SUPPLEMENT ARTICLE

Addressing Tri-Morbidity (Hepatitis C, Psychiatric Disorders, and Substance Use): The Importance of Routine Mental Health Screening as a Component of a Comanagement Model of Care

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Background. Recent studies suggest that most patients with hepatitis C virus (HCV) infection commonly present to medical clinics with active psychiatric and substance use disorders. However, routine screening for these disorders is generally not done.

Objectives. The purpose of our study was to assess prospectively the frequency of psychiatric and substance use disorders in patients presenting for initial assessment of a positive HCV antibody test result.

Methods. A sample of 293 patients represented the majority of patients scheduled for their initial hepatology clinic visit at the Portland Veterans Affairs Medical Center between September 2002 and September 2003. The patient screening questionnaire, Alcohol Use Disorders Identification Test-Consumption (AUDIT-C), and the Beck Depression Inventory (BDI-II) were administered to all patients.

Results. At screening, 93% of the patients had a current or past history of at least 1 psychiatric disorder, and 73% had ⩾2 disorders. The most common disorders included depression (81%), posttraumatic stress disorder (62%), any substance use disorder (58%), bipolar disorder (20%), and other psychotic disorders (17%). One hundred two patients (35%) had baseline BDI-II scores in the moderate-to-severe range of depression (>19), and 61 (21%) had AUDIT-C scores indicating current heavy alcohol use (⩾4).

Conclusions. Psychiatric and substance use disorders are highly prevalent among veterans with chronic hepatitis C. Thirty-five percent have significant symptoms of depression before the initiation of treatment with interferon (IFN). Routine screening for underlying psychiatric and substance use disorders and early treatment intervention before initiating antiviral therapy is essential to prevent worsening of depression and to optimize the outcome of treatment with IFN. Comanagement treatment models involving mental health care may expand the pool of patients eligible to receive treatment with IFN, as well as enhance treatment outcomes.

Chronic hepatitis C virus (HCV) infection is a major cause of liver disease and the leading indication for liver transplantation in the United States. It is estimated that 2.7 million Americans have chronic HCV infection [1]. Complications of chronic HCV infection include progressive liver fibrosis, cirrhosis, end-stage liver disease, and hepatocellular carcinoma [2]. The actual risk of developing cirrhosis is unclear; current research estimates that 10%–20% of those infected will develop cirrhosis 20–30 years after initial infection [3].

Effective treatments for HCV infection have only recently become available. At present, optimal treatment for HCV infection consists of combination antiviral therapy with pegylated IFN-α and ribavirin [4, 5]. Successful treatment is associated with a decrease in hepatic fibrosis and cirrhosis in these patients.

The adverse effects of IFN-α have been known for some time, are significant, and include flulike symptoms, such as fatigue, myalgias, arthralgias, fever, musculoskeletal pain, irritability, and depression [6]. Up to 50% of patients receiving treatment with IFN may experience neuropsychiatric adverse effects, in particular depression [7, 8]. Other neuropsychiatric adverse effects include anxiety, cognitive slowing, impaired con-

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centration, and insomnia, all of which are also symptoms of major depressive disorder. [9].

A recent prevalence study suggests that 5.4% of patients seen within the Veterans Health Administration (VA) system are infected with HCV [10], which is ~3 times the prevalence in the general population. Several studies have estimated the prevalence of mental health disorders in veterans with HCV infection. The majority of these studies have been retrospective chart reviews. An inpatient VA study identified >33,000 HCV-positive veterans with comorbid psychiatric and substance use disorders from a database of all VA patients hospitalized between 1992 and 1999 [11]. By a retrospective chart review, they found that 86.4% of HCV-infected patients had at least 1 psychiatric or substance use disorder diagnosis in their medical record. To date, few outpatient studies have examined the comorbidity of HCV and mental health diagnoses. One outpatient study examined the prevalence of psychiatric and substance use disorders in a cohort of 206 veteran patients with known HCV-related liver disease via retrospective chart review [12]; 89% of patients had documented psychiatric and/or substance use disorder diagnoses. Two other authors, who studied smaller numbers of patients presenting to hepatology clinics, identified psychiatric illness and substance use disorders with interviews and various screening questionnaires [13, 14]. A significant percentage of patients in both of those studies had psychiatric and substance use disorder diagnoses that made them ineligible for antiviral treatment for HCV when standard criteria for treatment were applied.

