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Psychiatric and Substance Use Disorders among Methadone Maintenance Patients with Chronic Hepatitis C Infection: Effects on Eligibility for Hepatitis C Treatment

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Abstract

We set out to describe the prevalence and severity of psychiatric and substance use disorders (SUDs) in methadone maintenance treatment (MMT) patients with chronic hepatitis C virus (HCV) infection and to measure the impact on HCV-treatment eligibility. Psychiatric disorders, SUDs, and HCV-treatment eligibility were assessed in 111 MMT patients prior to a controlled trial of HCV treatment.

Lifetime and current diagnosis rates, respectively, were: any non-SUD Axis I disorder: 82% and 57%, any mood disorder: 67% and 35%, any anxiety disorder: 63% and 22%, any psychotic disorder: 11% and 9%. Antisocial personality disorder was present in 40%. A total of 56% met criteria for current SUDs. A total of 66% received psychiatric medications prior to HCV treatment; over half were receiving antidepressants. Despite psychiatric and substance use comorbidity, only 15% of patients were ineligible for HCV treatment: 10% due to failure to complete the evaluation, and 5% due to psychiatric severity. Substance use did not lead to ineligibility in any participant. Multiple logistic regression showed the Beck Depression Inventory contributed significantly to predicting HCV treatment eligibility. Most MMT patients were eligible for HCV treatment despite current SUD and non-SUD diagnoses. Depression severity may be a more significant predictor of HCV treatment eligibility than is substance use.

INTRODUCTION

Hepatitis C virus (HCV) infection affects more than 170 million people worldwide and more than 3 million people in the United States alone.¹ HCV remains the primary reason for liver transplantation, with as many as 20% of those chronically infected developing cirrhosis and between 3% and 5% developing hepatocellular carcinoma.² Injection drug use accounts for

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

the majority (65–70%) of disease transmission in industrialized countries such as in Europe and the United States.² In the United States, 85% of HCV-infected persons have one of two risk factors: history of injection drug use or receipt of a blood transfusion before 1992.³ Worldwide HCV-prevalence rates in injection drug users (IDUs) are estimated to range from 28% to 90%.⁴ For example, in a California study, over 90% of IDUs receiving methadone maintenance treatment (MMT) were HCV antibody positive and over 60% had chronic infection,⁵ and Canadian national seroprevalence studies indicated that HCV exposure occurs in up to 90% of IDUs.⁶ At present, treatment for chronic HCV infection consists of a combination of weekly injected pegylated interferon (IFN α) and daily oral ribavirin for a period ranging from 24 to 48 weeks depending on HCV genotype. Treatment success rates range from 50% to 54% in patients with genotype 1 and 76% to 82% in those infected with genotypes 2 or 3.^{7,8} Unfortunately, IFN α is associated with significant adverse effects ranging from flu-like symptoms, nausea, irritability, and fatigue to neutropenia, thrombocytopenia, and thyroid disorders.⁹ Moreover, IFN α can cause significant neuropsychiatric side effects such as acute confusional states or cytokine-induced depression or mania.¹⁰ Treatment initiation may, therefore, be complicated by the high prevalence of psychiatric comorbidity that has been found in studies of opioid-dependent patients in MMT, with mood or anxiety disorders being most prevalent.^{11–15}

Psychiatric disorders have been cited as a significant barrier to HCV treatment for patients with substance use disorders (SUDs).^{16–18} Provider concerns regarding the risk of serious neuropsychiatric adverse effects from interferon therapy in patients with SUDs and psychiatric disorders may inhibit referral for treatment; therefore, standardized screening and referral for psychiatric disorders has been recommended in an effort to increase the likelihood of successful HCV treatment initiation.¹⁹ MMT clinics provide a useful setting for an integrated approach to assessing and treating both HCV and accompanying mental disorders. A systematic review conducted by Novick and Kreek found substantial evidence of successful HCV treatment among MMT patients.²⁰ HCV-infected patients with comorbid substance use and psychiatric disorders have been safely and successfully treated when using a multidisciplinary approach.^{21–26} Unfortunately, numerous barriers continue to impede HCV treatment engagement in this high-risk population.^{18,27–32}

The objective of the present report is to provide a comprehensive description of psychiatric and substance use diagnoses and symptom severity in MMT patients seeking HCV treatment and to assess the impact of substance use and psychiatric variables on HCV-treatment eligibility in these patients. The data for this report were obtained within the context of a NIDA-funded controlled trial of HCV treatment provided to MMT patients on-site (MMT clinic) versus off-site (gastroenterology clinic) (ClinicalTrials.gov Identifier NCT 00148031).

