Psychiatric Implications of Hepatitis-C Infection

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ABSTRACT: Hepatitis-C virus (HCV) has infected an estimated 130 million people worldwide, most of whom are chronically infected. Infection is marked by both treatment- and non-treatment-related psychiatric symptoms. Symptoms associated with antiretroviral therapy, interferon-alpha (IFN-α), include acute confusional states, delirium, depression, irritability, and even mania. These psychiatric symptoms are further complicated by the high rate of substance abuse and comorbid HIV infection inherent to this population. Even in the absence of IFN-α therapy, comorbid depression, cognitive decline, and especially fatigue are common in patients suffering HCV. These comorbidities have significant effects on both treatments and outcomes, and thus are reviewed herein.

KEY WORDS: Hepatitis C, depression, fatigue, interferon-alpha

I. PSYCHIATRIC ILLNESS ASSOCIATED WITH HCV TREATMENT

Although antiviral treatment for HCV infection is the current standard of care, side effects from this treatment include depression and other neuropsychiatric symptoms.1 Specifically, these effects arise from recombinant preparations of interferon-alpha (IFN-α), which have played an increasingly important role in the treatment chronic viral hepatitis. Although frequently of benefit in hepatitis-C virus (HCV), IFN-α has been consistently observed to cause various neuropsychiatric adverse effects in many patients.
who receive it. Additionally, these adverse effects increase the risk of poor treatment outcome, since they often result in dosage reduction and/or discontinuation of treatment. Nevertheless, due to appropriate recognition and management of IFN-α–induced neuropsychiatric adverse effects, the majority of patients are able to continue receiving treatment. There are six major genotypes of HCV. It is estimated that four million Americans have been infected with hepatitis C, and of those, ~70% are infected with HCV genotype 1, and ~30% are infected with HCV genotypes 2 and 3. The remaining genotypes, namely, 4, 5, and 6, are also found but at a much lower prevalence. Laskus et al. documented presence of HCV in the cerebrospinal fluid (CSF) of infected patients. The virus was associated with CSF cells, and in patients harboring different viral strains in serum and PBMC, it was more closely related to PBMC- than serum-derived virus, which suggests that HCV-infected leukocytes carry the virus into the CNS, although a preference of one HCV genotype for brain penetration has not been determined.

I.A. IFN-α–Induced Acute Confusional States and Delirium

There is experience for IFN-α–related neuropsychiatric adverse effects from another disease, which is cancer. Many cancer patients being treated with high dose IFN-α develop an acute confusional state consisting of disorientation, lethargy, somnolence, psychomotor retardation, difficulties with speaking and writing, and psychotic symptoms. Parkinsonian symptoms, as well as seizures, have also been reported in up to one-third of patients receiving intracerebroventricular (ICV) IFN-α for cancerous brain metastases. Such symptoms usually resolve with treatment discontinuation but may persist in some individuals. Significantly, confounding factors such as underlying illnesses (i.e., brain metastases) and concomitant treatments, such as brain radiation, may contribute to this symptom development. Nevertheless, concerning the large population of patients receiving IFN-α for HCV, acute confusional states appear infrequently, even at doses significantly higher than typically used.
Little is known about the underlying pathways involved in IFN-α–induced acute confusional states/delirium. In addition to stimulating endogenous IFN receptors, IFN-α activates CNS opioid receptors. The frequency in which opiates themselves produce delirium in medically ill patients still remains high. Supporting studies demonstrating the effectiveness of opioid antagonists in reversing IFN-α–induced analgesia and fever in rodents as well as restoring memory and concentration deficits in humans have been reported. Moreover, IFN-α and other inflammatory mediators induced by IFN-α may damage neurons through several mechanisms including the induction of cerebral edema, the generation of free radicals, and the promotion of glutamate release with ensuing excitotoxic cell death. There are no published treatment guidelines for IFN-α–induced confusional states or delirium, but strategies for the management of delirium in the medically ill are applicable.

I.B. IFN-α–Induced Depression

The majority of studies suggest IFN-α treatment represents a significant risk factor for the development of both depressive symptoms as well as major depression as defined by the DSM-IV. Importantly, either full-blow major depression and or isolated depressive symptoms such as anxiety and fatigue are primary reasons for treatment discontinuation. Rates of IFN-α–induced major or minor depression seem to be dose and duration dependent. Additionally, premorbid patient–related risk factors play a role in the prevalence of IFN-α–induced depression. In the past several years, a number of investigations have been performed to assess the prevalence of mood disturbance during IFN-α treatment. Whether assessed as DSM-IV–diagnosed major depression or as elevated scores on depression rating scales, depression is a significant concomitant of treatment in nearly all of these studies, with prevalence rates varying from 16 to 58%.

Most of these studies evaluated patients receiving IFN-α with or without ribavirin for HCV. Treatment with pegylated IFNα-2b (PEG Intron) and IFNα-2a (Pegasys) combined with the antiviral agent ribavirin is the standard of care for patients with HCV.
Pegylation involves addition of a polyethylene-glycol group to IFN-α, which increases its plasma half-life, allowing weekly administration and improving antiviral efficacy.\textsuperscript{2} Unfortunately, little is known about the relative ability of either pegylated IFN-α-2b or pegylated IFN-α-2a to cause depression compared to the older preparations of IFN-α. In large trials, the rate of depression during 52 weeks of treatment with pegylated IFN-α-2b was 31\%,\textsuperscript{27} while the rate of depression with pegylated IFN-α-2a over 48 weeks was 22\%.\textsuperscript{28} It is important to note that in these trials, depression was defined as a single symptom and was assessed by self-report as part of a generalized adverse effect screening program. Rates of other depression-related symptoms for pegylated IFN-α-2b were fatigue (64\%), insomnia (40\%), irritability (35\%), and weight loss (29\%). The rates for pegylated IFN-α-2a were fatigue (54\%), insomnia (37\%), irritability (24\%), and reduced appetite (21\%). The only study that directly compared rates of major depression between pegylated and nonpegylated forms of IFN-α revealed no differences between the two treatments.\textsuperscript{29,30}

