Mania During Treatment of Chronic Hepatitis C With Pegylated Interferon and Ribavirin

Chiadi U. Onyike, M.D., M.H.S.

John O. Bonner, R.N.

Constantine G. Lyketsos, M.D., M.H.S.

Glenn J. Treisman, M.D., Ph.D.

Infection with the hepatitis C virus is an important public health problem, causing about 170 million cases of chronic hepatitis C worldwide (1) and 2.7 million cases in the United States (2). The disease has become the leading cause of liver failure and liver transplantation in the United States (3) and accounts for more than $5.46 billion in treatment costs (4). Given the magnitude of these effects, it is not surprising that the medical community has devoted considerable resources to combating hepatitis C. These efforts have led to important clinical and pharmacological developments in the management of chronic hepatitis C (5).

"The time has come to develop and disseminate systematic approaches for the psychiatric management of patients with chronic hepatitis C."

The most effective pharmacological therapy for chronic hepatitis C is pegylated interferon-alpha (IFN-α) combined with ribavirin, which leads to sustained viral remission rates of 54%–80%, depending on hepatitis C virus genotype (6, 7). Unfortunately, interferon is associated with adverse effects that can lead to additional morbidity and noncompliance, dose reduction, or termination of treatment (8). These include neuropsychiatric symptoms and syndromes such as fatigue, irritability, emotional lability, anxiety, insomnia, depression, delirium, cognitive impairment, mania, and psychosis (9–12). Suicide attempts and completions have been reported (13–16). Serious neuropsychiatric complications such as severe depression, psychosis, and suicidal states usually lead to permanent discontinuation of interferon.

Until recently, physicians avoided prescribing interferon for patients with mental illness. In addition, stringent inclusion criteria excluded patients with mental illness from participation in treatment studies, thereby limiting the applicability of findings to their clinical care (17). On the positive side, high sustained viral remission rates and lack of treatment alternatives led to increasing pressure to offer interferon plus ribavirin to all patients, including those with psychiatric disorders (18) and ongoing substance use (19), and to broaden the inclusion criteria for treatment studies (17).

In 2002, a National Institutes of Health Consensus Development Conference (5) recommended that interventions and research be extended to previously excluded populations, such as individuals with mental illness and substance use disorders. These recommendations are timely for the following reasons. First, the prevalence of chronic hepatitis C virus hepatitis is high among patients with psychiatric disorders (20–24). Indeed, the most important risk factor for acquiring hepatitis C virus infection in the United States is injection drug use (2). Injection drug use accounts for about 50% of new hepatitis C virus infections, and 50%–60% of users acquire the infection within the first 3 months of regular use (25, 26). Second, there is evidence that patients with mental illness can successfully complete a course of treatment (27). Without treatment, many cases will progress to liver cirrhosis, liver failure, and, possibly, hepatocellular carcinoma. Liver transplantation is available to patients who develop these complications, but transplantation and post-transplantation care is more difficult to manage, less accessible, and costlier than a 24- or 42-week course of combination pegylated IFN-α and ribavirin therapy. Furthermore, hepatitis C virus recurrence is virtually universal in patients who undergo liver transplantation (28, 29).

Clearly, all patients with chronic hepatitis C should be offered pegylated IFN-α and ribavirin treatment. With the recent expert consensus, patients with chronic hepatitis C should now receive interferon and ribavirin regardless of psychiatric status. As more patients are treated, interferon-induced psychiatric illness will likely become an increasingly important clinical problem. At present, there are few data to guide the long-term treatment of patients with chronic hepatitis C who develop secondary psychiatric disorders during interferon treatment.

In this report, we present the case of Mr. C, who developed a psychotic mania in early February 2002, after receiving pegylated IFN-α and ribavirin for a few weeks. This case underscores the risk for manic psychosis during interferon treatment. More important, this case illustrates the difficulties associated with completing interferon treatment after an episode of severe psychosis. In the discussion we review these clinical issues and suggest strategies for the management of interferon-induced manic psychosis.

Case History

Mr. C is a 39-year-old African American man with a remote history of injection drug use who was referred to the general psychiatry inpatient unit of Johns Hopkins Hospital for evaluation and treatment of psychotic mania characterized by elation, irritability, grandiosity, impulsive generosity, insomnia, hypersexuality, delusions of external control, and excessive religiousness. These symptoms occurred within 3 weeks of his receiving treatment with pegylated IFN-α and ribavirin for chronic hepatitis C.

