

Hepatitis C among the mentally ill: Review and treatment update

Newer agents reduce the risk of treatment-induced depression

At approximately 3 to 4 million patients, hepatitis C virus (HCV) is the most common viral hepatitis in the United States. Patients with mental illness are disproportionately affected by HCV and the management of their disease poses particular challenges.

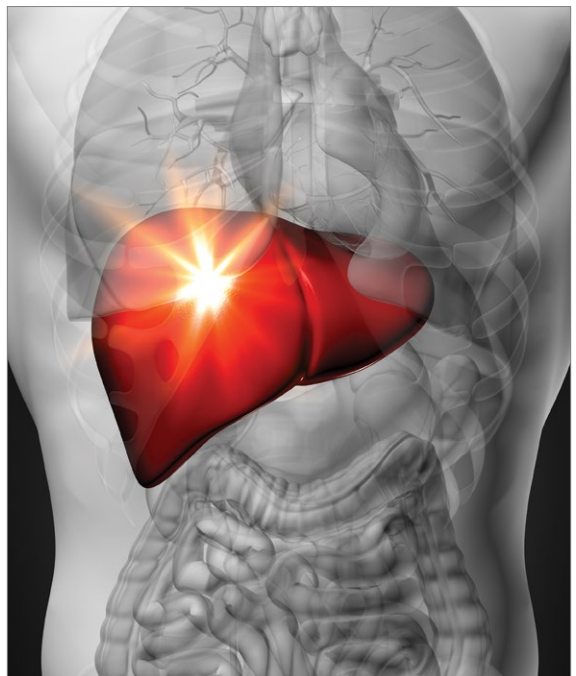
HCV is commonly transmitted via IV drug use and blood transfusions; transmission through sexual contact is rare. Most patients with HCV are asymptomatic, although some do develop symptoms of acute hepatitis. Most HCV infections become chronic, with a high incidence of liver failure requiring liver transplantation.

Hepatitis refers to inflammation of the liver, which could have various etiologies, including viral infections, alcohol abuse, or autoimmune disease. Viral hepatitis refers to infection from 5 distinct groups of virus, coined A through E.¹ This article will focus on chronic HCV (*Table 1, page 42*).

CASE

Bipolar disorder, stress, history of IV drug use

Ms. S, age 48, has bipolar I disorder and has been hospitalized 4 times in the past, including once for a suicide attempt. She has 3 children and works as a cashier. Her psychiatric symptoms have been stable on lurasidone, 80 mg/d, and escitalopram, 10 mg/d. Recently, Ms. S has been under more stress at her job. Sometimes she misses doses of her medication, and then becomes more irritable and impulsive. Her husband, noting that she has used IV heroin in the past, comes with her



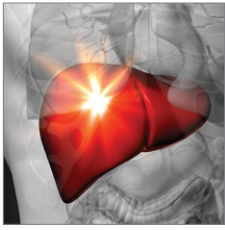
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Disclosure

The author reports no financial relationships with any company whose products are mentioned in this article or manufacturers of competing products.



Hepatitis C

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Educating patients about complications of viral hepatitis, such as liver failure, could be motivation to change risky behaviors



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Table 1

HCV in patients with psychiatric illness: Clinical highlights

Chronically mentally ill patients have higher rates of HCV infection
Patients should be counseled on risk factors for transmission (IV drug abuse, unprotected intercourse) and referred, when appropriate, for laboratory evaluation
All patients born between 1945 and 1965, whether risk factors are present or not, should be screened once for HCV
Treatment of HCV with IFN is associated with increased risk of depression. However, this is not an absolute contraindication to the use of IFN in patients with mental illness
Patients at higher risk of IFN-induced depression should be stabilized before initiating IFN and undergo close psychiatric monitoring throughout treatment. Selective serotonin reuptake inhibitors are safe and effective for IFN-induced depression
Because of their relative lack of neuropsychiatric side effects, IFN-free regimens employing direct-acting antivirals could be a safer alternative for patients with mental illness. Use of these newer regimens may be limited by cost and insurance formulary restrictions
Issues related to psychiatric comorbidity and supporting treatment adherence will continue to occupy psychiatrists involved in the care of these patients
HCV: hepatitis C virus; IFN: interferon

today and is concerned that she is “not acting right.” What is Ms. S’s risk for HCV?