Recent data from patients receiving high-dose IFN-α therapy for malignant melanoma suggest neurovegetative symptoms represent a subsyndrome that is distinct from the more depression-specific symptoms of depressed mood, anhedonia, and anxiety. A dimensional analysis revealed that neurovegetative symptoms of fatigue, psychomotor slowing, and loss of appetite occurred early in treatment and persisted, whereas depression-specific symptoms emerged later in treatment. Depression-specific symptoms were very responsive to treatment with paroxetine, while neurovegetative symptoms were only minimally responsive.\textsuperscript{31} These findings further support the notion that neurovegetative symptoms, while counting toward a diagnosis of depression, frequently occur in the absence of more depression-specific complaints.\textsuperscript{5}

Antidepressant pretreatment has been shown to protect against the development of major depression in patients receiving high-dose IFN-α for malignant melanoma.\textsuperscript{32} This treatment regimen in combination with the high rate of depression during IFN-α therapy has led many clinicians to pretreat patients with antidepressants prior to initiation of therapy. However, treatment with IFN-α, even at high doses, does not induce symptoms sufficiently severe to
qualify for major depression in at least 50% of patients. Therefore, this routine antidepressant pretreatment may expose patients to an unnecessary medication. Thus, studies evaluating risk factors involved in the development of IFN-α–induced depression may aid in the identification of patients who would be likely to benefit from antidepressant pretreatment.2

Risk factors for the development of depression can be divided into those inherent to IFN-α treatment itself and premorbid factors. Factors regarding the former include dosage and duration, as well as mode of IFN-α delivery, with adverse effects typically worsening as dosage duration increases.17,18,33 All neuropsychiatric adverse effects appear more commonly and more severe in patients receiving ICV and intravenous (IV) IFN-α (typically also at high doses) than in patients receiving IFN-α subcutaneously (as occurs in HCV treatment). Hence, patients receiving high-dose therapy administered either ICV or IV may especially benefit from antidepressant pretreatment.2 Several premorbid risk factors for development of IFN-α–induced depression have been reported. The most replicated risk factor is the presence of psychiatric illness just prior to initiating IFN-α treatment. Most studies that have addressed this issue show that baseline depression and/or anxiety, even when subclinical, predicts the development of psychiatric morbidity during IFN-α treatment.6,33–36 For example, patients receiving psychiatric treatment at the time of initiation of IFN-α appear at higher risk of developing depression.34–36 Conversely, other studies failed to find that past history of depression significantly increased the risk of neuropsychiatric disturbance or IFN-α treatment discontinuation.16–18,26 Furthermore, a past history of drug or alcohol abuse seems not to increase the risk of IFN-α–induced depression, as long as patients remain abstinent during the treatment period.6,30 This question of history is clearly a major issue in the treatment of drug abusers since their drug abuse as well as viral infection–related risks require intervention.37 Studies with IFN-α are divided between those that do38,39 and those that do not find gender to be a significant risk factor.30,40 Similarly, one study found that the very elderly may experience increased IFN-α–induced depression,41 although age has also not been found as a consistent risk factor.30

Of course, physical illness itself is a significant risk factor...
for the development of depression in all patients undergoing treatment. A large body of evidence indicates physiological processes inherent to most illnesses, and especially activation of the proinflammatory cytokine network may directly predispose toward the pathophysiology of depression via direct CNS effects. For example, in both humans and animals, administration of proinflammatory cytokines induces sickness behavior that is comprised of symptoms also commonly seen in depression including fatigue, anhedonia, social isolation, psychomotor slowing, decreased appetite, decreased libido, hyperalgesia, sleep disturbance, and neurocognitive impairment. These symptoms can be reduced or completely prevented by blocking CNS cytokine activity. Indeed, IFN-α is a potent inducer of proinflammatory cytokines and is likely to induce depression-related physical and emotional symptoms in patients already experiencing illness-related increases in proinflammatory cytokine production.

Activity of the hypothalamic-pituitary axis (HPA) may also pose a risk for the development of depression during IFN-α treatment. In support, patients who responded to a first dose of IFN-α with hyperactivity of corticotropin-releasing hormone (CRH) were significantly more likely to develop major depression during treatment than were patients with more modest stress system responses to the initial injection, even though none of the patients suffered major depression at baseline prior to treatment. Indeed, CRH hyperactivity is a central abnormality in major depression and is apparent in persons exposed to early life stress as well as for those who suffer from post-traumatic stress disorder.

Another physiologic mechanism thought to be involved in the development of IFN-α-related depression involves CNS serotonergic neurotransmission. Through activation of the proinflammatory cytokine network, IFN-α induces the enzyme indole-amine 2, 3-dioxygenase (IDO), which causes a diversion of the metabolism of tryptophan away from serotonin and toward kynurenine and quinolinate. Since tryptophan is not produced by the body, IDO-induced tryptophan depletion leads to reduced serotonin levels, a condition that rapidly induces dysphoria in many patients vulnerable to mood disorders. Indeed, various studies demonstrate correlations between reduced tryptophan levels and depression in
patients receiving IFN-α therapy. Moreover, evidence of both CRH and IDO hyperactivity positively correlated with depressed mood, anxiety, subjective memory, and attention difficulties, but not with neurovegetative symptoms, providing further support that depression during IFN-α therapy may actually be two separate syndromes. In addition to the CRH and serotonin pathways, other systems likely contribute to psychiatric symptoms during IFN-α treatment. Animal studies indicate IFN-α modulates CNS opioid, dopamine, and norepinephrine function. In addition, IFN-α increases free radical and glutamate production, inducing neuron cell damage. Interestingly, human studies demonstrate that carriers of the epsilon 4 allele of the apolipoprotein E (ApoE) gene might be at increased risk of developing many neuropsychiatric symptoms during IFN-α treatment, including anxiety, irritability, and depressive symptoms. The treatment of IFN-α-induced depression can be divided into prophylactic and symptomatic paradigms. That is, patients can be pretreated with an antidepressant to prevent or reduce the severity of the development of depression or patients can be monitored for signs of depression during IFN-α treatment and start antidepressant therapy only when indicated. Antidepressant treatment should not be discontinued for patients who are already taking an antidepressant for a psychiatric condition. Pretreatment is also a reasonable strategy for patients at high risk for developing depression during IFN-α therapy based on the criteria discussed above. This recommendation is based on the previously mentioned study showing that pretreatment with paroxetine significantly reduced development of major depression in patients receiving high-dose IFN-α for malignant melanoma. In this investigation, 40 patients were randomly assigned to receive paroxetine or placebo beginning two weeks before, and continuing during, treatment with IFN-α. After 12 weeks of IFN-α therapy, 45% of patients in the placebo group met criteria for major depression, versus 11% in the group receiving paroxetine. Furthermore, treatment with this SSRI was also efficacious in preventing treatment discontinuation due to neuropsychiatric adverse effects. Similar findings were shown in an open trial of pretreatment with the SSRI citalopram in patients receiving pegylated IFN-α plus ribavirin for HCV. Here, patients with a previous psychiatric history
who received citalopram pretreatment developed significantly less depression during IFN-α/ribavirin therapy than those with a psychiatric history who did not receive pretreatment.52

