Hepatitis C Treatment of Patients With Bipolar Disorder: A Case Series

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Background: Hepatitis C virus (HCV) chronic infection affects 10% to 15% of patients with bipolar disorder. Patients with HCV infection and comorbid psychiatric illness pose a tremendous clinical and therapeutic challenge. The cases presented in this report illustrate several critical issues facing clinicians who manage patients with comorbid HCV infection and bipolar disorder.

Method: Five cases are described in which patients with DSM-IV bipolar disorder were treated with interferon-α–based therapies and ribavirin to induce viral clearance of HCV. In all cases, the patients were treated using an integrated model of care, and the treatment decision was a consensus between the treating hepatologists and psychiatrists.

Results: In the first case, the patient had no significant neuropsychiatric adverse effects and had viral clearance. In 2 other cases, viral clearance of HCV was achieved through the delicate management of affective symptoms induced by interferon-α and ribavirin. Interferon-α and ribavirin treatment was halted due to mania and suicidal ideation in the 2 remaining cases.

Conclusion: These cases suggest that patients with hepatitis C and bipolar disorder should be evaluated for HCV antiviral treatments, as these patients can receive and tolerate these treatments if assessed meticulously, observed carefully, and followed extensively during interferon-α and ribavirin treatment. This case series will hopefully spark a dialogue about when HCV antiviral treatment should be withheld or delayed in these difficult cases.

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The presence of comorbid bipolar disorder presents considerable obstacles to clinicians caring for the 4 million Americans infected with the hepatitis C virus (HCV).[1,2] Interferon-α–based therapies (interferon-α) are used in combination with ribavirin to eradicate HCV infection and result in viral clearance rates of 54% to 56%.[1,3] Nonetheless, interferon-α–associated neuropsychiatric adverse effects have complicated the use of HCV therapies and reduced viral clearance rates. As a result, clinicians are often reluctant to prescribe interferon-α for patients with HCV infection and preexisting bipolar disorder due to the risk of precipitating or exacerbating neuropsychiatric symptoms.[4]

The prevalence rates of psychiatric and substance use disorders in patients with chronic HCV infection are higher than those in the general U.S. population.[5,6] Bipolar illness was found to be present in almost 1 out of 7 patients with HCV infection.[5,7] Furthermore, the prevalence of HCV infection in patients with serious mental illness and those admitted to psychiatric hospitals ranges from 8.5% to 18%,[8,9] rates that are 4 to 9 times higher than the prevalence of HCV infection in the U.S. general population.[1]

While the incidence, phenomenology, psychiatric workup, and clinical management of depression in patients with HCV infection treated with interferon-α have been well described,[10] considerably less attention has been paid to the interplay between HCV infection, bipolar disorder, and interferon-α.[11] Several reports have documented the course and psychiatric treatment of interferon-α–induced mania as well as mania induced by interferon-α withdrawal in patients with HCV infection.[12–15] However, there have been no reports documenting the administration of and successful treatment with interferon-α in patients with preexisting bipolar disorder.

There is a pressing need, therefore, to develop improved clinical management approaches for patients with HCV infection and comorbid bipolar disorder to ensure that they complete a full course of interferon-α treatment in an uninterrupted manner.[16] The purpose of this report is to demonstrate several important clinical issues facing hepatologists and psychiatrists who manage patients with comorbid HCV and bipolar disorder and to stimulate discussion about the optimum management of such patients,

as well as provide guidance in managing these challenging cases. I describe the clinical course of 5 HCV-infected patients with preexisting DSM-IV bipolar disorder type 1. The patients described were treated with pegylated-interferons and ribavirin. The decisions to treat all 5 patients with interferon-α were made by consensus between the hepatologist and the psychiatrist, and each patient received integrated medical and psychiatric care throughout his or her HCV treatment course.

CASE SERIES

Case 1

Mr. A was a 51-year-old single white man with HCV genotype 1. A course of standard interferon-α monotherapy in 1996 was not associated with adverse neuropsychiatric effects but failed to achieve viral clearance. A follow-up liver biopsy in 2000 revealed cirrhosis, and a 48-week course of pegylated-interferons and ribavirin was recommended.

