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Dr. Sostre: Identifying and managing psychiatric symptoms in HCV patients

Current PSYCHIATRY

Strategies for treating depression in patients with hepatitis C

Psychiatric symptoms can precede infection or be caused by HCV treatments

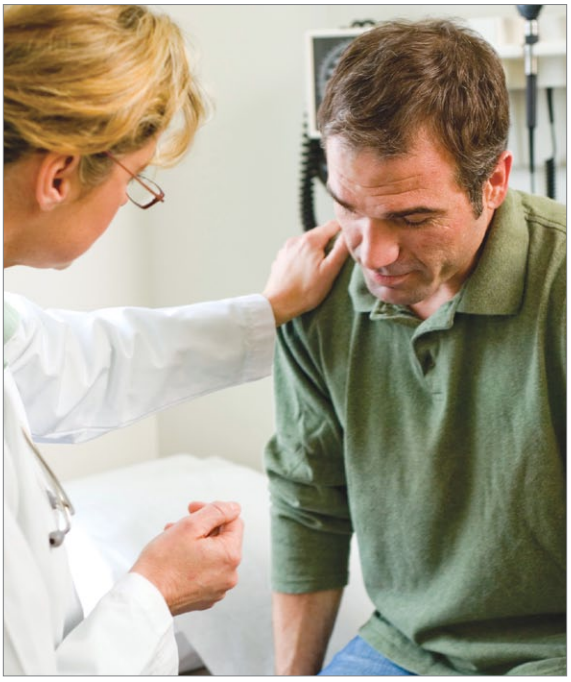
Mr. P, age 31, has been using heroin intravenously for 9 years. He smokes 1 pack of cigarettes daily, but denies using other substances, including alcohol. After an unintentional heroin overdose, Mr. P enrolls in a methadone maintenance treatment program (MMTP) that includes primary medical care and addiction medicine and psychiatric specialists, where he undergoes medical evaluation and screening for hepatitis C virus (HCV) and human immunodeficiency virus (HIV). Laboratory data reveal that although Mr. P is HIV negative, he has been exposed to HCV and treatment is indicated.

Among the approximately 3 million people in the United States with chronic HCV—an enveloped, single-stranded RNA virus—there's a high prevalence of premorbid psychopathology and substance abuse, as well as neuropsychiatric effects caused by HCV treatment.[1-3] Because underdiagnosing and undertreating psychiatric disorders contributes to morbidity and mortality in HCV patients, early identification and prompt treatment is critical.

IV drug use is the most common route for HCV infection, accounting for 65% to 70% of infections.[1] The prevalence of HCV among IV drug users is 28% to 90%.[1] Once exposed to HCV, 75% to 85% of patients do not clear the initial infection and become chronically infected.

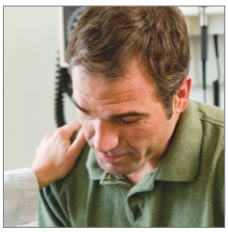
This article reviews the pathophysiology, identification, and management of psychiatric manifestations found among HCV patients and provides an understanding of how psychiatric symptoms manifest in HCV patients. This article also discusses HCV treatment and its neuropsychiatric side effects.

continued



Samuel O. Sostre, MD
Attending Psychiatrist
Psychosomatic Medicine and Addiction Psychiatry
Montefiore Medical Center
Bronx, NY

Gladys Tiu, MD
Attending Psychiatrist
Crozer-Chester Medical Center
Upland, PA



Clinical Point

Many HCV patients have psychiatric symptoms or disorders before HCV is detected or treatment is initiated

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Table 1

Tests to diagnose and evaluate HCV

Test	Results
HCV antibody	Determines prior exposure to HCV
HCV viral assay	Evaluates for current HCV infection
Liver biopsy	Assesses level of liver damage
HCV genotyping	Provides data to determine duration and intensity of treatment and likelihood of treatment success