Past History

Mr. C's father's personal and psychiatric history was unknown. His mother, who died in her 50s from complications of diabetes mellitus, had abused alcohol. Mr. C had seven siblings; six had abused illicit drugs (one brother died in drug-related violence and another was still in active addiction), but no sibling had any other psychiatric history. A maternal aunt suffered depression; another aunt died of Alzheimer's disease. Several cousins were addicted to heroin and cocaine.

Mr. C is the product of a normal pregnancy and birth. He had normal developmental milestones and a happy childhood. The family was lower-middle-class, his mother a single parent who worked two jobs. Mr. C dropped out of school in the 10th grade because of addiction to illicit drugs. He has worked as a truck driver for 12 years. He had a teenage son from his first marriage and lived with his fiancée, their infant son, and his two stepsons. A few years ago he was arrested for domestic violence, but charges were dropped. He has no current legal problems. He is a committed Christian who attends church services and Bible study regularly.

Mr. C smoked cigarettes occasionally in his early teens and started smoking marijuana at age 11 or 12. He started drinking alcohol at age 13 and abusing heroin and cocaine at age 14; physiological and psychological dependence on these substances quickly developed and continued until 1993. He has been abstinent from all substances, including cigarettes, for 11 years and is very actively involved in peer-led rehabilitation programs.

Mr. C vaguely recalled a positive hepatitis C virus antibody test, possibly when he was 19. He was rediagnosed with hepatitis C virus infection 5 years ago during a self-referred screening examination for sexually transmitted disease. He has chronic hepatitis C and is HIV negative. He is receiving dietary treatment for diabetes mellitus but has been treated with insulin in the past. He has no known environmental or medication allergies.

His medications at admission were fluoxetine, 40 mg, in the morning; pegylated IFN-α, 180 μg once a week; ribavirin, 1200 mg once a week; and zolpidem, 10 mg at bedtime (he had been taking up to 30 mg for several nights).

During the early months of recovery from addiction, Mr. C experienced euphoria and heightened optimism for a few weeks after a religious conversion. He did not experience irritability, grandiosity, insomnia, restlessness, elevated libido, or other phenomena that would suggest affective disturbance. He has since maintained a satisfying spiritual life. Five years ago, he broke up with a girlfriend because she was actively using illicit drugs. He grieved the loss of the relationship, struggled with drug cravings (but did not resume drug use), and developed feelings of anger and despair. He eventually became suicidal and homicidal and was hospitalized in a psychiatric unit for about 7 days. He was treated for depression with fluoxetine, 20 mg/day. He continued to take fluoxetine and experienced no further episodes of depression.

Present Illness

Mr. C saw a hepatologist early in 2001 as recommended by his physician; the workup included liver biopsy, which showed stage 3 precirrhotic disease. Treatment with IFN-α and ribavirin (three times a week) was started in August 2001. Within the first few weeks of treatment Mr. C developed fatigue and a flulike syndrome. He also developed sadness and tearful episodes. His physician increased the dose of fluoxetine to 40 mg/day, and his mood improved. There was some evidence of viral suppression after 4 months, at which time the hepatologist recommended a switch to pegylated IFN-α and ribavirin, which had recently become available. While trying to fill the new prescription, Mr. C missed enough doses of IFN-α and ribavirin to be given a drug holiday. The fatigue and the flulike symptoms remitted.

He started to take pegylated IFN-α and ribavirin injections (once weekly) in January 2002. Within 3 weeks, he developed restlessness and insomnia as well as episodes of unprovoked laughter, irritability, and tearfulness. These symptoms evolved into euphoria, impulsive generosity, increased libido, excessive religiousness, thought disorder (flight of ideas), ideas of reference, grandiose delusions, and delusions of external control (by mobile phone and telepathic communication).

He confronted colleagues at work over religion; later he obeyed a "telepathic message" and quit his job. In the week before his hospitalization, he went 4 days without eating. He was belligerent when his family confronted him regarding his bizarre behavior, and he threatened his fiancée for "having sex with others." He continued to take pegylated IFN-α and ribavirin despite instructions from his hepatologist to stop, and he did not comply with referral to a psychiatrist. After almost 2 weeks of psychosis, his fiancée took him to the emergency room for evaluation. He came to the emergency room in an agitated and disorganized state and was treated with haloperidol and diphenhydramine, with calming effect, before being involuntarily admitted to the inpatient unit.

On admission, Mr. C was a tall, overweight African American man. He was alert and cooperative. He was not agitated. He was talkative, and his associations were loose. He was euphoric and grandiose. He denied having hallucinations, and delusions were not elicited. He denied suicidal or homicidal ideation as well as aggressive impulses. He did not have obsessions, compulsions, or phobias. Insight and judgment were poor. He could not answer questions on the Mini-Mental State Examination (MMSE). On physical examination, vital signs were found to be normal, and he looked healthy. The remainder of the physical examination was unremarkable.