In many HCV patients, it is reasonable to initiate antidepressant treatment only if depressive symptoms begin to emerge once IFN-α therapy has commenced because most patients receiving IFN-α do not develop clinically significant depression, especially when IFN-α is administered in lower doses, or in pegylated preparations. In such cases, initiating antidepressant treatment when a patient receiving IFN-α has had at least one week of continuous depressive symptoms of mild or greater severity2 appears to be indicated. Support for treating patients symptomatically once IFN-α–induced depression has emerged is provided by data demonstrating that depressive symptoms can be effectively treated in patients receiving IFN-α/ribavirin treatment for chronic HCV.26 In an investigation of 39 patients with chronic HCV, 85% of individuals who developed major depression during treatment responded to citalopram.6 In a larger study, 79% of subjects who developed depression during IFN-α/ribavirin treatment were able to complete therapy after addition of paroxetine.7 In further support, depression scores declined significantly in all patients within one month of antidepressant initiation, even with ongoing IFN-α treatment. The results of these studies are in accord with those of various smaller open-label trials and case reports, indicating that all antidepressants are effective in the treatment of IFN-α–induced depression once it has emerged. However, these results should be considered preliminary, since none of these investigations employed a placebo control for antidepressant use.53–58 Finally, it should be mentioned that in one case report a melanoma patient with severe protracted depression induced by IFN responded rapidly to a course of methylphenidate. Indeed, this stimulant appeared to be effective in the treatment of neurovegetative symptoms of major depression induced by IFN. In summary, the available literature provides support for prophylactic as well as symptomatic antidepressant treatment of IFN-α–induced depression, although further placebo-controlled, double-blind trials are required.2 Even with this encouraging evidence, however, IFN-α therapy should be halted when the risks of the depression outweigh the benefits
of uninterrupted treatment. Several clinical scenarios are best addressed by suspending IFN-α treatment, including cases in which depression is associated with suicidal ideation with plan and the means. Although uncommon, IFN-α treatment has been associated with suicide attempts and suicide completions, usually in individuals with no psychiatric history. Therefore, all patients with depressive symptoms during treatment should be carefully screened for suicidal ideation. Other instances in which suspension of IFN-α treatment should be considered include the presence of depressive symptoms that pose an immediate threat to disruption of family relationships or inability to function at work. In such instances, IFN-α should be restarted after adequate pretreatment with an antidepressant.

There are several factors to consider when selecting an antidepressant. Selective serotonin reuptake inhibitors have been most frequently studied; however, available evidence indicates that all antidepressants are likely to be effective. Thus, it is reasonable to select an antidepressant for IFN-α–induced depression using the same principles for treatment of depression that are used generally (i.e., drug-drug interactions, adverse effect profile, and efficacy). In medically ill patients on many medications, treatment with tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) should be avoided, since they are lethal in overdose. Concerning the newer antidepressants, fluoxetine, paroxetine, fluvoxamine, and nefazodone are more likely to raise the plasma levels of other concurrent drugs metabolized via P450. Venlafaxine, mirtazapine, and citalopram seem to confer few effects on all isoenzymes of the cytochrome P450 (CYP) complex, although their metabolism can be affected by other medications that disrupt liver metabolism including protease inhibitors.

Fluoxetine, norfluoxetine, sertraline, and paroxetine are potent in vitro inhibitors of cytochrome P450 2D6 and are capable of causing marked elevations in plasma desipramine and nortriptyline concentrations. Fluoxetine, sertraline, and fluvoxamine are thought to inhibit cytochrome P450 2C because of observed interactions with phenytoin, diazepam, and other drugs metabolized by these enzymes in vivo. Bupropion is primarily metabolized by (CYP) 2B6 and inhibits metabolism of other medications at a similar
level to sertraline. Typical adverse effects of agents that block serotonin reuptake (citalopram, duloxetine, fluoxetine, fluoxetine, paroxetine, sertraline, and venlafaxine) are sexual dysfunction, gastrointestinal distress, anxiety, sweating, and headaches. Venlafaxine, at doses of ≥ 300 mg/day, has also been correlated with a low rate of hypertension.

In addition, one report suggests that HCV-positive patients with cirrhosis and portal hypertension or hepatic failure may be at an elevated risk for bleeding events when treated with an SSRI antidepressant, and especially when this is combined with nonsteroidal anti-inflammatory drugs (NSAIDs). Nefazodone has recently been associated with a low incidence of fatal liver failure and should not be given to patients receiving IFN-α for HCV. Adverse effects of bupropion, a noradrenergic and dopaminergic agent, include gastrointestinal distress and anxiety. Moreover, administration of bupropion in conjunction with drugs that block CYP isoenzymes (including certain antiretroviral agents) has been associated with seizures, which are of particular importance because IFN-α may lower the seizure threshold. In support, a report on patients receiving pegylated IFN-α-2b and ribavirin for HCV indicates that although the incidence of seizures was low, a disproportionate number of patients who had seizures during the treatment were also on bupropion therapy.

There are several factors to consider regarding the antidepressant efficacy in patients receiving IFN-α. Several lines of evidence suggest combining serotonergic and catecholaminergic or noradrenergic and dopaminergic activity may be more effective than serotonergic agents alone in the treatment of major depression. Other investigations suggest that addition of desipramine (a noradrenergic TCA) to an SSRI improves both the rate and magnitude of response. In accord with this, data indicate venlafaxine, duloxetine and milnacipran (serotonin/noradrenaline reuptake inhibitors) may be more effective than SSRIs for acute remission of depression. Moreover, such agents are reported to be more effective than SSRIs in diminishing chronic pain and in the treatment of fatigue, common symptoms in patients receiving IFNα, even in the absence of other depressive symptoms. When combined with reports indicating SSRIs are not especially effective
for IFN-α–induced fatigue and neurovegetative symptoms, the first-line use of agents that enhance the noradrenaline/dopamine functioning of patients with significant depression-related neurovegetative symptoms in the absence of additional depression-specific symptoms is suggested. Furthermore, first-line use of these agents, in the context of isolated neurovegetative symptoms, also confers the additional advantage of not causing sexual dysfunction that frequently accompanies treatment with SSRIs; a property that likely enhances IFN-α–associated sexual dysfunction.

