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Pharmacologic Therapies in Gastrointestinal Diseases

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KEYWORDS

• Hepatitis C virus • Direct acting antivirals • Irritable bowel syndrome • GERD
• Peptic ulcer disease

KEY POINTS

- Treatment of hepatitis C virus has radically changed in recent years and most patients are now treatment candidates and have a high likelihood of permanent cure of the virus.
- First-line treatment of irritable bowel syndrome is lifestyle modification for patients with mild-moderate symptoms, and pharmacotherapy for patients with moderate to severe symptoms.
- Proton pump inhibitors (PPIs) are the mainstay of therapy in gastric and duodenal ulcers, and in gastroesophageal reflux disease, although long-term use of PPIs carries the risk of several side effects.

PHARMACOTHERAPY FOR HEPATITIS C VIRUS

In the United States, hepatitis C virus (HCV) is the leading case of liver-related deaths, hepatocellular carcinoma (HCC), and liver transplant.[1] Until recently, treatment of HCV consisted of pegylated interferon plus ribavirin, a regimen that was complicated, highly toxic, poorly efficacious, and had multiple contraindications.[1] Most patients were not treatment candidates, and in total only 5% to 6% of US patients with HCV were successfully treated in the interferon era.[2]

Clinical Benefit of Achieving Sustained Virologic Response

The goal of HCV antiviral treatment is to achieve a sustained virologic response (SVR), defined as HCV RNA levels at less than the limit of detection in the blood at 12 or more weeks after completing antiviral treatment. There is compelling evidence that an SVR has clinically meaningful improvements in outcomes. Among patients with cirrhosis

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who achieved an SVR, compared with patients who did not achieve an SVR, those with an SVR had a significantly reduced risk of HCC, liver failure, death related to liver disease, and all-cause mortality.[3,4]

Direct-acting Antivirals

HCV treatment has undergone radical changes since interferon. Novel treatments that target specific parts of the HCV lifecycle are called direct-acting antivirals (DAAs). Since late 2013, multiple DAAs have been introduced, such as sofosbuvir, simeprevir, ledipasvir, ombitasvir, dasabuvir, paratapravir, and daclatasvir. These drugs are used in combination with each other, or in combination with ribavirin. The new regimens are interferon free and all oral. The DAA regimens are generally short courses, usually 12 weeks in duration, but in some situations are 8 weeks or 24 weeks. In clinical trials, the cure rates with the DAAs are generally more than 90% and reach 100% in some subgroups.[5–16] In general, patients who are treatment naive achieve higher SVR rates, but, with DAA regimens, treatment-experienced patients are seen to still achieve SVR rates of more than 90%, although usually requiring at least a 12-week duration and sometimes longer, and/or often adding ribavirin, especially if there is also the presence of cirrhosis.[9,12,13,15] In large observational real-world studies, SVR rates are also greater than 90%, similar to trial outcomes.[17] The oral medicines have very mild and tolerable side effect profiles; when ribavirin is included in the regimen, there are higher side effect rates.[8–10,14] Discontinuation rates in real-world studies have also seemed to be low, especially when ribavirin is not needed.[17] Overall, these new interferon-free DAA regimens have dramatically changed HCV treatment, with most of the HCV population predicted to now be medically eligible, and to have a high likelihood of treatment success (**Table 1**).

Principles for Patient Selection for Hepatitis C Virus Treatment

All patients with chronic HCV who do not have medical contraindications are potential candidates for antiviral treatment. The natural history of untreated chronic HCV is variable; fibrosis progression is nonlinear, and it is estimated that 20% to 30% of patients with chronic HCV ultimately develop cirrhosis.[1] The urgency for treatment should be highest for patients with cirrhosis and advanced fibrosis, and also patients with HCC awaiting liver transplant, extrahepatic manifestations of HCV, after transplant, and women planning to conceive a child in the near term.[18,19]

Table 1
HCV-specific targets and antiviral medications: US Food and Drug Administration (FDA) approved or in phase II or III trials as of 2015

NS3/4A Protease Inhibitors	NS5B Polymerase Inhibitors Nucleoside/Nucleotide	NS5B Polymerase Inhibitors Non–Nucleoside/Nucleotide	NS5A Inhibitors
Simeprevir[a]	Sofosbuvir[a]	Dasabuvir[a]	Ledipasvir[a]
Paritaprevir[a]	Mericitabine	Beclabuvir	Ombitasvir[a]
Grazoprevir	ACH-3422	GS-9669	Daclatasvir[a]
ABT-493	MK/IDX-459	TMC-055	Elbasvir
Sovaprevir	MK-3682	MK-8876	Velpatasvir
GS-9857			ABT-530
Danoprevir			ACH-3102
Vedroprevir			Samatasvir
			GSK-2336805
			MK-8408

[a] Currently FDA approved.

Evaluating a patient's potential adherence to the prescribed regimen is crucial to the patient selection process. Providers should incorporate strategies for measuring and supporting adherence. Ongoing substance use, including drinking alcohol, using illicit drugs (including marijuana), or participating in opioid replacement programs should not be an exclusion for HCV treatment.[18,19]

Pretreatment Evaluation

Before initiating antiviral therapy in a patient with chronic HCV, the information listed in **Box 1** should be obtained.[18,19]

Principles of Regimen Selection

The most important pretreatment considerations for selection of DAA regimen are (1) genotype and subtype; (2) the presence or absence of cirrhosis and, if cirrhosis, then a determination of Child-Turcotte-Pugh (CTP) class A, B, or C; and (3) any prior history of treatment experience (**Table 2**).

