Depression Comorbidity and Antidepressant Use in Veterans With Chronic Hepatitis C: Results From a Retrospective Chart Review

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Background: The 2002 National Institutes of Health Consensus Conference Statement recommended that both clinical and research efforts be made to increase the availability of hepatitis C virus (HCV) treatment to patients who were previously ineligible because of comorbid psychiatric illness and substance use disorders. However, little research on patients with HCV and comorbid depression has been conducted that can serve to inform and guide treatment of HCV. In this study we characterize the prevalence and severity of comorbid depression, as well as antidepressant and other psychotropic prescribing patterns, in a sample of U.S. veterans with HCV.

Method: Participants were recruited between November 2002 and July 2005 from the liver specialty clinic and from a 1-time HCV patient education class conducted through the Portland Department of Veterans Affairs Northwest Hepatitis C Resource Center. Patients who signed informed consent were asked to complete the Beck Depression Inventory, Second Edition (BDI-II), and their medical records were reviewed for information regarding active prescriptions for psychotropic medications and prior psychiatric diagnoses.

Results: Of the 881 veterans enrolled in the study, 783 (89%) completed the BDI-II. Approximately one third (34%, 264/783) of the veterans endorsed moderate to severe symptoms of depression (BDI-II score ≥ 20), and 37% (290/783) were prescribed an antidepressant; however, 48% (140/290) of veterans prescribed an antidepressant continued to endorse moderate to severe depressive symptoms. Furthermore, of all veterans endorsing moderate to severe symptoms of depression (N = 264), only about half (56%, 148/264) were prescribed an antidepressant.

Conclusion: On the basis of BDI-II scores, a significant proportion of veterans with HCV experience moderate to severe depressive symptoms. Although antidepressants were the most commonly prescribed psychotropic medication, many who were prescribed an antidepressant continued to experience high levels of depressive symptoms, an important consideration when deciding whether to initiate antiviral therapy to treat HCV.

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Approximately 3.9 million Americans, or 1.8% of the U.S. general population, are infected with the hepatitis C virus (HCV), making HCV a major public health concern. However, prevalence is known to vary depending upon age, gender, ethnicity, and military service.[1] Several studies have shown that veterans using Department of Veterans Affairs (VA) healthcare facilities have a higher prevalence of HCV as compared with the general population.[1–4]

Although there has been speculation that military service may be a risk factor for HCV infection, several studies show that this is not the case.[3,5] With the exception of combat medic work, infections are associated with long-established risk factors not exclusive to military service, such as blood transfusion, injection drug use, tattoos, incarceration, and multiple opposite-sex partners.[3] Furthermore, HCV-infection prevalence among active duty and reserve military personnel is lower than in the VA studies and the general civilian population younger than 40 years.[5]

Despite the lower numbers of HCV infections in active duty personnel and reservists, the prevalence of HCV infection in users of VA facilities has repeatedly been shown to be higher than in the general population.[1–4,6] Most recently, Dominitz et al.[6] found that an estimated 5.4% of veterans who access medical care through the VA are infected with HCV, a prevalence that is 3 times greater than that of the general population. However, veterans who access their health care through the VA are not representative of the general population or of veterans who do not use the VA. In general, veterans who access the VA health care system consist of a higher proportion of people who are at greater risk for HCV infection, including men, minorities, and those living below the poverty line.[7,8]

Veterans with HCV also frequently have comorbid psychiatric diagnoses. A retrospective study by el-Serag et al.[9] showed that 85% of veterans hospitalized in VA facilities between 1992 and 1999 had at least 1 current or past psychiatric or substance abuse diagnosis. Among those with a substance use disorder, 85% had been diagnosed with a depressive disorder and 71% had been diagnosed with an anxiety disorder. Other common comorbid diagnoses included posttraumatic stress disorder (43%), a psychotic disorder (42%), or bipolar disorder (30%), and many veterans had multiple diagnoses. In a more recent prospective study conducted by the Hepatitis C Resource Center at the Portland VA Medical Center in which HCV patients were screened for psychiatric illness when they attended their initial hepatology appointment, 93% screened positive for a current or past history of at least 1 psychiatric disorder, and 81% screened positive for depression.[10]