Historically, patients with mental health disorders have been excluded from antiviral treatment for HCV infection [15]. Comorbid psychiatric and substance use disorder diagnoses have constituted the most common reason patients have been denied treatment for HCV infection, particularly within the VA health care system [13, 16]. This exclusionary criterion was established because of concerns that IFN may worsen underlying psychiatric illness, resulting in premature discontinuation of antiviral treatment, noncompliance, suicide, and violence toward others. It is now recognized that patients with stable psychiatric illness who are engaged in mental health treatment can successfully complete treatment with IFN for HCV infection [17].

One of the primary goals of the Northwest Hepatitis C Resource Center is to remove barriers to treatment with IFN for HCV-positive patients with mental health and substance use disorders. An important aspect of this process has been to examine the prevalence and severity of psychiatric and substance use disorders in veterans with HCV infection who have been referred to the liver clinic at the Portland VA Medical Center. Pretreatment screening for psychiatric and substance use disorders is required of all patients referred to the liver clinic to identify, assess, and treat psychiatric and substance use disorders in HCV-positive patients before antiviral therapy. This mental health screening has become an integral component of care for hepatitis C in our hospital and has fostered an integrated comanagement model of care involving mental health and medical providers. The purpose of the present study was to determine prospectively the frequency of psychiatric and substance use disorders and the severity of depressive symptoms in a subgroup of veterans, which allowed us to aggregate and analyze our screening data. The 293 patients described here were all veterans receiving health care at the Portland VA Medical Center and were referred to the liver clinic between October 2002 and October 2003.

PATIENTS AND METHODS

Patients. The Portland VA Medical Center Institutional Review Board approved this study, and all patients signed informed consent to participate. Patients enrolled in primary care or mental health clinics at the Portland VA Medical Center are routinely screened for risk factors for HCV infection. These risk factors include receipt of blood transfusions before 1992, Vietnam-era service in the military, tattoos, history of iv or intranasal drug use, high-risk sexual practices, and occupational exposures. Any patient who has at least 1 risk factor at screening and who agrees to be tested has an order entered for testing for antibody to HCV. Patients without identifiable risk factors can request and receive testing as well. All patients with positive results for antibody to HCV have the presence of HCV RNA confirmed by use of PCR and are eligible for referral to the liver clinic for evaluation. At the first liver clinic appointment, patients are referred for participation in this ongoing prospective study and receive information regarding the study.

Although our population of patients is predominantly white and male, both male and female patients and patients of all racial backgrounds are eligible for and were enrolled in this study. There is no upper age limit for participation.

Screening instruments. After enrollment in the study, all patients were administered a screening questionnaire designed by the Northwest Hepatitis C Resource Center. This patient screening questionnaire (PSQ) was designed to detect current or past history of or treatment for psychiatric illness by addressing DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders,* 4th edition) diagnostic criteria, diagnostic history, and history of prescription medication for psychiatric illness. These questions may be answered "no" or "yes." Questions regarding the efficacy of prescribed medication are included and are scored "yes" or "no." The PSQ is a new instrument that the Northwest Hepatitis C Resource Center is validating in the population of veterans infected with HCV. Questions concerning current or past use of alcohol or other substances and quantity and frequency of such use are included as well.

Table 1. Demographic characteristics of 293 veterans admitted to a Portland, Oregon, liver clinic.

Characteristic	Value
Sex, no. of patients	
Male	279
Female	14
Age, mean ± SD (range), years	53 ± 6.3 (23–86)
Ethnicity, % of patients[a]	
White	80
African American	10
Other (Native American, Hispanic)	10
Period of service, % of patients	
Vietnam-era	71
Post-Vietnam	19
Persian Gulf I	4
World War II, Korea, Post-Korea pre-Vietnam	6

[a] Data with regard to ethnicity were available for only 100 patients. By law, veterans are not required to answer questions about ethnicity.

Copies of the PSQ may be obtained from the corresponding author.

All patients enrolled in the study also completed the Beck Depression Inventory (BDI-II) [18, 19] and the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) [20]. The BDI-II is a 21-question, self-report screening instrument used to measure characteristic attitudes and symptoms of depression. Each item is assigned a score of 0–3, with 3 indicating the most severe symptoms. A cumulative score is determined by adding the scores of the individual items. BDI-II cutoff scores were determined by using the guidelines set forth in the Beck Depression Inventory manual [19]. High and low scores were grouped so that a BDI-II total score of $\leqslant$19 indicated minimal-to-mild depressive symptoms and a BDI-II total score of >19 indicated moderate-to-severe depressive symptoms. Clustering of depressive symptoms was further examined by use of the specific somatic and cognitive-affective symptom dimensions described by Beck et al. [19].

The AUDIT-C is a 3-question screening test designed to detect heavy drinking, alcohol abuse, and alcohol dependence. AUDIT-C cutoff scores were determined by the guidelines set forth by Bush et al. [20], in which a score of $\geqslant$4 indicates the likelihood of heavy alcohol use, abuse, or dependence.