The initial formulation focused on Mr. C's mania superimposed on a previous history of depression. The religious conversion was felt to be an earlier episode of mania, and Mr. C was diagnosed with bipolar disorder, type I, manic episode. The possibility that pegylated IFN-α triggered this mania was considered, given the temporal

association and published reports of mania during interferon treatment. We did not think that fluoxetine precipitated the mania because he had been taking it for a few years and the dose increase had occurred several months earlier. Given his sustained alertness and a presentation typical for mania, delirium was considered unlikely. Resumption of heroin and cocaine use was excluded by history and laboratory testing during the emergency room evaluation.

The initial goals for Mr. C's treatment were to establish a diagnosis, interrupt the mania, encourage his participation in treatment (through discussion of the reasons for hospitalization, illness education, and family involvement), and initiate appropriate pharmacotherapy.

Admission laboratory tests included CBC with differential, metabolic panel, tests of liver and thyroid function, urinalysis, urine toxicology screen, serum vitamin B_{12} and folate levels, and RPR. Thyrotropin (TSH) level was 0.36 μIU/ml and a repeat TSH level was 0.53 μIU/ml (range=0.50–4.50); free T_4 and T_3 were normal. Alanine aminotransferase (ALT) was 47 IU/liter and aspartate aminotransferase (AST) was 43 U/liter. Urinalysis revealed gross hematuria. Results of other tests were negative. Brain computerized tomography (CT) was normal.

Mr. C cooperated with evaluation and treatment. Pegylated IFN-α, ribavirin, fluoxetine, and zolpidem were discontinued. He received haloperidol, 5 mg orally at bedtime, for the psychosis. The next day mild dystonia (jaw and neck stiffness) was relieved by a single oral 1-mg dose of benztropine, and the haloperidol dose was then decreased to 1 mg at bedtime. On the second hospital day, Mr. C gave voluntary consent for hospitalization. Lithium was prescribed at an initial oral dose of 150 mg twice daily. He participated actively in illness education, therapeutic groups, and occupational therapy.

Ultrasound and CT scan of the kidneys revealed a benign cyst in the right kidney and a smaller cyst in the lower pole of the left kidney. A repeat urinalysis showed resolution of the hematuria; further evaluation was deferred to his primary physician. By the third day, the mania had remitted. Lithium was increased to 300 mg twice daily. Serum ALT and AST levels were normal. On the fourth day, haloperidol was discontinued and he was discharged home. The discharge plan included follow-up care with his physician and his hepatologist.

Follow-Up

Mr. C was to see the outpatient psychiatrist a week later. A few days after discharge, he developed nausea, malaise, and abdominal cramping. The outpatient psychiatrist (C.U.O.) reduced the lithium dose to 300 mg/day, and the symptoms resolved. Mr. C was seen in the hepatitis psychiatry clinic several days later in the company of his fiancée, who reported that he had completely recovered and was in his usual mental and physical state.

During the office visit, Mr. C was calm, alert, attentive, and cooperative. He was talkative, but his verbal associations were normal. He had many questions about his recent mania and about lithium. He had a normal mood and a normal range of affect. Self-attitude, level of energy, and libido were normal. He denied suicidal, homicidal, and aggressive thoughts or impulses. He denied having hallucinations. Delusions and experiences of passivity were not elicited. He did not have obsessions, compulsions, or phobias. Insight and judgment were good. On the MMSE he scored 30 of 30.

Mr. C's psychiatric history was carefully reviewed during the initial office visit. He described his religious conversion 9 years earlier. That conversion experience differed qualitatively from the recent episode of mania. There had been no behavioral or perceptual disturbances, no grandiosity or delusions, and he had maintained his usual social and work habits. He had sought and received spiritual mentorship from his pastors, and under their guidance his spirituality had matured over the years. On the basis of this information, we concluded that he had not had a previous episode of mania. Thus the recent episode of mania was his first, attributable to treatment with pegylated IFN-α, and the DSM-IV diagnosis of substance-induced mood disorder, manic type, was made.

Mr. C did not want to take medication indefinitely unless absolutely necessary. We decided to continue lithium treatment until he had resumed work and had several additional months of social and psychological stability. Fluoxetine was not restarted because of our concern that doing so might lead to recurrence of mania. Mr. C agreed initially with this approach, but he stopped taking lithium a few weeks later. He continued follow-up visits and has remained stable at his pre-episode baseline since. He has returned to work, is now married, and he and his wife have another child.

