PRN OPINION PAPER

Provision of Clinical Pharmacist Services for Individuals With Chronic Hepatitis C Viral Infection

Joint Opinion of the GI/Liver/Nutrition and Infectious Diseases Practice and Research Networks of the American College of Clinical Pharmacy

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The objective of this opinion paper was to identify and describe potential clinical pharmacists' services for the prevention and management of patients infected with the hepatitis C virus (HCV). The goals of this paper are to guide the establishment and development of pharmacy services for patients infected with HCV and to highlight HCV research and educational opportunities. Recommendations were based on the following: a review of published data on clinical pharmacist involvement in the treatment and management of HCV-infected patients; a consensus of clinical pharmacists who provide direct patient care to HCV-infected patients and practice in different pharmacy models, including community-based and academic settings; and a review of published guidelines and literature focusing on the treatment and management of HCV infections. The recommendations provided in this opinion paper define the areas of clinical pharmacist involvement and clinical pharmacy practice in the treatment and management of patients with HCV. Clinical pharmacists can promote preventive measures and education about reducing HCV transmission, improve medication adherence, assist in monitoring clinical and adverse effects, recommend treatment strategies to minimize adverse effects and drug interactions, and facilitate medication acquisition and logistics that positively improve patient outcomes and reduce the health care system costs.

KEY WORDS hepatitis C virus, HCV, peginterferon, ribavirin, direct-acting antivirals, HCV protease inhibitors, nucleotide polymerase inhibitors, NS5A inhibitors, adverse effects, clinical pharmacists, drug interactions, adherence.

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Background

Approximately 170 million persons worldwide are affected by the hepatitis C virus (HCV), and 3.2 million are chronically infected in the United States.[1] About 75–85% of patients with untreated acute HCV infection will progress to chronic infection; of these, 45% will develop cirrhosis by 2030.[1, 2] In addition, 1–5% of deaths occur from HCV-related complications of cirrhosis or hepatocellular carcinoma (HCC).[1] HCV-related morbidity and mortality are expected to increase between 2030 and 2035, with 38,000 cases of end-stage liver disease (ESLD), 3,200 cases requiring referral for liver transplantation, and 36,100 deaths.[3] These statistics are not expected to improve if current screening rates, public awareness, and interventions to treat and manage HCV infection remain low.[3] Recent data from the 1999–2008 National Health and Nutrition Examination Survey (NHANES) found that "baby boomers" (persons born between 1945 and 1965) make up 76.5% of all HCV-infected adults in the United States.[4] Therefore, the Centers for Disease Control and Prevention (CDC), the U.S. Preventive Services Task Force, the American Association for the Study of Liver Disease (AASLD), and the Infectious Diseases Society of America (IDSA) recommend a one-time screening for HCV infection in all baby boomers who do not have any known risk factors for acquiring HCV infection.[1, 5] The Institute of Medicine (IOM) reports that in the next 10 years, about 2.7–3.9 million persons will be chronically infected, and of these, 75% are unaware of their infection.[6] The IOM report identified several key issues affecting existing efforts against viral hepatitis, including a lack of knowledge about HCV infection among the general public and health care providers.[6] Their findings emphasize the need for increased HCV screening and the capability to treat HCV-infected persons. Expansion of HCV testing sites, including community pharmacies, would allow earlier detection of infected individuals and more timely management before complications of liver disease ensue. The anticipated development and approval of more effective and tolerable HCV agents may significantly increase the number of individuals seeking HCV treatment.

The AASLD recommends initiating antiviral treatment in HCV-infected persons with bridging or septal fibrosis or with compensated liver cirrhosis observed on liver histology.[7] The goals of HCV therapy are to prevent liver disease progression to cirrhosis and development of complications (e.g., portal hypertension, HCC) and mortality. Identification of HCV genotype (1–7), including subtype (e.g., 1a, 1b), is essential to determine the appropriate therapy and length of treatment. In the United States, 75% of patients are infected with HCV genotype 1, followed by genotypes 2 and 3.[7, 8] The end point of HCV treatment is determined by surrogate virologic parameters rather than by clinical end points. The primary goal of treatment is to achieve a virologic cure or a sustained virologic response (SVR), currently defined as having an undetectable HCV RNA level 24 weeks after completion of therapy, although there is support for the identification of SVR as early as 12 weeks after treatment.[7, 9]

The AASLD practice guidelines for the management of chronic HCV have undergone significant revisions in the past few years based on emerging data from clinical trials of new HCV agents. The 2009 AASLD practice guidelines recommended the combination of ribavirin and peginterferon alfa-2a or -2b as standard therapy.[7] In clinical trials, standard therapy was associated with SVR rates of approximately 42–52% in patients with HCV genotype 1 and ~80% for genotypes 2 and 3.[10] In 2011, the first-generation direct-acting antivirals (DAAs), telaprevir and boceprevir, were U.S. Food and Drug Administration (FDA) approved only for genotype 1 infection. The addition of the first-generation DAAs to standard therapy increased SVR rates by 31% to 47% with telaprevir and by 25% to 38% with boceprevir (response-guided therapy).[10] Treatment using first-generation DAAs is not FDA approved for special populations, including human immunodeficiency virus (HIV)-HCV–coinfected patients and liver transplant recipients. However, SVR rates in HIV-HCV–coinfected patients are similar to those reported in HCV monoinfected patients. Potential benefits have also been observed in studies in liver transplant recipients; unfortunately,

This paper represents the opinion of the GI/Liver/Nutrition and Infectious Diseases Practice and Research Networks of the American College of Clinical Pharmacy (ACCP). It does not necessarily represent an official ACCP commentary, guideline, or statement of policy or position.