Side Effects of Direct-acting Antiviral Regimens in Phase 3 Trials

Side effects of current DAAs are common but generally mild.[5–16] Periodic laboratory monitoring of levels of liver enzymes, bilirubin, and hemoglobin is recommended for patients receiving HCV antiviral therapy (**Table 3**).[18,19]

Box 1
HCV DAA pretreatment evaluation

- HCV genotype and subtype
- HCV RNA (quantitative viral load) ideally within 6 months before start of treatment
- Fibrosis assessment – may be done by 1 or more of the following:
  - Liver biopsy
  - Liver Fibrosis imaging such as transient elastography (FibroScan)
  - Serum markers of fibrosis such as FibroSure, FibroTest, FIBROSpect
  - Clinical calculators of fibrosis such APRI[20,21] or FIB-4[22]
- Determination of the absence/presence of cirrhosis – may be done by 1 or more of the following:
  - Physical exam findings (splenomegaly, spider angioma, other)
  - Routine laboratory findings (thrombocytopenia, hypoalbuminemia, other)
  - Abdominal imaging findings (nodular surface of liver, splenomegaly, other)
  - Liver biopsy documentation of cirrhosis
  - Non-invasive fibrosis assessment consistent with cirrhosis (e.g., APRI > 2.0, FIB-4 > 3.25, elastography > 1.25 kilopascals)
- If cirrhosis is detected, the CTP class should be determined
- If cirrhosis is detected, HCC should be excluded by imaging within the previous 6 months
- HCV treatment history and outcome
- Human immunodeficiency virus (HIV) status and, if HIV seropositive, current antiretroviral regimen and degree of viral suppression

Documented use of 2 forms of birth control in patient and sex partners in whom a ribavirin-containing regimen is chosen.
Abbreviations: APRI, AST to Platelet Ratio Index; FIB-4, Fibrosis-4 Calculator.

Table 2
CTP classification of the severity of cirrhosis

	Class A	Class B	Class C
Total points	5–6	7–9	10–15
Factor (points)	1	2	3
Total bilirubin (μmol/L)	<34	34–50	>50
Serum albumin (g/L)	>35	28–35	<28
Prothrombin time/ International Normalized Ratio	<1.7	1.71–2.30	>2.30
Ascites	None	Mild	Moderate–severe
Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory)

Assessing Hepatitis C Virus Treatment Response

Assessment of HCV RNA during and after therapy is critical to determining treatment response. The goal of treatment is to achieve an HCV RNA level less than the level of detection (ie, undetectable). Consider checking HCV RNA starting at week 2 or week 4, and every 2 weeks until the level becomes undetectable. End-of-treatment HCV RNA is recommended but optional. HCV RNA levels at 12 weeks after the completion of treatment need to be obtained to determine whether SVR was achieved (**Box 2**).

Interpretation of Hepatitis C Virus RNA Results

Several assays are available for quantifying HCV RNA levels, with different lower limits of quantification and ranges of detection. The US Food and Drug Administration (FDA) recommends use of a sensitive, real-time, reverse-transcription polymerase chain reaction (RT-PCR) assay for monitoring HCV RNA levels during treatment with DAA agents. To assess treatment response, commercial assays that have a lower limit of HCV RNA quantification of less than or equal to 25 IU/mL are strongly recommended. Some assays have a lower limit of HCV RNA quantification of 12 IU/mL. For results greater than the lower limit of quantification for the assay being used (eg, >25 IU/mL), the result is quantified, commonly referred to as the viral load. However, low levels of virus close to the limit of quantification may mean that HCV RNA is detected by the assay but not

Table 3
Side effects of DAAs in phase 3 trials

HCV DAA Regimen	Headache (%)	Fatigue (%)	Nausea (%)	Diarrhea (%)	Insomnia (%)	Skin Reactions (%)
Daclatasvir + sofosbuvir	20	19	12	9	6	NR
Ledipasvir/sofosbuvir	13–18	11–17	6–9	3–7	3–6	—
Ombitasvir/paritaprevir/ ritonavir + dasabuvir ± ribavirin	—	34	16–22	—	12–14	13–18
Sofosbuvir + simeprevir ± ribavirin	21	25	14	—	—	11

Abbreviation: NR, not reported.

Box 2
HCV treatment monitoring

Test the HCV RNA level assessed at week 4 of treatment.

If the HCV RNA is quantifiable at week 4 or at any time point thereafter, reassess HCV RNA in 2 weeks. If the repeated HCV RNA increases, discontinuation of all treatment should be strongly considered.

HCV RNA should be tested at end of treatment

HCV RNA must be tested at 12 weeks after completion of treatment or thereafter to determine whether SVR was achieved.

quantifiable, and often these are reported as detected. This result should be interpreted as extremely low level of virus but still detectable. In addition, when no HCV RNA can be detected by the assay, then the report may read either as "Target not detected," or as "Undetected," or simply as "Less than 25 IU/mL"; for example, when 25 IU/mL is the lower limit for that assay. It is important that treating providers understand how to interpret the reporting of HCV RNA results by their laboratories (**Box 3**).

Drug Resistance in Direct-acting Antivirals

DAAs target the HCV virus at the NS3, NS5A, and NS5B areas, but amino acid polymorphisms can exist within these areas causing reduced efficacy of DAAs.[23] These polymorphisms are termed resistance-associated variants (RAVs). NS5A inhibitors and NS3/4A protease inhibitors are particularly susceptible to resistance. Although a low percentage of patients treated with DAAs fail to achieve SVR, testing for RAVs may become part of planning for retreatment after a DAA failure. With further study, recommendations on who and when to test for RAVs are expected to be developed.

Genotype 1

Genotype 1 in the DAA era has had extremely high response rates, consistently 90% and higher. Some DAA studies have also uncovered that there are significant differences between genotype 1a and genotype 1b for some regimens, with genotype 1a having been shown to be more likely to contain baseline RAVs (eg, Q80K)

Box 3
Definitions of HCV treatment response

Rapid virologic response: undetectable HCV RNA at 4 weeks during treatment.

End-of-treatment response: HCV RNA less than lower limit of quantification (LLQ) at the end of treatment.

SVR: HCV RNA less than LLQ at least 12 weeks after treatment completion.