Study Participants

Study participants were opioid-dependent patients enrolled in a Central New York MMT program who were seeking evaluation for HCV treatment within the context of the above-described primary study. All MMT clinic patients were eligible to participate if they had chronic HCV infection defined as a positive HCV ribonucleic acid (RNA) quantitative

polymerase chain reaction (PCR) test result, were 18 to 65 years old, enrolled in MMT for a minimum of 90 days, were willing to consider HCV treatment, and had some form of medical insurance. All participants were offered evaluation for HCV medical treatment, regardless of the presence of active drug or alcohol use or comorbid medical or psychiatric illness. Participants provided written consent and study procedures were approved by SUNY Upstate Medical University and Crouse Hospital Institutional Review Boards.

Procedures

One hundred and eleven participants ($n = 111$) were recruited and randomized into the study from July 2004 through August 2007. Three participants underwent random assignment but were lost to follow-up prior to initiation of the psychiatric evaluation process; thus, full psychiatric diagnostic data are described for 108 participants. Psychiatric evaluations were obtained at the first research visit that included a complete medical and psychiatric history, psychiatric medication and other treatment history, substance use history, and mental status examination. SUD and non-SUD psychiatric diagnoses were determined by the Structured Clinical Interview for DSM-IV Axis I (SCID-I)³³ and DSM-IV Axis-II (SCID-II) Antisocial Personality Disorder (ASPD) inventory.³⁴ SUD diagnoses were considered to be current if criteria had been present in the past 12 months. Research staff conducting these interviews received SCID training from Michael First, M.D.

Following completion of each psychiatric/SUD diagnostic assessment, the results were reviewed by the research psychiatrist (SLB) and each participant was assigned to one of three categories: having no psychiatric or SUD contraindication to HCV treatment (1); having a chronic persistent psychiatric or SUD contraindication to HCV treatment (2); or having a temporary psychiatric or SUD contraindication to HCV treatment (3) (defined as the presence of acute psychiatric or SUD symptoms that could be stabilized by further treatment within the constraints of the study time limitations). Participants in the third group were offered psychiatric treatment by the research psychiatrist (SLB) or a psychiatrist of their choosing for up to 6 months to determine whether psychiatric symptoms would improve sufficiently to allow for safe initiation of HCV treatment. Due to the time-limited nature of the study's funding period, participants were allowed a finite time frame of 6 months for completion of the medical and psychiatric assessment for HCV-treatment eligibility and resolution of contraindications. If, after 6 months from initial assessment, a participant continued to have a psychiatric condition that was a contraindication or failed to complete the evaluation process, then that participant was no longer considered eligible for HCV treatment. Psychiatric exclusion criteria were considered on a case by case basis according to American Association for the Study of Liver Diseases (AASLD) guidelines.⁹ Current SUDs and alcohol or drug use were not necessarily considered absolute exclusion criteria, unless they required inpatient detoxification or caused medical complications that were judged to place the patient at increased risk for adverse consequences from HCV treatment. Of note, no subjects were determined to be ineligible for HCV treatment due to SUDs or alcohol or drug use based on the above criteria.