Statistical analysis. BDI-II subscale scores were evaluated by use of *t* tests for dependent samples to detect somatic versus cognitive-affective score differences in depressed versus nondepressed groups and heavy versus nonheavy alcohol users. χ^2 and Pearson correlations were also computed to detect associations between depression and alcohol use. All confidence levels were set at 95%.

Dimensional analysis. Data for the specific symptom dimensions as described above were extracted from the BDI-II scores of the patients in the study. The items on the BDI-II relating to the somatic dimension include numbers 4, 10–13, and 15–21. Items 1–3, 5–9, and 14 relate to the cognitive-affective dimension of the BDI-II [19].

RESULTS

PSQ screening. The data reported here represent the results of screening for depression before initiation of any antiviral treatment for chronic hepatitis C (i.e., patients who have not as yet received IFN and/or ribavirin). The results reported here are for the first 293 patients who enrolled in the study and who completed the screening instruments outlined above. Approximately 90% of patients who were referred agreed to participate in this study and signed informed consent. All patients were positive for antibody to HCV, all were veterans, 95% (279) were male, and the mean (±SD) age was 53 ± 6.3 years (range, 28–86 years). Approximately 80% of the patients were white, 10% were African American, and the remainder were Native American or Hispanic. Approximately 71% of patients had served in the military during the Vietnam era. Demographic variables are summarized in table 1.

All 293 patients completed our screening questionnaire, the BDI-II, and the AUDIT-C. Ninety-three percent of patients ($n = 273$) reported current or past history of at least 1 psychiatric or substance use disorder; 73% ($n = 214$) had $\geqslant$2 disorders. Fifty-one percent ($n = 149$) reported both a psychiatric and a substance use disorder. Depression was the most common disorder in the sample (81%). Posttraumatic stress disorder was reported by 62%, alcohol or other substance use disorder by 58%, bipolar disorder by 20%, and schizophrenia and other psychotic disorders by 17% of patients. Twenty-one percent of patients ($n = 61$) reported current heavy alcohol use, as defined by an AUDIT-C score of $\geqslant$4. These results are summarized in figure 1.

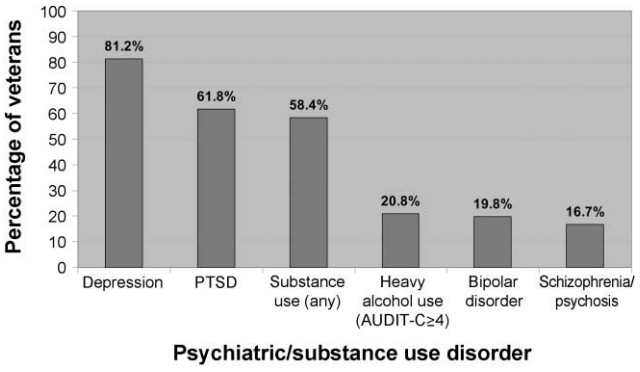

Figure 1. Percentage of veterans with chronic hepatitis C ($n = 293$) who reported a psychiatric or substance use disorder. PTSD, posttraumatic stress disorder; AUDIT-C, Alcohol Use Disorders Identification Test-Consumption.

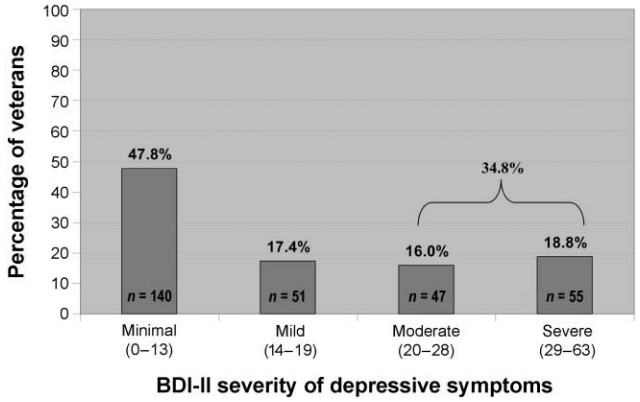

Figure 2. Severity of depression among 293 veterans, according to the Beck Depression Inventory-II (BDI-II) [19].

BDI-II. BDI-II scores are shown in figure 2. Of the 293 patients, 47.8% ($n = 140$) were essentially asymptomatic (BDI-II scores of 0–13), and 17.4% ($n = 51$) reported symptoms of mild depression (BDI-II scores of 14–19). Sixteen percent of patients ($n = 47$) had symptoms consistent with moderate depression (BDI-II scores of 20–28), and 18.8% ($n = 55$) reported severe symptoms of depression (BDI-II scores of ⩾29).