HCV in mental illness

Compared with the general population, HCV is more prevalent among chronically mentally ill persons. In one study, HCV occurred twice as often in men vs women with chronic mental illness.² Up to 50% of patients with HCV have a history of mental illness and nearly 90% have a history of substance use disorders.³ Among 668 chronically mentally ill patients at 4 public sector clinics, risk factors for HCV were common and included use of injection drugs (>20%), sharing needles (14%), and crack cocaine use (>20%).⁴ Higher rates of HCV were reported in hospitalized patients with schizophrenia and comorbid psycho-

active substance abuse in Japan.⁵ Because of the high prevalence in this population, it is essential to assess for substance use disorders. Employing a non-judgmental approach with motivational interviewing techniques can be effective.⁶

Individuals with mental illness should be screened for HCV risk factors, such as unprotected intercourse with high-risk partners and sharing needles used for illicit drug use. Patients frequently under-report these activities. At-risk individuals should undergo laboratory testing for the HIV-1 antibody, hepatitis C antibodies, and hepatitis B antibodies. Mental health providers should counsel patients about risk reduction (eg, avoiding unprotected sexual intercourse and sharing of drug paraphernalia). Educating patients about complications of viral hepatitis, such as liver failure, could be motivation to change risky behaviors.

CASE CONTINUED

During your interview with Ms. S, she becomes irritable and tells you that you are asking too many questions. It is clear that she is not taking her medications consistently, but she agrees to do so because she does not want to lose custody of her children. She denies current use of heroin but her husband says, “I don’t know what she is doing.” In addition to advising her on reducing risk factors, you order appropriate screening tests, including hepatitis and HIV antibody tests.

Screening guidelines

The U.S. Preventive Services Task Force and the CDC both recommend a 1-time screening for HCV in asymptomatic or low-risk patients born between 1945 and 1965.^{1,7} Furthermore, both organizations recommend screening for HCV in persons at high risk, including:

- those with a history of injection drug use
- persons with recognizable exposure, such as needlesticks
- persons who received blood transfusions before 1992
- medical conditions, such as long-term dialysis.

Table 2

Managing interferon-associated depression

Clinical concern	IFN treatment of hepatitis C is associated with a 25% risk of depression
Risk factors	Female sex, history of a major depressive episode or other psychiatric disorder, low educational level, baseline subthreshold depression symptoms
Management	Optimal stabilization of psychiatric symptoms is recommended before beginning IFN-based therapy. SSRIs are safe and effective for IFN-associated depression. Prophylactic use of antidepressants in average risk patients is not indicated
Future directions	Clinical concern about IFN-induced neuropsychiatric side effects may diminish as new IFN-free treatment regimens become more widely used

IFN: interferon; SSRIs: selective serotonin reuptake inhibitors

There is no vaccine for HCV; however, patients with HCV should receive vaccination against hepatitis B.

Diagnosis

Acute symptoms include fever, fatigue, headache, cough, nausea, and vomiting. Jaundice could develop, often accompanied by pain in the right upper quadrant. If there is suspicion of viral hepatitis, psychiatrists can initiate the laboratory evaluation. Chronic hepatitis, on the other hand, often is asymptomatic, although stigmata of chronic liver disease (eg, jaundice, ascites, peripheral edema) might be detected on physical exam.⁸ Elevated serum transaminases are seen with acute viral hepatitis, although levels could vary in chronic cases. Serologic detection of anti-HCV antibodies establishes a HCV diagnosis.