Mr. C has declined pegylated IFN-α and ribavirin because of the mania experience, and his physician concurs because liver transaminase levels were normal at follow-up several months ago. Mr. C still maintains an active spiritual life; his confidence in his spirituality was initially shaken—this came up in psychotherapy, and he also sought spiritual counseling from his pastor—but that has resolved. He still participates actively in substance abuse rehabilitation programs, and he now does voluntary guidance counseling for prisoners about to be released as well as recently released prisoners.

Discussion

Treatment of chronic hepatitis C can be very difficult for patients because of the many complications of interferon and ribavirin. The neuropsychiatric complications of interferon cause significant distress and morbidity and are among the most common reasons for treatment discontinuation (30). Until recently, mental illnesses were considered contraindications to interferon treatment because it was believed that they increased the risk for serious neuropsychiatric complications. Today there is wide agreement that all patients are eligible for interferon and ribavirin treatment, regardless of psychiatric, HIV, or other status (5).

Mr. C was offered treatment with pegylated IFN-α and ribavirin despite an earlier episode of interferon-related depression and a hospitalization for suicidal depression years earlier. Unfortunately, the emergence of psychotic mania led to discontinuation of treatment. Mania is an acknowledged complication of interferon treatment. The incidence remains unknown, but many cases have been described in the English-language literature (31–42).

There currently is no evidence that previous history of depression and taking antidepressants are risk factors for

the development of interferon-induced mania. However, cases have been reported of interferon-induced depression followed by mania (43, 44). Since mania usually occurred after *discontinuation* of interferon in these cases, these observations are ambiguous—they may represent the evolution of an interferon-induced bipolar disorder or the behavioral expression of putative neuropharmacological effects of interferon discontinuation.

Clinicians have also observed that the risk for mania (and other neuropsychiatric complications) during interferon treatment may be dose dependent (45) and may also be higher in patients with subclinical neurological abnormalities (46).

In Mr. C's case we note both that mania occurred during treatment with a higher potency formulation of interferon and followed an episode of interferon-induced depression by several months. It would not be unreasonable to ask if Mr. C may not have had a "latent" bipolar disorder, given the previous hospitalization for severe depression. The idea of a "latent" bipolar disorder seems attractive, but it does not explain the timing of mania here (and in other cases reported) unless one allows for interferon being the "trigger," which then leads back to the conclusion that interferon induced the mania. Ultimately, the precise mechanisms involved in the evolution of mania during interferon treatment remain a matter of speculation, but several lines of evidence have pointed to neuroendocrine, neurotransmitter, and cytokine pathways (47–49).

Dose reduction and discontinuation of interferon can be effective interventions for mania, depression, and other interferon-related neuropsychiatric syndromes (45), but when the psychopathology is severe or persistent, pharmacotherapy with psychotropic agents is necessary. Another approach is to treat mania without dose reduction or discontinuation of interferon. For example, in a prospective study of medical clinic referrals (50), 10 patients with mood disturbance, auditory hallucinations. and delusions completed IFN-α treatment after these syndromes were treated with neuroleptics, lithium, or carbamazepine. Another report (34) described three cases of mania during high-dose IFN-α treatment for malignant melanoma; one patient was acutely treated with perphenazine, lithium, and lorazepam, the other two with gabapentin. IFN-α treatment continued and was completed several months later, with the three patients stabilized on concurrent gabapentin treatment. Thus, interferon-induced mania responds to the pharmacological agents typically used for treating mania.

The reports above (34, 50) and several others (31, 33, 37, 38, 40, 41) document treatment successes with haloperidol and other "typical" neuroleptics, risperidone and olanzapine ("atypical" neuroleptics), lithium, gabapentin, and carbamazepine. There is only one report of treatment of interferon-induced mania with valproic acid (40), presumably because the risk of hepatotoxicity associated with the drug discourages its use; however, a recently reported retrospective analysis suggests that mentally ill patients with chronic hepatitis C can be treated safely with valproic acid (51).

Should Mr. C continue to take lithium (or other psychotropic medication) to prevent recurrence of mania? There is only one reported case of mania recurrence after IFN-α was stopped because of an interferon-induced first episode (37), but at least one case of persistent mania has also been reported (38). Most reports describe illness resolution within a month. One group (50) observed residual anxiety, insomnia, and hypothymia in two of 10 subjects with psychosis. In another case (31), haloperidol was discontinued after 1 month and the patient was doing well 6 months later. Another patient remained stable several months after psychiatric medicines were discontinued (36), and yet another remained asymptomatic at 12 months (33), although it is unclear from the report whether risperidone was discontinued.