I.C. IFN-α–Induced Irritability or Mania

Irritability is a classic symptom of mania and a common adverse effect of IFN-α treatment. Indeed, many reports indicate that IFN-α is capable of inducing mania. A recent European study found that 20% of patients receiving pegylated IFN-α and ribavirin for HCV demonstrated manic or hypomanic symptoms at some time point during six months of treatment. Since manic symptoms are composed of a spectrum from relatively mild hypomania to psychotic manias, delineating the true prevalence of IFN-α–induced mania very much depends on the criteria by which mania is defined. Up to 77% of patients receiving IFN-α plus ribavirin for HCV report fatigue during treatment. It is not currently known what percentage of patients with irritability may be better defined as dysphoric manic versus depressed versus fatigued. Consequently, it is important to note that both depression and states of chronic fatigue are commonly associated with irritability. Consistent with the idea that the majority of cases of IFN-α–induced irritability likely represent a depressive spectrum disorder, reports suggesting most cases of IFN-α–induced irritability are best treated with antidepressants. Moreover, this is consistent with data indicating that antidepressants, especially SSRIs, decrease irritability and anger.

When mania does occur, it requires an immediate treatment strategy quite different from depression. It is imperative that physicians who treat with IFN-α recognize the symptoms of mania, since time is crucial when dealing with these patients. Many manic
patients fail to demonstrate classic euphoric symptoms but instead display extreme irritability. Such cases are frequently difficult to diagnose because most physicians relate dysphoric individuals to depressive symptoms, especially in terms of IFN-α treatment in which all neuropsychiatric complaints are usually attributed to “depression.” A misdiagnosis here can have damaging results since antidepressants may induce or augment mania. Thus, if irritability occurs during a manic episode, addition of an antidepressant may worsen symptoms.

Key symptoms that tend to differentiate dysphoric mania from depression are as follows. Dysphoric mania is marked by rage, poor insight into condition, increased energy, hypersexuality, increase speech with increased rate, increased use of telephone, flamboyant style of dress, and commonly psychotic symptoms. On the other hand, depression is marked by mild irritability, good insight into condition, fatigue, loss of sexual interest, diminished expectations, diminished speech with decreased rate, decreased desire for social contact, drab clothing, and relatively low occurrence of psychosis. Risk factors for mania include family history of bipolar disorder or personal history of past manic or hypomanic episodes. In addition, evidence suggests that many patients with recurrent depression that commence early in life may also be at increased risk for mania. Emergency psychiatric consultation is imperative if a mania may be emerging in a patient while receiving an antidepressant. Additionally, because of the many risks associated with mania, it is recommended that the antidepressant also be discontinued. Effective antimanic mood stabilizers including lithium, valproate, and carbamazepine, as well as atypical antipsychotics, of which olanzapine has been the best studied, should be initiated. Benzodiazepines are useful to induce prolonged periods of sleep, which allows many manic patients to recover more rapidly.

I.D. Complication of Treatment Strategies by Substance Use Disorders

In addition to pre-existing affective or psychotic disorders, patients with comorbid substance abuse (SA) disorders are at increased risk for HCV infection and represent the vast majority of patients
with chronic HCV. Indeed, HCV occurs in up to 90% of injection drug users. Thus, mitigating this comorbidity represents a significant harm reduction in terms of both acquisition of HCV and also development of later neuropsychiatric comorbidities. To date, few studies have been completed that examine whether ongoing injection or noninjection drug use affects the course of HCV infection. Physicians have been reluctant to treat adults with comorbid SA disorders due to concerns that the neuropsychiatric side effects of IFN-α may increase the risk of relapse. Furthermore, clinicians may also be concerned that these patients are more likely to be noncompliant with treatment, although there is little empirical evidence to support this notion. In general, physicians withhold IFN-α therapy from HCV-infected alcohol or drug users until patients have maintained abstinence for at least six months.

These practices have resulted in a disproportionately low number of patients with SA disorders being enrolled in clinical trials or receiving IFN-α therapy. For example, in a retrospective study of 100 patients screened for psychiatric illness, SA disorders, or serious medical illness, were deemed ineligible for IFN therapy secondary to the presence of at least one of these disorders. In accord, in another investigation of 557 patients referred to an HCV clinic, 21% were ineligible for psychiatric disorders, 14% for current alcohol abuse, and 3.5% for current injection drug use. Moreover, a large retrospective study found that nearly one in six patients with HCV did not receive ongoing health care following the diagnosis of chronic HCV. Of the group not receiving follow-up care, 60% belonged to the “high-risk lifestyle group,” which included patients with a history of nasal (inhalation) or IV drug use, and 22.8% of this group were patients with current alcohol abuse, defined as > 50 g/day. Therefore, the initial barriers to treatment may be related to physicians’ negative attitudes about SA disorders in HCV infected individuals.

Little evidence exists to support the notion that a history of SA disorders precludes treatment tolerance or efficacy. On the contrary, in several recent studies with small patient cohorts, it has been shown that adequate viral response rates are achievable in injection drug users who are still actively using drugs. In a review of 10 clinical trials published between 2001 and 2004...
regarding antiviral therapy in substance users, the sustained viral response (SVR) and compliance rates did not differ from non–drug users infected with HCV.\textsuperscript{94} Other investigations indicate that while heavy drinking (> 70 to 80 g/day) is associated with poor SVR, patients with a history of mild to moderate alcohol use who abstain for a period prior to and during IFN therapy display SVR rates similar to those observed in individuals without a history of alcohol abuse.\textsuperscript{95–97}

