A Bitter Pill to Swallow: Why Medication Safety Is Critical in Hepatitis C Treatment

Karyn M. Sullivan, PharmD, MPH; Linda M. Spooner, PharmD, BCPS (AQ-ID), FASHP, FCCP; Emily Harris, PharmD; Kenneth Lowe, PharmD; and George M. Abraham, MD, MPH, FACP

ABSTRACT

Purpose: To provide medication safety tips to optimize the management of patients receiving treatment for chronic hepatitis C virus (HCV) infection.

Summary: Ensuring safe medication use in patients who receive treatment for HCV infection is a crucial component in providing optimal patient care. Because of the complexity of available treatment options, numerous challenges exist in preventing medication errors with HCV therapies. This article will focus on the selection of appropriate treatment options along with proper dosing and duration, awareness of concomitant disease states and drug interactions, identifying adverse drug reactions (ADRs) and patient counseling points, the provision of adherence counseling and prevention of treatment interruptions, improving communication with patients and between pharmacies, and recognizing the importance of a multidisciplinary approach.

Conclusion: Maintaining awareness of medication safety strategies geared toward HCV pharmacotherapy is critical for providing optimal care for patients while minimizing the opportunity for errors.

Keywords: hepatitis C virus (HCV), medication safety, medication errors

INTRODUCTION

Approximately 71 million people globally are chronically infected with HCV, resulting in 399,000 deaths each year from HCV-related complications.1 In the United States, more than three million people are chronically infected, resulting in treatment-related costs of approximately $8 billion annually.2 In addition to its tremendous economic burden, HCV treatment results in many opportunities for medication errors to occur. These errors can happen at any point during medication use, from prescribing to dispensing to administering to monitoring. The availability of multiple treatment options for the six HCV genotypes (GT1–GT6) contributes to the risk of medication-related adverse events. Medication errors may involve regimen selection, adherence, dispensing, and drug–drug interactions.

Overall costs for HCV treatment may become higher for payers if safety issues result in patient harm or lead to an additional course of therapy. This article addresses these and other safety challenges by providing recommendations to consider for patients receiving treatment for HCV infection. (See Figure 1 for a checklist of safety recommendations.)

MEDICATION SAFETY TIP #1
Ensure Appropriate Treatment Selection

HCV treatment recommendations are based on the genotypic diagnosis of the patient as well as on individual characteristics, including concomitant human immunodeficiency virus (HIV) or hepatitis B virus (HBV) infection; cirrhosis, renal impairment, or organ transplantation; and prior treatment experience/resistance testing (if any).3 Each regimen is associated with various medication combinations, treatment durations, and potential drug–drug interactions. Strategic development of a treatment regimen is crucial. In resource-limited settings, priority in initiating a regimen may need to be given to patients experiencing advanced fibrosis, HIV/HBV co-infection, extrahepatic manifestations, compensated cirrhosis or liver transplantation resulting from the progression of liver disease, and related complications in these patient populations. Specific guidance for HCV treatment based on genotype and special patient populations can be found at www.hcvguidelines.org.4 This frequently updated document, which is based upon consensus opinion from national infectious diseases and hepatology organizations, contains detailed tables of recommended and alternative regimens for HCV infection. It provides guidance for health care providers in confirming the selection of the proper medication regimen based on individual patient characteristics and supporting data from clinical trials, thus helping to prevent medication errors in the prescribing phase.

MEDICATION SAFETY TIP #2
Ensure Appropriate Dosage and Duration of Treatment

In addition to appropriate drug selection, health care providers must take into consideration proper dosing. Many treatment regimens are available as coformulated tablets (e.g., sofosbuvir/velpatasvir, ledipasvir/sofosbuvir), and others are available as single-ingredient products (e.g., daclatasvir, sofosbuvir). Glecaprevir/pibrentasvir dosing requires 3 tablets administered once daily.4 Proper drug dosing and appropriate formulation are important for optimizing HCV pharmacotherapy. HCV drug dosage may vary as a result of drug–drug interactions with...

Disclosures: Dr. Spooner has received past grant support (not for this article) from Gilead Sciences, Inc., and was on the Bristol Myers Squibb speakers’ bureau several years ago. The other authors report no commercial or financial interests in regard to this article.
A Bitter Pill to Swallow: Why Medication Safety Is Critical in Hepatitis C Treatment

The online guidance document (mentioned in Tip #1) provides a summary of the appropriate treatment duration for each recommended or alternative regimen. Also, it serves as a quick and easy method for practitioners to assess the appropriateness of a regimen that has already been chosen elsewhere. A review of this document is advisable whenever a treatment regimen is chosen, to prevent errors in therapy duration.

