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Psychiatric and Substance Use Disorders in Individuals with Hepatitis C

Epidemiology and Management

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Abstract

Hepatitis C virus (HCV) infection is a major health concern in the US as well as in other countries worldwide. Treatment issues and disease management

strategies are complicated by the extremely high rate of psychiatric and substance use disorders in those who have HCV. The majority of new and existing cases of HCV are related to injection drug use and, in this population, the prevalence of psychiatric comorbidity is high. Optimally, all patients with HCV should be screened for psychiatric and substance use disorders before initiation of antiviral therapy. If a patient screens positive, he or she should be referred to a mental healthcare provider or addiction specialist, assessed for the presence of a psychiatric or substance use disorder, and appropriately treated prior to initiation of antiviral (i.e. interferon) therapy. Although interferon-based therapies can lead to severe neuropsychiatric adverse effects, including in rare instances suicide, evidence suggests that many patients with comorbid psychiatric and substance use diagnoses can be treated safely and effectively using comanagement strategies. However, most patients with HCV are not treated with antiviral therapy. Therefore, we must expand our definition of HCV 'treatment' to include treatment of the comorbid psychiatric and substance use disorders that accompany HCV infection and precede antiviral therapy. This paper reviews the epidemiology and management of psychiatric and substance use disorders in patients with HCV, the issue of psychiatric and substance use disorders as contraindications for antiviral therapy, and current treatment strategies for HCV patients with these comorbid conditions.

Approximately 3–4 million Americans and >170 million people worldwide are infected with hepatitis C and have chronic hepatitis C virus (HCV) infection. The most common means of transmission are through injection drug use (65–70%), high-risk sexual behaviors, including sex with multiple partners (15–20%), or occupational exposure (5%)[1] (table I). Up to 20% of chronically infected patients will develop cirrhosis over the 20-year period following acute infection and approximately 3–5% of these patients will develop hepatocellular carcinoma. At particular risk are those who are heavy alcohol users, co-infected with HIV or hepatitis B virus, or older at the time of HCV infection.[2-4] Hepatitis C is also the most frequent cause of liver transplant in the US.[5]

Table I. Centers for Disease Control and Prevention recommendations on who should be tested for hepatitis C virus (HCV) infection[6]

HCV testing is recommended for the following people:
Persons who ever injected illegal drugs, including those who injected once or a few times many years ago
Persons who were treated for clotting problems with a blood product made before 1987
Persons who were notified that they received blood from a donor who later tested positive for HCV
Persons who received a blood transfusion or solid organ transplant before July 1992
Long-term haemodialysis patients
Persons who have signs or symptoms of liver disease (e.g. abnormal liver enzyme tests)
Children born to HCV-positive women
Healthcare workers after exposures (e.g. needle sticks or splashes to the eye) to HCV-positive blood on the job

Substance use and psychiatric disorders are common comorbidities in those who have HCV infection. Between 30% and 98% of injection drug users are infected with HCV,[7] and the prevalence of HCV among patients with comorbid alcohol use, abuse or dependence disorders both with and without cirrhosis is significantly higher than in individuals without alcohol use.[8] The occurrence of HCV infection is reported to be up to 11 times greater in people with serious mental illness than that found in the general population, and as high as 25% in some study samples of patients with serious mental illness.[9] Data collected on patients seen at any facility in the Northwest Veterans Integrated Service Network 20 (8 medical centers and 17 outpatient clinics in Alaska, Washington, Oregon and Idaho) suggest

that of those patients tested for HCV, 9.9% with schizophrenia/schizoaffective disorder and 31.1% with schizophrenia/schizoaffective disorder and comorbid substance use disorder were infected, compared with 5.3% of controls (patients without schizophrenia, schizoaffective or substance use disorders).[10] Importantly, this high prevalence of coexisting psychiatric and substance use disorders has been a significant barrier to HCV treatment for these patients. This paper reviews the epidemiology and management of psychiatric and substance use disorders seen in patients with HCV, the issue of psychiatric and substance use disorders as contraindications for antiviral therapy, and current treatment strategies for HCV patients with these comorbid conditions.

1. Epidemiology of Substance Use Disorders and Psychiatric Illness Comorbidity in Patients with Hepatitis C

1.1 Substance Use Disorders Comorbidity

HCV occurs in up to 90% of injection drug users.[11] Seroconversion to HCV in injection drug users can occur anytime in the course of drug use, but occurs in a majority of patients within the first 1–3 years of drug use.[12] It has been noted that host (e.g. sharing drug preparation and injection equipment), viral (e.g. high efficiency of HCV transmission via blood exposure), and environmental (e.g. there are large groups of HCV-infected injection drug users in many regions of the world) factors all support the rapid spread of HCV among injection drug users.[12,13] Relative to the general population, the incidence of HCV infection is also high among non-injection drug users. In a sample of >700 non-injection drug users (heroin, cocaine or crack) the prevalence of HCV ranged from 5% to 29%, depending on age, gender, study location and drugs used.[14] To date, few studies have been carried out to determine if ongoing injection or non-injection drug use affects the course of HCV infection.[15] However, unlike other drugs of abuse, alcohol use does significantly affect the course of HCV infection and liver disease progression.

Between 8% and 43% of patients who have alcohol use or abuse disorders and comorbid liver disease have evidence of HCV infection.[16-19] Heavy alcohol use is a risk factor for transmission of HCV and it increases the rate of liver disease progression. Alcoholic liver disease and HCV infection are both considered risk factors for the development of hepatocellular carcinoma.[20,21] Most epidemiological studies have shown that the effects of alcohol and HCV on liver disease progression are synergistic.[22] Furthermore, the more alcohol consumed, the worse the clinical outcome. Patients with HCV infection who drink >30g of alcohol per day have a higher risk of developing cirrhosis and fibrosis and a lower survival rate compared with those HCV patients who drink <30g of alcohol per day.[23,24] Although there are no studies to support the following speculation, interventions designed to decrease or stop alcohol use in moderate/heavy alcohol users with HCV may significantly reduce liver disease progression.