Overall, the evidence suggests that maintenance treatment with psychiatric medicines is not necessary for most patients with no previous history of psychosis. Patients with a previous history of psychiatric illness are usually maintained on their medications. As of October 2003, Mr. C had remained asymptomatic for more than 18 months after haloperidol and lithium were discontinued.

Should Mr. C receive interferon treatment in the future? Given that chronic hepatitis C is frequently progressive (52), disruption of treatment is a serious consequence of interferon-induced neuropsychiatric illness. Patients and their physicians are faced with a dilemma when interferon treatment is discontinued under such circumstances. However, there is evidence to support a rechallenge with interferon. As noted earlier, managing interferon-induced mania may not require discontinuation of interferon.

There are also suggestive data from the literature on interferon-induced depression. First, treatment with IFN-α does not necessarily increase the risk for depression in patients with preexisting mental illness (53, 54). Second, case reports (55–60) and prospective studies (61, 62) have shown that treating depression allows IFN-α treatment to continue. Third, successful resumption of IFN-α after treatment of interferon-induced mood disorder has also been reported. Schafer et al. (63) reported that addition of an antidepressant enabled a patient with schizoaffective psychosis who had developed depression to complete a course of IFN-α. Fourth, results from prospective studies (64, 65) indicate that antidepressant treatment may prevent interferon-induced depression.

There have been no systematic studies evaluating pharmacological prevention of interferon-induced mania or psychosis, but anecdotal data exist. One report described a patient with well-managed chronic schizophrenia who completed a course of IFN-α (66). In another case (43), psychiatric medicines were not prescribed: an episode of interferon-induced depression that resolved after IFN-α was stopped was followed by one of euphoric mania that remitted in 3 weeks, and then the patient resumed and completed a course of lower-dose IFN-α.

From the foregoing, it seems reasonable to consider continuing (or resuming) interferon treatment, as long as interferon-induced depression or mania has been treated and ongoing psychiatric care is available. When interferon is continued or resumed under such circumstances, three approaches are available: 1) Prescribe psychiatric medicines until interferon treatment is completed (whether this is treatment or "prophylaxis" depends on timing). 2) Prescribe a lower dose of interferon. 3) Combine a "watchful waiting" stance with close monitoring. Which approach is best is an empirical question that should be settled in clinical trials, but it is likely most psychiatrists would favor a "prophylactic" approach. If Mr. C eventually decides to resume pegylated IFN-α and ribavirin, we would certainly consider prophylaxis with lithium or low-dose haloperidol.

Recommendations

The literature reviewed in this report suggests an approach to the longitudinal management of first-episode mania in patients treated with interferon (summarized in Appendix 1). At present, screening of all patients with chronic hepatitis C for mental illness before the initiation of interferon treatment is not likely to be useful or cost-effective. There are no established risk indicators on which to base a strategy for identifying patients who may benefit from close monitoring by a psychiatrist. However, when a candidate for interferon treatment is known to have a mental illness, psychiatric monitoring is indicated. If the patient is unstable, preexisting mental illness should be treated before interferon is prescribed.

Obviously, further research is necessary for developing definitive guidelines for the short-term and long-term management of interferon-induced mania. Systematic studies are needed to determine risk estimates and risk indicators for the development (and recurrence) of interferon-induced mania. Studies will also be needed to facilitate early detection of the neuropsychiatric complications of interferon and to optimize therapeutic interventions for these conditions. It is also important to define the clinical criteria for maintaining or resuming interferon therapy when interferon-induced mania has occurred. Finally, identification of the molecular mechanisms by which interferon produces mania and depression may illuminate our general understanding of the pathophysiological processes underlying mood disorders.

Conclusions

As the population burden of chronic hepatitis C increases over the next two decades (67), increasing numbers of patients will receive pegylated IFN-α and ribavirin. Interferon treatment is associated with substantial risk for neuropsychiatric illness, including depression and mania. Since treatment for chronic hepatitis C will also be extended to previously neglected populations, including the mentally ill, psychiatrists can expect to have an increasingly important role in the management of this disease. Psychiatrists will treat preexisting mental illness, identify and refer patients for treatment of chronic hepatitis C, and manage neuropsychiatric complications of interferon. The time has come, therefore, to develop and disseminate systematic approaches for the psychiatric management of patients with chronic hepatitis C.