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these studies were small, single-center studies, and only early virologic response (EVR) data were available.[11] Additionally, telaprevir and boceprevir have significant drug interactions with calcineurin inhibitors, which limits use of these agents in transplant patients.[11] The AASLD 2011 guidelines recommended starting first-generation DAAs, in combination with peginterferon alfa and ribavirin, in patients with genotype 1 infection.[12]

In January 2014, joint AASLD and IDSA updated Web-based guideline recommendations were issued based on encouraging study results and preliminary data from ongoing trials with second-generation DAAs and newer agents.[5] First-generation DAAs are no longer recommended. The AASLD and IDSA joint guidelines recommend sofosbuvir- and simeprevir-based regimens, depending on HCV genotype and eligibility of peginterferon alfa therapy, over first-generation DAA regimens and peginterferon alfa and ribavirin combination therapy.[5] The second-generation DAAs, simeprevir (NS3/4A protease inhibitor) and sofosbuvir (nucleotide analog NS5B polymerase inhibitor), were both approved by the FDA for the treatment of HCV genotype 1 infection (including cirrhosis) at the end of 2013.[13, 14] Sofosbuvir was also FDA approved in patients with HCV genotype 2, 3, or 4 infection; patients with HCC; patients with HCV–HIV-1 coinfection; and those awaiting liver transplantation.[13] Sofosbuvir should be combined with ribavirin for HCV genotype 2 or 3 and with peginterferon alfa and ribavirin for HCV genotype 1 or 4 infection. Sofosbuvir could also be combined with simeprevir with or without ribavirin (off-label use) in patients with genotype 1 infection who are ineligible to receive peginterferon alfa therapy. A major advantage of sofosbuvir-based therapy is its shorter total treatment duration of 12–24 weeks, compared with first-generation DAA therapy (24–44 weeks). However, patients with genotype 3 infection who received 12 weeks of sofosbuvir and ribavirin had worse SVR rates (30%) than those observed with peginterferon alfa and ribavirin therapy (~60%).[15] In the VALENCE study of 250 patients with genotype 3 infection, SVRs of 91% and 68% were achieved among those without and those with cirrhosis, respectively.[16] Therefore, genotype 3 patients should receive 24 weeks of sofosbuvir and ribavirin to improve SVR rates.[13, 15, 16] Similar to telaprevir and boceprevir, 12 weeks of simeprevir should be used in combination with peginterferon alfa and ribavirin for a total treatment duration of 24–44 weeks. Unfortunately, some of these newer regimens still include ribavirin and peginterferon alfa, which are associated with significant adverse effects; however, studies showed that newer regimens are associated with SVR rates greater than 90% (~60% with genotype 3 infection) and fewer adverse effects compared with first-generation DAAs and combination peginterferon alfa and ribavirin therapy.[17]

Multiple investigational agents are being studied in interferon-free regimens with or without ribavirin (e.g., paritaprevir/ritonavir, dasabuvir, ombitasvir, fixed-dose combination of sofosbuvir and ledipasvir) and all-oral, interferon-free, and ribavirin-free regimens (e.g., daclatasvir, asunaprevir, and BMS-791325 therapy) with promising results (SVR rates > 90%).[17–20] Emerging agents with activity against genotype 1 infection include the following: (i) ledipasvir, an HCV NS5A inhibitor with activity also against genotype 4 infection; fixed-dose, coformulated ledispasvir and sofosbuvir for genotype 1 infection[21–23]; (ii) paritaprevir/r, an NS3/4A protease inhibitor that is combined with ritonavir to increase its half-life, allowing once-daily dosing; (iii) ombitasvir, an NS5A replication complex inhibitor; (iv) dasabuvir, a nonnucleoside NS5B polymerase inhibitor; (v) daclatasvir, an HCV NS5A replication complex inhibitor with pangenotypic activity against genotypes 2–6[24]; and (vi) asunaprevir, an NS3 protease inhibitor with antiviral activity against genotypes 2–6.[25, 26] With expanded HCV testing and approval of new HCV agents and treatment regimens associated with impressive SVR rates and better tolerability, the demand for HCV treatment is likely to increase.

Although the current medications used to treat HCV are effective in achieving SVR, several limitations are associated with their use. Significant adverse effects associated with the administration of peginterferon alfa (e.g., depression, flu-like symptoms, neutropenia, and thrombocytopenia) and ribavirin (e.g., hemolytic anemia, rash, and teratogenicity) have resulted in treatment discontinuation rates of 10–14% and poor SVR rates.[10, 12] The addition of first-generation DAAs produced new toxicities (e.g., telaprevir-induced rash; boceprevir-induced anemia and dysguesia), worsened standard therapy toxicities, and had complicated drug interactions (substrates and inhibitors of cytochrome P450 [CYP] 3A, P-glycoprotein [P-gp], and organic anion-transporting polypeptide [OATP] 1B1 and

