and are deeply grateful for the enormous amount that these therapists have taught us about suicidal patients and their treatment.

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Interferon for Hepatitis C Patients With Psychiatric Disorders

TO THE EDITOR: We read with great interest the recent clinical case conference by Chiadi U. Onyike, M.D., M.H.S., et al. (1). Practicing psychiatrists are increasingly asked to assist gastroenterologists in making risk-benefit assessments regarding interferon alpha (IFN-α) treatment of patients with chronic hepatitis C virus infection. Reluctance to treat patients with hepatitis C virus and psychiatric illnesses with IFN-α is certainly understandable because of concerns of precipitating or worsening psychiatric comorbidity. However, the exclusion of patients with comorbid hepatitis C virus infection and psychiatric illnesses is not justifiable without a comprehensive risk-benefit analysis.

Although Mr. C came to the psychiatry service after the decision to treat him with a second course of IFN-α had been made, Dr. Onyike et al. appropriately raised the question of whether he should be offered yet another trial of IFN-α in the future despite neuropsychiatric toxicity associated with his first two courses of IFN-α. The authors suggested that the answer was yes. We contend that critical information regarding this determination is missing from the case discussion. Specifically, Mr. C's hepatitis C virus genotype and viral load bore directly on this risk-benefit analysis.

It is estimated that 70% of the U.S. population with hepatitis C virus is infected with genotype 1, and the remaining 20%–30% are infected with genotypes 2 or 3 (2). Pegylated IFN-α with ribavirin achieves sustained virological response (i.e., complete eradication of hepatitis C virus; absent hepatitis C virus viral load 6 months after IFN-α treatment is completed) in 50%–59% of the patients with genotype 1 and 80%–90% of the patients with genotypes 2 and 3 (2, 3). These sustained response rates, however, were derived from large clinical trials (3–5) and may not be applicable to the hepatitis C virus-infected population with psychiatric illness because these trials excluded all patients with a history of psychiatric illness and substance abuse. The following factors have all been associated with reduced sustained virological response rates: male gender, African American race, high body mass index, advanced age (>40 years), high hepatitis C viral load, and hepatitis C virus genotype 1 (6).

Similarly, several risk factors are thought to increase the probability of emergent psychiatric comorbidity during IFN-α treatment (7–9). Those factors include the following: a previous history of any psychiatric illness, a history of substance abuse, a family history of psychiatric illnesses, and a history of suicidal ideation (8). Although these factors are not well validated, they were used as exclusion criteria in several large hepatitis C virus clinical trials (3–5). The patient described by Dr. Onyike et al. would have had an estimated 50%–60% chance of achieving sustained virological response if infected with genotypes 2 or 3 but only a 10%–20% chance of achieving sustained virological response if infected with genotype 1. These predictions factor in the lower remission rates for an African American man and for patients with a higher body mass index (6). Furthermore, this patient would have had a greater likelihood of developing psychiatric complications because of his previous and family psychiatric histories (7, 9). The high probability of IFN-α-induced psychiatric comorbidity coupled with a hepatitis C virus genotype 1 and a high viral load would make the case for a future course of IFN-α difficult to justify.

The practice of excluding patients with hepatitis C virus and psychiatric illnesses from IFN-α treatment is stigmatizing (8) and will result in substantial morbidity and mortality for a vulnerable population no less deserving of treatment than patients with hepatitis C virus without psychiatric illnesses. Nonetheless, evidence-based patient selection is paramount when endeavoring to treat patients with comorbid psychiatric illnesses and hepatitis C virus to minimize the morbidity and mortality associated with IFN-α treatment. Despite the absence of a consensus regarding when IFN-α treatment should be withheld (either because of the low estimated likelihood of sustained virological response and/or the high probability of psychiatric morbidity), clinicians must still make an individualized and balanced risk-benefit analysis incorporating hepatitis C virus disease-specific factors as well the potential for psychiatric complications before offering IFN-α treatment.

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TO THE EDITOR: We read with interest the report by Dr. Onyike et al. involving a patient who developed mania while being treated with pegylated IFN-α and ribavirin. This is important since pegylated IFN-α is used in the treatment of chronic hepatitis C and other viral illnesses and has been associated with a significantly lower incidence of depression in comparison to unmodified IFN-α (1). While pegylated IFN-α may also be associated with a reduced incidence of mania, it is important for clinicians to be aware of this potential side effect. Neuropsychiatric disturbances usually occur after repeated IFN-α exposure (days or months) or upon treatment discontinuation. The latter may have been an important factor in the reported case since the patient missed many doses of IFN-α before starting the new course of pegylated IFN-α. Since preclinical studies have shown that IFN-α decreases dopamine in the brain (2), a sudden withdrawal from IFN-α may have induced a surge of this neurotransmitter, which has been hypothesized to be important in mania.

The authors minimized the likelihood that the selective serotonin reuptake inhibitor (SSRI) fluoxetine may have been implicated in the switching process since it was initiated years earlier and the dose was doubled over 4 months before this mood alteration. We take the opposite view, suggesting that fluoxetine may have contributed to the switching process. This opinion is partially based upon recent work by Ramasubbu (3), who described two depressed patients—one with unipolar depression and the other with dysthymia. In both instances, the patient became hypomanic when the SSRI (sertraline and paroxetine, respectively) dose was significantly increased, and the hypomania resolved with subsequent dose reduction. In these cases, the switching occurred approximately 1 month after the dose increase, similar to the case by Dr. Onyike et al., in which mania developed 4 months after the SSRI dose increase.

In addition to less serious side effects (e.g., gastrointestinal symptoms), antidepressants, including SSRIs, are capable of inducing hypomanic/manic episodes (4). This is a particular concern in patients with a history of bipolar disorder but has also been described in nonbipolar depressives (3), including the patient presented by Dr. Onyike et al. Patients with a previous history of IFN-α-induced depression may also prove to be especially vulnerable.

Gastroenterologists frequently treat patients with chronic hepatitis C with a history of bipolar or major depressive disorder. These physicians should consider consultation with a psychiatrist since many of these patients are already taking antidepressants and/or necessitate prescriptions of antidepressants to prevent and/or treat IFN-α-induced depression. A psychiatrist would more effectively be able to monitor and/or intervene if a hypomanic/manic episode occurred.

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TO THE EDITOR: The article by Dr. Onyike et al. detailing the case of mania caused by pegylated IFN-α with ribavirin was a thorough review. It will be particularly useful for those who have not yet treated a patient experiencing these adverse psychiatric consequences from IFN-α.

However, I saw one recommendation in the review that I disagree with. In the appendix of the article, there was a table with treatment recommendations for a patient experiencing manic symptoms from IFN-α treatment. I noticed that gabapentin was one of the agents. Although there have been numerous case reports and open-label studies citing the usefulness of gabapentin for mania, a double-blind, placebo-controlled trial is the gold standard and the ultimate "litmus test." In 2000, Pande and colleagues (1) observed no difference between gabapentin and placebo for the adjunctive treatment of mania. If this trial failed to show an effect as an adjunct, I don't see how gabapentin could be used as monotherapy either.

When considering that the National Public Radio network has broadcast to the general public four times in 2003 alone regarding a lawsuit involving gabapentin for bipolar disorder (2), I believe it is inadvisable to use this agent for mania—medication-induced or not.

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Dr. Onyike and Colleagues Reply

TO THE EDITOR: We agree with Dr. Rifai et al. that a decision to prescribe pegylated IFN-α 2a with ribavirin to patients with a history of psychiatric disorder requires a comprehensive risk-benefit assessment. However, exactly which data should go