1.2 The Trimorbidity of Substance Use Disorders, Psychiatric Illness and Hepatitis C

The prevalence of trimorbidity (substance use and psychiatric illness and HCV infection) is particularly common among veterans treated within the Veterans Affairs Medical Centers (VAMCs), compared with other patient populations. In a study that used the national Veteran's Health Administration database, the prevalence of HCV was found to be 1.77% (33 824 of 1.9 million veterans hospitalised between 1992 and 1999).[25] According to discharge diagnoses, 85% of these HCV-infected veterans had at least one past or present psychiatric or substance use diagnosis and 62% had comorbid psychiatric and substance use disorders. Very few veterans with HCV infection had a comorbid psychiatric illness without also having a comorbid substance use disorder. Among those HCV patients with comorbid psychiatric and substance use disorders, 85% were diagnosed with a depressive disorder, 71% with an anxiety disorder, 43% with post-traumatic stress disorder (PTSD), 42% with a psychotic disorder, and 30% with bipolar disorder.[25]

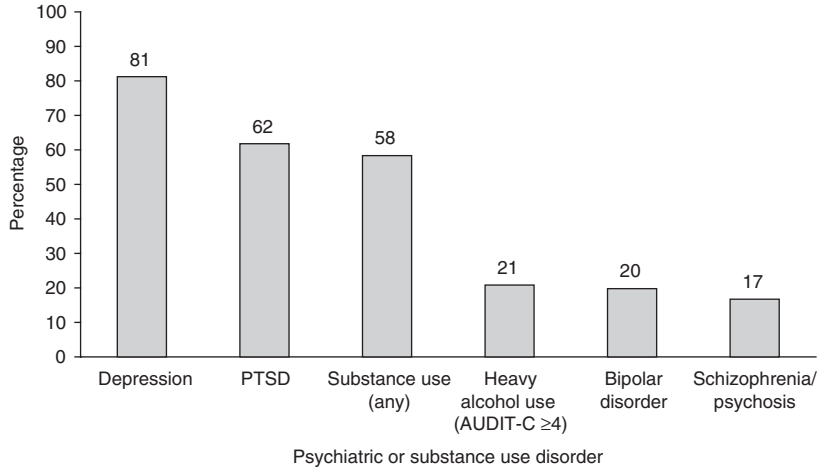

Fig. 1. Percentage of veterans with chronic hepatitis C virus infection (n = 293) who reported a psychiatric or substance use disorder in a prospective clinical study.[27] **AUDIT-C** = Alcohol Use Disorders Identification Test-Consumption; **PTSD** = post-traumatic stress disorder.

In another study designed to determine the incidence of psychiatric and substance use comorbidities among 120 veterans with HCV infection, the level of depression, anxiety, PTSD and alcohol use were assessed. Standardised rating scale scores indicated that many of the patients had clinically significant levels of depression (44.2%), anxiety (38.1%), PTSD (20.8%) and alcohol-related problems (26.7%). Coexisting psychiatric disorders and/or recent substance use was found in 73.4% of these patients.[26] Similarly, a prospective study conducted at the Portland VAMC assessed the frequency of psychiatric and substance use disorders in 293 patients presenting for initial assessment of a positive HCV antibody test. Ninety three percent of the patients screened positive for a history of at least one current or past psychiatric or substance use disorder, and 73% had two or more disorders[27] (figure 1).

In contrast to these studies conducted at VAMCs, other reports indicate that the rates of psychiatric and substance use disorders in patients with HCV infection seen at other hospital settings are much lower, but still of clinical significance. In a study conducted at a large Midwestern teaching hospital, 322 patients diagnosed with HCV infection were recruited; 26.4% had a previous psychiatric diagnosis and 36.3% had recent or active substance abuse.[28] Similarly, in a study conducted in the Hepatology Clinics at the University of Michigan Medical Center (n = 206), psychiatric comorbidities alone were reported in 3% of the participants with HCV infection.[29]

Collectively, these reports highlight the need to develop comanagement models of care so that healthcare providers can expand the numbers of patients eligible for HCV treatment, including patients with psychiatric and substance use disorders (see section 3.).

2. Antiviral Therapy for the Treatment of Hepatitis C

2.1 Overview

Interferons (IFNs) are a class of cytokines produced by human blood cells that act as host defense proteins and modulate the immune system.[30] Therapeutic uses of exogenously administered IFNs are derived from these functions. IFN-based therapies are the treatment of choice for patients with HCV infection[31,32] and success of treatment is based on a sustained viral response (SVR) [defined as no detectable virus 6 months post treatment].

There are three common genotypes of HCV in the US. The recommended duration of IFN therapy is 48 weeks for patients with HCV genotype 1 and 24 weeks for patients with HCV genotypes 2 or

3.[33,34] Although genotype 1 is most common in the US, it is less responsive to antiviral therapy than genotypes 2 or 3, and therefore requires a longer duration of treatment.[35,36] A recent article in the *New England Journal of Medicine* suggests that an even shorter course of therapy (12 weeks) may be indicated for some patients with genotypes 2 or 3.[37] This is important for injection drug users with HCV because younger patients are often infected with the genotype 2 or 3. Shorter durations of treatment may increase the number of patients able and willing to undergo treatment for HCV and decrease the overall prevalence of the disorder within the intravenous drug-using community.

In addition to IFN, the combination of IFN plus ribavirin therapy often results in higher SVR rates than with IFN monotherapy.[32,34] Ribavirin is another antiviral drug and, although the exact mechanisms of its action in the treatment of HCV are unknown, it is thought to interfere with the production of viral DNA and RNA, which are critical to the replication and survival of the virus.[38] Research suggests that the viraemia relapse rate after therapy is almost twice as high among patients treated with IFN alone than among patients given combination therapy.[39] However, clinical adverse events associated with combination therapy are comparable to those seen with IFN monotherapy.[34,40]

More recently, pegylated IFN has been shown to be effective and can be used safely, as it has an adverse-effects profile similar to IFN.[40] Studies indicate that pegylated IFN therapy in combination with ribavirin has superior anti-HCV effects to those seen with IFN monotherapy[41] and may have superior SVR rates compared with regular IFN and ribavirin combination therapy.[42] Thus, combination therapy with pegylated IFN and ribavirin is the currently the recommended treatment strategy for eligible HCV-infected patients.[42-45]