OATP2B1 [only with telaprevir]).[27] Newer FDA-approved DAAs have been associated with fewer toxicities compared with first-generation DAAs. The most common reported adverse effects with simeprevir are rash, photosensitivity reactions, pruritus, and nausea. Fatigue and headache have been reported with sofosbuvir coadministered with ribavirin, and fatigue, headache, nausea, insomnia, and anemia have been reported with sofosbuvir, peginterferon alfa, and ribavirin.[13, 14] Unfortunately, sofosbuvir and simeprevir are associated with significant drug interactions, although to a lesser extent compared with those associated with first-generation DAAs. Sofosbuvir is a P-gp substrate associated with significant but fewer drug interactions, primarily with potent P-gp inducers (e.g., rifampin, carbamazepine, St. John's wort).[13] Simeprevir has the potential for significantly more drug interactions than sofosbuvir since it is a substrate and inhibitor of intestinal CYP3A, P-gp, and OATP 1B1/3.[14] Currently, several interferon-free and ribavirin-free regimens have been studied and were associated with fewer adverse effects and drug interactions compared with current therapy.[17–20] Previously, limited data were available about retreatment with DAAs in patients who were failing or intolerant to initial DAA-based regimens; however, the combination of daclatasvir and sofosbuvir in patients with HCV genotype 1 was associated with SVR rates of 98% in patients who did not achieve an SVR with telaprevir or boceprevir.[24]

Purpose

The purpose of this opinion paper is to describe the practice and scope of professional services of clinical pharmacists in the prevention and management of HCV infection. This paper was written as a guide to developing and maintaining clinical pharmacy services for persons with HCV infection. It should not necessarily be expected to serve as a standard of care, nor is it designed to limit the scope of clinical pharmacy practice in this setting.

A clinical pharmacist should be a prominent member of the interdisciplinary team providing pharmaceutical care for patients with chronic HCV infection. The roles and responsibilities of the clinical pharmacist may vary, depending on the health care setting; federal, state, and local laws; and institution policies and procedures. However, we believe that the involvement of a clinical pharmacist can promote preventive measures and education on reducing HCV transmission, improve medication adherence, assist in initiating HCV treatment, assist in monitoring clinical and adverse effects, recommend treatment strategies for minimizing adverse effects, and facilitate medication acquisition and logistics that positively improve patient outcomes and reduce health care system costs.

Establishing Pharmacy Involvement in the Area of HCV

Identifying Roles and Activities

Several factors should be considered before initiating HCV treatment, including overall drug cost, contraindications, treatment benefits, efficacy and duration, drug interactions, pharmacogenomics, and adverse effects. A clinical pharmacist can prevent and minimize costs related to adverse effects and drug interactions. HCV is the most common chronic blood-borne infection in the United States, and it is associated with a significant financial burden to the health care system.[28] It is expected that direct costs alone will exceed $10.7 billion by 2019.[28, 29] The majority of the economic resources directed toward HCV are associated with medications, laboratory monitoring, and management of adverse effects. However, the cost of caring for HCV-infected patients increases ~18% with disease progression (e.g., advanced liver disease) and may exceed $100,000 annually in patients requiring liver transplantation.[30]

Medication costs, especially with DAAs, are important to consider before starting HCV therapy. Currently, the cost of DAAs can range from $26,400 to $80,000, depending on the DAA prescribed and the duration of therapy. Pharmacogenomics may also influence therapy costs and assist patients and clinicians in making the decision to pursue therapy. Patients with interleukin (IL)-28B genotype cytosine-cytosine (CC) were more likely to achieve an undetectable HCV RNA level after 4 weeks (rapid virologic response [RVR]) of peginterferon alfa and ribavirin compared with individuals carrying one or two copies of the thymine (T) allele (e.g., TT or CT).[31] In addition, patients with the Q80K polymorphism are less likely to respond to simeprevir therapy, and screening for this polymorphism is strongly recommended before initiation of simeprevir for HCV genotype 1a infections.[14]

The cost of adverse effects can significantly impact the overall economic analysis associated with HCV treatment. Peginterferon alfa and ribavirin are associated with numerous adverse effects (as described earlier), and the addition of DAAs can potentiate these toxicities as well as incur new toxicities.[10, 12] Although ribavirin dose reduction is the preferred initial management strategy, severe anemia could necessitate the use of erythropoietin-stimulating agents (ESAs) and transfusions and/or result in hospitalization.[10, 12] For patients receiving ribavirin-based therapy, ribavirin dose reduction to 600 mg/day can effectively manage anemia without compromising SVR rates and without the added expense of ESAs.[5, 10, 12]

Although costs associated with drug acquisition and management of HCV-related adverse effects are high, especially with the addition of DAAs, these costs are offset by preventing advancing liver disease in patients who successfully complete treatment.[3] In one study, compared with standard therapy, triple therapy with boceprevir or telaprevir, peginterferon alfa, and ribavirin reduced lifetime risk for histological changes by 38% and 28% and increased quality-adjusted life expectancy by 3% and 8%, respectively, in patients with HCV who had mild and advanced fibrosis.[32] Overall, clinical pharmacists can play a crucial role within the interprofessional team to facilitate successful completion of HCV drug treatment by implementing cost-effective therapies (e.g., optimizing treatment response) and effectively managing adverse effects to prevent worsening of these events and potential hospitalization. All of these activities are essential in containing health care costs.

Managing drug toxicity aggressively and appropriately is critical to ensure successful completion of HCV therapy. Treatment discontinuation rates have been reported to be as high as 14%, especially with peginterferon alfa and ribavirin therapy.[10, 12] Adherence, especially with the addition of the first-generation DAAs, is reduced due to the pill burden and complexity of drug dosing, duration of treatment, and multitude of adverse effects.[33] DAA therapy, especially with first-generation DAAs, is further complicated by many drug interactions.[27] As drug experts, clinical pharmacists should be an integral part of the interprofessional team to facilitate successful HCV therapy by monitoring for and addressing drug toxicities, improving adherence, and identifying and addressing drug interactions before, during, and after HCV therapy. Clinical pharmacists can also perform HCV pretherapy screening and education to prepare patients for treatment, which might minimize nonadherence.