These findings are particularly concerning for at least 2 reasons. First, interferon-based therapy (including interferon-alpha [IFN-alpha], IFN-alpha plus ribavirin, pegylated IFN-alpha, and pegylated IFN-alpha plus ribavirin) is the only U.S. Food and Drug Administration–approved treatment for patients with chronic HCV infection. However, in addition to their therapeutic effects, IFN-alpha–based therapies are associated with a range of neuropsychiatric side effects, in particular depression, which can compromise and sometimes prevent successful completion of antiviral therapy.[11–13] Studies show that approximately 20% to 30% of patients will develop depression during the course of IFN-alpha therapy.[14–18] Thus, it is important to screen patients prior to the start of IFN-alpha therapy so uncontrolled depression can be treated before IFN-alpha therapy is initiated.[19,20] Although there is some controversy in the literature, several studies in HCV patients show that depression symptom rating scores before IFN-alpha therapy initiation may be predictive of the development of IFN-alpha–induced depression.[14,21,22]

The second concern is that patients with prior psychiatric diagnoses have historically been excluded from IFN-alpha therapy because initial treatment guidelines have cautioned against treating these individuals. The argument has been that patients with psychiatric and substance use disorders pose a higher risk of treatment noncompliance and may experience worsening of their psychiatric condition. However, there is limited evidence to exclude those patients with comorbid psychiatric disorders from antiviral therapy. This fact is reflected in the 2002 National Institutes of Health Consensus Conference Statement, which specifically states that both clinical and research efforts be made to increase the availability of hepatitis C treatment to patients who were previously ineligible because of comorbid psychiatric illness and substance use disorder.[23]

Interferon therapy has now become an appropriate option for patients who may have previously been excluded from treatment because of comorbid depression. Because those patients with depression were previously considered poor treatment candidates, there is little research in patients with HCV and comorbid depression to inform and guide treatment. In this study we characterize the prevalence and severity of comorbid depression, as well as antidepressant and other psychotropic prescribing patterns, in a sample of U.S. veterans with chronic HCV infection.

METHOD

Subjects

Study participants were recruited from an optional one-time "Living with Hepatitis C" education class conducted through the Portland VA Northwest Hepatitis C Resource Center and from hepatology clinics. Between November 2002 and July 2005, 881 veterans gave informed consent (approved by the Portland VA Medical Center Institutional Review Board) to allow data extraction from their electronic medical records.

Screening Instruments

Participants were asked to complete the Beck Depression Inventory, Second Edition (BDI-II)[24] upon study entry. The BDI-II is a 21-item self-report questionnaire developed to assess symptoms of depression consistent with the diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition.[25,26] The BDI-II was selected because of the measure's history of correlation with other common measures of depression, as well as its sensitivity and specificity for predicting major depression in patients who are undergoing IFN-alpha therapy.[27] Also, as a practical matter, the BDI-II is a frequently used measure, and the clinicians in our facility are familiar with its administration and interpretation.

In addition, each participant's pharmacy records were reviewed for information regarding active prescriptions

Table 1. Psychotropic Medications Used in the Search of Pharmacy Records

Antidepressants, SSRI	Antidepressants, tricyclic
Citalopram[a]	Amitriptyline[a]
Escitalopram	Amoxapine
Fluoxetine[a]	Clomipramine
Fluvoxamine	Desipramine[a]
Paroxetine[a]	Doxepin[a]
Sertraline[a]	Imipramine
Antidepressants, other	Nortriptyline[a]
Bupropion[a]	Protriptyline
Duloxetine	Trimipramine
Maprotiline	Antidepressants, MOAI
Mirtazapine[a]	Isocarboxazid
Nefazodone[a]	Phenelzine sulfate[a]
Trazodone[a,b]	Tranylcypromine
Venlafaxine[a]	Sedatives/hypnotics, other
Benzodiazepine derivative sedatives/hypnotics	Buspirone[a]
Alprazolam[a]	Chloral hydrate[a]
Chlordiazepoxide[a]	Dexmedetomidine
Clorazepate	Eszopiclone
Diazepam[a]	Ethchlorvynol
Estazolam	Meprobamate
Flurazepam	Zaleplon
Lorazepam[a]	Zolpidem[a]
Midazolam	Lithium salts: lithium[a]
Oxazepam[a]	Antipsychotics
Quazepam	Aripiprazole[a]
Temazepam[a]	Clozapine
Triazolam	Haloperidol[a]
Anticonvulsants[c]	Loxapine[a]
Carbamazepine[a]	Molindone
Divalproex[a]	Olanzapine
Lamotrigine	Quetiapine[a]
Valproate sodium	Risperidone[a]
Valproic acid[a]	Ziprasidone[a]