Although combination therapy with pegylated IFN and ribavirin is the current standard of care for patients being treated for HCV in the US, it is important to note that the mental health interventions may vary based on the particular type of antiviral therapy used. In one study of 531 IFN-naive patients treated with either pegylated IFN or standard IFN, it was found that patients receiving pegylated IFN experienced significantly less fatigue and better quality of life than those receiving standard IFN.[46] Another study compared groups receiving combination therapy with ribavirin. Quality-of-life measures were compared in 1121 patients who received pegylated IFN and ribavirin or standard IFN and ribavirin. Patients in the pegylated IFN group demonstrated superior quality-of-life scores and tolerance to therapy. In particular, these patients experienced less fatigue and had significantly improved measures on several health-related quality-of-life measures, including improved social and physical function, decreased physical role limitations and increased vitality.[47] This suggests that patients who are treated with standard IFN, with or without ribavirin, may benefit from additional monitoring for changes in their quality of life and appropriate treatment interventions.

Antiviral therapy response rates among individuals can be highly variable and dependent on a number of factors. Section 4 reviews some of these factors, in particular, those most relevant to patients with psychiatric and substance use disorders. However, in general, clinical trials show that depending on their viral genotype, 40–80% of patients treated with a combination of pegylated IFN and ribavirin clear the HCV infection (average response rate for genotype 1 is 40–50% vs ≈80% for non-genotype 1).[42,45]

2.2 Neuropsychiatric or CNS Adverse Effects of Antiviral Therapy

In addition to the therapeutic effects of IFN, it also induces a range of neuropsychiatric and other adverse effects (table II). Most common are 'flu-like' symptoms such as chills, fever and muscle soreness.[48] It is also well accepted that IFN can cause significant neuropsychiatric adverse effects, including symptoms of depression, fatigue, anxiety, irritability, sexual dysfunction, anorexia, hypersomnia, anhedonia, psychomotor retardation, impaired concentration, apathy and confusion.[49-53] The majority of IFN therapy discontinuations that

Table II. CNS adverse effects associated with interferon and ribavirin therapy

Adverse effect	Patients reporting adverse effect (%)	References
Anxiety/irritability	24–47	42,55-57
Concentration impaired	10–17	56,57
Depression	20–30	49,53,55,58
Dizziness	14–21	42,56,57
Insomnia	30–40	42,55-57
Mania	<1–10	59-61
Vision disorders	5	56,57
Seizures	≈1	62-64
Auditor toxicity	≈1	65

occur in HCV-infected patients are related to the development of IFN-induced depression.[54]

Given that a number of the adverse effects associated with IFN therapy are dose dependent, one strategy that healthcare providers have used to decrease the adverse effects is to reduce the dosage of ribavirin and/or IFN.[66] However, this strategy may not be optimal, as decreasing the dosages of these drugs may negatively impact SVR rates, especially for those patients infected with HCV genotype 1[33,34,42,67] (see section 3.3).

Rates of IFN-induced depression range from 0% to 44%.[49,68,69] Occasionally, attempted or successful suicides occur during IFN therapy, but the incidence is believed to be rare and putatively not different than in untreated patients with HCV infection.[70] While these depressive adverse effects usually resolve after the completion of IFN therapy or treatment with antidepressants, they can persist or reappear with dose escalation and lengthy treatment. Taken together, the data show that IFN-induced depression is common and suggest that healthcare providers should monitor patients on IFN therapy for the development of major depressive disorder, particularly between the second and fifth months of IFN therapy (see section 3.2), even in patients without a history of psychiatric illness.

2.3 Barriers to Treatment

In a retrospective study of Medicaid patients designed to assess the prevalence of selected factors that could influence initiation of IFN therapy, it was found that liver biopsy, a diagnosis of mild liver disease, a diagnosis of psoriasis, antidepressant use and classification of race/ethnicity as 'other' increased the likelihood of IFN therapy. A decreased likelihood of antiviral therapy was associated with age ≥65 years, a diagnosis of kidney disease and one or more emergency department visits.[71] Although substance abuse and dependence and psychotropic drug use were among the predictor variables analyzed, these factors did not appear to significantly influence the initiation of IFN therapy. However, barriers to HCV treatment do exist and are serious concerns for individuals with comorbid substance use and psychiatric disorders.[72]

According to a large retrospective study conducted in France, almost one in six patients with HCV infection did not receive ongoing healthcare following the diagnosis of chronic hepatitis C.[73] These data suggest that one of the initial barriers to treatment may be related to engaging the patients successfully in treatment. Close to 60% of the non-followed patients belonged to the 'high-risk lifestyle group', which included patients with a history of nasal or intravenous drug use and 22.8% of the non-followed group were patients with current alcohol abuse (defined as >50 g/day).[73] Most physicians withhold antiviral therapy from HCV-infected alcohol or drug users until substance use has stopped and patients have maintained abstinence for a period of at least 6 months.[74] This requirement is unrealistic given that substance use disorders are chronic illnesses and are characterised by frequent relapses. Furthermore, a recent review provided evidence to show that 6 months of alcohol cessation before the initiation of IFN therapy may be insufficient to negate the influence of lifetime daily alcohol use or abuse.[22]

Other barriers to antiviral therapy for patients with hepatitis C may include social instability and comorbidities associated with drug use, insufficient access to expertise about HCV, and the high cost of comprehensive care and treatment.[72]

Common arguments against using IFN therapy to treat HCV-positive individuals with psychiatric and

substance use disorders are listed below, although not all arguments are widely supported in the literature.[75]

1. The increased risk of potentially serious psychiatric complications secondary to IFN therapy in patients with a past or present psychiatric illness compared with patients without psychiatric illness.

2. Concerns that substance users will not adhere to treatment plans.

3. Concerns that intravenous drug users will become re-infected with the virus.

4. Return to alcohol or drug use will accelerate liver disease, as heavy alcohol consumption accelerates the progression of HCV-related chronic liver disease and may reduce the efficacy of IFN therapy.