Approximately 35% of patients ($n = 102$) had baseline BDI-II scores in the range of moderate-to-severe depressive symptoms (BDI-II scores of >19). Approximately 28% of patients ($n = 81$) endorsed some level of suicidal ideation on BDI-II item 9, and 7.5% ($n = 22$) scored ⩾2 on item 2, which measures hopelessness and suggests increased suicide risk [19].

BDI-II and PSQ scores. Patients who reported current or a history of depression on the PSQ had significantly higher BDI-II scores than did patients who did not screen positive for depression. The mean (±SD) BDI-II score for patients reporting current or a history of depression was 18.48 ± 11.34, compared with 5.47 ± 5.55 for those reporting no history of depression ($t = 8.27$; $P < .001$).

Symptom dimensions. The total sample scored significantly higher on the somatic dimension of depressive symptoms than on the cognitive-affective dimension ($t = 8.88$; $P < .01$). Patients with moderate-to-severe depressive symptoms (BDI-II scores of >19) did not demonstrate any significant difference in the severity of the somatic versus cognitive-affective subscale symptoms ($t = .98$; *P*, not significant). However, patients with minimal-to-mild depressive symptoms ($t = 11.36$; $P < .01$) did show significantly greater somatic than cognitive-affective symptoms of depression. These results are shown in figure 3.

Results of the AUDIT-C. The AUDIT-C results were examined as part of this study because of the concern that concurrent alcohol use may mimic depressive symptoms. Approximately 21% of patients did report heavy alcohol consumption (defined by an AUDIT-C score of ⩾4) at the time of their initial appointment at the liver clinic. There was no significant difference in mean BDI-II total score for heavy (AUDIT-C score of ⩾4) versus nonheavy (AUDIT-C score of <4) alcohol users (mean ± SD BDI-II score, 16.15 ± 11.93 vs. 15.62 ± 10.68), and no significant correlation was found between BDI-II and AUDIT-C scores (*P*, not significant).

DISCUSSION

The neuropsychiatric adverse effects of treatment with IFN-α, including the high incidence of depression, are well known. Current or past psychiatric illness and/or substance use disorder have historically been contraindications to treatment with IFN because of concerns that IFN will worsen the psychiatric disorder or cause relapse of the substance use disorder [15]. Premature discontinuation of treatment, noncompliance, suicide, violence, and relapse with use of alcohol and drugs are cited as concerns in this population of patients. However, although IFN can lead to severe neuropsychiatric adverse effects, including suicide ideation, the published evidence and our own experience suggest that many patients with dual-diagnosis disorders (i.e., both psychiatric disorders and substance abuse disorders) can be treated safely and effectively [14, 21–24].

Other authors have examined the prevalence of psychiatric and substance use disorders in several different cohorts of veterans [11–13, 25]. In all of those studies, the prevalence of substance use disorder and psychiatric illness was >60%. However, no studies to date have prospectively examined all new patients presenting to liver clinics for outpatient evaluation and treatment of chronic hepatitis C. In the present study, >90% of veterans screened positive for past substance use and/or psychiatric disorder, and >80% screened positive for depression. Posttraumatic stress disorder was reported by 62% of

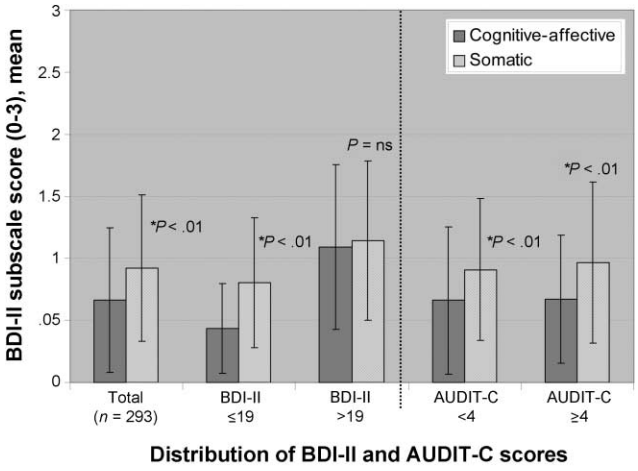

Figure 3. Mean Beck Depression Inventory-II (BDI-II) [19] cognitive vs. somatic subscale scores among a sample of veterans ($n = 293$). AUDIT-C, Alcohol Use Disorders Identification Test-Consumption; ns, not significant.

patients, alcohol or other substance use disorders by 58%, bipolar disorder by 20%, and psychotic disorders by 17%. The vast majority of patients (73%) reported ⩾2 disorders, and 51% reported both a psychiatric and substance use disorder. Thirty-five percent of all patients had a current BDI-II score of >19, indicating moderate-to-severe depressive symptoms, and >20% reported current hazardous alcohol use, as defined by an AUDIT-C score of ⩾4.