[a]Medications prescribed in this sample.
[b]Trazodone was not counted as an antidepressant in analyses.
[c]Only anticonvulsants used for treatment of bipolar disorder were included.
Abbreviations: MAOI = monoamine oxidase inhibitor, SSRI = selective serotonin reuptake inhibitor.

for psychotropic medications. Specifically, we examined charts for current use of antidepressants, antipsychotics, benzodiazepines, other sedatives, and mood stabilizers (lithium and certain anticonvulsants) on the basis of the formulary used by the VA. See Table 1 for a list of medications in the formulary. Trazodone was prescribed for problems with sleep, not as an antidepressant. For purposes of these analyses, trazodone was not counted as an antidepressant.

Electronic medical records of each participant were also examined to determine prior psychiatric diagnoses of major depressive disorder, dysthymic disorder, posttraumatic stress disorder, and substance abuse and to determine whether participants had been treated with psychotherapy for depression.

Statistical Analysis

Group means and standard deviations were calculated for the demographic information and BDI-II scores.

Table 2. Demographic and Clinical Characteristics of Veterans With Hepatitis C Virus Included in the Study (N = 783)

Characteristic	Value
Age	
Mean (SD), y	54 (6.4)
Range, y	29 to 87
Race[a]	
White, N (% of known)	255 (79)
Black, N (% of known)	28 (9)
Other, N (% of known)	38 (12)
Unknown, N	462
Gender, N (%)	
Male	758 (97)
Female	25 (3)
Mood disorders, N (%)[b]	
Major depressive disorder	491 (63)
Dysthymic disorder	205 (26)

[a]Data on ethnicity were available for 321 patients. By law, veterans are not required to answer questions about ethnicity.
[b]Categories not exclusive.

Fisher exact test was performed to determine the relationship between antidepressant medication use and BDI-II scores. Chi square tests were conducted to assess the frequency of specific antidepressants and other psychotropic medications used in patients with a BDI-II score less than 20 versus patients with a BDI-II score of 20 or more. A 1-way analysis of variance was conducted to examine the difference in BDI-II scores in patients prescribed an antidepressant versus not prescribed an antidepressant. All statistical calculations were done using SPSS for Windows, Version 11 (SPSS Inc., Chicago, Ill.).

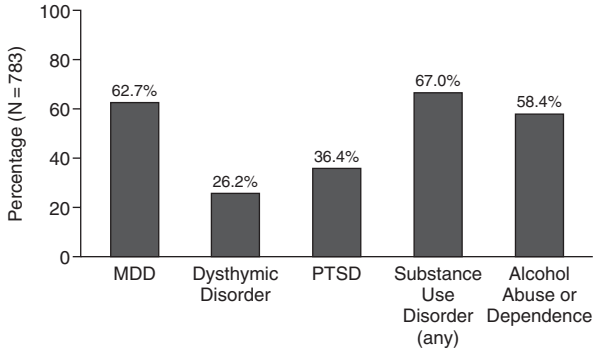
RESULTS

Of the 881 veterans enrolled in the study, 783 (88.9%) completed the BDI-II. The 98 who did not complete a BDI-II did not differ from those who completed the BDI-II on variables of gender, race, or age (data not shown). Reasons for not completing the BDI-II included lack of time in the clinic to complete the questionnaire or inadvertent failure to fully complete the questionnaire (i.e., not completing the back side). These participants have been excluded from further analyses. See Table 2 for demographic information of the sample of 783 participants.