Roles of the Clinical Pharmacist and Description of Activities

The management of HCV infections is centered on pharmacotherapy, making the clinical pharmacist appropriately suited as part of the patient's care team. Current HCV guidelines provide recommendations on its diagnosis, treatment, and management; however, specific recommendations involving clinical pharmacists in HCV care do not exist.[5] Literature documenting the clinical pharmacist's role in the management of HCV describes activities developed within the ambulatory setting, but most can be easily extrapolated to the inpatient environment. In both the outpatient and inpatient setting, the clinical pharmacist's roles and activities include the following: (i) preventive care, (ii) comprehensive medication and disease evaluation, (iii) patient education, counseling, and adherence evaluation, (iv) cost evaluation and distribution of medication, (v) pretreatment laboratory assessment and adverse toxicity management, (vi) HCV dosing and treatment recommendations and assessment of treatment efficacy, and (vii) transitions of care activities.

Preventive Care

The clinical pharmacist has an opportunity to play a key role in the prevention of HCV by increasing public and individual awareness.[6] Additionally, the clinical pharmacist may be involved in the provision of hepatitis A and B virus immunizations for those infected with chronic HCV.[5, 10] Patients with known liver disease are at increased risk of morbidity and mortality should they be infected with other hepatotrophic viruses (e.g., hepatitis A and B viruses).[5, 10, 12] Additionally, patients with chronic liver disease should receive an annual influenza vaccine and pneumococcal polysaccharide vaccine. Other vaccines that can be considered on an individual basis include tetanus/diphtheria/pertussis (whooping cough), varicella zoster, and measles/mumps/rubella. At a minimum, clinical pharmacists should review the patients' immunization history and assess the

need for hepatitis A virus, hepatitis B virus, influenza, and pneumococcal vaccinations.

Comprehensive Medication and Disease Evaluation

Clinical pharmacists should prospectively evaluate all drug therapy for appropriate indications, dosages, and drug interactions and intervene as needed. An assessment of the patient's current medications affords the opportunity to address four major medication-related issues: (a) identifying medications known or likely to cause drug interactions with HCV treatment medications, (b) identifying and assessing the use of complementary and alternative medicine (CAM) therapies, (c) identifying and assessing drug–disease interactions, and (d) optimizing management of underlying disease states.

(a) Numerous commonly used medications interact with DAAs (e.g., simeprevir- and ritonavir-containing antivirals) with varying clinical relevance. Documented and potential drug interactions should be identified, and recommendations for monitoring, dosage adjustments, or changes in therapy should be anticipated.[27] Additionally, the number and clinical implications of the interactions need to be evaluated when considering which DAA is selected. Additional dosage adjustments and monitoring recommendations should be reviewed in the prescribing information for DAAs; however, not all potential drug interactions have been evaluated and/or listed in the prescribing information. To supplement this information, pharmacokinetic properties of medications may be analyzed for the extent and pathway of metabolism. The clinical significance of drug interactions is not always evident, and clinical pharmacists can aid in interpreting and guiding therapy. In the instances where there are no viable therapeutic alternatives, close and frequent monitoring of the interacting medication and dose titration should be considered.

(b) In addition to reviewing prescription and nonprescription medications, it is important for clinical pharmacists to evaluate the use of CAM, which is common among patients with chronic liver disease.[34] One study showed that silymarin (milk thistle) was commonly used in patients with chronic HCV (16% had used previously and 17% used regularly) to modestly improve HCV treatment response and decrease adverse effects.[35] Concomitant use of silymarin with simeprevir has been shown to increase levels of simeprevir; therefore, clinical pharmacists should recommend against combining these agents.[14] Another CAM to consider is St. John's wort, as it has been shown to decrease serum concentrations of DAAs.[13, 14, 27] Currently, there are no data regarding drug interactions with other CAM therapies in patients receiving DAA therapy. In addition to CAM therapies, clinical pharmacists should consider drug–food interactions with DAA therapy (e.g., grapefruit juice with simeprevir); however, this information is limited.

(c) Drug–disease interactions should also be evaluated by clinical pharmacists in patients infected with HCV, especially in assessing appropriate drug use and dosing in patients with existing hepatic dysfunction.[36, 37] For example, patients with cirrhosis often use nonsteroidal antiinflammatory drugs (NSAIDs) as a replacement for acetaminophen for pain management. However, NSAIDs can cause kidney dysfunction, reduce the efficacy of diuretics, and increase the risk of upper gastrointestinal hemorrhage, which are all significant concerns in these patients. If acetaminophen must be used, clinical pharmacists should review specific recommendations regarding acetaminophen dosing in patients with liver disease (especially used concurrently with alcohol) and limit the daily dosage to no more than 2 g. In addition to assessing home medications used in patients with cirrhosis, it is important to assess the use of HCV agents in patients with cirrhosis (e.g., indication of certain agents in patients with cirrhosis, such as with simeprevir) and consider the challenges when managing these agents in these patients (e.g., worsening underlying thrombocytopenia with peginterferon alfa). Also, the extent of existing hepatic dysfunction in patients with cirrhosis should be evaluated and used to guide appropriate drug use and dosing. In addition to assessing the use of HCV agents in patients with cirrhosis, clinical pharmacists should also be involved in determining the patient's eligibility for peginterferon alfa therapy based on the patient's psychiatric history, risk of psychiatric complications, and risks of peginterferon alfa toxicities. Patients should be evaluated for depression before starting treat-

ment and regularly during therapy for exacerbation of depression, anxiety, or other psychiatric illness, especially if receiving peginterferon alfa therapy.[36, 37] Even in patients not receiving interferon, underlying depression can affect adherence to therapy.[38] Clinical pharmacists can also assist in evaluating both men and women for appropriate contraception before initiating HCV treatment regimens that include ribavirin, a known teratogen with a long half-life. With the wealth of drug knowledge that clinical pharmacists possess, these clinicians are well positioned to make these recommendations.