Depression is one of the most common chronic conditions encountered by general medical practitioners. It is estimated that at least 10% of general medical outpatients have major depression. Our finding that 81% of our patients had current or past depression and that 35% had BDI-II scores of >19 (suggesting moderate-to-severe depressive symptoms) is consistent with these findings.

The results of our dimensional comparison show a high incidence of somatic symptoms in those with only mild depressive symptoms. This is not surprising, because this is a sample of patients with chronic medical illnesses. All of our patients have diagnoses of HCV infection, and many have other comorbid chronic medical illnesses, including cardiovascular disease and diabetes. Thus, a high incidence of somatic symptoms might be expected. However, the patients with moderate-to-severe depressive symptoms appear to demonstrate both the cognitive and somatic symptoms of depression, which are symptoms that might be expected in patients with a clinical diagnosis of major depression.

The results of the AUDIT-C are included with this analysis because of the concern that heavy alcohol use may mimic depressive symptoms, particularly in patients with chronic hepatitis C [26]. Despite its significant frequency at the time of presentation to the liver clinic, heavy alcohol use did not appear to be a confounding factor, and these patients did not appear to have a higher frequency of more-severe depressive symptoms.

There are several limitations to the present study. First, the study examined a population of veterans; thus, the vast majority of our patients are male, and their average age is 53 years. It is suspected that the majority of patients in this study have had chronic hepatitis C for >10 years. The ethnicity of our patient population reflects the ethnic composition of the Portland, Oregon, metropolitan area: most patients are white. Thus, results cannot be generalized to nonveterans, younger populations, women, patients newly infected with HCV, or non-white patients. In addition, we did not study homeless, incarcerated, or otherwise disenfranchised patients, which are populations known to have a high prevalence of chronic hepatitis C.

The results of the present study support the utility of routine screening of HCV-positive patients for psychiatric and substance use disorders. Routine screening will assist in prompt identification and referral for treatment of patients with active psychiatric and substance disorders. With active treatment and stabilization of their psychiatric and substance use disorders, these patients may become eligible for antiviral treatment for chronic hepatitis C. In addition, it is important to identify and provide close follow-up for patients with a history of psychiatric or substance use disorder who may be at risk for relapse during antiviral treatment. Ultimately, these strategies may increase the pool of patients eligible for antiviral treatment and decrease noncompliance with treatment and dropout because of treatment-emergent psychiatric symptoms. Furthermore, the morbidity and mortality of IFN-related neuropsychiatric complications may be decreased.

In summary, the results of the present study confirm the extremely high prevalence of psychiatric and substance use disorders among outpatients with hepatitis C who present for initial evaluation and treatment. Historically, these diagnoses would be contraindications for antiviral treatment for chronic hepatitis C for these patients, and therefore, the majority of patients with chronic hepatitis C would actually be excluded from receiving treatment with IFN. Successful antiviral treatment is associated with an improvement in hepatic fibrosis and cirrhosis and, in high-risk patients (e.g., active iv drug users), may also result in decreased transmission of HCV in the general population. Because of the high incidence of comorbidity, routine screening of these patients for underlying psychiatric and substance use disorders is necessary. In addition, it is important to expand the opportunity for antiviral treatment for chronic hepatitis C to patients with comorbid psychiatric and substance use disorders. Routine screening for psychiatric and substance use disorders allows for identification and treatment of these comorbid conditions before antiviral therapy is begun. It is anticipated that such a strategy will expand the pool of patients eligible for antiviral therapy and enhance treatment outcomes.

Unfortunately, few programs or treatment models are designed to manage systematically the substance abuse and psychiatric comorbidity of people with HCV infection immediately before and during treatment with IFN. Health care providers now recognize the need for a systematic approach to hepatitis C that addresses the comorbidity of psychiatric and substance use disorders, an approach that demands active participation from mental health care providers. A first step toward developing comanagement strategies involving mental health and chemical dependency professionals and hepatologists may be to broaden the definition of "treatment" for chronic hepatitis C to incorporate the treatment of the psychiatric and substance use disorders that precede and accompany the liver disease due to HCV infection. Only then can we hope to develop multidisciplinary treatment models in which patients can receive coordinated mental health, chemical dependency, and medical care for chronic hepatitis C in a single clinic location.

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