Depression, anxiety, and mania symptom severity were assessed with the Beck Depression Inventory (BDI),³⁵ the Beck Anxiety Inventory (BAI),³⁶ and the Young Mania Rating Scale

(YMRS),³⁷ respectively. Fatigue severity at study entry was evaluated using the Fatigue Severity Scale³⁸ with a calculated score between 0 (no fatigue) and 7 (severe fatigue). The Addiction Severity Index—Lite (ASI-Lite)³⁹ was used to measure substance use severity and past 30-day substance use frequency. Urine drug testing for opioid and cocaine was performed using the Jant Accutest Multidrug three-panel test for opioids, cocaine, and tetrahydrocannabinol (THC) (Jant Pharmacal Corporation, Encino, CA). All research-related substance use self-reports and urine drug test results were kept confidential from MMT clinic staff.

Statistical Analysis

Demographic characteristics were compared using chi-square analysis for measures of association among dichotomous variables or *t*-test comparisons of means when appropriate. Mann-Whitney U median test was used for comparisons of ordinal outcomes. Block multiple logistic regression was used to assess the extent to which blocks of predictors increased predictive accuracy of HCV-treatment eligibility. The model started with a *demographics* block, including age, gender (1 = female), and race (1 = African American). A second *substance use* block included an indicator for whether any SUD was diagnosed, and a second indicator for presence of positive cocaine or opioid urine results. Our last block, *psychiatric disorders*, included an indicator for whether the subject had a diagnosed mood disorder, anxiety disorder, or psychotic disorder (1 = yes), and their BDI score. The dependant variable was HCV-treatment eligibility (eligible, not eligible), and we report the odds ratios (OR), 95% confidence intervals of the OR, and significance values for the full model.

RESULTS

Demographics and HCV Medical Characteristics

Participants' demographic characteristics are summarized in Table 1. Participants were mainly male (60%) and white (80%). The mean age was 43 ($\pm$ 10) years. The primary source of health insurance was Medicaid (74%). A minority (24%) were married or living as married. The average level of education was 12 years ($\pm$ 2). Eighty percent were unemployed with one-third receiving public assistance and one-third receiving SSI/SSD. Twenty-nine (26%) of the 111 participants had started treatment at the MMT clinic within 6 months prior to study entry.

Most participants (78%) had a current primary care provider, but only 18% had ever consulted a hepatologist. All had chronic HCV infection as evidenced by HCV RNA quantitative testing and 5% had HIV coinfection. Eighty-two percent had HCV genotype 1 disease and nearly half (45%) had HCV viral load levels $\leq$ 2 million IU/mL.

Substance Use Characteristics

The average age of first opioid use was 20 ($\pm$ 6) years and the average duration of opioid use was 23 years. Almost all (93%) reported a history of injection drug use. Ninety percent reported a history of cocaine use. MMT chart review of observed urine drug testing within the 90 days prior to study entry (n = 111) showed that 24% of participants had a urine test

positive for opioids, 35% for cocaine, and 23% for THC. ASI-Lite³⁹ self-report of past 30 days of alcohol and drug use indicated use of alcohol by 17%, illicit opioids by 15%, cocaine by 17%, and cannabis by 14% of participants ($n = 109$).

Substance Use Disorder Diagnoses

Current substance use abuse or dependence diagnoses (SUD) were determined by Structured Clinical Interviews for DSM-IV Axis I (SCID-I).³³ As noted above, because three participants failed to complete the evaluation process, SUD diagnostic data are available for 108 participants. SUDs were considered to be current, if criteria were met in the previous 12 months. All participants met lifetime criteria for diagnosis of opioid dependence on agonist therapy by virtue of their participation in MMT. Over half (56%) also met diagnostic criteria for current substance abuse or dependence despite participation in MMT. Forty-seven percent were diagnosed as having current opioid or cocaine dependence or abuse. Seventeen percent of participants were diagnosed with current alcohol dependence or abuse, 17% were abusing or dependent on sedatives, and 16% were diagnosed with cannabis abuse or dependence. Table 2 provides a summary of SCID substance use diagnoses.