Treatment recommendations

All patients who test positive for HCV should be evaluated and treated by a hepatologist. Goals of therapy are to reduce complications from chronic viral hepatitis, including cirrhosis and hepatic failure. Duration and optimal regimen depends on the HCV genotype.⁸ Treatment outcomes are measured by virological parameters, including serum aminotransferases, HCV RNA levels, and histology. The most important parameter in treating chronic HCV is the sustained virological response (SVR), which is the absence of HCV RNA 12 weeks after completing therapy.⁹

Treatment is recommended for all persons with chronic HCV infection, according to current treatment guidelines, which are updated regularly by the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America.¹⁰ Until recently, treatment consisted of IV pegylated interferon (PEG-IFN) in combination with oral ribavirin. Success rates with this regimen are approximately 40% to 50%. The advent of direct-acting antivirals (DAAs) has revolutionized treatment of chronic HCV. These agents include simeprevir, sofosbuvir, ledipasvir, and the combination of ombitasvir-paritaprevir-ritonavir plus dasabuvir (brand name, Viekira Pak). Advantages of these agents are oral administration, high treatment success rates (>90%), shorter treatment duration (12 weeks vs up to 48 weeks with older regimens), and few serious adverse effects⁹⁻¹¹; drawbacks include the pricing of these regimens, which could cost upward of ≥\$100,000 for a 12-week course, and a lack of coverage under some health insurance plans.¹² The manufacturers of 2 agents, telaprevir and boceprevir, removed them from the market because of decreased demand related to their unfavorable side-effect profile and the availability of better tolerated agents.

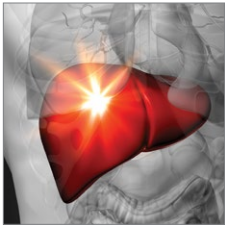
Treatment considerations for interferon in psychiatric patients

Various neuropsychiatric symptoms have been reported with the use of PEG-IFN. The range of reported symptoms include:

- depressed mood
- anxiety

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Goals of therapy for HCV are to reduce complications from chronic viral hepatitis, including cirrhosis and hepatic failure



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Depressive symptoms can present as early as 1 month after starting treatment, but typically occur at 8 to 12 weeks

Table 3

Recommended initial treatment regimens for HCV without cirrhosis

HCV genotype

Regimen

1a	Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks
	Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks
	Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dasabuvir (250 mg) with weight-based ribavirin for 12 weeks
	Daily simeprevir (150 mg) plus sofosbuvir (400 mg) for 12 weeks
	Daily daclatasvir (60 mg ^a) plus sofosbuvir (400 mg) for 12 weeks
1b	Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks
	Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks
	Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) for 12 weeks
	Daily simeprevir (150 mg) plus sofosbuvir (400 mg) for 12 weeks
	Daily daclatasvir (60 mg ^a) plus sofosbuvir (400 mg) for 12 weeks
2	Daily sofosbuvir (400 mg) and weight-based ribavirin for 12 weeks
	Daily daclatasvir (60 mg ^a) plus sofosbuvir (400 mg) for 12 weeks
3	Daily daclatasvir (60 mg ^a) plus sofosbuvir (400 mg) for 12 weeks
	Daily sofosbuvir (400 mg) and weight-based ribavirin plus weekly PEG-IFN for 12 weeks

^aThe dosage of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively

HCV: hepatitis C virus; PEG-IFN: pegylated interferon

Source: Reference 10

- hostility
- slowness
- fatigue
- sleep disturbance
- lethargy
- irritability
- emotional lability
- social withdrawal
- poor concentration.^{13,14}

Depressive symptoms can present as early as 1 month after starting treatment, but typically occur at 8 to 12 weeks. A systematic review and meta-analysis of 26 observational studies found a cumulative 25% risk of interferon (IFN)-induced depression in the general HCV population.¹⁵ Risk factors for IFN-induced depression include:

- female sex
- history of major depression or other psychiatric disorder
- low educational level
- the presence of baseline subthreshold depressive symptoms.