MEDICATION SAFETY TIP #3
Be Aware of Concomitant Disease States

Another consideration that affects medication safety is the presence of coexisting disease states that a patient may have during HCV treatment. The reactivation of HBV has been reported in co-infected patients who receive HCV treatment but are not receiving suppressive treatment for HBV. Therefore, patients should be screened for HBV infection before starting treatment for HCV infection to determine how to proceed. Also, HCV-induced hepatic dysfunction can be problematic when using nonprescription medications, which could lead to adverse effects. For example, this can occur in patients with hepatic dysfunction who use nonsteroidal anti-inflammatory drugs (NSAIDs) in place of acetaminophen for the treatment of pain. The prolonged use of NSAIDs may lead to other side effects such as renal dysfunction or upper gastrointestinal bleeding. Health care providers should review the patient’s coexisting conditions to determine how they may affect HCV treatment in order to prevent adverse outcomes.

MEDICATION SAFETY TIP #4
Recognize Potential Drug–Drug Interactions

Potential interactions between prescribed HCV therapy and current prescription and nonprescription medications must be assessed during the medication reconciliation process. It is important to review interactions that affect the absorption, metabolism, and any other pharmacokinetic/pharmacodynamic considerations of the particular HCV regimen. For example, daclatasvir is routinely dosed at 60 mg once daily. When used with a strong cytochrome P450 (CYP) 3A4 inhibitor, the dosage must be reduced to 30 mg once daily. Conversely, when used with a CYP3A4 inducer, the dosage must be increased to 90 mg once daily. Other regimens, including glecaprevir/pibrentasvir and elbasvir/ grazoprevir, contain protease inhibitors that affect the CYP isoenzyme systems, resulting in numerous contraindications and dose adjustments. Overlooking dosing adjustments such as this may lead to medication errors with subsequent poor treatment outcomes or toxicity.

A patient’s use of nonprescription products and complementary and alternative medications is another source of drug interactions with HCV therapies. For example, nonprescription acid reducers can greatly affect the absorption of ledipasvir/sofosbuvir and velpatasvir/sofosbuvir, which require an acidic environment to be absorbed. And, when administered with the majority of HCV medications, the use of St. John’s wort, which is an inducer of CYP3A4 and drug transporters such as P-glycoprotein results in subtherapeutic serum concentrations and subsequent treatment failure. Providers are advised to consult appropriate resources containing information on drug–drug interactions with HCV therapies, including subscription drug databases and no-cost resources such as the HEP Drug Interactions website www.hep-druginteractions.org. These concomitant medications, which will be discussed in Tip #4.

Another potential source of medication errors in HCV pharmacotherapy is inappropriate treatment duration. For patients with GT1 infection, the duration of treatment can vary from 8 weeks to 16 weeks, depending upon treatment history, HCV ribonucleic acid (RNA, also known as viral load), the presence or absence of cirrhosis, and the concomitant use of ribavirin. If too short a course of treatment is selected for an individual patient, the chance of a sustained virologic response (SVR) will be compromised. If treatment extends beyond the recommended guidelines, it may expose patients to a greater risk of adverse effects as well as to substantial increases in drug costs. The online guidance document (mentioned in Tip #1) provides a...
databases permit the screening of all concomitant medications that a patient is taking, along with HCV pharmacotherapy, allowing for the correct selection of and any required adjustments to the treatment regimen.

MEDICATION SAFETY TIP #5
Identify Potential Adverse Drug Reactions (ADRs)

ADRs with HCV therapies can result in the premature withdrawal of therapy for many patients. Understanding how ADRs occur with HCV medications ultimately benefits both the patient and the health care system through the reduced costs associated with symptom management and the discontinuation/modification of treatment. ADRs with HCV therapies generally occur for several reasons, including side effects caused by the treatment itself, as well as the previously discussed issues of drug–drug interactions and drug–disease interactions.