Non-SUD Psychiatric Diagnoses and Symptom Severity

More than three quarters (77%) of participants had a history of mental health treatment, with 29% having a history of psychiatric hospitalizations. Of the 108 HCV-infected MMT participants who completed the SCID, 82% met criteria for one or more lifetime non-SUD Axis I disorders, and 56% had at least one current non-SUD Axis I disorder as shown in Table 3. Mood disorders were the most frequent lifetime diagnoses, found in 67%, with 42% having met criteria for lifetime major depressive disorder and 12% with lifetime substance-induced mood disorder. Lifetime anxiety disorders ranked a close second to mood disorders, present in 63% of participants, with lifetime rates of 25% for posttraumatic stress disorder (PTSD), 22% for generalized anxiety disorder, 21% for panic disorder with agoraphobia, and 21% for social phobia. Lifetime psychotic disorders were present in 11%. Axis II ASPD was diagnosed in 40% of subjects.

Current mood and anxiety diagnoses were also common. At least one current anxiety disorder was found in 44% of participants. PTSD was diagnosed in 17%, social phobia in 13%, and panic disorder with agoraphobia in 8%. At least one current mood disorder was found in 35% of subjects, with current major depressive disorder in 22%, bipolar I disorder in 6%, and bipolar II disorder in 3% of participants.

Depression and anxiety symptom severity levels were in the mild to moderate range, with a mean BDI of $17 (\pm 12)$, and a mean BAI of $16 (\pm 13)$. The mental health subscore and component score of the Medical Outcomes Study Short Form 36-item health survey (SF-36)⁴⁰ were used to further assess psychiatric symptom severity. Participants had a substantially poorer mental health subscore ($56, SD \pm 25$) and mental health component score ($38.3, SD \pm 14.5$) than the U.S. normative population ($75.2, SD \pm 17.6$; $50, SD \pm 10$, respectively). Fatigue severity scores³⁸ were moderately elevated ($n = 87, 4.13, SD \pm 1.8$). Those with current mood disorders ($p = .01$) and those with current anxiety disorders ($p = .$

001) had higher median pretreatment fatigue severity scores than those without these diagnoses.

Psychiatric Medications

Two-thirds (66%) of participants were taking at least one psychiatric medication at study entry. Over half (56%) were taking antidepressant medications, of which over half (56%) were selective serotonin reuptake inhibitors. A smaller proportion (11%) of this cohort was taking antianxiety medication (including benzodiazepines, antihistamines, and pregabalin). Twelve percent of the participants were taking mood stabilizers. Twenty percent were taking an antipsychotic medication, even though only 9% had a psychotic disorder diagnosis.

Hepatitis C Treatment Eligibility and Predictors of Hepatitis C Treatment Eligibility

Ninety-four (85%) of this cohort ($n = 111$) of MMT patients with chronic HCV infection were found to be medically and psychiatrically eligible for initiation of HCV treatment with pegylated interferon and ribavirin. The most frequent reason for ineligibility was failure to complete the evaluation process in 11 (10%), followed by severe psychiatric illness severity in 6 (5%) due to either unstable mood (4 subjects) or psychotic disorder (2 subjects). No subjects were considered to be ineligible due to alcohol or substance use. Block multiple logistic regression was used to assess the extent to which *demographic*, *substance use*, and *psychiatric disorder* blocks of predictors improved the predictive accuracy of HCV-treatment eligibility (Table 4). The *demographics-only* model achieved a poor, though marginally significant ($p < .05$) coefficient of determination⁴¹ of .10. Adding the *substance use* block did not improve the model significantly (Nagelkerke $R^2 = .12$); however, adding the *psychiatric disorder* block of predictors that included an indicator for mood, anxiety, or psychotic disorders, and BDI scores doubled the coefficient (Nagelkerke $R^2 = .24$), resulting in significant improvement in predictive accuracy ($p < .03$).

This model accurately predicted treatment eligibility for 75.9 cases and treatment ineligibility for 63.3 cases, achieving a generalized coefficient of determination of .24 ($\chi^2 = 11.34$, $p < .01$).⁴¹ While the overall predictive model performed well, clearly the psychiatric disorder block made the largest contribution to model accuracy, with BDI score contributing the majority of influence on the model (Table 4). Increased BDI depression scores were associated with decreased likelihood of HCV treatment eligibility.