Mr. A had been diagnosed with bipolar disorder during his late adolescent years. His first manic episode resolved promptly with lithium carbonate, and he suffered only 1 subsequent manic episode (when he was unable to obtain medication while traveling abroad). His manic symptoms had been quiescent for the last 10 years. During this time, he had routine monthly visits to his psychiatrist and had been compliant with his prescribed psychiatric medications (lithium carbonate 450 mg twice a day [serum lithium level = 0.9 mEq/L] and trazodone 50 mg and clonazepam 2 mg, both at bedtime).

Given the presence of severe liver disease and bipolar disorder, a psychiatric consultation was requested to assist with Mr. A's clinical management before and during HCV treatment. Mr. A understood the risks (including the development of affective instability) and the potential benefits of interferon-α treatment. His brother agreed to act as a substitute decision-maker in the event that the patient's mental status was altered during interferon-α treatment such that he lacked the functional capacity to make decisions for himself. The HCV treatment course was commenced, but week 7 was marked by the development of mild affective instability without frank depressive or manic symptoms. HCV viremia was absent at 12 weeks, and HCV treatment was continued. He completed 48 weeks of HCV treatment and achieved a sustained viral response. He continued to have a stable psychiatric illness and when seen 1 year later was free of HCV infection and any psychiatric symptoms.

Case 2

Ms. B was a 32-year-old married white woman who contracted HCV genotype 1 infection as a result of a blood transfusion. Ms. B had suffered from bipolar disorder type 1 for 12 years and had been hospitalized at age 20 due to an episode of mania. Lithium carbonate 450 mg twice a day (serum lithium level = 0.7 mEq/L) resulted in mood stabilization for 5 years, after which she suffered an episode of depression that responded to paroxetine 30 mg/day.

Ms. B and her supportive husband were planning to have children, but a liver biopsy showed significant inflammation, and Ms. B was concerned about transmission of HCV infection to her child. The treating hepatologist was initially reluctant to offer her treatment for HCV infection due to her psychiatric illness. After consultation with Ms. B and her family, both the treating psychiatrist and hepatologist agreed in January 2002 to proceed with a 48-week course of pegylated-interferons and ribavirin with the following stipulations: first, she would have to comply with appointments every 2 weeks with her psychiatrist; second, her pegylated-interferons injections and use of other psychotropics would be monitored by her husband to ensure adherence; and third, her husband would be the holder of her durable power of attorney for health care decisions in case of her psychiatric decompensation.

During week 10 of HCV treatment, Ms. B developed depressive symptoms and anhedonia. Her symptoms responded to an increase in her paroxetine dose to 50 mg during the following 2 weeks. Her HCV treatment course remained uneventful until week 30, when she developed racing thoughts, elevated mood, and grandiosity. Her dose of lithium was increased to 1150 mg (serum lithium level = 1.0 mEq/L), and her paroxetine dose was lowered to 30 mg. These changes resulted in the complete resolution of her symptoms, and she completed her HCV treatment course.

When seen 6 months later, Ms. B was free of both psychiatric symptoms and HCV infection, and lithium was substituted with lamotrigine. Two years later, she was seen in follow-up and had a healthy 6-month-old child who was free of HCV infection.

Case 3

Mr. C was a 52-year-old white man who was diagnosed with HCV genotype 3 infection in the context of a workup for persistently elevated liver function. This workup was prompted by symptoms of polyuria and polydipsia and showed an elevated fasting glucose level confirming the diagnosis of type 2 diabetes mellitus. Over a period of 4 months, diet and exercise resulted in improved blood glucose control.

Mr. C also had a history of bipolar disorder and had been stable on his treatment regimen (quetiapine 600 mg q.h.s.) for 5 years. His first manic episode was 25 years earlier and resulted in hospitalization. His only other psychiatric hospitalization was due to an exacerbation of his mania symptoms precipitated by a switch in his psycho-

tropics from valproate to quetiapine. At the time of presentation, Mr. C was in a stable marriage, worked full-time as an engineer, and was followed routinely by his psychiatrist.

A liver biopsy revealed marked inflammation with fatty infiltration. The evaluating gastroenterologist recommended treatment with a 24-week course of pegylated-interferons-α and ribavirin and required visits every 2 weeks with the treating psychiatrist. Mr. C decided to pursue treatment and appointed his wife as the holder of his durable power of attorney. HCV treatment was initiated in March 2002, and during week 6, Mr. C became depressed and had increased anhedonia and fatigue. Citalopram was added and its dose increased to 40 mg by week 10. This resulted in full improvement in the patient's affective symptoms.