Relapse: HCV RNA less than LLQ during treatment and/or at the end of treatment, but subsequent quantifiable HCV RNA following treatment cessation.

Partial response: greater than or equal to 2 $\log_{10}$ reduction from baseline HCV RNA at week 12, but virus remains detectable through week 24 or treatment end with peginterferon and ribavirin.

Nonresponse: detectable HCV RNA throughout treatment.

Null response: less than 2 $\log_{10}$ reduction from baseline HCV RNA during peginterferon and ribavirin treatment.

and patients with genotype 1a requiring either a longer duration and/or the addition of ribavirin with some regimens, such as the regimen of paritaprevir/ritonavir/ombitasvir plus dasabuvir, compared with patients with genotype 1b.[11–14] Learning the subtype of a patients with genotype 1 can be relevant depending on which DAA is being used. By the end of 2015, there were 3 FDA-approved all-oral regimens for genotype 1: ledipasvir/sofosbuvir,[8–10] paritaprevir/ritonavir/ombitasvir plus dasabuvir plus/minus ribavirin,[11–14] and sofosbuvir plus simeprevir plus/minus ribavirin.[15] Other regimens are under FDA review and are anticipated to be introduced in 2016, and additional agents are also still in development at this time (**Table 4**).

Genotype 2

Current all-oral FDA-approved treatment of genotype 2 is sofosbuvir plus ribavirin for 12 weeks.[6,7] There are some data to show that extending to 16 weeks significantly improves outcomes for cirrhotics and treatment-experienced patients.[24] At this time, there have not been FDA-approved all-oral regimens that do not require ribavirin for genotype 2, but there are trials of ledipasvir/sofosbuvir and daclatasvir plus sofosbuvir for genotype 2,[25,26] both of which would not require ribavirin (**Table 5**).

Table 4
Genotype 1: 2015 recommended treatment options of FDA approved DAAs

Treatment History and Cirrhosis Status	Genotype 1 Recommended Regimens in 2015
Treatment naive Without cirrhosis	Ledipasvir/sofosbuvir × 12 wk Ledipasvir/sofosbuvir × 8 wk: if baseline viral load <6 million IU/mL Ombitasvir/paritaprevir/ritonavir + dasabuvir × 12 wk Genotype 1a: add ribavirin Genotype 1b: ribavirin not required
Treatment naive Cirrhosis	Ledipasvir/sofosbuvir × 12 wk (CTP A, CTP B[a] and C[a]) Ombitasvir/paritaprevir/ritonavir + dasabuvir (CTP A)[b] Genotype 1a: add ribavirin; × 24 wk Genotype 1b: ribavirin not required × 12 wk
Treatment experienced (prior peginterferon/ribavirin experienced only) Without Cirrhosis	Ledipasvir/sofosbuvir × 12 wk Ombitasvir/paritaprevir/ritonavir + dasabuvir × 12 wk Genotype 1a: add ribavirin Genotype 1b: ribavirin not required
Treatment experienced (prior peginterferon/ribavirin experienced only) Cirrhosis	Ombitasvir/paritaprevir/ritonavir + dasabuvir × 12 wk[b] (CTP A) Genotype 1a: add ribavirin Genotype 1b: ribavirin not required. Ledipasvir/sofosbuvir + ribavirin × 12 wk[a] (CTP A, B, C)
Treatment experienced (prior NS3/4A inhibitor or sofosbuvir + pegylated interferon + ribavirin) With or without cirrhosis	Ledipasvir/sofosbuvir + ribavirin × 12 wk[a]

[a] Not FDA approved.
[b] FDA warning against using in patients with advanced cirrhosis.

Table 5
Genotype 2: 2015 recommended treatment options of FDA approved DAAs

Treatment History and Cirrhosis Status	Genotype 2 Recommended Regimens in 2015
Treatment naive Without cirrhosis	Sofosbuvir + ribavirin × 12 wk
Treatment naive Cirrhosis	Sofosbuvir + ribavirin × 16 wk
Treatment experienced Without cirrhosis	Sofosbuvir + ribavirin × 12 wk[a]
Treatment experienced Cirrhosis	Sofosbuvir + ribavirin × 16 wk[a]

[a] FDA approved for 12 weeks. Not FDA approved for 16 weeks.

Genotype 3

Genotype 3 has had much more difficulty consistently achieving outstanding SVR rates.[27] Baseline and treatment emergent RAVs may be more relevant in patients with genotype 3, especially for NS5A RAVs,[23] and guidelines are now recommending baseline RAV testing for patients with genotype 3 to help guide selection of regimen.[18,19] At the end of 2015, the most effective interferon-free regimens for genotype 3 were daclatasvir plus sofosbuvir with ribavirin,[16] or ledipasvir/sofosbuvir with ribavirin, which is not FDA approved at this time.[28] These regimens have achieved 90% to 100% SVR among noncirrhotic patients, but in cirrhotic patients SVR rates have been much lower, and treatment must be extended to increase likelihood of SVR. Treatment with sofosbuvir plus pegylated interferon and ribavirin has the highest SVR rate for patients with genotype 3 with cirrhosis[24] and patients do not develop NS5A resistance, but the regimen requires interferon. At this time, patients with genotype 3 with cirrhosis and prior treatment experience are proving to be an especially challenging group, although more effective therapies are anticipated as early as 2016 (**Table 6**).[29]

Hepatitis C Virus–Human Immunodeficiency Virus Coinfection

Patients coinfected with HCV–human immunodeficiency virus (HIV) have SVR rates similar to those in patients not infected with HIV in the DAA era[30–34] and should receive the same HCV antiviral regimen as patients not infected with HIV, regardless of genotype.[18,19] Potential drug interactions are of greater concern for coinfected patients,