(d) A thorough medication evaluation offers an opportunity to recommend alternative treatments to optimize comorbidities, especially if patients are working toward candidacy for HCV treatment but have poorly controlled underlying disease states. Additional responsibilities of clinical pharmacists include identifying strategies to reduce pill burden, recognizing compliance and adherence issues, and motivating patients to become active participants in their treatment. Optimizing therapy for underlying disease states (e.g., diabetes mellitus) and general lifestyle interventions including weight loss and cessation or reduction of alcohol, marijuana, and tobacco, which have been associated with worsening liver damage, should also be implemented.[39] For example, a clinical pharmacist can evaluate underlying disease states at each appointment and reach out to the patient's health care providers (e.g., primary care physician) to make recommendations to optimize treatment for these disease states as needed.

Patient Education, Counseling, and Adherence Evaluation

The shortage of primary care providers and the sparse availability of specialized clinics designed specifically for HCV management may limit a prescriber's ability to dedicate sufficient time to provide extensive disease state and medication counseling. Many health care providers may avoid treating patients with HCV because of the complexity and unfamiliarity of the treatment regimen. Significantly improved clinical outcomes, patient satisfaction, and pharmacoeconomics have been reported when clinical pharmacists provide disease state counseling and medication education for multiple chronic diseases.[40] An interprofessional approach involving clinical pharmacists in HCV management demonstrated community-based SVR rates comparable to those achieved in clinical trials.[41] As an integral clinician on the interprofessional team, clinical pharmacists could provide patient-specific drug and disease state education during initial and follow-up visits for HCV treatment. Effective counseling has been shown to positively impact patient adherence to HCV therapy, increasing SVR rates to 60% in patients who received combination therapy with peginterferon alfa and ribavirin.[36] Additionally, patients infected with chronic HCV genotype 1 who were adherent to more than 80% of their treatment doses of peginterferon alfa and ribavirin achieved higher SVR rates.[33] Overall, improvement in adherence could impact viral resistance and efficacy of future treatment options.

Adherence has been a common concern with HCV therapy, historically due to significant pill burden and complex dosing regimens. Although current treatments are substantially easier and new therapies are expected to be even more so, new concerns for adherence have arisen, especially in the context of medication costs and patients taking medications for multiple comorbidities. Clinical pharmacists are well suited to help patients incorporate HCV therapy into their daily activities and to make treatment recommendations based on their assessment of the patient's risk of nonadherence. Clinical pharmacists should use any tools available to assist patients in achieving compliance, including the use of pill boxes and reminder alarms and engaging supportive family members. Clinical pharmacists should also assess whether patients have adequate medication storage areas (e.g., a functional refrigerator) and stress the important of appropriate storage of HCV medications.

Another component of patient education is instructing patients on how to safely and effectively administer injections, such as peginterferon alfa and growth factors (e.g., ESAs and granulocyte colony-stimulating factor [G-CSF]). A review of proper injection techniques can be provided by the clinical pharmacist at therapy initiation and reiterated at follow-up visits. Additionally, the clinical pharmacist may educate patients on potential adverse effects that may

develop during the course of HCV therapy, encourage patients to actively participate in their medical care, and discourage self-discontinuation of these essential medications. Chronic disease support groups and educational classes focusing on HCV infection are also effective settings for the clinical pharmacist to provide expert knowledge on managing HCV while providing the patient and family members a comfortable environment to ask questions and address any treatment concerns.[42]

Cost Evaluation and Distribution of Medication

Involvement in procurement and distribution of medication offers another opportunity for clinical pharmacists to optimize therapy in patients with HCV and to ensure treatment adherence.[37] Clinical pharmacists can identify patients at risk for nonadherence based on refill histories of other medications. A clinical pharmacist involved in the distribution and dispensing of medication can ensure that the patient receives medications on time, streamline the prior authorization process, and ensure that all medications are updated in the pharmacy system to review for potential drug interactions. In addition to assisting with medication distribution, clinical pharmacists should identify and address cost-related issues before the patient starts HCV treatment. Health care providers might overlook the patient's inability to afford HCV medications due to lack of insurance, high deductibles, or high copayments. As mentioned previously, medications used to treat HCV are extremely expensive, and when cost-related issues arise, clinical pharmacists can identify potential cost-saving sources (e.g., medication assistance programs or copay card programs).

Pretreatment Laboratory Assessment and Adverse Toxicity Management

Review of baseline laboratory results (e.g., HCV viral load, pharmacogenomics testing, hemoglobin, and hematocrit) allows a clinical pharmacist to gauge treatment response and to predict potential adverse effects that may occur with HCV therapy. For example, anemia is an expected adverse event that can occur with HCV therapy, especially when ribavirin is used. In an anemic patient, investigation and management of the anemia should be performed before the initiation of HCV treatment to prevent further decline.