APPENDIX 1. An Approach to the Management of First-Episode Mania in Patients Receiving Pegylated Interferon for Chronic Hepatitis C

- Consider maintaining interferon while treating mania; reduce dose or discontinue interferon when mania is severe.
- Mania can be treated with typical or atypical neuroleptics, lithium, gabapentin, or carbamazepine. Valproic acid should be used cautiously because of the risk for hepatotoxicity.
- Decide whether to resume interferon therapy after mania has remitted (relevant data include seriousness of the manic episode and severity of liver disease).
- Psychotropic medications should be continued (or resumed) if interferon treatment is restarted.
- Psychotropic medications can be discontinued within a month of mania resolution if interferon treatment has been abandoned.
- Psychotropic medications should be discontinued soon after completion of interferon treatment.
- Follow-up should be maintained for 6–12 months after discontinuation of psychotropic medications.
- Indefinite psychiatric follow-up is indicated for patients with persistent symptoms or preexisting mental illness.

Received April 25, 2003; revision received Oct. 14, 2003; accepted Oct. 31, 2003. From the Department of Psychiatry and Behavioral Sciences and the Department of Medicine, School of Medicine, and the Department of Mental Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore. Address correspondence to Dr. Onyike, Osler 320, Johns Hopkins Hospital, 600 North Wolfe St., Baltimore, MD 21287; conyike1@jhem.jhmi.edu (e-mail).

The authors thank the patient whose case is presented for his support and encouragement of this work.

References

1. Global surveillance and control of hepatitis C: report of a WHO consultation organized in collaboration with the Viral Hepatitis Prevention Board, Antwerp, Belgium. J Viral Hepat 1999; 6:35–47
2. Alter MJ, Kruszon-Moran D, Nainan OV, McQuillan GM, Gao F, Moyer LA, Kaslow RA, Margolis HS: The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med 1999; 341:556–562
3. Lauer GM, Walker BD: Hepatitis C virus infection. N Engl J Med 2001; 345:41–52
4. Leigh JP, Bowlus CL, Leistikow BN, Schenker M: Costs of hepatitis C. Arch Intern Med 2001; 161:2231–2237
5. Management of Hepatitis C: 2002: Consensus Statements: NIH Consensus Development Program, vol 19, number 1. Bethesda, Md, National Institutes of Health, 2002, pp 1–44
6. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albrecht JK: Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial. Lancet 2001; 358:958–965
7. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL Jr, Haussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J: Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002; 347:975–982
8. Fried MW: Side effects of therapy of hepatitis C and their management. Hepatology 2002; 36(5, suppl):S237–S244