HCV: hepatitis C virus

Source: Reference 4

Testing for HCV

Chronically infected HCV patients may have few, if any, specific physical complaints, and often are diagnosed during screenings or other routine laboratory evaluations. The presence of risk factors, such as a history of injection drug use or receiving a blood transfusion before 1992,[1] guides the decision to screen for HCV. Normal liver function test results should not preclude testing because many HCV-positive patients have transaminases within the normal range.[4] Initial screening is via an antibody-mediated immunoassay that is highly specific and sensitive for past exposure to HCV (***Table 1***).[4] However, a positive screen does not indicate the presence of active infection. Evidence of the virus via a viral assay will identify active HCV, but does not indicate need for treatment. Liver biopsy confirms the presence of liver injury and quantifies its extent. The severity of liver damage will determine whether treatment is needed. HCV genotyping determines the appropriate duration and dosage of pharmacotherapy.

CASE CONTINUED

Mood improves, but fatigue persists

As part of pre-HCV treatment evaluation, Mr. P undergoes a psychiatric evaluation. He describes periods of low mood while actively engaged in drug use but has never received psychiatric treatment, experienced suicidal ideation, or attempted suicide. Since starting opioid agonist therapy, he reports improved mood but endorses continued mild fatigue and difficulty falling sleep. The psychiatrist determines Mr. P does not meet criteria for an axis I diagnosis other than a substance use disorder.

Although most HCV patients have few, if any, nonspecific physical symptoms, many have psychiatric symptoms or disorders before the HCV diagnosis is made or treatment is initiated; substance use disorders are most common. Batki et al[1] found that 56% of HCV patients in an MMTP met criteria for a nonsubstance axis I disorder and 82% met criteria for such a disorder during their lifetime. Additionally, 66% of patients were taking psychiatric medications. ***Table 2***[1,5,6] lists the rates of other psychiatric disorders found in patients with untreated HCV.

Many patients with chronic HCV complain of chronic fatigue and deficiencies in attention, concentration, higher executive functions, learning ability, and memory that result in significant reduction in quality of life (***Box, page 36***).[7-9] These findings have been found to be independent of the degree of liver disease and are seen in HCV patients with normal liver function.[7,8]

CASE CONTINUED

Motivated and compliant

Since joining the MMTP 6 months ago, Mr. P has been motivated and compliant with all appointments and treatments. Routine urine toxicology screening supports his claim of abstinence. Mr. P begins HCV treatment while continuing follow-up with addiction medicine and psychiatric clinicians and maintains open communication with all treatment providers.

For many years the standard HCV treatment was pegylated interferon-α (IFN-α) and ribavirin. IFN-α is a proinflammatory cytokine with antiproliferative, antiviral, and immunoregulatory properties. The half-life of IFN-α significantly increases with pegylation, which allows for weekly injections.[10,11] IFN-α usually is combined with ribavirin, which increases its efficacy as measured by the sustained virological response (SVR) compared with IFN-α alone. Depending on the virus genotype,

Table 2

Rates of psychiatric disorders in patients with untreated hepatitis C virus

Disorder(s)	Current rate	Lifetime rate
Mood disorders	34% to 35%	67%
Major depressive disorder	22% to 28%	42%
Anxiety disorders	26% to 44%	63%
Antisocial personality disorder	No rates; lifetime diagnosis	16% to 40%
Psychotic disorders	9% to 17%	11%
Substance use disorder	56%	56% to 86%

Source: References 1,5,6

treatment lasts 24 to 48 weeks; SVR rates range from 40% to 82%.[11-13] In 2011, the FDA approved 2 agents—telaprevir and boceprevir—for adjunctive treatment of HCV genotype 1 infection. These 2 agents are protease inhibitors that when added to IFN-α and ribavirin increase the SVR rate in genotype 1 infection from 40% to 50% to approximately 75%.[14,15]