With regard to psychiatric disorders, a review of clinical trials that focused on the treatment of chronic HCV in patients with substance use disorders found that psychiatric comorbidity did not negatively influence adherence or treatment outcomes.[76] Sylvestre[77] also assessed the impact of preexisting psychiatric diagnoses on HCV treatment outcomes and found that 35% of the patients who did not report a prior psychiatric disorder had SVRs, compared with 22% of the patients who reported a prior psychiatric condition. However, there was no difference in dropout rates between the two groups. In separate studies, Ho et al.[78] and Pariante et al.[79] compared the incidence of major CNS adverse events between patients with and without active psychiatric illness. Both studies found that a psychiatric illness did not increase the risk of major CNS adverse events. In a study of 39 HCV patients, those who developed IFN-induced major depressive disorder (33%) were not more likely to have a history of psychiatric or substance use disorders,[58] suggesting that a history of substance use or major depression did not predict development of IFN-induced depression and, therefore, should not automatically exclude HCV-infected patients with psychiatric and substance use disorders comorbidity from IFN therapy.

Kraus et al.[80] assessed compliance with IFN therapy in patients with hepatitis C. Substance use was not identified as a predictor of poor compliance. In a long-term study designed to assess IFN therapy outcomes in former HCV-positive injection drug users, 33% of former users with SVR returned to injection drug use in the 5 years following antiviral therapy, and all but one patient (who admitted to frequently sharing needles) remained HCV negative.[81] Similarly, in a study of 50 HCV-positive inpatients with substance use histories, no cases of re-infection were found, even though approximately 80% of patients returned to injection drug use. There was no significant difference in IFN SVR rates for patients who relapsed compared with those who did not.[82]

There has been some discussion of the appropriateness of treating active substance users with acute HCV infection. Treatment can eradicate HCV in most patients with acute hepatitis and prevents the evolution of the infection into a chronic form, which will occur in 50–84% of patients.[83] However, the treatment model for acute hepatitis C differs significantly from that of chronic hepatitis C. In particular, those with chronic HCV infection have time to weigh the risks and benefits of treatment, relative sobriety, treatment for any underlying mental illness, housing or other types of stability, and develop a relationship with the treatment team. In a recent study of 27 patients with acute HCV infection, only 8 completed treatment or received >80% of the scheduled drug. Seven of these eight obtained an SVR, but effectiveness was severely limited by withdrawals from treatment. Patients who were at particular risk of not completing treatment were injection drug users and women.[84] However, obtaining sustained viral clearance in this high-risk group may prevent subsequent infection in partners or associates who share needles with infected patients.

On the basis of a recent review of ten clinical trials published between 2001 and 2004 concerning antiviral therapy in substance users, SVR and adherence rates are not different from non-users with hepatitis C. The authors of this review concluded that it is important to (i) treat depression as early as possible; (ii) advise to start substitution therapy, if

applicable; and/or (iii) increase substitution therapy in those who are already receiving it.[85]

Another study compared HCV treatment between all risk groups (patients with psychiatric disorders [n = 21], methadone substitution [n = 23], former drug addiction [n = 21] vs non-psychiatric patients with HCV [n = 23]). This study found that the group at greatest risk of ceasing treatment was the group with former drug addition (43%); this risk was statistically increased over all other groups. Patients with psychiatric disorders and those receiving methadone maintenance did not show a higher withdrawal rate than the control group (non-psychiatric patients with HCV). This suggests that both those with psychiatric illness and those receiving methadone maintenance may do well in treatment, and that those with a previous drug addiction may benefit from additional screening and monitoring.[86]

The Organization to Achieve Solutions in Substance-Abuse (OASIS) provides medical treatment to recovering injection drug users in Oakland, CA (see section 3.1). In a study of 59 methadone patients who were treated at OASIS and who completed IFN therapy, 54% achieved an end-of-treatment response and 28% achieved an SVR, modestly lower than rates observed in non-opioid-dependent patients. Further, the overall withdrawal rate for this sample was 24%, similar to the 20–21% withdrawal rate typically observed in IFN therapy clinical trials.[87] In a related paper, data were collected from a larger sample of patients with HCV undergoing methadone maintenance therapy (n = 76). Although 56% of the patients had at least one of the characteristics potentially associated with poorer treatment outcomes, 76% of the patients completed IFN therapy and 28% had SVRs.[77]

Another study examined 50 patients receiving methadone maintenance and 50 patients with no injection drug use or methadone maintenance for 5 years. Although the group receiving methadone maintenance had a greater withdrawal rate during treatment, the groups were comparable with regard to adverse events and SVR, and neither group had a serious psychiatric event.[88] These findings suggest that, once established in treatment, those patients receiving methadone can do as well as those who are in sustained recovery from substance abuse. However, this and other studies assessing antiviral therapy in patients on active methadone treatment were conducted using selected patient samples undergoing prospective evaluation. The feasibility of treating patients with active substance use disorders in general practice remains to be determined.

Collectively, emerging evidence shows that, other than the potential acceleration of liver disease in alcohol drinkers[75,89] (see section 4.0), few data support withholding treatment from eligible individuals with psychiatric and substance use disorders. It is important to note that uncontrolled psychiatric and substance use disorders can be associated with significant morbidity and mortality. In a large, community-based longitudinal study, viral clearance and end-stage liver disease were investigated in persons who acquired HCV from injection drug use. Drug overdose, as opposed to liver disease, accounted for 19% of deaths and the incidence of end-stage liver disease was higher in patients who drank the equivalent of three or more drinks per day.[90] As is reviewed in section 3, patients with psychiatric and substance use comorbidities should always be monitored closely during antiviral therapy for the emergence of adverse effects, exacerbation of psychiatric symptoms, changes in substance use and treatment compliance, preferably in collaboration with a mental healthcare provider.