Table 6
Genotype 3: 2015 recommended treatment options of FDA approved DAAs

Treatment History and Cirrhosis Status	Genotype 3 Recommended Regimens in 2015
Treatment naive Without cirrhosis	Ledipasvir/sofosbuvir plus ribavirin × 12 wk[a] Daclatasvir + sofosbuvir × 12 wk
Treatment naive Cirrhosis	Daclatasvir + sofosbuvir + ribavirin × 12 wk (CTP A) Daclatasvir + sofosbuvir + ribavirin × 24 wk (CTP B and C)
Treatment experienced Without cirrhosis	Sofosbuvir + pegylated interferon + ribavirin × 12 wk[a] Ledipasvir/sofosbuvir + ribavirin × 12 wk[a]
Treatment experienced Cirrhosis	Sofosbuvir + pegylated interferon + ribavirin × 12 wk[a] Daclatasvir + sofosbuvir + ribavirin × 12 wk (CTP A) Daclatasvir + sofosbuvir + ribavirin × 24 wk (CTP B and C)

[a] Not FDA approved.

and the choice of HIV regimen and HCV DAA regimen need to be carefully considered to avoid toxicities and development of drug resistance (Table 7).

Summary

HCV treatment has undergone extensive change in the past 2 years. There are now multiple regimens of drugs that have extremely high success rates and that are all-oral, short courses with mild side effects. Physicians and providers who treat patients with HCV need to be familiar with the evaluation of patients with HCV for treatment and how to select treatment course and monitor appropriately, especially when the field is still rapidly evolving.

PHARMACOTHERAPY FOR IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal (GI) disorders worldwide. Estimates of the US population prevalence of IBS have varied greatly across studies, ranging from 3.1% to 20.4%,[35] because of varying survey methodologies and the application of different diagnostic criteria. Chronic abdominal pain and altered bowel habits are the primary characteristic clinical features of IBS and these patients are broadly classified as those with constipation-predominant symptoms (IBS-C) and those with diarrhea-predominant symptoms (IBS-D).[36,37] IBS and other functional disorders account for substantial morbidity and cost.[38,39] Although lifestyle modifications and dietary manipulation remain as the initial management strategy for patients with mild to moderate symptoms that do not impair the quality of life, pharmacotherapy plays a significant role as an adjunctive treatment. This article focuses on the pharmacotherapy for IBS.

Approach to Pharmacotherapy for Irritable Bowel Syndrome

Pharmacologic therapy is initiated in patients with moderate to severe symptoms that impair quality of life. In the management of IBS, various treatments have been used, such as[35] fiber,[36] interventions that modify the microbiota (eg, probiotics, prebiotics, antibiotics),[37] antispasmodics,[38] antidiarrheals,[39] antidepressants,[40] psychological therapies,[41] prosecretory agents,[42] osmotic and stimulant laxatives,[43] narcotic and non-narcotic analgesics, and[44] antibiotics. The choice of agents depends on the dominant symptom and the subtype of IBS. Pharmacologic agents should be used to supplement lifestyle modifications as an adjunctive therapy (Table 8).

There are several trials comparing specific agents with placebo, resulting in mixed results. In a survey of 1966 patients with IBS by Drossman and colleagues,[40] patients with IBS took at least 2 drugs on average (range, 0–13), and the most commonly prescribed medications were non-narcotic analgesics (31%), antidepressants (30%), antidiarrheal agents (23%), antispasmodics (18%), and opiates (18%). The use of

Table 7
Studies of DAA combination regimens in HIV-HCV coinfected patients

Study	N	Treatment	SVR Rates (%)
ION-4	335	Ledipasvir/sofosbuvir × 12 wk	94–97
ALLY-2	127	Daclatasvir + sofosbuvir × 12 wk	91–98
TURQUOISE-1	63	Ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin × 12–24 wk	83–95
C-EDGE	218	Grazoprevir/elbasvir × 12 wk	94–100

Table 8
Pharmacotherapy in IBS

Treatment	Benefits	Common Adverse Effects
Over-the-counter Agents		
Fiber: psyllium	Effective for IBS-C	Bloating, gas
Laxative	Beneficial for constipation in IBS-C, but not global symptoms	Bloating, gas, cramping, diarrhea
Antidiarrheal: loperamide	Beneficial for diarrhea in IBS-D, but not global symptoms	Constipation
Probiotics	Unclear benefit	Similar to placebo
Antispasmodic: peppermint oil	Beneficial for global symptoms and cramping	GERD, constipation
Prescription Drugs		
Antidepressants: TCAs, SSRIs, SNRIs	Improve global symptoms and pain	Dry eyes/mouth, sedation, constipation
Antispasmodics	Some benefit in global symptoms and pain	Dry eyes/mouth, sedation, constipation
Prosecretory agents Linaclotide Lubiprostone	Improve global abdominal and constipation symptoms in IBS-C	Nausea, diarrhea
Antibiotics: rifaxamin	Improve global abdominal and constipation symptoms in IBS-D	Similar to placebo
5-HT_3 antagonists Alosteron Ondansetron	Improve global abdominal and constipation symptoms in IBS-D	Constipation, rarely ischemic colitis
Eluxadoline	Improves abdominal pain and diarrhea with IBS-D	Constipation, nausea, rarely pancreatitis

Abbreviations: 5-HT_3, 5-hydroxytryptamine; GERD, gastroesophageal reflux disease; SNRIs, serotonin norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

pain medications (both narcotic and non-narcotic) and antidepressants reemphasizes that chronic pain is the predominant symptom reported by patients with IBS.[40] The adverse effects of these medications were greatest with narcotics, antidepressants, and anticonstipation drugs.