During week 19 of treatment, Mr. C developed racing thoughts and decreased sleep as well as erratic behavior. In an attempt to continue interferon-α treatment (given early viral clearance during week 12), his quetiapine dose was increased to 800 mg q.h.s., which resulted in partial improvement of his symptoms during the next week, but not full resolution of his racing thoughts. His pegylated-interferon dose was reduced by half, and lithium carbonate was added at 300 mg b.i.d. (serum lithium level = 0.5 mEq/L). His psychiatric symptoms completely resolved during week 21 of HCV treatment. During week 22 of treatment, his full pegylated-interferons dose was resumed. Mr. C completed the full 24-week course of interferon-α treatment without further complications and attained viral clearance.

Lithium was withdrawn gradually over the 6 months following HCV treatment, and the patient's quetiapine dose was tapered downward to 600 mg q.h.s. without complications. One year following completion of HCV treatment, a repeat liver biopsy showed a resolution of the inflammation and regression of fatty infiltration.

Case 4

Mr. D was a 51-year-old African American man with HCV genotype 1 infection whose liver biopsy showed significant inflammation but no cirrhosis, and his treating hepatologist recommended a 48-week course of pegylated-interferons and ribavirin.

Mr. D had a 20-year history of bipolar disorder and numerous hospitalizations due to episodes of mania (predominantly during the first 13 years of his illness). He subsequently experienced 2 episodes of depression, which resulted in hospitalization due to suicidal ideation. For the next 5 years, he had been followed routinely at the local community mental health facility and had been stable on his medication regimen of lithium carbonate 600 mg b.i.d. (serum lithium level = 0.9 mEq/L), sertraline 75 mg/day, and levothyroxine 0.075 mg/day. He lived alone, had never been married, and was employed part-time.

The treating psychiatrist expressed concerns about Mr. D's eligibility for HCV treatment due to his history of depression, suicidal ideation, and lack of social support. Mr. D agreed to receive his interferon-α injections under supervision at the community mental health clinic once weekly and continue to see his psychiatrist every 2 weeks. One of his cousins agreed to be the holder of his durable power of attorney for health care decisions. Mr. D's psychiatrist agreed to communicate closely with the patient's hepatologist. Treatment began in June 2002, and 4 weeks into treatment, Mr. D developed mild to moderate psychomotor retardation and affective flattening with depressive symptomatology, which responded to an increase in his dose of sertraline to 150 mg. He remained free of depression, mania, or behavioral symptoms until week 10, when he developed hypomania with some fleeting suicidal ideation. His hypomania responded to the addition of quetiapine 300 mg at bedtime, although he continued to have fleeting suicidal ideation. The 11th week of treatment was marked by an increase in suicidal ideation despite the increase in the dose of sertraline to 200 mg. Given the presence of suicidal ideation and persistent HCV viremia (without a significant decrease in HCV RNA counts), HCV treatments were stopped, and Mr. D was hospitalized for 10 days with no change in his psychotropic regimen. He was discharged free of suicidal ideation and continued to have persistent HCV viremia.

Case 5

Ms. E was a 47-year-old divorced white woman diagnosed with HCV genotype 1 infection after undergoing hepatitis serology testing due to abnormal liver function test results. A liver biopsy showed significant fibrosis, and treatment with a 48-week course of pegylated-interferons and ribavirin was recommended.

Ms. E had suffered from bipolar disorder for 20 years and also had a history of polysubstance dependence and intravenous drug use. She had been hospitalized numerous times due to episodes of mania and psychosis (often associated with alcohol use, intravenous heroin injection, and medication noncompliance). She completed an inpatient substance abuse treatment program at age 42, which was followed by regular attendance of Narcotics Anonymous meetings and compliance with her psychiatric follow-up and medication regimen (risperidone 4 mg q.h.s. and sodium divalproex 1000 mg q.h.s.) and had remained abstinent from substance use. The treating gastroenterologist was initially reluctant to offer her treatment for HCV infection due to her psychiatric history. However, at the time of evaluation, the patient had been free of hospitalizations or psychiatric symptom exacerbations for the past 5 years and was employed.

Ms. E and her supportive family strongly requested HCV treatment, as the patient had a brother who died from liver cirrhosis due to HCV infection and alcohol dependence. Her gastroenterologist and psychiatrist agreed to treat her with the following stipulations: first, she would have to comply with weekly appointments with her psychiatrist and agree to undergo random urine drug screens; second, her pegylated-interferons injections and ribavirin doses were to be given to her by her parents to ensure adherence; and third, her father would be the holder of her durable power of attorney for health care decisions in case of her psychiatric decompensation.