3. Hepatitis C Treatment Strategies for Individuals with Psychiatric and Substance Use Disorders

Emerging research studies and treatment guidelines suggest that IFN therapy should be considered for patients with ongoing drug use (other than alcohol) if such patients are likely to comply with treatment and do not have other contraindications.[91-93] The 2002 National Institutes of Health (NIH) Consensus Statement on the Management of Hepatitis C, the Veterans Health Administration: Treatment Recommendations for Patients with Chronic Hepatitis C, and the 2004 Practice Guidelines for the Management of Hepatitis C recommend that deci-

sions about treatment of HCV infection in people with psychiatric and substance use disorders, including injection drug users, be made on a case-by-case basis, and advise that drug use itself is not an absolute contraindication to IFN therapy for HCV infection.[94-96]

Several studies show that patients with histories of current or past psychiatric and substance use disorders can successfully complete a course of IFN therapy and that SVR rates are similar to those without such difficulties.[53,77,78,87,97,98] In one study, 22% of all patients had a history of a suicide attempt but did not have suicide attempts during IFN therapy.[53] Collectively, the patients in these studies had diagnoses of PTSD, major depression and bipolar disorder, as well as personality disorders and histories of substance use disorders.

It is important not to forget how difficult it is to engage HCV-infected patients in treatment. Several studies, both VA as well as non-VA, indicate that no-show rates for initial appointments are approximately 50% and, of the patients who make the initial visit, most are not considered treatment candidates, usually because of a comorbid psychiatric or substance use diagnosis.[99,100] Of the patients who begin antiviral therapy, a significant proportion withdraw or are discontinued from antiviral therapy because of neuropsychiatric adverse effects. In a retrospective chart review of 293 000 veterans seen in the Northwest Veterans Integrated Service Network 20 between 1998 and 2003, only 13–14 % of veterans with HCV underwent antiviral therapy.[10] The vast majority of these veterans with HCV continued to receive care and, in particular, mental healthcare. Often stabilisation of their psychiatric or substance use disorder is a prerequisite to antiviral therapy.

Thus, in order to increase the proportion of patients with underlying psychiatric and substance use disorders who may become treatment candidates, it is essential that we broaden our definition of 'HCV treatment' to include management of comorbid psychiatric and substance use disorders in patients with HCV and not confine our definition of 'treatment' solely to antiviral therapy.

3.1 Treatment Team Models

Given the very high frequency of comorbid psychiatric and substance use disorders among patients with HCV and the likelihood that antiviral therapy can exacerbate symptoms of psychiatric illness, regular screening and a comanagement model of care that uses frequent psychiatric symptom monitoring are optimal. An ideal multidisciplinary team would include the perspectives of primary care physicians, hepatologists, nurse practitioners, mental health professionals and substance abuse specialists.

An increasing number of programmes are successfully integrating HCV care for patients with psychiatric and substance use disorders into healthcare settings, including primary care, methadone treatment and other substance abuse treatment programmes, infectious disease clinics and clinics in correctional facilities.[72,77,96] Figure 2 and figure 3 illustrate examples of multidisciplinary clinical pathways used at the Portland VA Medical Center to facilitate treatment decisions for patients with HCV

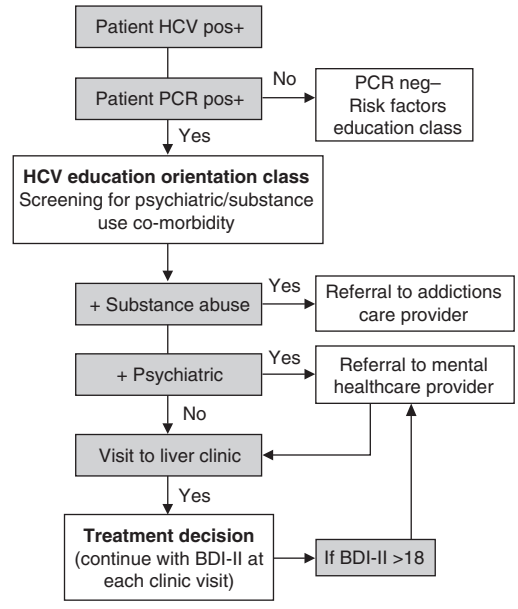

Fig. 2. Northwest Hepatitis C Resource Center Clinical Pathway: comanagement of comorbid populations. Refer to table III for a list of recommended psychiatric and substance use monitoring instruments. **BDI-II** = Beck Depression Inventory II; **HCV** = hepatitis C virus; **MHCP** = mental healthcare provider; **PCR** = polymerase chain reaction.

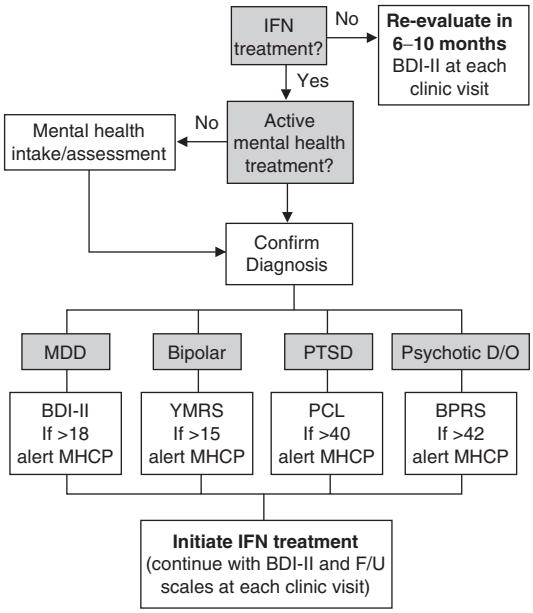

Fig. 3. Northwest Hepatitis C Resource Center Special Populations Clinical Pathway: psychiatric comorbidity. **BDI-II** = Beck Depression Inventory II; **BPRS** = Brief Psychotic Rating Scale; **F/U** = follow-up; **IFN** = interferon; **MHCP** = mental healthcare provider; **MDD** = major depressive disorder; **PCL** = PTSD checklist; **PTSD** = post-traumatic stress disorder; **YMRS** = Young Mania Rating Scale.

infection, which we have found to be effective in our particular clinical setting. Readers should note that 'cut-off values' for the recommended scales are not validated for patients with HCV infection.[101]

The liver damage that occurs as a result of chronic HCV infection can take as long as 10–15 years to become clinically significant. Consequently, it is rarely imperative to begin antiviral therapy quickly. Because of the detrimental adverse effects associated with treatment, healthcare providers and their patients should plan antiviral therapy carefully, including the need for mental healthcare in patients who have active comorbid psychiatric and substance use disorders. In certain instances, non-mental healthcare providers who are comfortable prescribing psychotropic medications can be guided by the use of various psychiatric symptom rating scales (see section 3.2). Non-mental healthcare providers should be cautious when prescribing antidepressants for IFN-induced depression, as antidepressants can cause mania induction or rapid cycling in patients with bipolar disorder.[102] Specific recommendations for non-mental healthcare providers, including a reference manual for the management of psychiatric and substance use disorders in patients with HCV can be found at the Department of Veterans Affairs Hepatitis C Resource Centers website.[103]