Adverse effects have been reported, in varying severity, in up to 94% of patients receiving peginterferon alfa and ribavirin therapy, limiting completion of the HCV treatment course.[36, 37] However, one study involving clinical pharmacists in the treatment of patients infected with the HCV genotype 1 showed that only 12% of patients required medical treatment of their adverse effects, and early discontinuation of HCV therapy occurred in 6% of patients.[37] Clinical pharmacists at the point-of-care and point-of-dispensing can identify these adverse effects early and initiate appropriate strategies to minimize complications and treatment discontinuation. For example, clinical pharmacists can assist health care providers in monitoring laboratory test results, specifically for anemia, neutropenia, and thrombocytopenia. If adjunctive therapies are required, such as ESAs or G-CSF, the clinical pharmacist can identify and resolve cost issues of these expensive drugs (e.g., insurance coverage or cost to the patient) and recommend an appropriate drug regimen. Clinical pharmacists can also assist other health care providers in managing the development or exacerbation of emotional or cognitive impairment, such as depression or irritability, as patients with chronic HCV have higher rates of these conditions.[43] Psychiatric adverse effects have been reported frequently with peginterferon alfa, including worsening of underlying psychiatric illnesses.[38] Depression from peginterferon alfa has been reported to be a risk factor for treatment failure and to negatively impact treatment adherence and quality of life.[38] Therefore, patients should be evaluated for depression before starting treatment and regularly during therapy for exacerbation of depression or psychiatric illness.[10] Antidepressants are often prescribed to prevent and ameliorate interferon-induced depressive symptoms and allow successful completion of HCV therapy; however, some of these medications interact with DAA therapy.[27, 36, 44] Clinical pharmacists can assist other health care providers in implementing and managing an effective antidepressant regimen to minimize any potential adverse effects and/or drug interactions, thereby affording patients the best chance of achieving treatment success.[36, 44] Interferon-free and interferon and ribavirin–free regimens will likely minimize the concerns for psychiatric adverse effects. Clinical pharmacists can assist in making recommendations on an appropriate treatment regimen for these patients.

HCV Dosing and Treatment Recommendations and Assessment of Treatment Efficacy

Clinical pharmacists, in collaboration with the primary health care provider, should recommend therapy and initial dosing of medications. For example, in patients with prior rash history, simeprevir might be avoided when a recurrence of rash would be especially challenging. Patients with multiple comorbidities and concomitant medications may be better suited to start sofosbuvir because of its shorter treatment duration and fewer drug interactions, thereby limiting the number of potential drug interactions and time frame of intolerance. Clinical pharmacists should also determine appropriate concomitant HCV medications to use with DAA therapy. Appropriate duration of HCV therapy and use of HCV therapy in special patient populations (e.g., patients with HIV-HCV coinfection, HCC, or cirrhosis, or liver transplant recipients) should also be evaluated by clinical pharmacists before initiation of therapy. Insurance companies cover certain HCV medications based on specific indications and costs. For example, an insurance company could approve sofosbuvir in patients infected with HCV genotype 1, 2, or 4, while limiting HCV therapy to combination peginterferon alfa and ribavirin in patients infected with HCV genotype 3. Clinical pharmacists must consider insurance and institutional formularies when selecting specific HCV agents.

Additionally, before the initiation of HCV therapy, clinical pharmacists should evaluate pharmacogenomics that may influence treatment efficacy and costs. Testing for the IL-28B genotype may be considered for peginterferon-alfa–eligible patients, whereas the Q80K polymorphism should be screened for in genotype 1a–infected patients receiving simeprevir, especially those failing first-generation DAAs who may harbor mutations. In addition to pharmacogenomics, clinical pharmacists may consider evaluating the patient for resistance mutations, especially since these mutations show cross-resistance to many HCV drugs.[31]

During and after HCV treatment, clinical pharmacists should assess treatment efficacy. In patients with HCV genotype 1, serum HCV RNA levels are measured during treatment depending on the HCV regimen to assess patient response. This test should be repeated at the end of treatment to document the end-of-treatment response (ETR). Final testing should be done after treatment to determine whether an SVR has been achieved.[10, 12] For genotypes 2–6, HCV RNA testing may be performed for RVR and EVR, but it should be performed in all patients for ETR and SVR.[7, 10, 12] Clinical pharmacists can ensure that patients who do meet the futility rules (i.e., rules developed during clinical trials that specify the HCV RNA threshold [e.g., > 1000 IU/ml] at the specific week of therapy for when to discontinue a given treatment to prevent needless drug exposure and minimize development of resistance) should discontinue HCV therapy.

Transitions of Care Activities

The clinical pharmacist can play a vital role in the management of HCV in patients transferring from one health care setting to another (e.g., from home to hospital). Patients receiving HCV care may be managed by HCV specialists, and if admitted to the hospital, these patients are cared for by general medicine practitioners or hospitalists. Clinical pharmacists have the opportunity to educate health care providers about the importance of HCV treatment continuation, adverse events, and drug interactions. HCV medications might be discontinued during a hospital admission; however, clinical pharmacists are well positioned to ensure therapy continuation by identifying these medications through medication reconciliation and by facilitating medication acquisition. Studies have shown that more accurate and comprehensive medication histories are obtained by pharmacy personnel compared with other health care professionals.[45, 46] Facilitating medication acquisition is important, especially if hospitalized patients forget to bring in their HCV medications from home. This is crucial, since missed doses of HCV medications, especially first-generation DAAs, may result in HCV resistance and treatment failure. HCV medications are costly; therefore, many hospitals do not have these drugs readily available on their formulary, forcing treatment interruptions. Clinical pharmacists can assist these practitioners or hospitalists by identifying and managing issues associated with HCV medications to ensure successful and safe continuation of HCV treatment. Clinical pharmacists can also assist in evaluating HCV therapies to include in-hospital and health system formularies to ensure appropriate use of these medications and drug availability.