Because of the risk of inducing depression, there was initial hesitation with providing IFN treatment to patients with

psychiatric disorders. However, there is evidence that individuals with chronic psychiatric illness can be treated safely with IFN-based regimens and achieve results similar to non-psychiatric populations.^{16,17} For example, patients with schizophrenia in a small Veterans Affairs database who received IFN for HCV did not experience higher rates of symptoms of schizophrenia, depression, or mania over 8 years of follow-up.¹⁸ Furthermore, those with schizophrenia were just as likely to reach SVR as patients without psychiatric illness.¹⁹ Other encouraging results have been reported in depressed patients. One study found similar rates of treatment completion and SVR in patients with a history of major depressive disorder compared with those without depression.²⁰ No difference in frequency of neuropsychiatric side effects was found between the groups.

Presence of a psychiatric disorder is no longer an absolute contraindication to IFN treatment for HCV. Optimal control of psychiatric symptoms should be attained in all patients before starting HCV treatment, and close clinical monitoring is warranted. A

review of 9 studies showed benefit of antidepressants for HCV patients with elevated baseline depression or a history of IFN-induced depression.²¹ The largest body of evidence supports the safety and efficacy of selective serotonin reuptake inhibitors for treating IFN-induced depression. Although no antidepressants are FDA-approved for this indication, the best-studied agents include citalopram, escitalopram, sertraline, and paroxetine.

A review of 6 studies on using antidepressants to prevent IFN-induced depression concluded there was inadequate evidence to support this approach in all patients.²² Pretreatment primarily is indicated for those with elevated depressive symptoms at baseline or those with a history of IFN-induced depression. The prevailing approach to IFN-induced depression assessment, prevention, and treatment is summarized in *Table 2* (page 43).

CASE CONTINUED

Ms. S tests positive for the HCV antibody but negative for HIV and hepatitis B. She immediately receives the hepatitis B vaccine series. Her sister discourages her from receiving treatment for HCV, warning her, "it will make you crazy depressed." As a result, Ms. S avoids following up with the hepatologist. Her psychiatrist, aware that she now was taking her psychotropic medication and seeing that her mood is stable, educates her about new treatment options for HCV that do not cause depression. Ms. S finally agrees to see a hepatologist to discuss her treatment options.

IFN-free regimens

With the arrival of the DAAs, the potential now exists to use IFN-free treatment regimens,¹⁰ which could eliminate concerns about IFN-induced depression.

Clinical trials of the DAAs and real-world use so far do not indicate an elevated risk for neuropsychiatric symptoms, including depression.¹¹ As a result, more patients with severe psychiatric illness likely will be eligible to receive treatment for HCV. However, as clinical experience builds with these new agents, it is important to monitor the experience of patients with psychiatric

comorbidity. Current treatment guidelines for HCV genotype 1, which is most common in the United States, do not include IFN-based regimens.¹⁰ Treatment of genotype 3, which affects 6% of the U.S. population, still includes IFN. Therefore, the risk of IFN-induced depression still exists for some patients with HCV. *Table 3*¹⁰ describes current treatment regimens in use for HCV without cirrhosis (see *Related Resources*, page 46, for treating HCV with cirrhosis).

Evolving role of the psychiatrist

The availability of shorter, better-tolerated regimens means that the psychiatric contraindications to HCV treatment will be eased. With the emergence of non-IFN treatment regimens, the role of mental health providers could shift toward assisting with treatment adherence, monitoring drug–drug interactions, and managing comorbid substance use disorders.¹⁰

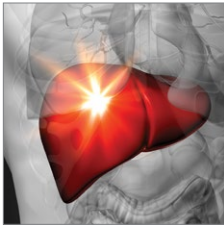
The psychiatrist's role might shift away from the psychosocial assessment of factors affecting treatment eligibility, such as IFN-associated depressive symptoms. Clinical focus will likely shift to supporting adherence to HCV treatment regimens.²³ Because depression and substance use disorders are risk factors for non-adherence, mental health providers may be called upon to optimize treatment of these conditions before beginning DAA regimens. A multi-dose regimen might be complicated for those with severe mental illness, and increased psychiatric and community support could be needed in these patients.²³ Furthermore, models of care that integrate an HCV specialist with psychiatric care have demonstrated benefits.^{6,23} Long-term follow-up with a mental health provider will be key to provide ongoing psychiatric support, especially for those who do not achieve SVR.