Pharmacotherapy in Constipation-predominant Irritable Bowel Syndrome

Bulking agents

Increased intake of dietary fiber is recommended to improve constipation-related symptoms in IBS-C. However, insoluble fiber (found in the seeds and skins of fruit) may exacerbate symptoms, causing more bloating, and provide little relief; soluble fiber (the type of fiber included in oatmeal, nuts, beans, apples, and blueberries) such as psyllium (ispaghula husk) in particular, provides relief in many patients. The authors suggest starting psyllium at a low dose of 1.2 gm daily and titrate up in dose and frequency based on the symptom response.[41] Psyllium should always be consumed mixed with water or other liquids, and not be swallowed dry because it may cause esophageal impaction.

If there is inadequate response to the initial management with dietary fiber, laxatives are the first choice for patients with IBS-C.

Osmotic laxatives

Polyethylene glycol Although there is no randomized controlled trial (RCT) showing a beneficial effect of polyethylene glycol (PEG) laxatives on IBS-related global symptom relief, the efficacy of PEG in increasing the frequency of bowel movements has been well shown and therefore PEG laxatives are useful in patients with IBS-C for specific symptom relief of constipation.[42,43] The usual dose is to start with 17 g of powder dissolved in 235 mL (8 oz) of water once daily and titrate up or down (to a maximum of 34 g daily) to effect. There are very few reported adverse effects with PEG and the cost is very low.

Other osmotic laxatives, such as lactulose and sorbitol, cause more bloating and flatulence and therefore should be avoided in patients with IBS.[44]

Stimulant laxatives

Stimulant laxatives include senna, bisacodyl, and sodium picosulfate. These laxatives cause fluid and electrolyte secretion by the colon mucosa and induce peristalsis, thereby producing a bowel movement. These drugs are used in chronic idiopathic constipation and are not indicated in IBS.[41]

Prosecretory agents

Linaclotide and lubiprostone are the two novel prosecretory agents that are FDA approved for use in IBS-C.[45,46] These drugs are similar in their pharmacokinetics and have negligible systemic absorption.[47]

Linaclotide Linaclotide is a peptide that activates guanylate cyclase-C receptors on the lumen of intestinal epithelium, which results in secretion of bicarbonate, chloride, and water into the lumen as well as stimulating colon transit. Linaclotide (Linzess) is administered at a dose of 290 μg daily and the most common adverse event is diarrhea.[46]

Lubiprostone Lubiprostone is a locally acting chloride channel activator that enhances chloride-rich intestinal fluid secretion. Lubiprostone (Amitiza) at dose of 8 μg twice daily is FDA approved to treat IBS-C in women 18 years and older.[45] The most common adverse effect is nausea.

The American Gastroenterological Association (AGA) recommends using linaclotide and lubiprostone (compared with using no drugs) in patients with IBS-C.[42]

Pharmacotherapy in Diarrhea-predominant Irritable Bowel Syndrome

Loperamide

Loperamide (Imodium) is a nonabsorbable opioid receptor agonist that acts on mu-opioid receptions in the myenteric plexus of the large intestine. The usual starting dose is 2 mg and can be titrated up to 12 mg safely.[48,49] Although the RCTs have not shown clear benefit in composite symptom end points in IBS, because of its low cost, wide availability, and minimal adverse effects, loperamide is widely used as an adjunct to other IBS-D therapies.[50]

Eluxadoline

Eluxadoline (Viberzi) is a novel mixed mu-opioid receptor agonist and delta-opioid receptor antagonist that acts locally in the GI tract with low systemic absorption.[51] Eluxadoline, at dosage of 100 mg twice daily, was shown to be effective in simultaneously relieving the symptoms of abdominal pain and diarrhea with IBS-D over 6 months in 2 large prospective phase 3 trials, and it was FDA approved in May 2015.[52,53] The most common side effects noted were constipation, nausea, and abdominal pain, and the most serious adverse effect noted was the risk of spasm in the sphincter of Oddi, which can result in pancreatitis.

Rifaximin

IBS is thought to be caused by alteration of gut microbial flora. Rifaximin, a minimally absorbed antibiotic, proved more effective than placebo for global symptoms and bloating, and was well tolerable, in patients with IBS.[54–56] Rifaxamin (Xifaxan) at a dosage of 550 mg 3 times daily has been recently approved by the FDA for IBS-D.[53] After a 2-week course, the efficacy persisted for up to 12 weeks.[55]

Tricyclic antidepressants and selective serotonin reuptake inhibitors

Antidepressants provide a statistically significant benefit compared with placebo for abdominal pain, global assessment, and IBS symptom score. Several RCTs showed a modest improvement in global symptom relief, with tricyclic antidepressants such as amitriptyline, desipramine, and imipramine. These are low-cost options that can be used as adjunctive therapy with caution, paying attention to the adverse effects such as sedation, prolongation of QT interval, urinary retention, and glaucoma.[42] Pooled results from 5 RCTs after durations of 6 to 12 weeks of selective serotonin reuptake inhibitors (SSRIs) showed no improvement in symptoms in IBS. The AGA recommends against using SSRI for patients with IBS.[42]

Antispasmodics

Antispasmodics decrease the smooth muscle contractions and reduce motility and secretions, thereby giving relief for abdominal pain and diarrhea.[50] Spasmolytic agents compared with placebo provided a statistically significant benefit for abdominal pain, global assessment, and IBS symptom score. The commonly used antispasmodics agents are dicyclomine, hyoscine (ie, scopolamine), and L-hyoscyamine (ie, active L-isomer of atropine). These agents are preferably used to treat IBS-D because of the side effect of constipation, although they can also be used as add-on agents for IBD-C.