Although direct-acting antiviral therapies are much better tolerated than the previously available interferon-based therapies, adverse reactions can still be observed. For example, patients receiving simeprevir or elbasvir/grazoprevir can experience adverse effects such as fatigue, headache, nausea, rash, photosensitivity, and itching. Some patients have also reported side effects lasting up to six months post-treatment with ribavirin, owing to its extensive half-life. When considering a patient’s therapy plan, it is important to be aware of the possible side effects that may occur with HCV medications and understand how they may affect patient adherence and counseling. This is discussed further in the tips below.

MEDICATION SAFETY TIP #6
Provide Optimal Adherence Counseling

Patients’ adherence to their regimen is critical in the treatment of HCV. Therefore, health care providers must counsel patients on the importance of following treatment schedules to improve SVR rates. In studies of a two-drug regimen, as many as 50% of the patients had failed to take 80% of their prescribed doses. These numbers increased when patients moved to a three-drug regimen, presumably as a result of the more complex scheduling requirements. In some cases, even missing a few days of medication can lead to treatment failure and, subsequently, the inability to get a new treatment regimen approved by the patient’s insurance company. Every interruption in therapy causes a greater risk for failure to achieve SVR because of the potential for the development of drug resistance.

Counseling for HCV therapy should emphasize the importance of not missing any doses. Helpful recommendations for establishing a weekly dosing routine include using a pillbox organizer, setting a reminder alarm, using a smartphone medication-adherence app, or linking therapy to other daily activities. Dosing schedules should be individualized to match the lifestyle of the patient. Some patients with HCV have described their schedules as “ritualistic,” as they attempt to adhere to their therapy. Patient adherence should be assessed at each follow-up visit, and using adherence tools like the Morisky Scale can help to identify potentially problematic areas in patients’ regimens.

The timely refilling and acquisition of medications is also an important aspect of adherence. Providing clear instructions for obtaining medications is vital for preventing delays or interruptions in treatment; therefore, new and current patients should be asked about their process for refilling medications at follow-up visits. Also, let patients know how they are to receive their medications: HCV medications are dispensed primarily by specialty pharmacies, and medications may be mailed to patients directly or sent to the clinic for patients to pick up. All health care providers for patients with HCV can serve as “cheerleaders” to promote adherence to medication regimens, as well as follow-up appointments and lab work reminders, and provide encouragement throughout the entire treatment process.

MEDICATION SAFETY TIP #7
Recognize the Potential for Treatment Interruptions

As discussed in Tip #6, interruptions to HCV therapy can have devastating effects on treatment goals. Health care providers must be alert to the possibility of interruptions by noticing verbal cues during their discussions with patients. These cues may include the mention of an upcoming vacation or planned hospitalization, temporary living situations such as shelters or halfway houses, changes in medical or pharmacy insurance coverage, and concerns about having sufficient funds to pay for office visits or prescription refills. Paying attention to such cues increases the likelihood of preventing future interruptions. Supplying patients with advice and options for dealing with unanticipated interruptions—emergency-room visits, hospitalization, or incarceration—can help them to handle situations with little impact on their therapy. In such cases, patients should make every effort to bring their medications with them or have a family member deliver them as soon as possible. Furthermore, remind patients to inform their HCV providers every time they have been advised to change their concomitant medication regimen, or their HCV regimen, in response to a personal health emergency.

MEDICATION SAFETY TIP #8
Provide Comprehensive Patient Education

Health care providers can address the many factors that lead to successful and safe HCV treatment by using educational materials and patient counseling. Advise patients to get vaccinations for both hepatitis A and hepatitis B to prevent coinfection and the consequent risk of hepatic decompensation. Education regarding alcohol use is crucial in preventing accelerated fibrosis and the consequent compensation of the liver, with faster progression to end-stage liver disease. Patients should avoid using alcohol when diagnosed with HCV infection. Inform patients about safe sexual practices, such as the correct and consistent use of barrier methods of contraception to prevent the transmission of the virus and possible reinfection, especially for those who engage in high-risk behavior involving multiple partners. For patients who are known to be injection-drug users, discourage illicit drug use and consider their current habits when contemplating the timing of initial therapy. Instruct patients about harm-reduction practices, such as the use of sterile injecting equipment and proper disposal of needles, which may prevent re-infection with or transmission of the hepatitis C virus.
A Bitter Pill to Swallow: Why Medication Safety Is Critical in Hepatitis C Treatment

HCV providers should also ask their patients to report the use of new medications or over-the-counter products so that potential drug–drug interactions and ADRs can be more easily identified. In addition, providers should encourage patients to actively participate in their care and maintain open communication about any treatment concerns they may have. Patients should be instructed to contact their provider about any adverse drug effects before they discontinue any medication.