\textbf{I.E. Implications of Comorbid HIV and HCV Infection}

As stated earlier, HCV occurs in 52–90\% of injection drug users.\textsuperscript{84} Importantly, injecting drugs is one of the most common means by which individuals acquire HIV infection as well. On sub group analysis, HIV-positive hemophiliacs are nearly all HCV positive. On the other hand, HCV infection is rare (2–10\%) in HIV patients who acquired HIV by homosexual contact. In general however, in the HIV-positive patient population, the prevalence of HCV coinfection ranges from 30\% to more than 50\%.\textsuperscript{84} The implications of this comorbidity are serious since HCV infection is more aggressive in HIV-infected persons, leading to hepatotoxicity at a more rapid rate, and consequently increases risk of cirrhosis, hepatocellular carcinoma and ultimately liver failure, and death. Indeed, this extended survival of HIV patients allows for decompensation of previously undiagnosed cirrhosis in coinfected patients. This is so common that in fact end-stage liver disease is now the leading cause of death in the HIV-infected population. Moreover, the treatment of comorbidity infected patients is complicated by drug-drug interactions. All recommended HAART regimens include at least three different antiretroviral drugs.\textsuperscript{98,99} Some regimens combine up to six different drugs.\textsuperscript{100} Since many HIV patients take medications for comorbid psychiatric disorders, the potential for multiple drug-drug interactions is great. In fact, two large retrospective studies of inpatients with HIV showed that approximately one-half of patients who were taking a PI were taking at least one other drug that could result in a drug interaction.\textsuperscript{101,102} In the second study, about 50\% of the drug interactions were considered potentially
serious or even life threatening. Many neuropsychotropic agents and antiretroviral drugs are metabolized by the cytochrome P450 systems. As examples, fluoxetine, norfluoxetine, sertraline, and paroxetine are potent in vitro inhibitors of cytochrome P450 2D6 and are capable of causing marked elevations in plasma desipramine and nortriptyline concentrations. Fluoxetine, sertraline, and fluvoxamine are thought to inhibit cytochrome P450 2C because of observed interactions with phenytoin, diazepam, and other drugs metabolized by these enzymes in vivo. Interactions between these drugs are usually the result of induction or inhibition of these P450 enzymes. As an example, among the PI, ritonavir was demonstrated to confer the greatest inhibitory action on CYP 3A4 and has been associated with many drug interactions—including inhibitory effects on the metabolism of other antiretroviral agents. Indeed, this is being used to enhance the half-life and decrease dosing frequency of these drugs. Various in vitro data suggest some anticonvulsants; in particular, valproate might increase viral replication. Importantly, the clinical implications of these findings seem to be nonexistent thus far. A recent retrospective study of 11 HIV patients taking valproate for manic syndromes did not appear to increase viral load, as long as their antiretroviral treatment was adequate. Challenges in preventing deleterious drug-drug interactions include the considerable individual variation observed in the degree to which cytochrome P450 enzymes can be induced or inhibited and the extent to which antiretroviral agents and other drugs induce or inhibit cytochrome P450 enzymes. These problems are further compounded when patients take multiple drugs, which makes predicting clinical drug interactions difficult in most cases.

II. Non–treatment Related Mental Illness Associated with Hepatitis-C Virus (HCV) Infection

II.A. Infection and Replication in the Brain by HCV

HCV belongs to the Flaviviridae family, which includes several well-known neurotropic viruses (e.g., yellow fever, dengue, and
tick-borne encephalitis viruses), and reports have suggested HCV as a cause of various CNS and peripheral nervous system pathologies.\textsuperscript{108–110} Thus, it is not surprising that infection of the brain itself may impart neuropsychiatric symptoms. Also, HCV RNA has been detected in the CSF from both HIV-positive and HIV-negative patients as stated earlier,\textsuperscript{111} and viral sequences have been amplified directly from brain tissue from a patient diagnosed with progressive encephalomyelitis.\textsuperscript{108} However, the presence of viral sequences in any particular compartment cannot be regarded as evidence for replication; and to prove the latter, the presence of replicative intermediates was first established in 2001 by Radkowski et al.\textsuperscript{112} They analyzed HCV RNA in autopsy brain tissue from six subjects, three of whom were HIV-1 positive. In addition to strand-specific detection of HCV RNA negative strands, they compared viral sequences amplified from various CNS structures and serum, assuming that in the presence of independent viral compartments they could be different, much like what has been described for HIV-1.\textsuperscript{113} Tests for the presence of HCV RNA were positive in serum and in every sample of brain tissue analyzed from all six patients, the only exception being patient number 3, from whom viral sequences could not be amplified from medulla oblongata. HCV RNA negative strands (the viral replicative intermediary) were detected in brain tissue in three patients. In two of these patients, serum- and brain-derived viral sequences were different and classified as belonging to different genotypes. In one of the latter patients, HCV RNA negative strands were detected in lymph node and, while being different from serum-derived sequences, were identical to those present in brain, thus suggesting HCV can replicate in the CNS, probably in cells of the macrophage/monocyte lineage.\textsuperscript{112}

\textbf{II.B. Depression in HCV Infection}

Both major mild forms of depression are common even among non-IFN-treated HCV-infected patients, and specifically symptoms of fatigue are common.\textsuperscript{29,114,115} Lee et al.\textsuperscript{115} reported major depression in nearly one-quarter of untreated HCV patients and more
than 60% were taking antidepressants when first seen. Moreover, because the study was retrospective, the frequency of depression could have been underestimated. Two possibilities to explain the high frequency of depression in their population were stated: (i) patients may be relatively young and suffer from reactive depression secondary to extreme fatigue and/or concern for their long-term well-being and/or (ii) patients with intrinsic depression might have greater risk factors for infection with HCV such as illicit drug use. A study by Dwight et al. supported the former. In their sample of chronic HCV patients, severity of depressive symptoms was highly associated with fatigue severity even after controlling for severity of hepatic disease and medical comorbidity. Thus, patients suffering the most severe form of depression, major depressive disorder (MDD), largely demonstrated the highest fatigue ratings. As in previous studies, there was no correlation between severity of hepatic disease, as measured by biopsy, and any symptom or function measure. Goulding, using the hospital anxiety and depression scale (HADS), found a total of 45.3% of HCV patients (n = 75) scored in the possibly or probably clinically depressed range (depression score > 8) in a frequency at tenfold (45.3%) at over tenfold the rate of controls (4%; n = 25). Subjects in the HCV group were also more than twice as likely as controls to score clinically significant anxiety levels.