Although the neuropsychiatric side effects of telaprevir and boceprevir have not been determined, treating chronic HCV with IFN-α and ribavirin has been associated with multiple psychiatric symptoms, including depression, mania, suicidality, anxiety, and psychosis.[11-14] Psychiatric symptoms are a common reason for discontinuing or reducing HCV treatment. Because of the high frequency of neuropsychiatric complications, some clinicians believe HCV patients with preexisting affective, psychotic, or substance use disorders should be excluded from HCV treatment. This has led to many HCV patients being untreated despite a lack of prospective, controlled data to support this opinion.[12] To improve outcomes and decrease morbidity, providing appropriate psychiatric services appears to be more important than attempting to select lower-risk patients for antiviral therapy.[1,12,16] The goals of psychiatric treatment should be to alleviate symptoms and allow patients to complete IFN-α therapy without interruption.[16,17]

Studies of high-risk patients who attend multidisciplinary treatment programs that can monitor adherence and efficacy and control side effects before and during HCV treatment have found psychiatric patients have similar adherence, compliance, and SVR rates and were not at increased risk of worsening depressive or psychotic symptoms compared with patients without a psychiatric history.[12,18] Additionally, HCV patients with a psychiatric history are not at an increased risk of suicide.[13,16] Similar findings have been observed in patients with active IV drug use or those receiving opioid agonist therapy. When HCV and substance use are treated simultaneously, patients can successfully complete HCV treatment with SVR rates comparable to those of patients not receiving opioid agonist therapy.[19-21]

CASE CONTINUED

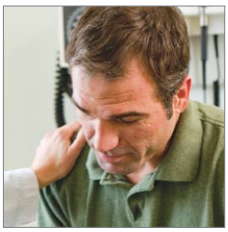
Worsening symptoms

During a psychiatric follow-up 12 weeks after starting HCV treatment, Mr. P reports worsening depressive symptoms with low mood, decreased enjoyment of activities, poor sleep, low appetite, and fatigue. He shows no evidence of psychosis and denies suicidal ideation. We continue his HCV treatment, schedule more frequent psychiatric visits, and initiate citalopram, titrated to 40 mg/d.

Depressive symptoms, the most common neuropsychiatric manifestation of HCV, typically begin early in treatment, usually within the first 12 weeks. Two distinct symptom clusters are noted. A neurovegetative cluster characterized by reduced energy, anorexia, and psychomotor retardation typically begins within the first few months of treatment. Months later, a

Clinical Point

Treating chronic HCV with IFN-α and ribavirin has been associated with depression, mania, suicidality, anxiety, and psychosis



Clinical Point

Depressive symptoms in HCV patients typically begin early in treatment, usually within the first 12 weeks

See this article at CurrentPsychiatry.com for more information on the role of serotonin metabolism and genetic polymorphisms in depression in HCV patients

depression-specific syndrome appears that includes depressed mood, anxiety, and cognitive impairment.[22]

Depressive symptoms may occur in up to 60% of patients treated with IFN-α.[11] When more rigorous depression measures are used, rates decrease to approximately 20% to 30%.[11,13] Accurate diagnosis and treatment of emerging depressive symptoms is essential because untreated depression can lead to postponing or excluding patients from antiviral treatment.[2] Screening instruments such as the Beck Depression Inventory-Second Edition (BDI-II) can be used to measure depressive symptoms in HCV patients with high sensitivity. However, because specificity has been low and somatic symptoms of chronic illness and depression often overlap, the BDI-II and other inventories may overestimate depression. Some researchers have suggested that focusing on questions targeting cognitive and affective symptoms rather than somatic ones may be a more valid measure of depression in patients undergoing immunotherapy for HCV.[2]

The immune system is implicated in IFN-α-induced depression because depressive symptoms share many features with a constellation of somatic and behavioral symptoms termed "sickness behavior."[11] These behaviors can occur when patients are exposed to cytokines that lead to a depressed level of functioning, which may allow the body to devote more energy to fighting illness. IFN-α, a cytokine, stimulates the immune system, which can lead to increases of interleukin (IL)-2, IL-6, and IL-10. Increased circulating levels of these ILs have been correlated with higher depression scores. Additionally, studies have found that patients who develop depression during IFN-α treatment have higher SVR rates, suggesting a more robust immune response.[11,22] For a discussion of how serotonin metabolism and genetic polymorphisms also may help explain the prevalence of depression in patients with HCV, see this article at CurrentPsychiatry.com.