Planning and Implementation

Clinical pharmacist involvement in the care of patients infected with HCV is specific to a practice setting; thus, design and required resources will depend on patient and provider needs. The business plan is the first critical step and should take into account the practice environment and its needs. It should contain the clinical pharmacist's scope of practice and location of services. The services should be marketed to the right clients, and obtaining input from key stakeholders is paramount in the planning process. Implementing services with physicians or practices makes fine-tuning the program and measuring outcomes easier. Demonstrating positive outcomes will improve extension to more physicians and practices. Potential outcomes may include improving adherence, patient satisfaction, improved SVR rates, and/or economic benefit by freeing up clinicians to perform other clinic-related functions. There should be continuous quality improvement to evaluate and improve the services provided.[47]

Documentation

Clinical pharmacists involved in the treatment of HCV should document all interventions and recommendations including pretreatment visits and evaluation of a patient's baseline medications (e.g., prescription and nonprescription medications as well as CAM) and assessment of any existing or potential drug interactions with HCV therapy. Additionally, clinical pharmacists should document all activities related to patient counseling and adherence. During HCV treatment, clinical pharmacists should consult with other health care providers and provide clear recommendations for dosage adjustments of HCV therapy and concurrent medications, and the use of supportive medications (e.g., growth factors).

Education of Other Health Care Professionals

In 2010, the IOM released a report on the state of HCV in the United States identifying major gaps in knowledge regarding viral hepatitis, not only among the general public but also among health care and social service providers.[6] Clinical pharmacists can facilitate the screening of HCV-positive patients to improve awareness of HCV, especially with a focus on the CDC's current recommendations for the birth-cohort (baby boomers) HCV screening. Although not all patients may be candidates for therapy, education regarding HCV can help minimize the risks of transmission. Clinical pharmacists are well positioned to provide education regarding HCV treatment and its complications to other health care professionals. Patients with HCV are usually cared for by hepatologists, gastroenterologists, infectious diseases specialists, and other providers when admitted to the hospital or when followed in the outpatient setting. More outpatient clinicians (e.g., primary care physicians) are prescribing and monitoring HCV treatment, and this trend may continue as peginterferon alfa and ribavirin use declines with more effective oral regimens. Knowledgeable clinical pharmacists are well positioned to provide education to patients and providers and to help address the complex issues with HCV therapy.

Research

Treatment of HCV affords various research opportunities. As therapy evolves, clinical pharmacists should be involved in clinical trials of new therapies and contribute to the literature regarding the use of current therapies in various patient populations. There are ongoing trials evaluating the use of DAA therapy in HIV-HCV–coinfected patients and in liver transplant recipients. Significant drug interactions limited the use of DAAs in these patients, especially after liver transplantation. Although sofosbuvir is FDA approved in patients with HIV-HCV coinfection who are receiving antiretroviral agents, sofosbuvir should not be coadministered with ritonavir-boosted tipranavir. In addition, concrete recommendations on dosage adjustments for concomitant medications during DAA therapy are unavailable, and general recommendations exist (i.e., "caution should be used and dose reduction should be considered"). Also, there are limited data regarding the outcomes of these drug interactions in patients with HCV. Understanding the drug interaction potential of new agents is critical for effective and safe management of HCV.[11] Moreover, new therapies are anticipated within the next 1–5 years that will likely pose new challenges and revise the current context of therapy. Clinical pharmacists should initiate and/or actively collaborate with other health care providers on various types of research, including efficacy and safety, pharmacokinetic, and pharmacoeconomic studies.[48] Clinical pharmacists can contribute to HCV research in several ways that include, but are

not limited to, the following: (i) participate in research design and data analysis, (ii) secure funding to conduct research, and (iii) report results of clinical research and pharmacoeconomic analyses at regional and national meetings, and publish findings in journals disseminated to clinical pharmacists and other health care professionals.

Resources

At a minimum, the clinical pharmacist should have several resources such a computer and telephone and adequate private space for interviewing and educating patients. In an ambulatory clinic, allocating this type of space can be a challenge. If a local pharmacy dispenses the medications, patients can be educated at the pharmacy. The area needs to be private and large enough to accommodate a patient with or without family members, or several patients if group teaching is provided. However, being able to interview patients and provide patient education in the ambulatory setting is ideal and allows the clinical pharmacist to build rapport with their health care providers and staff. Procedures for the office staff to schedule patients and communicate patient needs to the clinical pharmacist when he or she is off site should be developed. Teleconferences provided by specialty pharmacies and ambulatory clinics may be an option to provide education and a resource for patients at off hours and/or when the clinical pharmacist is off site or for patients residing in rural areas. Education materials tailored to the site are necessary and can supplement the teaching material provided by pharmaceutical companies. These materials should include specific drug-related information but also adverse effect management. Pocket cards with the medication dosing schedule or battery-operated timers can remind patients to take their medication. A patient's consent is recommended to document the patient's understanding of the need for adherence, routine laboratory testing, office visits, adverse effects, and two methods of birth control. Providing a calendar of laboratory dates and a packet containing the patient's laboratory orders for the duration of treatment will likely increase adherence to monitoring.

Electronic medical records allow the clinical pharmacist to view patient charts, communicate with health care providers and staff, and document clinical activities from any location. Also, a robust computer program that tracks the status of a patient's prescription is particularly useful to the ambulatory-based clinical pharmacist. The process of insurance approval with prior authorization and the frequent need for patient assistance programs can take several weeks. At any given time, patients will be in different stages of the procurement process. A real-time system organizes this process and is appealing to outpatient ambulatory clinics.