Taken together, there is a large burden of neuropsychiatric impairment associated with chronic HCV infection, but whether this is a direct consequence of the viral infection or whether it is related to associated factors remains unclear. The mechanism for a biological effect of the virus conferring depressive symptoms has yet to be established, although there is evidence for direct replication and effects in the brain as stated earlier. Furthermore, it may be more likely that patients with depression may have a higher incidence of HCV infection since the greatest reservoir of HCV infection is in IV drug users, many of whom already suffer clinical depression. On the other hand, depression may occur secondary to HCV infection itself in the form of a reactive depression. This might be related to the diagnosis and concerns over long-term health, or may be secondary to fatigue and cognitive impairment. Occurring in conjunction with these psychosocial factors, a biological effect of
HCV that imparts depression can not as yet be ruled out, especially since the virus infects and replicates in the CNS.

II.C. Fatigue in HCV Infection

Many uncontrolled surveys have reported the prevalence of fatigue in HCV patients, which is likely the most common psychiatric symptom in chronic HCV infection. Using the fatigue impact scale (FIS), Goh et al. found that the perceived functional impact of fatigue on quality of life was significantly higher in patients with chronic HCV infection compared to healthy controls, a phenomenon unrelated to degree of hepatitis and the coexistence of autoimmune disorders alone. Interestingly, their results also indicated that IFN treatment had no significant impact on fatigue. Barkhuizen et al. examined the frequency of fatigue in HCV compared with other liver diseases via chart review for diagnoses, amino-transferases, histology, treatment, and presence of HCV by second-generation ELISA and/or PCR. They found that 67% of patients in the HCV group developed significant fatigue compared with 44% in other liver diseases. For example, fatigue was significantly more frequent among patients with isolated HCV than among those with isolated alcoholic liver disease or hepatitis B (66%, 30%, and 29%, respectively). Cacoub et al. assessed the prevalence of fatigue in HCV patients prior to any therapy, as well as on prolonged follow-up of both treated (n = 355) and untreated patients (n = 76). A self-report questionnaire was completed every six months for a total of 18 months. At baseline, fatigue was present in 59% (n = 254) of patients. Fatigue was significantly improved in 29 of 83 (35%) responders (those with successful IFN treatment) compared to 75 of 348 (22%) patients with detectable HCV RNA (p = 0.01). The impact of virologic response on fatigue significantly persisted after adjusting for age, gender, fibrosis stage, and depression (odds ratio: 0.34, p < 0.001). In contrast to the previous study, antiviral treatment here seemed associated with a reduction in fatigue.

Thus, although improvements in fatigue have been reported after treatment, it does appear to persist in some individuals despite a
virological response. As was seen in studies of depression in HCV, many of the studies in the HCV-related fatigue field can be criticized for inadequate control of salient confounders including multiple social, behavioral, psychological, and personality factors.\textsuperscript{116,126,127} Because the majority of studies have been methodologically flawed by failing to account for all confounding factors, the statement cannot be made that HCV causes fatigue.\textsuperscript{128} Indeed, in one controlled retrospective study, no excess fatigue in HCV-infected patients compared to noninfected blood donors was observed.\textsuperscript{129} Of note, the prevalence of fatigue in the “healthy” blood donors was 70%, suggesting the fatigue rating instrument might have been oversensitive. Thus, it is likely that fatigue reported by HCV-infected patients is the result of multiple causes. Furthermore, as with non-treatment-induced depression in HCV patients, the relative contribution of a biological mechanism remains uncertain.\textsuperscript{118}

**II.D. Cognitive Impairment in HCV Infection**

Confounders are particularly important when discussing cognitive impairment in HCV, namely, chronic hepatic encephalopathy (CHE). This is a neuropsychiatric syndrome typically associated with portal-systemic shunting secondary to cirrhosis of the liver, but may also exist in patients with surgical portal-systemic shunts.\textsuperscript{130} Signs and symptoms of hepatic encephalopathy include an altered level of consciousness, asterixis, ataxia, confusion, spatial disorientation, and visual hallucinations.\textsuperscript{131} Several investigations into impairments in patients with cirrhosis but no appreciable clinical signs of CHE have demonstrated selective deficits of psychomotor speed, visual perception, and attention with preserved verbal ability. This syndrome is termed minimal hepatic encephalopathy (MHE). Therefore, HCV infection may result in cognitive impairment prior to development of cirrhosis, and may be unrelated to a history of illicit drug use or mood disorder in some patients.\textsuperscript{132} Such phenomena are described herein.

Since cognitive impairment in the form of MHE is frequently detectable in patients with cirrhosis, any study that tests for a direct effect of HCV infection on cognitive function should either
exclude patients with advanced liver disease/cirrhosis or have sufficient power to allow subgroup analyses. The published studies to date have considered and controlled for the presence of advanced liver disease, medical comorbidity, and drug abuse to varying degrees. However, inconsistencies exist in the use of control groups and definitions of impairment, resulting in varying conclusions about prevalence and severity of cognitive impairment due to chronic HCV infection.

Forton examined antiviral treatment–naive patients (n = 27) with confirmed minimal HCV hepatitis compared to a control group of patients (n = 16) who had been exposed to HCV but were negative for HCV RNA on repeated testing. A historical healthy control group was also included. Groups were matched for education and history of illicit drug use. None of the patients were taking central nervous system (CNS)–altering medications or illicit drugs at the time of the study, and patients were classified as nonusers if a history of major drug usage was unequivocally absent. HCV-infected patients displayed deficits on more tasks (performance more than one standard deviation below the normative mean) than the HCV RNA–negative patients and historical controls. These included selective impairments of attention, concentration, and working memory. No significant differences were observed between individuals with and without a history of recreational drug usage. Furthermore, the HCV-infected patients had higher levels of depression, but this failed to correlate with the cognitive test scores. The authors concluded that mild neurocognitive impairment was evident in a proportion of patients with histologically mild chronic HCV infection, and that it was unrelated to depression, fatigue, or a history of illicit drug use.