9. Trask PC, Esper P, Riba M, Redman B: Psychiatric side effects of interferon therapy: prevalence, proposed mechanisms, and future directions. J Clin Oncol 2000; 18:2316–2326
10. Lerner DM, Stoudemire A, Rosenstein DL: Neuropsychiatric toxicity associated with cytokine therapies. Psychosomatics 1999; 40:428–435
11. Nozaki O, Takagi C, Takaoka K, Takata T, Yoshida M: Psychiatric manifestations accompanying interferon therapy for patients with chronic hepatitis C: an overview of cases in Japan. Psychiatry Clin Neurosci 1997; 51:175–180
12. Yokoyama A, Kimura Y, Shigemura J: Psychiatric side effects of interferon. J Toxicol Sci 1996; 21:93–96
13. Fukunishi K, Tanaka H, Maruyama J, Takahashi H, Kitagishi H, Ueshima T, Maruyama K, Sakata I: Burns in a suicide attempt related to psychiatric side effects of interferon. Burns 1998; 24: 581–583
14. Ademmer K, Beutel M, Bretzel R, Jaeger C, Reimer C, Clemens J: Suicidal ideation with IFN-alpha and ribavirin in a patient with hepatitis C. Psychosomatics 2001; 42:365–367
15. Janssen HL, Brouwer JT, van der Mast RC, Schalm SW: Suicide associated with alfa-interferon therapy for chronic viral hepatitis. J Hepatol 1994; 21:241–243
16. Fattovich G, Giustina G, Favarato S, Ruol A: A survey of adverse events in 11,241 patients with chronic viral hepatitis treated with alfa interferon. J Hepatol 1996; 24:38–47
17. Strader DB: Understudied populations with hepatitis C. Hepatology 2002; 36(5, suppl 1):S226–S236
18. Van Thiel DH, Friedlander L, Molloy PJ, Fagiuoli S, Kania RJ, Caraceni P: Interferon-alpha can be used successfully in patients with hepatitis C virus-positive chronic hepatitis who have a psychiatric illness. Eur J Gastroenterol Hepatol 1995; 7:165–168
19. Edlin BR: Prevention and treatment of hepatitis C in injection drug users. Hepatology 2002; 36(5, suppl 1):S210–S219
20. el-Serag HB, Kunik M, Richardson P, Rabeneck L: Psychiatric disorders among veterans with hepatitis C infection. Gastroenterology 2002; 123:476–482
21. Nguyen HA, Miller AI, Dieperink E, Willenbring ML, Tetrick LL, Durfee JM, Ewing SL, Ho SB: Spectrum of disease in US veteran patients with hepatitis C. Am J Gastroenterol 2002; 97:1813–1820
22. Yovtcheva SP, Rifai MA, Moles JK, Van der Linden BJ: Psychiatric comorbidity among hepatitis C-positive patients. Psychosomatics 2001; 42:411–415
23. Rosenberg SD, Goodman LA, Osher FC, Swartz MS, Essock SM, Butterfield MI, Constantine NT, Wolford GL, Salyers MP: Prevalence of HIV, hepatitis B, and hepatitis C in people with severe mental illness. Am J Public Health 2001; 91:31–37
24. Dinwiddie SH, Shicker L, Newman T: Prevalence of hepatitis C among psychiatric patients in the public sector. Am J Psychiatry 2003; 160:172–174
25. Garfein RS, Vlahov D, Galai N, Doherty MC, Nelson KE: Viral infections in short-term injection drug users: the prevalence of the hepatitis C, hepatitis B, human immunodeficiency, and human T-lymphotropic viruses. Am J Public Health 1996; 86:655–661
26. Thomas DL, Vlahov D, Solomon L, Cohn S, Taylor E, Garfein R, Nelson KE: Correlates of hepatitis C virus infections among injection drug users. Medicine (Baltimore) 1995; 74:212–220
27. Van Thiel DH, Friedlander L, De Maria N, Molloy PJ, Kania RJ, Colantoni A: Treatment of chronic hepatitis C in individuals with pre-existing or confounding neuropsychiatric disease. Hepatogastroenterology 1998; 45:328–330
28. Rosen HR: Hepatitis C in the liver transplant recipient: current understanding and treatment. Microbes Infect 2002; 4:1253–1258
29. Berenguer M: Natural history of recurrent hepatitis C. Liver Transpl 2002; 8(10, suppl 1):S14–S18
30. Kraus MR, Schafer A, Csef H, Faller H, Mork H, Scheurlen M: Compliance with therapy in patients with chronic hepatitis C: associations with psychiatric symptoms, interpersonal problems, and mode of acquisition. Dig Dis Sci 2001; 46:2060–2065
31. Altindag A, Ozbulut O, Ozen S, Ucmak H: Interferon-alpha-induced mood disorder with manic features. Gen Hosp Psychiatry 2001; 23:168–170
32. Bozikas V, Petrikis P, Balla A, Karavatos A: An interferon-alpha-induced psychotic disorder in a patient with chronic hepatitis C. Eur Psychiatry 2001; 16:136–137
33. Garcia-Pares G, Domenech C, Gil M: Psychosis induced by interferon-alpha. Psychosomatics 2002; 43:428–429
34. Greenberg DB, Jonasch E, Gadd MA, Ryan BF, Everett JR, Sober AJ, Mihm MA, Tanabe KK, Ott M, Haluska FG: Adjuvant therapy of melanoma with interferon-alpha-2b is associated with mania and bipolar syndromes. Cancer 2000; 89:356–362
35. Iancu I, Sverdlik A, Dannon PN, Lepkifker E: Bipolar disorder associated with interferon-alpha treatment. Postgrad Med J 1997; 73:834–835
36. Kanno A, Yamada M, Abe M, Okamoto Y: A case of interferon alpha-induced manic psychosis in chronic hepatitis C. Tohoku J Exp Med 1999; 187:79–82
37. Monji A, Yoshida I, Tashiro K, Hayashi Y, Tashiro N: A case of persistent manic depressive illness induced by interferon-alfa in the treatment of chronic hepatitis C. Psychosomatics 1998; 39:562–564
38. Schafer M, Boetsch T, Laakmann G: Psychosis in a methadone-substituted patient during interferon-alpha treatment of hepatitis C. Addiction 2000; 95:1101–1104
39. Strite D, Valentine AD, Meyers CA: Manic episodes in two patients treated with interferon alpha. J Neuropsychiatry Clin Neurosci 1997; 9:273–276
40. Howes OD, McKenzie KJ: Manic psychosis induced by long term alpha-interferon treatment for hepatitis. Int J Psychiatry Clin Pract 2000; 4:161–162
41. Thome J, Knopf U: Acute psychosis after injection of pegylated interferon alpha-2a. Eur Psychiatry 2003; 18:142–143
42. Kingsley D: Interferon-alpha induced "tertiary mania." Hosp Med 1999; 60:381–382
43. Carpiniello B, Orru MG, Baita A, Pariante CM, Farci G: Mania induced by withdrawal of treatment with interferon alfa. Arch Gen Psychiatry 1998; 55:88–89
44. Rossi A, Renzetti D, D'Albenzio L, Gianfelice D, Kalyvoka A, Rinaldi O: Case of mania induced by withdrawal of interferon-alpha in a patient affected by bipolar disorder. Psychiatry Clin Neurosci 2002; 56:647–648
45. Renault PF, Hoofnagle JH, Park Y, Mullen KD, Peters M, Jones DB, Rustgi V, Jones EA: Psychiatric complications of long-term interferon alfa therapy. Arch Intern Med 1987; 147:1577–1580
46. Adams F, Fernandez F, Mavligit G: Interferon-induced organic mental disorders associated with unsuspected pre-existing neurologic abnormalities. J Neurooncol 1988; 6:355–359
47. Licinio J, Kling MA, Hauser P: Cytokines and brain function: relevance to interferon-alpha-induced mood and cognitive changes. Semin Oncol 1998; 25(1, suppl 1):30–38
48. Valentine AD, Meyers CA, Kling MA, Richelson E, Hauser P: Mood and cognitive side effects of interferon-alpha therapy. Semin Oncol 1998; 25(1, suppl 1):39–47
49. Taylor JL, Grossberg SE: The effects of interferon-alpha on the production and action of other cytokines. Semin Oncol 1998; 25(1, suppl 1):23–29
50. Hosoda S, Takimura H, Shibayama M, Kanamura H, Ikeda K, Kumada H: Psychiatric symptoms related to interferon therapy for chronic hepatitis C: clinical features and prognosis. Psychiatry Clin Neurosci 2000; 54:565–572