The critical elements of care for HCV patients with comorbid psychiatric and/or substance use disorders (which span several medical disciplines) are reviewed in the following subsections and include (i) education; (ii) screening and evaluation for psychiatric and substance use disorders comorbidities; (iii) coordination of substance abuse treatment services, mental healthcare and social support; (iv) assessment of liver disease; and (v) antiviral therapy, when appropriate. It is additionally advised that patients with injection drug use receive testing for HIV as well as vaccination against hepatitis A and hepatitis B.[10,72]

3.2 Screening and Monitoring Strategies

It is recommended that patients with hepatitis C and a known psychiatric history receive psychiatric consultation and psychiatric symptom rating scale measures before beginning antiviral therapy.[96,104] In HCV-infected and malignant melanoma patients treated with IFN therapy, some reports suggest that depression symptom rating scores before IFN therapy initiation may be predictive of the development of IFN-induced depression.[53,58,105,106] Therefore, screening for symptoms of depression before IFN therapy initiation may help to identify patients at risk for developing IFN-induced depression.

For the purposes of screening patients for depression before IFN therapy, various self-rated or clinician-rated scales can be used (table III). Some of the more commonly used self-rated instruments are the Zung Self-Rating Depression Scale,[107] the Beck Depression Inventory (BDI),[108] and the self-rating version of the Montgomery Asberg Depression Rating Scale.[109] In a study that examined the sensitivity and specificity of the BDI and other instruments for predicting eventual psychiatric and antidepressant treatment during IFN therapy, the BDI performed best in this analysis and is now the preferred

screening tool at VAMCs.[53] These tools can provide increased accuracy in assessing patients' depressive symptomatology as well as objective measurements of changes in mood states during the course of IFN therapy.[104,110]

To reliably identify substance use disorders prior to IFN therapy, all patients should undergo careful evaluation for current substance use disorders.[96] Screening for alcohol use should include measures of quantity and frequency as well as screens for alcohol abuse or dependence. The Alcohol Use Disorders Identification Test (AUDIT) is a brief, well-validated and self-administered instrument that screens for both at-risk drinking and for alcohol abuse and dependence[116] (table III). The AUDIT-C is composed of the first three items of the AUDIT and can serve a similar function with fewer items to score.[118] When patients have a positive screen for a substance use disorder, they should be referred to an addiction specialist for consultation and recommendations on how to manage substance use prior to IFN therapy. Patients who are using heroin or other opioids should be specifically referred for opioid agonist therapy.[72,96]

In addition to assessing patients for psychiatric and substance use disorders comorbidities prior to the initiation of IFN therapy, regular monitoring of psychiatric symptoms and substance use during the course of treatment is also recommended (figure 3). Treatment guidelines for individuals with HCV infection suggest that patients not exhibiting depression before treatment should be evaluated for depression at least monthly and preferably every 2 weeks during the initial few months of antiviral therapy. Patients with depression scores indicating moderate-to-severe depression should be considered for antidepressant treatment (see section 3.3) and preferably followed by a mental health professional.[96] For patients with histories of substance use disorders, regular monitoring and the coordination

Table III. Screening/monitoring instruments for psychiatric and substance use disorders during the course of interferon therapy[a]

Rating scale	Purpose	Cut-off scores	Resource information	References
Psychiatric disorders				
BDI, BDI-II	Monitor depressive symptoms	>18	www.psychcorp.com	108,111
BPRS	Identify and monitor the severity of psychiatric symptoms such as delusions, hallucinations, thought disorders, anxiety and depression	>42	www.psychrehab.com	112
MADRS	Monitor symptoms of depression	>25		109
PCL	Monitor symptoms of PTSD	>40	www.pdhealth.mil	113
YMRS	Monitor symptoms of mania for patients with bipolar disorder	>15		114
Zung Self-Rating Depression Scale	Monitor symptoms of depression	>50	www.fpnotebook.com/psy85.htm	107
Substance use				
AASE	Monitor alcohol cravings	N/A	www.niaaa.nih.gov/publications/aase.htm	115
AUDIT	Screen for alcohol use	>8	www.niaaa.nih.gov/publications/insaudit.htm	116
ASI	Assess attitudes toward changing problem behaviors related to substance use disorders	N/A	www.niaaa.nih.gov/publications/urica.htm	117

a The Northwest Hepatitis C Resource Center developed the Patient Screening Questionnaire Screening (PSQ; available online at www.portland.med.va.gov/Mood-Disorders-Center) to identify psychiatric and substance use disorders prior to the start of antiviral therapy.

AASE = Alcohol Abstinence Self-Efficacy Scale; **ASI** = Addiction Severity Index; **AUDIT** = Alcohol Use Disorders Identification Test; **BDI** = Beck Depression Inventory; **BPRS** = Brief Psychiatric Rating Scale; **MADRS** = Montgomery Asberg Depression Rating Scale; **PCL** = post-traumatic stress disorder checklist; **YMRS** = Young Mania Rating Scale.

of care with addiction specialists are also recommended.