5-Hydroxytryptamine Receptor Antagonists

Alosetron

Alosetron, a 5-hydroxytryptamine (5-HT_3) receptor antagonist, has been shown to have good tolerability with clinical efficacy in women with refractory IBS-D symptoms that are severe and unresponsive to other agents.[57] Alosteron was initially approved by the FDA in 2000 at a dosage of 1 mg twice daily, and then, because of reports of complications such as constipation and ischemic colitis, it was withdrawn from the market, and has now been reintroduced for use only under a specific physician-based risk management program.[42,58]

Ondansetron

Patients with IBS-D have faster transit times than healthy controls.[59] Ondansetron, a 5-HT_3 receptor antagonist, a commonly used antiemetic, was shown to reduce colonic transit time in healthy individuals many years ago.[60] In a recent randomized trial of 120 patients, significant improvement in stool form and urgency was seen with ondansetron compared with placebo; however, there was no change in pain and bloating.[59] Considering the chronic nature of the disease, the results from this 5-week study should be approached with cautious optimism and could be considered when treating selected patients with IBS-D.[61]

Summary

Most recommendations on pharmacotherapy in IBS are based on low-quality to moderate-quality evidence. No single IBS therapy is uniformly effective for all patients, and the treatment should be personalized for each patient based on the symptom. Recognizing the risk of adverse effects, and the unclear benefit for global symptom

relief, pharmacotherapy should be initiated only to patients with moderate to severe symptoms that impair the quality of life.

PHARMACOTHERAPY FOR GASTROESOPHAGEAL REFLUX DISEASE AND PEPTIC ULCER DISEASE

Gastroesophageal reflux disease (GERD) is one of the most prevalent diseases worldwide, and approximately 20% of the US population has GERD.[62–64] The prevalence of GERD is much less in Asia (5%) compared with the Western world.[63] Peptic ulcer disease (PUD) is another common GI disease with considerable morbidity and complications such as GI bleeding. Many environmental factors, such as nonsteroidal antiinflammatory drugs (NSAIDs), smoking, and *Helicobacter pylori*, have been strongly related to PUD. There is a downtrend in the incidence of PUD and related complications in recent decades because of better management of PUD.[65–69] Patients often have overlapping symptoms of GERD (ie, regurgitation and heartburn) and PUD (pain or discomfort localized to the upper abdomen) and it is important to distinguish between them, because this has important diagnostic and therapeutic implications. Lifestyle and dietary modification, and avoiding offending agents, are basic initial recommendations for both these diseases before initiating pharmacotherapy. This article focuses on pharmacotherapy for GERD and PUD.

Medical Management of Gastroesophageal Reflux Disease

Medical management of GERD should be initiated in patients who fail initial lifestyle interventions such as weight loss; head-of-bed elevation; avoidance of late evening meals; tobacco and alcohol cessation; and cessation of chocolate, caffeine, spicy foods, citrus, and carbonated beverages.[70–74]

Although antacids, histamine2-receptor antagonists (H_2RA), and proton pump inhibitors (PPIs) are the agents available to treat GERD, the cornerstone of GERD therapy is to decrease the esophageal acid exposure by decreasing gastric acid secretion.[75] Therefore PPIs remain the first-line therapy to achieve this goal[75] (**Table 9**).

Proton Pump Inhibitors

PPIs are the most potent inhibitors of gastric acid secretion by irreversibly inhibiting the final common step in acid secretion via hydrogen-potassium (H-K) ATPase pump. PPIs have been shown to be superior to H_2RA, antacids, and sucralfate in many clinical trials and meta-analyses.[75,76] PPIs have shown a significantly faster healing rate of peptic ulcers (12%/wk) versus H_2RAs (6%/wk) and provided faster, more complete heartburn relief (11.5%/wk) versus H_2RAs (6.4%/wk).[77] In patients who have erosive reflux disease, PPIs seem to give better relief than in patients with nonerosive reflux disease (NERD).[78] Even in patients with NERD, PPIs provided better heartburn relief than H_2RA.[78]

Which Proton Pump Inhibitor, When to Administer, What Dose, and How Long?

Among the 6 currently available PPIs (rabeprazole, pantoprazole, esomeprazole, dexlansoprazole, omeprazole, lansoprazole), omeprazole and lansoprazole can be obtained over the counter without a prescription. There is no significant difference in efficacy between different PPIs.[79] Although some studies show differences in esophageal reflux using pH monitoring, clinically superior outcomes have not yet been shown.[80,81]

Any form of PPI for an 8-week course is the initial first line of therapy for symptom relief in GERD. In general, PPIs are more effective when administered 30 to 60 minutes before

Table 9
Antisecretory agents in GERD and PUD

Drug Name	Dose (mg)	Interaction	Potential Adverse Effects
H_2RA	Dosage adjustment is required for patients with renal insufficiency	—	Cytopenias, rash, GI intolerance, and arrhythmias
Cimetidine	800 BID or 400 QID	Multiple drug interactions	—
Famotidine	20 BID or 40 QD	Multiple drug interactions	—
Nizatidine	150 BID or 300 QD	Multiple drug interactions	—
Ranitidine	150 BID or 300 QD	Multiple drug interactions	—
PPIs	No dosage adjustment needed for renal impairment May require lower dosage in hepatic impairment	—	GI symptoms (abdominal pain, diarrhea, nausea), headache, rash, liver toxicity, osteoporosis, community-acquired pneumonia
Omeprazole	20–40 QD	↓ Absorption of clopidogrel, ketoconazole ↑ Absorption of digoxin ↓ Clearance of diazepam, warfarin, phenytoin	—
Pantoprazole	40 QD or 40 BID	Not many drug interactions	—
Lansoprazole	15–30 QD or 30 BID	Not many drug interactions	—
Esomeprazole	20–40 QD	↓ Absorption of clopidogrel, ketoconazole ↓ Clearance of diazepam, warfarin, phenytoin	—
Dexlansoprazole	30–60 QD	Not many drug interactions	—

Abbreviations: BID, twice a day; QD, every day; QID, 4 times a day; TID, 3 times a day.

the first meal of the day for maximal pH control, because the amount of H-K–ATPase present in the parietal cell is greatest after a prolonged fast. However, the newer dexlansoprazole, which is in a dual delayed-release form, can be taken any time of the day regardless of food intake.[82] The PPI should be titrated down to the lowest possible effective dose based on the symptom control during long-term therapy.[83,84]

Can Proton Pump Inhibitors be Used as On-demand Therapy?