Electronic medical records of veterans were examined to determine prior diagnoses of major depressive disorder, dysthymic disorder, posttraumatic stress disorder, and substance abuse. See Figure 1 for percentages of veterans who have a prior diagnosis in their medical record. Note that categories are not exclusive.

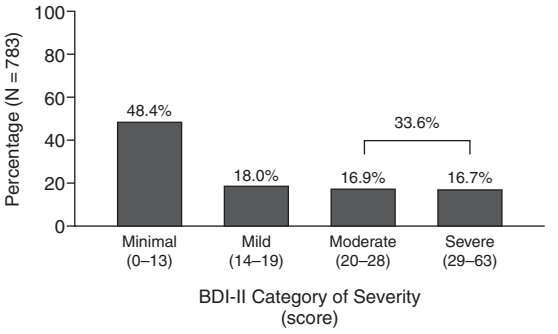
A BDI-II score of 20 or higher is generally accepted as an indication of moderate to severe depression.[24] Approximately one third (34%, 264/783) of veterans who completed the BDI-II scored 20 or higher. The mean ± SD BDI-II score for this group was 30 ± 8.2. Of 264 veterans with moderate to severe depressive symptoms, 44%

Figure 1. Depression, Posttraumatic Stress Disorder, and Substance Use Disorders in Veterans With Hepatitis C Virus



Abbreviations: MDD = major depressive disorder, PTSD = posttraumatic stress disorder.

Figure 2. Breakdown of Beck Depression Inventory, Second Edition (BDI-II) Scores by Category of Severity[a]



[a]Note: Approximately 27% of patients (N = 214) endorsed some level of suicidal ideation on BDI-II item 9 and 11% (N = 86) scored 2 or higher on item 2 (hopelessness), suggesting increased suicide risk.

(N = 116) were not prescribed an antidepressant. See Figure 2 for a breakdown of BDI-II scores by severity.

Electronic medical records of the veterans were examined to determine which patients were taking antidepressant medication prior to completing the BDI-II. Thirty-seven percent (290/783) of veterans were taking an antidepressant (excluding trazodone) at the time they were screened. Twenty-six patients were taking trazodone as their only psychotropic medication. None of the participants in this sample were on IFN-alpha therapy at the time of this study.

Of the 290 participants prescribed an antidepressant, 48% (N = 140) endorsed moderate to severe depressive symptoms (BDI-II score ≥ 20). In addition, 25% of participants not prescribed an antidepressant (124/493) also endorsed moderate to severe depressive symptoms. The mean ± SD BDI-II score of participants prescribed an antidepressant (N = 290) was 20.4 ± 12.2, as compared to a score of 13.4 ± 10.6 for veterans not taking an antidepressant (N = 493) ($F = 71.75$, $df = 1781$, $p < .0001$).

Pharmacy data were also examined for other commonly prescribed medications that either directly or indirectly affect mood, including benzodiazepines, other sedatives, antipsychotics, lithium, and anticonvulsants prescribed for psychiatric purposes. Fifty-eight percent (154/264) of patients with BDI-II scores greater than or equal to 20 were taking psychotropic medication (including antidepressants) versus 35% (180/519) of patients with BDI-II scores less than 20 ($\chi^2 = 40.02$, $df = 1$, $p < .0001$).

Overall, antidepressants were the most frequently prescribed medication, with 37% (290/783) of patients taking an antidepressant. The next most commonly prescribed medications were antipsychotics (7%, 54/783) and benzodiazepines (7%, 53/783). Table 3 summarizes psychotropic usage for the portion of the sample with an active prescription (N = 334).

Table 3. Psychotropic Usage by Class Among Patients Taking Psychotropic Medication[a] at the Time of Screening

	Total (N = 334)		BDI-II < 20 (N = 180)		BDI-II ≥ 20 (N = 154)	
Drug Class[b]	N	%	N	%	N	%
Benzodiazepines	53	16	32	18	21	14
Other sedatives/hypnotics	31	9	16	9	15	10
Antidepressants, all	290	87	150	83	140	91
SSRIs	177	53	90	50	87	56
Tricyclic antidepressants	36	11	23	13	13	8
Other antidepressants	170	51	82	46	88	57
Antipsychotics	54	16	32	18	22	14
Lithium salts	4	1	2	1	2	1
Anticonvulsants (for psychiatric purposes)	15	4	5	3	10	6

[a]Excludes trazodone.
[b]Veterans may be prescribed medication in more than 1 drug class.
Abbreviations: BDI-II = Beck Depression Inventory, Second Edition; SSRI = selective serotonin reuptake inhibitor.