3.3 Medication Management

The primary reason for a lack of adherence to antiviral therapy is the onset of adverse effects[66] (see also section 2.2). For example, the main adverse effect of ribavirin is dose-related haemolytic anaemia.[119] Haematological adverse effects, including neutropenia, thrombocytopenia and anaemia are the most common reasons for dose reductions in patients receiving combination therapy with pegylated IFN and ribavirin.[42,120] However, reducing the doses of ribavirin and/or IFN may have an adverse effect on antiviral therapy outcomes. In a study comparing response rates of patients treated with pegylated IFN and ribavirin compared with standard IFN and ribavirin, the likelihood of SVR increased as the ribavirin dose increased.[42] Nevertheless, treatment-related adverse effects may necessitate dose reductions or discontinuation of therapy. This section reviews medication interventions that may help patients adhere to therapy more successfully and decrease the need for dose reductions. For more detailed information regarding adverse effect management strategies, please refer to the VA's HCV Treatment Guidelines[96] or reference manual, Management of Psychiatric and Substance Use in Patients With Hepatitis C.[103]

3.3.1 Antidepressants

Although antidepressants are commonly prescribed for IFN-induced depression, to date no controlled studies have been published regarding their efficacy in a large sample of patients receiving IFN therapy.[49] Several case reports and relatively small sample size studies suggest that antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), can reverse or reduce IFN-induced depression.[53,58,121-123]

Few studies have evaluated the possible utility of antidepressants in preventing the development of depression during IFN therapy. Results from these reports suggest that pretreatment with antidepressants appears to be an effective strategy for minimising IFN-induced depression; however, these prophylactic treatment studies were conducted in patients on IFN therapy for malignant melanoma (not HCV).[106,124] Recently, Kraus et al.[101] investigated the efficacy and safety of SSRI prophylaxis in HCV-positive patients who previously developed IFN-induced depression during an unsuccessful course of antiviral therapy. All patients receiving SSRI prophylaxis (n = 8) were able to complete IFN re-therapy, and depression scores were significantly lower during IFN re-therapy with SSRI prophylaxis. A recent study by Schaefer et al.[125] compared patients with psychiatric disorders pretreated with citalopram, and patients with and without psychiatric disorders who were not pretreated with citalopram. Those in the pretreated group were found to have significantly fewer depressive episodes.

The use of antidepressant treatment in conjunction with IFN therapy may serve to facilitate treatment compliance and reduce the risk of drug relapse in patients with substance use diagnoses (see De Bie et al.[91] for review). SSRIs can be effective for treating alcohol dependence,[126] although these findings are controversial. However, SSRIs have been shown to reduce alcohol relapse in patients with concomitant depressive symptoms. Similarly, compared with placebo, short-term treatment with fluoxetine significantly decreased craving for amphetamine, and intermediate-term treatment with imipramine significantly increased the duration of adherence to treatment.[127] In patients with HCV infection and substance use disorders, potential IFN-induced drug cravings and the risk for drug use escalation could seriously compromise their HCV treatment and recovery. In a study of HCV-infected patients receiving methadone maintenance, 56% were receiving psychiatric medications prior to the start of IFN therapy, and 88% were taking a psychiatric medication by the end of treatment.[87]

3.4 Substitution/Maintenance Therapy

Substitution therapy with methadone or buprenorphine is effective in treating heroin addicts. It has been suggested that maintenance therapy with opioid agonists on an outpatient basis could provide

a foundation for successful treatment for HCV.[77,88] In support of these findings, a recent review recommends that for patients with opioid dependence the usual dose of methadone can be continued in patients with stable chronic liver disease, including advanced cirrhosis, and that modest increases in methadone dose may be appropriate for some patients.[128] In addition, it was noted that buprenorphine could cause liver dysfunction, in particular after intravenous administration. Thus, it is advised to follow liver function tests during buprenorphine treatment and to warn the patients regarding the intravenous use of buprenorphine. Importantly, neither methadone nor buprenorphine were found to influence the antiviral effects of IFN therapy.[128]

3.5 Anticraving Agents

Heavy alcohol drinking accelerates HCV-related liver damage and is a contraindication to IFN therapy. In addition, abstinence has been associated with improved response rates to IFN therapy (see section 4.2). Disulfiram produces a sensitivity to alcohol and may be useful for alcohol-dependent patients with HCV infection. Data indicate that disulfiram may slow hepatic injury by eliminating alcohol consumption as well as help establish abstinence, which is frequently required to qualify for IFN therapy.[129,130] In a retrospective medical record review, aminotransferase levels were compared across several timepoints for patients with (n = 26) and without (n = 20) HCV infection who were also receiving disulfiram 1500mg weekly. There were no significant differences between the groups. In particular, patients with HCV infection showed no significant elevations in liver enzymes at any of the timepoints assessed, suggesting that with close monitoring disulfiram can be safely used in patients with HCV.[129] Saxon et al.[131] found that patients with elevated baseline transamine levels and HCV were more likely than patients with moderately elevated baseline levels to have significant increases in transaminase levels while receiving disulfiram. However, it was noted that most study participants did not experience other adverse effects with disulfiram.

Additional anticraving agents for patients with alcohol use disorders have been identified, such as naltrexone or acamprosate; however, more research is needed to determine the safety and efficacy of these pharmacological approaches to craving in patients with hepatitis C.[132-134]

3.6 Pain Management

HCV infection as well as IFN therapy are associated with, and may trigger or exacerbate, various extrahepatic manifestations. These include, among others, rheumatic manifestations such as arthritis, arthralgias and fatigue, as well as musculoskeletal pain.[135,136] The use of opioid medications in the management of chronic nonmalignant pain is common even though there are only a limited number of studies that examine the outcomes of long-term opioid therapy for HCV patients. Additionally, few data address the concern that using opioid medications for HCV-related analgesia may be associated with the development of physical dependence, tolerance or addiction, especially in individuals with a history of substance use disorders. As reviewed in section 1.0, the majority of patients with HCV infection have comorbid substance use disorders, including injection opioid drug use. However, opioid analgesics are commonly prescribed to HCV-infected patients for chronic pain. In a retrospective study of 478 patients with HCV, 42% were prescribed opioid analgesics (excluding methadone used for maintenance purposes) in the last year and 54% in the last 3 years. However, patients with opioid abuse or dependence diagnoses were prescribed opioids (other than methadone) less often than those without, and patients receiving IFN therapy in the last year were not significantly more likely to be prescribed narcotics than those who were not.[137]

4. Factors Affecting Sustained Viral Response Rates

4.1 Viral and Related Factors

Considerable efforts have been devoted to identifying factors that are predictive of response or nonresponse to IFN therapy. Individuals who are infect-

ed with genotype 1, in more advanced stages of fibrosis, co-infected with HIV, or have high HCV viral loads are less likely to achieve a SVR.[94,138]