MEDICATION SAFETY TIP #9
Improve Communication Between Community and Specialty Pharmacies

A possible source of problems with HCV treatment is the lack of communication between community and specialty pharmacies. Patients can obtain HCV medications from a specialty pharmacy or from a community pharmacy that also offers specialized care programs and services for managing HCV treatment. When patients elect to obtain their HCV medications from a specialty pharmacy, it is likely that they also use a community pharmacy to obtain any non–HCV-related medications. Problems can arise when the community pharmacy staff does not have the HCV medications on the patient’s medication profile simply because they are unaware of them. Communication between community and specialty pharmacies should be improved to ensure effective screening for drug–drug interactions with HCV medications. Specialty pharmacy staff can help bridge this gap by identifying the community pharmacy used by the patient and notifying the pharmacy about the patient’s current HCV medications.

MEDICATION SAFETY TIP #10
Recognize the Utility of an Interprofessional Approach to Care

One of the most important aspects of HCV treatment is the fact that it is rarely the exclusive domain of any one type of health care provider. An interprofessional team approach is the best way to ensure optimal treatment results. Vu et al. described the value of patient navigators for managing the prior authorization process for HCV medications. Navigators can assist patients by collaborating with nurses and specialty pharmacies to obtain the prior authorizations needed for insurance coverage. In one interferon-based study performed by Carrión et al., results showed that an HCV care team with two hepatologists, two nurses, one pharmacist, and several psychiatric professionals achieved a higher SVR and significantly higher adherence rates for their patients than those without the team. The SVR rate was 77.1% in patients treated with the multidisciplinary team compared to an SVR rate of 61.9% (P < 0.05) in patients treated without the team. The adherence rate was 94.6% for patients treated with the multidisciplinary team versus 78.9% (P < 0.05) for patients without the team.

One example of the effective workflow of an interprofessional team took place at the ambulatory clinic at Froedtert Hospital in Milwaukee, Wisconsin. The team consisted of hepatologists, physician assistants, hepatology nurses, and a clinical pharmacist. After receiving their diagnosis, patients were referred to one of three on-site community pharmacies that included specialty medication processing and medication therapy management services. Patients began by seeing a hepatologist, or a physician assistant if they were returning for a follow-up appointment. After patients received approval for treatment, they visited with a hepatology nurse and clinical pharmacist for specialized education. The team also worked on behalf of the patients to obtain any necessary prior authorizations for the prescribed HCV medications. To ensure compliance, patients were encouraged to return at four-week intervals for appointments with a physician assistant to monitor laboratory values. Overall, patients were satisfied with this multidisciplinary approach to care.

MEDICATION SAFETY CHALLENGES WITH HCV TREATMENT

Medication error-reduction strategies should focus on the design of systems to mitigate human error. The most effective strategies include automation or constraints that force the correct action every time. Standardization and checklists to avoid reliance on memory are also effective, although weaker, error-reduction strategies. Creating policies and providing patient education are less effective, but are still vitally important within medication-use systems. Implementing error-reduction processes for HCV treatment is exceptionally challenging because of its complexity and interprofessional nature. The development of electronic order sets to guide prescribing is a well-known safety recommendation for promoting the standardization of care. The guidance on the website mentioned in Tip #1 acts as an order set, but it also allows for the customization of therapy (based on liver status, treatment history, genotype, and concomitant medications), which is crucial for the care of patients with HCV. Counseling and education are weak error-reduction strategies, but should not be undervalued in the treatment of HCV infection. Checking that patients comprehend instructions at each visit with each care provider is of paramount importance. Traditional safety strategies need to be tailored for HCV therapy because the medication safety concerns in this disease state are nontraditional in nature.

CONCLUSION

Caring for patients with HCV is a complex process involving the prescription, administration, and monitoring of treatment in order to avoid medication errors. In addition, patients require an abundance of safety-related recommendations to ensure the best possible treatment outcome. Consider targeted HCV medication safety strategies to minimize the risk for errors throughout the health care process.

REFERENCES

4. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America (AASLD-IDS). Recommendations for testing, managing, and treating hepatitis C. Avail-
Medication Safety in Hepatitis C Treatment