Treating depressed HCV patients

Antidepressants are the treatment of choice for IFN-α-induced depression. Most currently used antidepressants are effective[22] and selective serotonin reuptake inhibitors are considered first choice.[16] Antidepressant choice should be guided by principles similar to those used for patients without HCV: using side effects profiles to target specific symptoms and being mindful of pharmacokinetic properties.

Two treatment approaches have been investigated: prophylactic and symptomatic. A 2012 study[23] of 181 HCV patients with no history of mental illness determined escitalopram, 10 mg/d, effectively reduced the incidence and severity of interferon-associated depression. Other studies examining prophylactic treatment of all patients who were to undergo interferon treatment found this approach did not prevent depressive episodes.[24,25] However, antidepressants have been beneficial for patients with subsyndromal depressive symptoms at baseline[26] and after clinically significant depressive symptoms emerge.[27] Electroconvulsive therapy also has been reported to effectively treat de-

Box

Pathophysiology of fatigue and cognitive deficits in HCV

The pathophysiology of fatigue and neurocognitive dysfunction in hepatitis C virus (HCV) infection is unclear. However, the improvement of chronic fatigue in patients with HCV who receive ondansetron, a 5-hydroxytryptophan-3 receptor antagonist, has implicated abnormal monoaminergic function. Single-photon emission CT studies have found decreased midbrain serotonergic and striatal dopaminergic transmission in some HCV patients with cognitive deficits.[7]

Recently, data have been mounting on a direct neuropathic effect of HCV, with viral elements found in autopsy brain tissue and cerebrospinal fluid.[8] Researchers have suggested that HCV may enter the CNS via a Trojan horse-like mechanism inside infected mononuclear cells.[8] More recently, human brain microvascular endothelium, the major component of the blood-brain barrier, has been found to express all major viral receptors that would allow HCV infection of the CNS.[9]

pression in HCV patients undergoing antiviral therapy.[28]

CASE CONTINUED

Lingering symptoms

Mr. P responds to citalopram with an improvement in mood, anhedonia, and appetite, but he continues to complain of low energy and poor concentration. In an effort to target these symptoms, methylphenidate, titrated to 30 mg/d in divided doses, is added to his regimen, which rapidly improves his symptoms. Insomnia is treated successfully with trazodone, 50 mg/d. Mr. P frequently visits his psychiatrist, who monitors his depressive symptoms using the BDI-II. Mr. P completes HCV treatment without recurrence of depressive symptoms or relapse to heroin use.

Although antidepressants are effective for treating affective and cognitive symptoms, they are not as effective for fatigue and other neurovegetative symptoms.[16,29] The psychostimulants methylphenidate and dextroamphetamine and the nonstimulant modafinil have been studied for treating depressive symptoms in medically ill patients and can be used to treat IFN-α-induced fatigue.[16,22,29]

IFN-α's effect on serotonin metabolism leads to a tryptophan-deficient state because of increased catabolism as a result of activation of indoleamine-2,3-dioxygenase (IDO). This has led to use of tryptophan supplementation, either as augmentation or monotherapy, for managing depressive symptoms in patients treated with IFN-α. Schaefer et al[30] reported 3 cases where tryptophan supplementation significantly decreased depressive symptoms. Other researchers have argued that supplementing tryptophan in the context of IDO activation can lead to greater production of kynurenine and quinolinic acid, which have been linked to increased depressive symptoms in patients receiving IFN-α.[31] They argue that supplementation of 5-HTP, which is available as a dietary supplement without a prescription, can lead to increased serotonin levels and improvement in depressive symptoms.[31]