In a study by Hilsabeck et al., a battery (visuocostructional skills, learning, forgetting, sustained visual attention/concentration, psychomotor speed, visual scanning/tracking, and mental flexibility) was administered to HCV-infected individuals (n = 66; 44 without cirrhosis). Results indicated that the proportion of impaired performance ranged from 0%, on a design copy task, to 49%, on a measure of sustained attention. As in the previous study, impairment was defined as performance one standard deviation below the normative mean. This study was confounded by the
fact that 27% of the HCV-infected patients were taking psychiatric medication and 23% were undergoing IFN therapy at the time of testing. The HCV-infected patients were compared with patients affected by liver disease of other etiologies \((n = 14)\). In this study, no excess of cognitive impairment was seen in the HCV group. However, it must be taken into account that the comparison group included patients with alcoholic liver disease and may have been insufficiently powered. Thus, it was concluded that progressive liver injury might result in cognitive deficits in patients with HCV, even prior to development of cirrhosis. The same research group utilized a similar test battery in an independent sample of HCV-infected patients \((n = 21)\) and examined more thoroughly the association of neuropsychiatric symptoms, including self-reported cognitive dysfunction, with objective neuropsychological test data.\(^{134,135}\) The cohort was similarly heterogeneous as in their previous study: 33% had cirrhosis, 19% had alcoholic hepatitis by liver biopsy, 9% had comorbid HIV infection, 24% were on antiviral therapy, and 55% were on psychiatric medication at the time of testing. Similar rates of impairment in concentration, complex attention, and working memory were observed. No significant differences on any of the cognitive measures between individuals reporting higher and lower levels of fatigue, depression, or cognitive dysfunction were found. These results are similar to those of Forton et al.\(^{133}\) However, because of the heterogeneity of their cohort, and thus the high likelihood of confounding, the authors’ conclusion that a significant proportion of patients with chronic HCV infection experience cognitive difficulties is not strongly convincing. Indeed, it is not clear that the impairments described were directly attributable to HCV infection. Moreover, the lack of an association between cognitive measures and fatigue or depression in these studies makes the clinical significance of the impairments uncertain.

This concern is addressed by a study of patients with HCV infection without cirrhosis or advanced liver disease \((n = 30 \text{ and } 44, \text{ respectively})\) compared to healthy controls \((n = 15)\). Medical and psychiatric comorbidity, active drug abuse, and treatment with any CNS-altering medication were exclusion criteria in this investigation. The study sought to determine whether patients’ self-reported fatigue was accompanied by objective evidence of
cerebral dysfunction. A well-validated battery of neuropsychological tests was utilized with the fatigue impact scale, the functional activities questionnaire, and the hospital anxiety and depression scale. HCV-infected patients were further subdivided into mild and moderate fatigued groups based on the fatigue impact scale scores. In support of earlier studies, HCV-infected patients demonstrated attention deficits, slight memory disturbances, functional impairments in activities of daily living, and depression. These deficits were present in the mildly fatigued patients, but more pronounced in the moderately fatigued group. The cognitive deficits reflected attentional processes and higher executive functions. Of note, visuoconstructive abilities and motor performance, which are often impaired in MHE, were preserved. Since these deficits were selective rather than global, it was concluded that rather than being a consequence of mood disturbance, they were objective evidence of CNS involvement in HCV. Unfortunately, no conclusions can be drawn here regarding the prevalence of CNS involvement in the broader population of HCV-infected patients because the study subjects were recruited from a tertiary care center.133

This potential deficit in generalizability was addressed by an investigation in 2003 in patients with chronic hepatitis, who were incidentally found to be HCV infected on screening for blood donation.136 The study was designed to evaluate cognitive function and quality of life in chronic hepatitis, secondary cirrhosis without previous decompensation, and cirrhosis with previous decompensation. Patients were allowed into the study only if no overt encephalopathy was present at the time of testing. Patients ($n = 120$) were compared with age, sex, and educationally matched controls. Quality of life was measured using the SF-36, and cognitive testing was performed using a battery of standardized tests measuring memory, attention, executive function, visual perception, and psychomotor function. In disagreement with prior investigations, the authors found no evidence of cognitive impairment in HCV-infected patients without cirrhosis or those with compensated cirrhosis. Impairments were only detected in patients with previous hepatic decompensation, which was most likely caused by MHE. There was however a nonsignificant trend toward impaired executive function in the precirrhotic group.
Several factors may explain these results. First, the majority of patients in the noncirrhotic and compensated cirrhotic groups were enrolled after HCV infection was diagnosed on blood donation. Thus, they were positively selected for good health because symptomatic individuals are unlikely to volunteer for blood donation. Indeed, this is reflected in the SF-36 quality-of-life scores of the chronic HCV group, who differed significantly from the control group in only one out of the eight scores. Second, patients with overt cognitive dysfunction as assessed by the mini–mental status test were excluded. Third, the battery employed was broad, covering five neuropsychological domains, which may not all be relevant to chronic HCV. The other studies indicated attention to be the most relevant domain, and this was tested using three tests in this study: Trail A, Symbol Digit Oral, and Stroop. Importantly, the Symbol Digit Oral and Stroop tests were of low sensitivity in precirrhotic individuals in one previous study (20–23% impairment) and were insensitive in another. Fourth, the study used strict criteria for cognitive impairment by performing statistical analyses on raw scores compared with a healthy control group instead of defining impairment by comparison with population norms. These elements, taken together with sensitivity differences in the paper-based tests versus with the computer-based recording of reaction times, might explain the discrepant findings in the study. The investigation was, however, consistent with earlier studies in that no association was found between cognitive function and physical and mental quality of life as measured by SF-36. Notwithstanding the salient differences of patient characteristics, control groups, methodology, and statistical analysis in these studies, there is a consensus that, in patients with chronic HCV infection, mild cognitive impairment is common. Further investigation is required to shed light on the prevalence, clinical significance, and etiology of these.

Thus, as with fatigue, several factors may involved in the cognitive dysfunction observed in HCV patients. First is the aforementioned presence of MHE. Second may be the effect of personality or HCV acquisition–associated factors such as a history of major recreational drug usage, presence of affective disorders, and of subjectively experienced symptoms such as fatigue. Third, there may also be a biological effect of HCV infection on the CNS. These
factors may not be mutually exclusive and might interact. Much evidence exists for a deleterious effect of active drug use on cognitive function;\textsuperscript{138} however, few studies have addressed the effect of prolonged abstention from recreational drug use.\textsuperscript{118} Investigations have indicated that neuropsychological impairment in the first few weeks of abstinence, especially from opiates and sedatives,\textsuperscript{139} may persist for up to three months. Conversely, there is also evidence that neurocognitive function improves during abstinence.\textsuperscript{140}

Importantly, no consistent correlation between cognitive impairment and depression in HCV-infected patients has been shown, even though most studies included patients with mild depression. It has been suggested that the self-reported mild mood disturbance is a part of a neuropsychological syndrome associated with HCV infection, and may actually be a result of physical or cognitive symptoms or the shock of diagnosis and illness perception.\textsuperscript{29,123} Thus, further studies are needed to determine cognitive status in patients without any depressive features.