In general PPIs have a half-life of ~1 hour, although some newer PPIs, like lansoprazole, have slightly longer half-lives than the prototype omeprazole. Because only the actively acid-secreting proton pumps are inhibited, and only a few pumps may be active during the brief interval when PPIs are present (all PPIs have plasma half-lives of 1–2 hours), the antisecretory action increases on daily dosing and the full steady-state acid inhibition is achieved only after 4 to 5 days. Therefore, PPIs should be administered daily as a course rather than on demand, as in the case of antacids.[85]

Is Maintenance Therapy After the Initial 8 Weeks Necessary?

PPIs should be continued as daily maintenance therapy for patients who continue to have symptoms after PPIs are discontinued and in patients with complications, including erosive esophagitis and Barrett esophagus.[83,84,86] Almost two-thirds of patients with NERD and moderate to severe esophagitis have relapse of symptoms over a period of time when PPIs are discontinued.[87,88]

Histamine Receptor Antagonists

H_2RAs cause competitive (ranitdine) and noncompetitive (famotidine) inhibition of the histamine2 receptor on the gastric parietal cell and decrease the acid secretion. They soon develop tolerance, which limits their use in maintenance therapy for GERD.[89] The role of H2RAs in GERD is mainly as an adjunctive therapy, as additional bedtime H_2RA along with PPIs for patients with symptoms refractory to PPI. This bedtime H_2RA approach has been shown to be effective in decreasing nocturnal acid breakthrough in patients with GERD.[90] If clinical tolerance for H_2RA is encountered, intermittent or on-demand H_2RA could be helpful, although there are no data to support such a strategy.

Antacids

Antacids have a limited role in management of GERD. They tend to provide immediate short-term relief of heartburn by neutralizing the gastric acid, thereby limiting the acid reflux to the esophagus. However, this relief is temporary, lasting only for a few minutes to an hour and is therefore not recommended for definitive therapy.[91]

Pharmacotherapy for Nonresponders or Partial Responders to Proton Pump Inhibitors

For patients with refractory symptoms while on PPIs, the emphasis should be on lifestyle adjustments, and then referral for further evaluation with possible endoscopy. The initial step in management of refractory GERD is optimization of the dose and timing of administration of the PPI.[92] The dose could be doubled, nighttime H_2RAs could be added along with the PPIs, and it could be reemphasized that patients should take the PPI 30 to 60 minutes before the first meal of the day. Sometimes a trial of switching to a PPI from a different group provides better relief to some patients.[93]

Baclofen for Refractory Gastroesophageal Reflux Disease

A small subset of patients with refractory GERD have nonacid reflux. Refractory GERD can be defined as failure of symptom resolution despite twice-daily PPIs and

additional bedtime H_2RA therapy. In these patients, the gamma-aminobutyric acid B agonist baclofen has been shown to decrease reflux episodes and symptoms during PPI therapy.[94] Randomized trials comparing baclofen and surgical fundoplication are currently underway.[95]

Adverse Effects of Proton Pump Inhibitors

For minor common adverse effects, such as headache, dyspepsia, and diarrhea, clinicians should consider switching to a different class of PPI. During long-term PPI use, significant gastric acid reduction can lead to development of reactive hypergastrinemia and hypochlorhydria, which can result in development of atrophic gastritis, which is a precursor for gastric cancer.[96] There are convincing data establishing the association between PPI use with an increase in *Clostridium difficile* colitis, although the magnitude of risk is very low.[97] The FDA has issued a warning that long-term use of PPIs can decrease calcium absorption and increase the risk of osteoporotic fractures in the elderly.[96,98] The data on an increased risk for community-acquired pneumonia (CAP) in association with PPI therapy are still conflicting, and PPI therapy should not be withheld in patients requiring therapy because of a potential risk of CAP.[84,86,99] Although there are no worrisome issues, drug-to-drug interactions are to be considered when using PPIs. Recent studies have shown that PPI therapy does not need to be altered during concomitant clopidogrel use because no increased risk for adverse cardiovascular events has been found.[100–102] Because of the potential teratogenicity, PPIs should be avoided in pregnancy and instead sucralfate could be used.

Medical Management of Peptic Ulcer Disease

The initial management of PUD varies based on the clinical presentation and likely cause. The treatment options include empiric antisecretory therapy and empiric therapy for *H pylori* infection, along with avoiding the possible causative agents, such as NSAIDs.

Eradication of Helicobacter pylori

Apart from patients who are taking NSAIDs, most patients with duodenal ulcers and at least two-thirds of patients with gastric ulcers are infected with *H pylori*. Therefore, the current recommendation is to test for *H pylori* in all patients with active PUD and with confirmed history of peptic ulcer disease (not previously treated for *H pylori*).[103] First-line therapies for *H pylori* include a PPI, clarithromycin, and amoxicillin or metronidazole (triple therapy), and a bismuth/tetracycline-based quadruple therapy[103] (**Table 10**). In areas where clarithromycin resistance is high (>15%–20%), the effectiveness of this triple combination therapy is less than 70% to 80% and so metronidazole should be given instead of clarithromycin.

Table 10
First-line therapies for *H pylori*

Type of Regimen	Drugs	Frequency	Duration (d)
I	PPI	BID	10–14
	Clarithromycin 500 mg	BID	
	Amoxicillin 1 g or METRONIDAZOLE 500 mg	BID	
II	PPI	QD	10–14
	Tetracycline 500 mg	QID	
	Bismuth subsalicylate 525 mg	QID	
	Metronidazole 250 mg	QID	

Table 11
Sequential therapy for *H pylori*

Duration (d)	Drug	Frequency
First 5	PPI + amoxicillin 1 g	BID
Next 5	PPI + clarithromycin 500 mg + tinidazole 500 mg	BID

The treatment is usually recommended for 10 to 14 days, because shorter regimens are shown to have lesser eradication rates.[104] The eradication rates with PPI-based triple therapy and quadruple therapy are similar.[105,106] It is therefore reasonable to start empiric triple therapy (PPI, clarithromycin, and amoxicillin) in patients who have not previously received clarithromycin and who are not allergic to penicillin. If the patient is allergic to penicillin, metronidazole can be substituted for amoxicillin. If the patient is allergic to penicillin or has previously been treated with clarithromycin, bismuth quadruple therapy should be considered[105] (see **Table 10**).