DISCUSSION

Summary of Findings

Despite MMT, over half of this cohort of HCV-infected MMT patients met criteria for a current SUD diagnosis (past 12 months), most often involving continued opioid or cocaine dependence or abuse. These results are in concert with other research findings examining current SUD diagnoses among opioid-dependent patients.^{12,13,42} The rates of lifetime and current non-SUD psychiatric diagnoses in our sample were similar to other findings indicating high levels of mood, anxiety, and personality disorders in patients with SUD diagnoses.^{43,44}

Despite the high prevalence of current psychiatric disorders, only 5% of the patients in this cohort demonstrated severe enough psychiatric illness to prevent eligibility for HCV treatment initiation. As noted by McGovern et al. and Sacks et al. in their evaluations of SUD treatment facilities, while there is a high rate of co-occurring psychiatric illness among SUD patients, severity tends to be low enough to allow the majority to receive mental health treatment services within their respective substance abuse treatment programs.^{44,45} However, psychiatric factors such as depression may have contributed to the failure of some patients to complete the process of evaluation for HCV-treatment eligibility. Ineligibility for HCV treatment in our sample was due more to failure to complete the evaluation process (11%) than to specific psychiatric disorders (5%). Furthermore, use of a multiple logistic regression model revealed that current depression severity, as assessed by the BDI, made a significant contribution to the prediction of HCV-treatment eligibility. This result points to the importance of pretreatment assessment of depression severity as an indicator of HCV-treatment eligibility in opioid-dependent MMT patients with untreated chronic HCV infection.

Study Strengths and Limitations

Although a number of studies have examined psychiatric disorders in HCV-infected substance users,^{19,21,23,25,46–51} few studies^{22,26,52} have examined psychiatric diagnosis and symptom severity in MMT patients with chronic HCV infection. Even fewer¹⁵ have used structured diagnostic interviews to assess psychiatric disorders. A strength of this study, therefore, is its use of the SCID to examine psychiatric diagnoses in MMT patients with chronic HCV infection *prior* to initiation of HCV treatment. Another strength of this study is its maximally inclusive entry criteria allowing as many HCV-infected MMT patients as possible to access HCV treatment, in contrast with entry criteria for previous HCV treatment studies that have typically excluded patients with comorbid active substance use or mental illness. The low threshold to study entry provided the opportunity for the investigators to conduct comprehensive standardized psychiatric evaluations of a broad range of MMT patients with chronic HCV-infection who were interested in HCV treatment. The inclusion of patients with co-occurring psychiatric and substance use disorders enhances this study's ability to naturalistically reflect the actual universe of treatment-seeking MMT patients with HCV infection and, thereby, increases the generalizability of our findings.

Limitations of this study include the sample size (111 participants) and use of one large central New York MMT clinic as the recruitment site. These factors may limit the ability to generalize our findings to other clinics and other regions. However, our psychiatric diagnostic findings largely agree with data from other studies that examined psychiatric disorders in MMT patients with HCV infection.^{15,22,26,52} Although our study design attempted to be as inclusive as possible, this study limited entry to those HCV-infected MMT patients who were willing to consider HCV treatment and who had some form of medical insurance or willingness to pay out of pocket for medical treatment. This may somewhat limit the generalizability of our findings regarding psychiatric diagnoses and severity to those HCV-infected MMT patients who had interest in HCV treatment or were insured or willing to pay out of pocket for their medical care.

High rates of psychiatric disease have been documented in MMT patients and in others with opioid dependence,^{11–13,42,53,54} as well as in patients with chronic HCV infection.²⁷ Our findings contribute to scientific knowledge regarding psychiatric diagnoses and disease severity in HCV-infected MMT patients; however, we did not compare psychiatric diagnoses or disease severity of our cohort to MMT patients who were not HCV infected.