Finally, electronic medical records were examined to determine the percentage of veterans who had received psychotherapy for depression. Of the 783 veterans in the sample, 276 (35%) had 1 psychotherapy visit for major depressive disorder; 108 (14%) had 3 or more psychotherapy visits for major depressive disorder.

DISCUSSION

Overall, we found that antidepressants were the most commonly prescribed psychotropic medication in veterans with chronic HCV infection. Of interest, patients taking an antidepressant (37%, 290/783) reported more depressive symptoms, compared to patients not taking an antidepressant. Approximately one third (34%, 264/783) of all veterans in our sample scored 20 or higher on the BDI-II, suggesting they have moderate to severe depressive symptoms. Furthermore, only about half (53%, 140/264) of these patients were prescribed an antidepressant, and

only 14% (108/783) participated in 3 or more psychotherapy sessions for depression. These data suggest that a significant portion of patients with chronic HCV experience symptoms of depression that are not treated or not treated adequately prior to the first liver clinic appointment. The high rate of depressive symptoms suggests a possible overlap between having a medical illness and depression. Also, the finding of a high rate of *untreated* depressive symptoms suggests it is important to examine current practices and explore possibilities for improvement in services.

There are several possible reasons for the high rate of untreated depressive symptoms in this study. First, most patients attending the "Living with Hepatitis C" education group and hepatology clinic in our study are referred from primary care clinics. This particular referral base represented 73% of our sample. Patients in primary care have a higher risk of being chronically depressed[28] compared to patients in psychiatry specialty clinics. Within VA primary care, Kirchner et al.[29] examined the rate of diagnosis for depression between 1997 and 2001 and determined that the screening and diagnosis of occult depression has been increasing. However, it is still well below what is expected despite established VA guidelines for diagnosis and treatment of major depression.[29] There have been recent efforts in the VA system to improve both the recognition and treatment of depression in primary care.[30,31] Although VA systems have been designed for screening patients for depression and there has been an increase in the percentage of veterans identified with depression, our data suggest further improvements may be warranted. Such improvements may include regularly screening patients for depression and integrating mental health services with specialty and primary care clinics.

Second, there is significant overlap between medical illnesses and symptoms of depression. Activation of the immune system by infectious agents can precipitate the development of depression (e.g., depressive symptoms seen in patients who are taking interferon therapy for HCV). Both Akiskal[32] and Gilmer et al.[28] found a relationship between general medical illness burden and chronic depression. Patients with chronic HCV infection often experience fatigue, muscle and joint aches, and problems with sleep. Fatigue, changes in sleep and appetite, and problems with concentration are all symptoms of depression as well as common symptoms of so-called sickness behaviors. While it may be that medical symptoms mimic symptoms of depression, it is also possible that the presence of a chronic medical illness may obscure recognition and treatment of depression. It is unclear whether symptoms of depression in this sample are due to a lack of recognition and treatment of depression or whether they are due to the additional burden of having a medical illness. This distinction will require further study.

Third, it may be that there are widespread negative attitudes about psychotropic medications in the general population. Benkert and his group[33] surveyed 2176 people about their attitudes toward psychotropic drugs as compared to cardiovascular drugs. In his sample, people expressed greater fear of losing control, of side effects, and of becoming addicted to the psychotropic drugs as compared to the cardiovascular drugs.

Fourth, patients with depression and HCV may go untreated because many patients with HCV are concerned about taking any medications that may jeopardize their liver health. Despite counseling about the relative safety of antidepressants in liver disease, many choose not to take any medication that is not absolutely required.