HCV treatment began in January 2003, and during week 5, Ms. E developed grandiose delusions with auditory and visual hallucinations. An increase in her risperidone dose to 4 mg twice a day did not ameliorate her symptoms during the following week. In an attempt to manage her psychiatric symptoms and allow her to continue HCV treatment, the dose of sodium divalproex was increased to 1500 mg q.h.s. and then 2000 mg q.h.s. during the seventh week of interferon treatment. These efforts were not successful, and by week 8 of her treatment, both parents agreed that the patient had become more manic and agitated. Treatment with pegylated-interferons and ribavirin was stopped, and Ms. E was involuntarily admitted to a psychiatric inpatient unit for 5 days, during which time her sodium divalproex dose was increased to 2250 mg per day. Her manic symptoms abated rapidly and completely, and she was discharged home to her parents' care.

Six months later, Ms. E was free of psychiatric symptoms. Despite the abbreviated course of interferon-α treatment, her liver function test results normalized, and a follow-up liver biopsy 1 year later showed some improvement in the degree of inflammation.

DISCUSSION

These cases illustrate several medical and psychiatric challenges pertaining to the management of patients with comorbid bipolar disorder and HCV infection. Patients with HCV and bipolar disorder represent 10% to 15% of all U.S. patients infected with HCV.[5,6] The exclusion of patients with HCV infection and bipolar illness from consideration of HCV treatment is understandable, but not always justifiable. Such practice is stigmatizing and will result in substantial morbidity and mortality for a particularly vulnerable population no less deserving of HCV treatment than patients with HCV infection who are free of psychiatric illness.[17]

Several reports warn of the potential worsening or new onset of mania during HCV treatment.[18–22] Others, however, suggest that preexisting psychiatric illness should not automatically exclude patients from HCV treatment.[23–25] Nonetheless, clinicians remain hesitant to initiate interferon-α treatment due to concerns about precipitating mania or worsening affective symptoms. Recent reports[26–28] and the cases described here demonstrate that some patients (up to 30%) with preexisting psychiatric disorders (affective and psychotic disorders) will complete their HCV treatment course with no significant worsening in their psychiatric symptomatology.

Clinical experience in patients with HCV infection and comorbid bipolar disorder indicates that interferon-α–emergent neuropsychiatric side effects (e.g., depressive syndromes, mania, and psychotic symptoms) can be effectively managed when monitored appropriately, identified early, and treated aggressively.[26,29] The risk-benefit analysis for patients with bipolar disorder and evidence of HCV-related cirrhosis may justify HCV treatment with interferon-α. Furthermore, patients with bipolar disorder who receive HCV treatment without achieving viral clearance may still achieve normalization of liver function test results and some improvement in liver pathology. Long-term follow-up studies are needed, however, to identify whether this benefit for interferon-α nonresponders also translates into a reduction in the incidence of liver cirrhosis or hepatocellular carcinoma.[30] If such benefits were confirmed, this would strengthen the argument to treat patients with HCV and bipolar disorder with interferon-α.

Interferon-α treatment of patients with HCV infection and bipolar disorder highlights the importance of an integrated medical and psychiatric care model.[31] The medical management of HCV is complex, and the decision to treat with interferon-α requires the consideration of numerous factors. It is estimated that 70% of HCV-positive Americans are infected with HCV genotype 1, and the viral clearance rates in response to pegylated-interferons-α treatment are 50% to 60%.[1] In contrast, viral clearance rates for genotypes 2 and 3 are as high as 80% to 90%. However, HCV genotypes 2 and 3 affect only 20% to 30% of the U.S. population infected with HCV.[1] Other factors associated with poor response rates to interferon-α treatment include the following: advanced age (> 40 years), increased body mass index, nonwhite race, human immunodeficiency virus coinfection, and higher HCV viral loads.[32] Consequently, the threshold for treating patients who are infected with HCV genotypes 2 and 3 and who suffer from bipolar disorder may be lower than that for patients infected with HCV genotype 1.