In recent years, there has been a decline in eradication rates with clarithromycin-based triple therapy or bismuth-based quadruple therapy. Studies show eradication rates greater than 90% with sequential therapies based on PPIs, and amoxicillin for 5 days followed by a PPI, clarithromycin, and tinidazole for an additional 5 days[107](**Table 11**).

Treatment of Persistent Helicobacter pylori Infection (Salvage Therapy)

After failed first-line therapy, a thorough review of the patient's previous treatment regimen is prudent to avoid the same antibiotics. Also, it is important to assess for medication nonadherence and to reinforce the importance of adhering to the regimen. because most patients are treated with clarithromycin-based triple therapy as first line, bismuth-based quadruple therapy is considered an accepted salvage therapy in patients not treated previously with metronidazole.[108] However, with persistent infection, levofloxacin-based therapy (levofloxacin, omeprazole, nitazoxanide, and doxycycline [LOAD]) for 10 days has been shown to be an alternate option, although no validation studies have so far been done in the United States[103,108,109] (**Table 12**).

Antisecretory Therapy

Antisecretory therapy is mandatory for all the patients with peptic ulcers, independent of cause, to aid ulcer healing. PPIs are a mainstay of antisecretory therapy because

Table 12
Salvage therapy for persistent *H pylori* infection

	Frequency	Duration (d)
Bismuth quadruple therapy		
PPI	QD	7–14
Tetracycline, bismuth, metronidazole	QID	—
LOAD	—	10
Levofloxacin 250 mg	QD	—
PPI	BID	—
Nitazoxinide 500 mg (Alinia)	BID	—
Doxycycline 100 mg	QD	—

Box 4
Long-term maintenance PPI therapy in PUD

1. Continued NSAID use
2. Failure to eradicate *H pylori*
3. Frequent recurrent peptic ulcers
4. Large ulcer (>2 cm) with multiple comorbid conditions

they are the most potent inhibitors of acid secretion and are superior to antacids, H_2RAs, prostaglandins, and sucralfate. There are 6 currently available PPIs (discussed earlier). As mentioned earlier, PPIs should be taken 30 to 60 minutes before the first meal of the day when the proton pumps and parietal cells are active. A longer duration of antisecretory therapy is recommended with gastric ulcers (8–12 weeks) compared with duodenal ulcers (4–6 weeks).

Long-term maintenance antisecretory therapy for an indefinite period is recommended in high-risk patients with complicated ulcers, and continued use of NSAIDs (**Box 4**).

Among the 4 H_2RAs available (cimetidine, ranitidine, famotidine, and nizatidine), only ranitdine (Zantac) and famotidine (Pepcid) are commonly used. Famotidine is a noncompetitive inhibitor of histamine and so is slightly more effective than the others, which are competitive inhibitors. Also, famotidine has the longest duration of action of them all. All the agents are renally excreted and therefore dose is to be adjusted in patients with renal failure. Tolerance to the antisecretory effects of H_2RAs develops quickly and frequently. Although PPIs are the first-line antisecretory medications, H_2RAs can be used when PPIs cannot be used for reasons such as adverse effects, allergies, and drug-drug interactions.[110] A single bedtime dose of an H_2RA can heal the peptic ulcers in 8 weeks.

Treatment of Nonsteroidal Antiinflammatory Drug Ulcers

NSAIDs should be discontinued wherever possible. If NSAID therapy cannot be discontinued, dose reduction of the NSAID should be considered, along with initiation of additional long-term-PPI therapy. PPIs have been shown to be more effective than $H_2$2RAs in reducing NSAID-induced ulcers.[110,111]

Misoprostol Use in Nonsteroidal Antiinflammatory Drug Ulcers

Misoprostol, a prostaglandin analogue, has been used as a gastroprotective agent during concomitant NSAID use. There is evidence that the ulcerogenic effect of NSAIDs correlates with prostaglandin synthesis. Misoprostol is the only prostaglandin analogue approved by the FDA for prevention of NSAID-induced ulcer disease. Misoprostol has been shown to be more effective than H_2RAs in preventing NSAID-induced mucosal injury.[112] Misoprostol at a dose of 800 μg daily is equally effective as PPI in ulcer prevention with NSAID use.[113] However, its usefulness is limited by its GI side effects; especially diarrhea.

Antacids

Antacids have no proven efficacy in healing ulcers. Some studies have shown ulcer healing with antacid alone, which is thought to be by binding bile, inhibiting pepsin, and promoting angiogenesis.[114] However, ulcer healing requires high doses of antacids, which often lead to adverse side effects and therefore are rarely used in practice to treat PUD.[115]

Summary

Although most patients respond well to pharmacologic agents, lifestyle modifications should be part of the initial management of GERD before initiating pharmacotherapy. Patients with refractory GERD who do not respond to any pharmacologic therapy may be considered for surgical antireflux procedures, such as Nissen fundoplication and laparoscopic sphincter augmentation. A subset of patients with PUD, such as *H pylori*–negative disease, NSAID-negative ulcer disease, refractory peptic ulcers, and recurrence of peptic ulcers, should be treated with indefinite maintenance antisecretory therapy and also be investigated for rare causes of ulcer disease, such as Zollinger-Ellison syndrome, Crohn disease, ischemia, sarcoid, lymphoma, eosinophilic gastroenteritis, and immunoglobulin G4–related sclerosing disease.

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