Requirements and Development of Clinical Pharmacists

Clinical pharmacists providing care to patients infected with HCV should demonstrate competency in the knowledge and skills to serve this unique population. Postgraduate training will provide a foundation for providing clinical services to patients in various settings. However, specific experiences in caring for patients with HCV may be limited or not available throughout the postgraduate training. Therefore, programs and other experiences should be used to ensure that clinical pharmacists obtain essential information before providing proficient pharmaceutical HCV care to these patients. Important information to obtain before caring for these patients includes pathophysiology of the disease, recognition and management of drug toxicity and potential drug interactions, injection training, and effective patient counseling techniques. Guideline documents and online modules (e.g., the American College of Clinical Pharmacy's Ambulatory Care Self-Assessment Program chapter on viral hepatitis[49]) can be used for the didactic portion of the program, with an assessment activity to document successful completion. In addition, sufficient opportunity for experience in the practice environment to develop competency in the area of HCV is essential. Training or mentoring by a clinical pharmacist with practice-related experience in hepatology or infectious diseases is ideal. A future certificate program for treatment of chronic HCV could prepare a larger number of clinical pharmacists in a consistent fashion.

Barriers

Although significant opportunities exist for clinical pharmacists to provide pharmaceutical care to patients with chronic HCV infection, several common barriers exist that must be overcome to establish a successful pharmacy service. Time, provider awareness of clinical pharmacists'

value and expertise, clinical pharmacists' confidence and skill, medical record documentation, and the lack of provider billing status can all be potential barriers that must be planned for and addressed.

Educating individual patients initiating treatment for chronic HCV is a lengthy process. Time and financial constraints might necessitate group training instead of private training. In a group setting, patients might feel uncomfortable asking questions and causing personal needs not to be addressed or met. After treatment begins, frequent patient contact is necessary to manage adverse effects and monitor adherence.

Providers might be unaware of the value that clinical pharmacists can provide to the chronically infected HCV patient. Although it may not represent the prevailing opinion of all practicing providers, several medical organizations have expressed concern that clinical pharmacists are encroaching on areas traditionally performed by other health care providers.[50] Clear communication, scope of practice, and involvement of providers in the planning process are important to demonstrate the value of clinical pharmacists in HCV care and avoid negative interactions.[50] A collaborative, multidisciplinary approach to the management of common and complex disease states, such as HCV, is encouraged.

Clinical pharmacists may lack the confidence and expertise to manage a HCV-infected patient without appropriate training or mentoring, which consists of postgraduate training in addition to clinical experiences in caring for these patients. The cost and logistics of developing and delivering a program to clinical pharmacists with different levels of experience can be substantial. Conferences and online courses are available to clinical pharmacists wanting to learn more about HCV infection; Appendix 1 provides a listing of available resources. In addition, health care delivery models such as Project ECHO can provide HCV expertise and support in HCV management.

Clear and effective methods of communicating recommendations, accessible clinic notes, and provider education are critical to the successful HCV pharmacy service. In large specialty pharmacies, telecommunication is common, but there can be significant communication barriers with this style (e.g., lack of visual assessment of patient comprehension). Not all ambulatory care clinics have electronic health records, making remote access to the patient chart impossible. A paper chart must be physically obtained, and documentation of outcomes is more tedious.

Conclusion

The demand for HCV treatment is predicted to increase with expanded HCV testing and the approval of new HCV drugs associated with impressive SVR rates and better tolerability. Current medications used to treat HCV-infected patients are effective in achieving SVR. Unfortunately, these drugs are associated with significant adverse effects (e.g., depression, flu-like symptoms, anemia, neutropenia, and thrombocytopenia), significant drug interactions with DAAs (especially with simeprevir and regimens that include ritonavir), high risk of patient nonadherence and treatment discontinuation, and significant medication- and therapy-related costs. Due to these pharmacological challenges with HCV treatment, clinical pharmacist involvement in the treatment of HCV is critical. There is a shortage of clinicians to manage and treat the HCV epidemic, and this gap in the health care system is an opportunity for increased involvement by clinical pharmacists. In addition, the field of HCV therapy is rapidly evolving and will require an interprofessional approach to judiciously and effectively guide pharmacological therapy. Clinical pharmacists can play a critical role within the multidisciplinary team to facilitate successful completion of HCV therapy by implementing cost-effective treatment of HCV (e.g., assessing treatment response), managing adverse effects effectively, predicting and managing drug interactions, and averting potential treatment discontinuation and hospitalizations. The inclusion of a clinical pharmacist can promote preventive measures on reducing HCV transmission, improve medication adherence, monitor clinical and adverse effects, optimize HCV medication dosing, improve management of adverse effects, aid in medication acquisition and logistics, and subsequently positively affect patient outcomes.

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Appendix 1. Available Resources on Hepatitis C Viral Infection

Associations:

American Association for the Study of Liver Diseases (AASLD)
American College of Gastroenterology (ACG)
American Gastroenterological Association (AGA)
American Liver Foundation

Web sites:

http://www.clinicaloptions.com/Hepatitis.aspx
http://www.hep-druginteractions.org/
http://echo.unm.edu/
http://www.liverfoundation.org/
http://www.hepatitis.va.gov/
http://www.hcvguidelines.org
http://hepatitisc.uw.edu/index.php
http://www.aasld.org/LiverLearning%C2%AE/Pages/LiverProgramforPrimaryCareProviders.aspx

Meetings:

Digestive Disease Week (www.ddw.org): occurs annually, usually in May
The Liver Meeting (www.aasld.org): occurs annually, usually in November