Patients with HCV and bipolar disorder should be educated about their diagnosis and prognosis and be actively engaged in their treatment decision-making. To ensure adherence with HCV treatment and an understanding of the risks involved, a full and comprehensive assessment of the patient's cognition, judgment, and reasoning should be performed before treatment is offered. An integrated risk-benefit assessment incorporating information from

the psychiatric evaluation, liver biopsy, HCV disease parameters, available psychosocial support, and the patient's treatment preferences may allow the hepatologist and the psychiatrist to more confidently recommend either the initiation or the postponement of HCV treatment. This is particularly true in the case of infection with HCV genotype 1. Such analysis offers the patient the opportunity to participate in the discussion and make an informed decision about interferon-α treatment. In cases in which HCV treatment is postponed, emphasis should be placed on abstaining from alcohol and drug use and maintaining the health of the liver.[33]

From a psychiatrist's perspective, the following factors would influence patient selection for HCV treatment: the clinical course of the bipolar illness, compliance with medications, frequency of previous hospitalizations, and presence of a functional emotional and psychosocial support system.[2,33] A next-of-kin or significant other can closely monitor the patient for symptom exacerbation and may provide substituted decision-making in cases of incapacitation. Another factor to consider is that comorbid substance abuse may be present in as many as 50% of patients with HCV and bipolar disorder,[5,6] and abstinence from substance use for at least 6 months not only is recommended by the National Institutes of Health consensus guidelines for treatment of HCV but has been found to improve the probability of achieving viral clearance.[34,35] Random urine drug screens may be justified in such high-risk patients to ensure that they remain abstinent, as interferon-α therapy might induce a relapse into substance use.[34,35]

There are no systematic studies on the use of mood stabilizers (i.e., lithium, lamotrigine) in patients with HCV infection; however, agents that are renally excreted are thought to be safe in patients with HCV infection. Recently, the use of valproate with careful monitoring of liver function tests has been found to be safe in patients with HCV.[36] The concomitant use of carbamazepine and oxcarbazepine with interferon-α is contraindicated due to the increased risk of bone marrow suppression. The use of antidepressants for the treatment of interferon-α–induced depression in HCV has been studied extensively and found to be generally acceptable. Several open-label studies have found that citalopram and paroxetine were effective in the treatment of and prophylaxis against interferon-α–induced depression.[28,37,38] However, a prophylactic approach using antidepressants to prevent interferon-α–induced affective symptoms may not be justified in all patients on the bases of the current literature and clinical experience. Such prophylactic approaches may expose too many patients to the potential adverse effects of antidepressants in a population with already compromised liver function and a propensity toward coagulopathies.[39,40]

There are no systematic studies on the use of typical and atypical antipsychotics in patients with HCV infection. Clinical experience suggests that their use is generally safe and well tolerated when they are given to patients with HCV or coadministered with interferon-α–based therapies. However, the following 2 exceptions are noteworthy: first, the concomitant use of interferon-α and clozapine significantly increases the risk for neutropenia and fatal agranulocytosis and is contraindicated[41]; second, the metabolic adverse effects of olanzapine (and to a lesser degree other atypical antipsychotics like risperidone, quetiapine, aripiprazole, or ziprasidone) may be particularly problematic in patients with HCV.[42] Both HCV infection and atypical antipsychotic use have been associated with abnormal glucose metabolism and the development of diabetes mellitus. These associations demand attention to patient selection and frequent monitoring of fasting glucose when using atypical antipsychotics in patients in HCV infection.

I urge that readers use caution when applying the experience from these case reports to the treatment of patients with HCV infection and comorbid bipolar disorder. A closely integrated medical and psychiatric care model needs to be in place before HCV treatment is offered, as these patients may deteriorate rapidly if not monitored closely. Patient selection should be conducted in an interdisciplinary fashion incorporating factors relevant to both HCV and the psychiatric illness. There is a need for more research to establish the optimum management strategies (e.g., preemptive dose increase of mood stabilizers or atypical antipsychotics, use of prophylactic antidepressants, preemptive hospitalization). Future advances may improve HCV clearance rates and thus justify treating all HCV patients regardless of psychiatric comorbidity.

Drug names: aripiprazole (Abilify), carbamazepine (Equetro, Carbatrol, Tegretol, and others), citalopram (Celexa and others), clonazepam (Klonopin and others), clozapine (Clozaril, Fazaclo, and others), lamotrigine (Lamictal and others), levothyroxine (Synthroid, Novothyrox, and others), olanzapine (Zyprexa), oxcarbazepine (Trileptal), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), ribavirin (Rebetol, Ribasphere, and others), risperidone (Risperdal), sertraline (Zoloft), ziprasidone (Geodon).

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