis of all adverse events showed fewer events with rifaximin than with control (OR 0.27, 95% CI 0.12 to 0.59; nine trials; <math>I^2=69\%</math>). Serum ammonia: Seven trials reported a statistically significant reduction in serum ammonia at the end of treatment in both groups. There was no statistically significant difference between the groups in the meta-analysis of all trials or of subgroups with disaccharides or antibiotics as the control. Statistical heterogeneity was very high for all serum ammonia analyses (<math>I^2=83\%</math> or more). Psychometric parameters: Rifaximin improved electroencephalographic characteristics (WMD -0.21, 95% CI -0.33 to -0.09; four trials; <math>I^2=0</math>) and portosystemic encephalopathy (WMD -2.33, 95% CI -2.68 to -1.98; three trials; <math>I^2=21\%</math>). There was no statistically significant difference between rifaximin and control for improvement in mental status and asterixis. Trials with a high risk of bias were excluded from all analyses and the results remained consistent.</p>	<p>but the reliability of the conclusions may be affected by the observed statistical variation and the lack of participant information.</p>
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