The studies have also not demonstrated a consistent association between fatigue and cognitive impairment, although Weissenborn et al.\textsuperscript{141} reported greater cognitive dysfunction in more fatigued patients. Two possibilities have been suggested to explain this phenomenon.\textsuperscript{118} First, slowed mentation and psychomotor speed, along with reduced attention, might result in routine tasks taking longer to complete. This reduced performance for a given amount of effort may be interpreted by the individual as fatigue. Second, fatigue and cognitive impairment may both be caused by a third unidentified factor.

\textbf{II.E. The Impact of Coinfection with HIV as an Etiology of Neuropsychiatric Impairment}

The implications of this comorbidity with HIV-1 infection are serious because HCV infection is more aggressive in HIV-infected persons, leading to hepatotoxicity at a more rapid rate and consequently increased risk of cirrhosis, hepatocellular carcinoma and ultimately liver failure, and death. Indeed, this extended survival of HIV patients allows for decompensation of previously undiag-
nosed cirrhosis in coinfected patients. This is so common that, in fact, end-stage liver disease is now the leading cause of death in the HIV-infected population.

As stated earlier, HCV occurs in 52–90% of injection drug users. Importantly, injecting drugs is one of the most common means by which individuals acquire HIV infection as well. On sub group analysis, HIV-positive hemophiliacs are nearly all HCV positive. On the other hand, HCV infection is rare (2–10%) in HIV patients who acquired HIV by homosexual contact. In general, however, in the HIV-positive patient population, the prevalence of HCV coinfection ranges from 30% to more than 50%. Not only does the shared mode of transmission make this comorbidity common, but also the success of highly active antiretroviral therapy (HAART) in prolonging the survival of HIV-infected patients.

Coinfection with HIV may also affect the course of neurobehavioral outcomes of HIV infection. HIV infection can facilitate extrahepatic HCV replication, and both viruses are present in monocytes/macrophages, cells that are known to migrate to the brain and release toxic proinflammatory mediators such as quinolinate, leading to considerable dysregulation of immune responses. Indeed, HCV augments neuropsychiatric deficits associated with HIV infection and methamphetamine use. Furthermore, neuropsychiatric dysfunction has been linked to HCV infection in HIV-positive patients. These works have pointed to a phenomenon whereby HIV and HCV might interact in the CNS to promote greater neurological damage.

Indeed, coinfection with both viruses presents a possible additive or synergistic increase in risk for neuropsychiatric problems. In a recent study, the distribution of HCV was analyzed in brains of well-characterized HIV patients. The presence of HCV antigens in the CNS of patients infected with HIV was demonstrated in atrocities and per vascular macrophages; two key cell populations mediating brain inflammation that is a central cause of both HCV- and HIV-related cognitive impairment. This study further suggests that HCV traffics into the CNS of patients infected with HIV and that the presence of HCV antigens is associated with cognitive impairment. It should be noted that in the context of HIV infection, which many HCV-infected drug abusers are subject to,
quinolinate elevations have been demonstrated as well and may be associated with HIV-associated dementia (HAD).

Letendre examined postmortem brain tissue from 12 people who had HCV/HIV coinfection and 13 HIV-infected people who were HCV negative. They found HCV RNA in the brain tissue of all the HIV HVC–coinfected individuals, but none of the HCV-negative individuals. Antibodies to HCV were also found in the CNS of patients with coinfection. Most interestingly, it was found that presence of HCV RNA was significantly associated with considerable cognitive impairment as well as the presence of encephalitis, further supporting the notion that replicating HCV can cause or enhance neurological damage caused by HIV. Previous works suggested that glutamate transport is defective in patients with HCV infection and HIV is also known to impair glutamate transport, suggesting HCV and HIV might be working together to block glutamate clearance from synapses of patients with coinfection, possibly leading to structural damage in the brain and therefore possible neuropsychiatric symptoms. Coinfection with both viruses must also be considered in terms of CYP modulation by anti-HIV drugs and neurotropics. Treatment of chronic HCV with IFN-α is relatively contraindicated in patients with psychiatric disorders because of possible severe psychiatric side effects. Previous studies evaluating the effect of IFN treatment on drug metabolism have been conducted with the doses used to treat hepatitis (i.e., 3–6 million units, three times per week). It was shown that IFN treatment adversely affects drug metabolism. The clearance of antipyrine, a probe of hepatic oxidative metabolism that is metabolized by multiple CYP enzymes, was evaluated in patients on IFN with the results showing a decrease in antipyrine clearance of ~20%. High-dose IFN differentially impairs CYP-mediated metabolism, having no effect on some enzymes (CYP2E1) and substantial effects on others (CYP1A2; median 60% decrease). A significant association was found between the magnitude of CYP inhibition and the occurrence of side effects including fever and neurological toxicity in melanoma patients. Activities of CYP1A2, CYP2D6, and CYP2C19 were decreased, whereas CYP2E1 was not changed. The clinical implication of these findings in high-dose therapy may be applied to HCV, for safety, although doses in HCV are
much lower. Overall, it can be assumed that the clearance of drugs predominately metabolized by CYP1A2, CYP2D6, and CYP2C19 enzymes would be decreased, which may result in increased drug exposure and therefore increased potential for adverse effects. Thus, the drug-cytokine interaction observed during IFN-α therapy may have significant clinical consequences. CYP1A2, CYP2D6, and CYP2C19 are involved in the metabolism of sedatives, narcotics, psychotherapeutics, antiepileptics, beta-blockers, proton pump inhibitors, anesthetics, bronchodilators, and antibiotics.\textsuperscript{145,147–153} Thus, much caution is advised when agents whose metabolism is inhibited by IFN are being used during and after IFN therapy.

III. CONCLUSIONS

HCV infection poses unique challenges to clinicians due to both non-treatment- and treatment-related\textsuperscript{153–155} psychiatric comorbidities including depression,\textsuperscript{156–158} mania, cognitive impairment, and especially isolate neurovegetative symptoms. Antidepressants, particularly SSRIs,\textsuperscript{159,160} have shown significant efficacy in treating depressive symptoms in both treatment-related and non-treatment-related cases. It is important to assess the current and future risk of suffering these ill effects by carefully screening for past and current mental illness and substance abuse in order to make a determination regarding initiation of IFN-α therapy and the risk of inducing psychiatric symptoms versus the benefit of improved hepatic status.

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