Psychotropic drug–drug interactions with DAAs

Both sofosbuvir and ledipasvir are substrates of P-glycoprotein and not metabolized by cytochrome P450 (CYP) enzymes.²⁴ Therefore, there are no known contraindications with psychotropic medications. However, co-

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There are no known contraindications with sofosbuvir and ledipasvir and psychotropic medications

Related Resources

- CDC. Viral hepatitis: hepatitis C information. www.cdc.gov/hepatitis/HCV/index.htm.
- American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. HCV guidance: recommendations for testing, managing, and treating hepatitis C. www.hcvguidelines.org.
- U.S. Department of Veterans Affairs. Interferon and ribavirin treatment side effects. www.hepatitis.va.gov/provider/reviews/treatment-side-effects.asp.

Drug Brand Names

Boceprevir • Victrelis	Lurasidone • Latuda
Buprenorphine • Buprenex	Ombitasvir-paritaprevir-ritonavir plus dasabuvir •
Buprenorphine/naloxone • Suboxone, Zubsolv	Viekira Pak
Carbamazepine • Tegretol	Paroxetine • Paxil
Citalopram • Celexa	Ribavirin • Rebetol
Daclatasvir • Daklinza	Ritonavir • Norvir
Elbasvir/grazoprevir • Zepatier	Sertraline • Zoloft
Escitalopram • Lexapro	Simeprevir • Olysio
Interferon-alpha • Intron A	Telaprevir • Incivek
Ledipasvir/sofosbuvir • Harvoni	

administration of P-glycoprotein inducers, such as St. John's wort, could reduce sofosbuvir and ledipasvir levels leading to reduced therapeutic efficacy.

Because it has been used for many years as an HIV treatment, drug interactions with ritonavir have been well-described. This agent is a "pan-inhibitor" and inhibits the CYP3A4, 2D6, 2C9, and 2C19 enzymes and could increase levels of any psychotropic metabolized by these enzymes.²⁵ After several weeks of treatment, it also could induce CYP3A4, which could lead to reduced efficacy of oral contraceptives because ethinylestradiol is metabolized by CYP3A4. Ritonavir is primarily metabolized by CYP3A4 (and CYP2D6 to a smaller degree). Carbamazepine induces CYP3A4, which may lead to decreased levels of ritonavir.²³

Bottom Line

Individuals with mental illness are at higher risk of hepatitis C, primarily because of substance abuse. Although pegylated interferon is associated with a risk of treatment-induced depression, direct-acting antivirals lack neuropsychiatric side effects and may be a safer modality for patients with psychiatric illness. Be aware of possible drug–drug interactions with these agents and collaborate with a hepatologist to monitor adherence.

This, in turn, could reduce the likelihood of attaining SVR and successful treatment of HCV.

Boceprevir, telaprevir, and simeprevir inhibit CYP3A4 to varying degrees and therefore could affect psychotropic medications metabolized by this enzyme.^{23,26,27} These DAAs are metabolized by CYP3A4; therefore CYP3A4 inducers, such as carbamazepine, could lower DAA blood levels, increasing risk of HCV treatment failure and viral resistance.

Daclatasvir is a substrate of CYP3A4 and an inhibitor of P-glycoprotein.²⁸ Concomitant buprenorphine or buprenorphine/naloxone levels may be increased, although the manufacturer does not recommend dosage adjustment. Elbasvir and grazoprevir are metabolized by CYP3A4.²⁹ Drug–drug interactions therefore may result when administered with either CYP3A4 inducers or inhibitors.

CASE CONCLUSION

Ms. S sees her new hepatologist, Dr. Smith. She decides to try a 12-week course of ledipasvir/sofosbuvir. Dr. Smith collaborates frequently with Ms. S's psychiatrist to discuss her case and to help monitor her psychiatric symptoms. She follows up closely with her psychiatrist for symptom monitoring and to help ensure treatment compliance. Ms. S does well with the IFN-free treatment regimen and experiences no worsening of her psychiatric symptoms during treatment.

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