Finally, there is growing popularity of the use of complementary and alternative medications and treatments for hepatitis C and associated depression.[34] These treatments may be perceived as either safer or more effective than allopathic treatments.[35]

Overall, antidepressants were the most commonly prescribed psychotropic medication (87% of patients taking any psychotropic medication were prescribed an antidepressant), followed by antipsychotics (16%), benzodiazepines (16%), other sedatives/hypnotics (9%), lithium (1%), and anticonvulsants (4%). Of interest, despite being prescribed antidepressants, 140 patients continued to have elevated BDI-II scores (≥ 20), suggesting that many moderately to severely depressed patients were undertreated or not responding to prescribed antidepressants.

Limitations of our study include that our sample is mostly male (97%) and mostly white (79%) and composed entirely of U.S. veterans, which will limit its generalizability to other nonveteran clinic populations. Another limitation is that participants were volunteers, as opposed to a true cross-sectional study, resulting in possible bias. It is possible that patients who are more depressed, medically ill, or actively using illicit substances may be less likely to attend an HCV education group and thereby less likely to be recruited for studies. Also, as the BDI-II is a self-report instrument, the potential exists for both underreporting symptoms (for example, marking all zeros to complete the task) or exaggerating symptoms (due to secondary gain).[36,37]

Recent studies have shown that higher depression ratings prior to initiating IFN-alpha therapy are associated or correlated with an increased likelihood of developing IFN-alpha–induced depression during treatment.[27] It may be that there is a spectrum of depressive subtypes and that certain subgroups of depressive symptoms (cognitive or somatic) may be predictive of success or failure on IFN-alpha therapy. A review of the clinical literature suggests that 2 types of depressive syndromes may be associated with IFN-alpha therapy: (1) a neurovegetative syndrome characterized by psychomotor slowing and

fatigue, which appears early during IFN-alpha therapy; and (2) a mood/cognitive syndrome that appears late during IFN-alpha therapy and is generally responsive to antidepressant treatment.[38]

In summary, many patients with chronic HCV infection experience depressive symptoms. Because depression is a common side effect of IFN-alpha therapy and a common reason for IFN-alpha dose modification or discontinuation,[36] screening for and treatment of depression are important in patients who are being considered for IFN-alpha therapy.[20,27,39] Our study suggests that many patients with HCV who come to their first liver clinic appointment are likely to have significant symptoms of depression that are undiagnosed and untreated. Also, patients with HCV who already have been diagnosed and treated for depression may be taking suboptimal doses of antidepressants or may be refractory to treatment. It is important to screen and ensure adequate response to antidepressant therapy in order to optimize their opportunity for IFN-alpha treatment. Screening patients in specialty clinics and including mental health professionals on the treatment team are 2 suggestions for addressing this need. Also, future studies are needed in order to elucidate the possible reasons for poor antidepressant response.

Drug names: alprazolam (Xanax, Niravam, and others), aripiprazole (Abilify), bupropion (Wellbutrin and others), buspirone (BuSpar and others), carbamazepine (Carbatrol, Equetro, and others), chlordiazepoxide (Librium and others), citalopram (Celexa and others), clomipramine (Anafranil and others), clorazepate (Gen-Xene, Tranxene, and others), clozapine (FazaClo, Clozaril, and others), desipramine (Norpramin and others), dexmedetomidine (Precedex), diazepam (Diastat, Valium, and others), divalproex (Depakote), doxepin (Sinequan, Zonalon, and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), eszopiclone (Lunesta), fluoxetine (Prozac and others), flurazepam (Dalmane and others), haloperidol (Haldol and others), imipramine (Tofranil and others), isocarboxazid (Marplan), lamotrigine (Lamictal and others), lithium (Lithobid, Eskalith, and others), lorazepam (Ativan and others), loxapine (Loxitane and others), mirtazapine (Remeron and others), molindone (Moban), nortriptyline (Pamelor and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), phenelzine sulfate (Nardil), protriptyline (Vivactil), quazepam (Doral), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft and others), temazepam (Restoril and others), tranylcypromine (Parnate and others), triazolam (Halcion and others), trimipramine (Surmontil and others), valproate sodium (Depacon and others), valproic acid (Depakene and others), venlafaxine (Effexor and others), zaleplon (Sonata), ziprasidone (Geodon), zolpidem (Ambien and others).

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