CONCLUSIONS

The majority of our sample of MMT with chronic HCV infection patients had psychiatric disorders and substance use conditions that are often considered to be barriers to HCV-treatment eligibility.^{17,18,27,29,32} However, 85% of these HCV treatment-seeking MMT patients were found to be eligible for initiation of HCV treatment despite having psychiatric disorders and active substance use. Only 11% of subjects failed to complete the complex process of evaluation for HCV-treatment eligibility, which may be an indicator of the benefit of colocating psychiatric and medical assessment services within substance use treatment clinics, particularly MMT programs. Our finding that depression severity was a more significant predictor of HCV-treatment eligibility than substance use suggests a pivotal role for assessment and treatment of depression in preparation for HCV-treatment eligibility in MMT patients with chronic HCV infection.

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TABLE 1Demographic characteristics ($n = 111$)

Age (mean yrs $\pm$ SD)	43 ($\pm$ 10)
Male	60%
Race	
Caucasian	80%
African American	14%
Native American	2%
Hawaiian/Pacific islander	
Mixed/other ethnicity	4%
Hispanic	20%
Medical Insurance	99%
Medicaid	74%
Private	18%
Medicare	7%
No insurance	1%
Married	24%
Independent Living	67%
Income Source	
Employment	20%
SSI/SSD	32%
Public assistance	33%
No income/other support	15%
Not employed	80%
Education	12 years ($\pm$ 2)

TABLE 2SCID substance use diagnoses—past 12 months ($n = 108$)

Any substance dependence or abuse	61 (56%)
Opioid or cocaine dependence or abuse	51 (47%)
Cocaine dependence	32 (30%)
Opioid dependence	37 (34%)
Cannabis dependence	10 (9%)
Sedative dependence	14 (13%)
Amphetamine dependence	2 (2%)
Hallucinogen dependence	0 (0%)
Alcohol dependence	6 (6%)
Polysubstance dependence	5 (5%)
Cocaine abuse	9 (8%)
Opioid abuse	4 (4%)
Cannabis abuse	8 (7%)
Sedative abuse	4 (4%)
Amphetamine abuse	2 (2%)
Hallucinogen abuse	2 (2%)
Alcohol abuse	12 (11%)
Polysubstance abuse	0 (0%)

TABLE 3SCID Non-SUD psychiatric diagnoses ($n = 108$)

Diagnosis	<i>N</i> (%) Current (past 30 days)	<i>N</i> (%) Lifetime
Any Axis I non-SUD diagnosis	61 (56%)	89 (82%)
Antisocial personality disorder	N/A	43 (40%)
Mood disorders		
Any mood disorder	38 (35%)	72 (67%)
Major depressive disorder	24 (22%)	45 (42%)
Bipolar I disorder	6 (6%)	11 (10%)
Bipolar II disorder	3 (3%)	3 (3%)
Dysthymic disorder	N/A	12 (11%)
Substance-induced mood disorder	1 (1%)	13 (12%)
Anxiety disorders		
Any anxiety disorder	48 (44%)	68 (63%)
Generalized anxiety disorder	N/A	24 (22%)
Panic disorder with agoraphobia	9 (8%)	23 (21%)
Panic disorder without agoraphobia	7 (6%)	14 (13%)
Social phobia	14 (13%)	23 (21%)
PTSD	18 (17%)	27 (25%)
Substance-induced anxiety disorder	3 (3%)	4 (4%)
Psychotic disorders		
Any psychotic disorder	10 (9%)	12 (11%)
Schizophrenia	1 (1%)	1 (1%)
Schizoaffective disorder	5 (5%)	7 (7%)
Psychotic disorder	4 (4%)	4 (4%)
NOS		
Major depression with psychotic features	3 (3%)	3 (3%)

TABLE 4

Logistic regression coefficients predicting treatment eligibility

		95% CI for OR		
	OR	Lower	Upper	p-value
Demographic block				
Age	.98	.93	1.03	.51
Female	.79	.32	1.96	.61
African American	.28	.07	1.11	.07
Substance use block				
Any SUD	1.52	.57	4.05	.40
Cocaine or opiate positive urine past 90 days	.66	.26	1.72	.40
Psychiatric disorder block				
Current mood, anxiety or psychotic disorder	.53	.25	2.07	.53
BDI score*	.49	.30	.79	.003

*
 $p < .01$