4.2 Alcohol Use

Concurrent alcohol use has been considered a contraindication during IFN therapy, as continued alcohol consumption decreases the response to IFN therapy in patients with HCV.[89,139,140] Loguercio et al.[141] found that the number of sustained responders decreased as the amount of alcohol consumption increased. In another study, age, previous alcohol intake and HCV genotype 1 were found to be independent predictors of non-response to IFN therapy.[142] Several proposed mechanisms of decreased responsiveness to IFN therapy in alcoholics include, but are not limited to, impaired immune function, high HCV RNA levels and increased hepatic iron stores.[22,143,144]

The effect of alcohol use on SVR may be a reflection of increased non-compliance with antiviral therapy. Data from a multicentre study (n = 726) found that there was no significant difference in end-of-treatment response and SVR rates between alcohol users and non-users.[145] However, recent alcohol users (within the past 12 months) had a higher rate of treatment discontinuation compared with non-users. On the basis of these findings, the authors concluded that patients with HCV infection and a history of previous alcohol use disorders should not be excluded from antiviral therapy. Recent alcohol users may require additional screening and support to ensure their ability to complete treatment.[145]

4.3 Depression

As previously discussed (see section 2.2), depression occurs in approximately 20–30% of patients with HCV during IFN therapy (table I). Raison et al.,[146] in a retrospective chart review, recently reported that patients with HCV infection who experienced increased depressive symptoms during the course of IFN therapy were less likely to clear the virus.

In contrast, two independent prospective studies conducted to examine the incidence and course of depression associated with IFN-based therapies in patients with HCV found the opposite relationship.[58,147,148] As a part of these studies, response rates of patients who developed depression during IFN therapy were compared with those patients who did not. At both study sites, end-of-treatment response and SVR rates were significantly higher in the patients who developed major depressive disorder during IFN therapy, compared with those who did not, suggesting that IFN-induced depression may be a predictor of a positive response to antiviral therapy or an indication of optimal dose administration. These two prospective studies differed from the retrospective chart review in that patients with IFN-induced depression were identified early during the course of their depression and treated with antidepressants, thus allowing continuation of antiviral therapy. More research regarding the effects of depression on antiviral responsiveness is needed. Collectively, these results show that with regular monitoring, early symptom detection and appropriate antidepressant treatment intervention, patients who develop depression during HCV treatment can successfully complete a course of IFN therapy and may have improved SVR.

5. Future Directions

Comorbid psychiatric and substance use disorders are very common among individuals with hepatitis C. Historically, many of these patients have been excluded from IFN therapy. Of foremost importance is (i) to develop safe and effective comanagement models of care for those who have previously been underserved; and (ii) to expand treatment availability for patients with psychiatric and substance use disorders through safe and effective interventions based on regular symptom monitoring and early detection of relapse. More research is needed to better understand the effects of alcohol, other substance use and psychiatric illness on IFN treatment outcomes in patients infected with HCV.

Future research should identify behavioral and pharmacological interventions that will enhance ad-

herence to antiviral therapy, and reduce the re-emergence of psychiatric symptomatology and substance use. As reviewed in section 2.2, depression is one of the most common and problematic adverse effects of IFN therapy for patients with HCV infection. There are no established risk factors that predict the development of IFN-induced depression. Studies show that IFN can alter tryptophan, serotonin and kynurenine levels as well as the activity of indoleamine 2,3-dioxygenase (an enzyme that converts tryptophan to kynurenine).[149] Importantly, these IFN-induced biochemical changes have been associated with increases in depression rating scores.[150,151] Recently, Wichers et al.[152] reported that it was the ratio of kynurenine/kynurenic acid (which is hypothesised to represent the neurotoxic challenge to the brain) that plays a role in the pathophysiology of IFN-induced depression. In addition, early increases in the vegetative symptoms of depression (such as decreased appetite, fatigue and hypersomnia) may be predictive of subsequent cognitive symptoms of depression in patients treated with IFN.[153] More research is needed to develop a targeted strategy which will enable healthcare providers to predict and then prevent IFN-induced depression.

We are currently involved in a multicentre research project designed to identify genetic predictors and associated biochemical markers (including nitric oxide, tryptophan, serotonin and cortisol levels[150,151,154-156]) of IFN-induced depression.[157] Results from this research may identify specific genetic predictors suggestive of a vulnerability to develop IFN-induced depression, and thus may allow us to target our psychiatric interventions, including prophylactic antidepressant treatment, towards a subgroup of patients at risk. Understanding the potential genetic factors and biochemical mechanisms involved in IFN-induced depression may also be relevant to the depressive symptoms that accompany other chronic medical conditions (including cancer and autoimmune disorders) where cytokines are elevated.

6. Conclusion

Hepatologists and other healthcare providers appreciate the need for a systematic approach to HCV infection that addresses the common comorbidities of psychiatric and substance use disorders, one that demands active participation from mental healthcare providers. Research findings and clinical experience gleaned from settings such as the VA, community clinics and other medical centres that treat large numbers of patients with HCV infection have contributed to the development of the following treatment strategies: (i) patients infected with HCV should have access to mental healthcare and substance use treatment providers; (ii) standardised screening and monitoring tools for recognising and assessing depressive symptoms and problematic substance use should be used regularly to identify patients who need referral or adjunctive mental healthcare before or during antiviral therapy; (iii) systems for referring patients with opiate addiction to appropriate treatment facilities, in particular those offering maintenance therapy with opioid agonists, are essential; and (iv) without more definitive data regarding the impact of occasional or infrequent alcohol use on HCV treatment outcomes, hepatologists should provide patients with information about and assistance in reducing alcohol consumption, but they should not insist on abstinence as a criterion for antiviral therapy.

The NIH Conference Consensus Statement specifically calls for efforts to "increase the availability of the best current treatments" to patients with chronic HCV infection who "have been ineligible for trials because of injection drug use, significant alcohol use, age, and a number of comorbid medical and neuropsychiatric conditions". Therefore, it is important to develop a targeted and comprehensive strategy to treat patients with comorbid psychiatric and substance use disorders, as treatment of HCV infection is likely to increase in the next decade. This information will ultimately contribute to the longer-term goal of improving treatment efficacy and minimising its adverse effects on the millions of patients infected with chronic HCV infection.

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