IFN-α treatment also is associated with mania and psychosis. The incidence, pathophysiology, and management of these treatment-emergent symptoms are not as well studied as IFN-α-induced depression. Mania and hypomania have been reported with interferon treatment, discontinuation of interferon, and use of antidepressants for interferon-induced depression.[29,32] Psychosis, in association with mood symptoms or alone, has been reported to occur in <1% of treated patients.[33] Treatment for mania and psychosis consists of decreasing or discontinuing immunotherapy and adding mood stabilizers and antipsychotics. Once immunotherapy is discontinued, mania and psychosis usually resolve, but prolonged duration of symptoms has been reported.[29,32,33]

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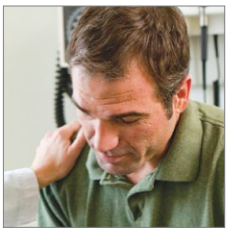
Clinical Point

Depressive symptoms may occur in up to 60% of patients treated with IFN-α; SSRIs are the treatment of choice



Clinical Point

Psychostimulants might be helpful for treating IFN-α-induced fatigue

Related Resources

- Centers for Disease Control and Prevention. Hepatitis C information for health professionals. www.cdc.gov/hepatitis/hcv/index.htm.
- Hep C Connection. www.hepc-connection.org.
- United States Department of Veterans Affairs. Hepatitis C. www.hepatitis.va.gov.

Drug Brand Names

Boceprevir • Victrelis
Citalopram • Celexa
Dextroamphetamine • Dexedrine
Escitalopram • Lexapro
Interferon-α • Intron
Methadone • Dolophine, Methadose
Methylphenidate • Ritalin, Methylin, others
Modafinil • Provigil
Ondansetron • Zofran
Ribavirin • Copegus, Rebetol, others
Telaprevir • Incivek
Trazodone • Desyrel, Oleptro

Disclosure

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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Bottom Line

Identifying and appropriately treating psychiatric disorders in patients with hepatitis C virus (HCV) is essential to reduce morbidity and mortality. The risk of neuropsychiatric side effects with use of interferon-α (IFN-α) in patients with premorbid psychiatric or substance use disorders should not prevent HCV patients from receiving IFN-α if indicated. Neuropsychiatric side effects of IFN-α can be adequately managed with psychopharmacology and close psychiatric follow-up.

Box

The role of serotonin metabolism and genetic polymorphisms in depression among hepatitis C virus patients

Altered serotonin metabolism has been linked to depression in hepatitis C virus (HCV) patients treated with interferon-α (IFN-α). Tryptophan can be metabolized towards serotonin via tryptophan hydroxylase and niacin via indoleamine-2,3-dioxygenase (IDO) with kynurenine (KYN) and quinolinic acid (QUIN) as intermediaries. Introduction of IFN-α activates IDO, causing preferential conversion of tryptophan towards the niacin arm away from serotonin and leads to elevated levels of KYN and QUIN. KYN and QUIN are available centrally, are neurotoxic, and have been correlated with increased depressive symptoms in IFN-α-treated patients.[a,b] A tryptophan-deficient state is created, with less tryptophan being converted to serotonin and subsequently to its metabolite, 5-hydroxyindoleacetic acid (5-HIAA). Decreased levels of 5-HIAA in cerebrospinal fluid have been associated with higher depressive symptoms and higher rates of suicide.[a,b]

Several genetic polymorphisms may help identify patients at risk for developing IFN-α-induced depression. Genes for the 5' promoter of the serotonin transporter (5-HTTLPR) have been investigated for roles in depression development in patients undergoing immunotherapy. Studies have found that persons with the short allele in the 5-HTTLPR gene are more likely to develop depression than those with the long allele. However, this has not been consistent across racial or ethnic groups.[a,b] Research also has associated the serotonin (5-HT) transporter, interferon receptor-A1, apolipoprotein ε4 allele, cyclooxygenase 2, and phospholipase A2 with development of a specific subgroup of symptoms.[a]

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