51. Felker BL, Sloan KL, Dominitz JA, Barnes RF: The safety of valproic acid use for patients with hepatitis C infection. Am J Psychiatry 2003; 160:174–178
52. Alberti A, Chemello L, Benvegnu L: Natural history of hepatitis C. J Hepatol 1999; 31(suppl 1):17–24
53. Pariante CM, Orru MG, Baita A, Farci MG, Carpiniello B: Treatment with interferon-alpha in patients with chronic hepatitis and mood or anxiety disorders. Lancet 1999; 354:131–132
54. Mulder RT, Ang M, Chapman B, Ross A, Stevens IF, Edgar C: Interferon treatment is not associated with a worsening of psychiatric symptoms in patients with hepatitis C. J Gastroenterol Hepatol 2000; 15:300–303
55. Gleason OC, Yates WR: Five cases of interferon-alpha-induced depression treated with antidepressant therapy. Psychosomatics 1999; 40:510–512
56. Levenson JL, Fallon HJ: Fluoxetine treatment of depression caused by interferon-alpha. Am J Gastroenterol 1993; 88:760–761
57. Schramm TM, Lawford BR, Macdonald GA, Cooksley WG: Sertraline treatment of interferon-alfa-induced depressive disorder. Med J Aust 2000; 173:359–361
58. Goldman LS: Successful treatment of interferon alfa-induced mood disorder with nortriptyline. Psychosomatics 1994; 35: 412–413
59. Valentine AD, Meyers CA: Successful treatment of interferon-alpha-induced mood disorder with nortriptyline. Psychosomatics 1995; 36:418–419
60. Farah A: Interferon-induced depression treated with citalopram. J Clin Psychiatry 2002; 63:166–167
61. Kraus MR, Schafer A, Faller H, Csef H, Scheurlen M: Paroxetine for the treatment of interferon-alpha-induced depression in chronic hepatitis C. Aliment Pharmacol Ther 2002; 16:1091–1099
62. Hauser P, Khosla J, Aurora H, Laurin J, Kling MA, Hill J, Gulati M, Thornton AJ, Schultz RL, Valentine AD, Meyers CA, Howell CD: A prospective study of the incidence and open-label treatment of interferon-induced major depressive disorder in patients with hepatitis C. Mol Psychiatry 2002; 7:942–947
63. Schafer M, Schmidt F, Amann B, Schlosser S, Loeschke K, Grunze H: Adding low-dose antidepressants to interferon alpha treatment for chronic hepatitis C improved psychiatric tolerability in a patient with schizoaffective psychosis. Neuropsychobiology 2000; 42(suppl 1):43–45
64. Hauser P, Soler R, Reed S, Kane R, Gulati M, Khosla J, Kling MA, Valentine AD, Meyers CA: Prophylactic treatment of depression induced by interferon-alpha. Psychosomatics 2000; 41:439–441
65. Musselman DL, Lawson DH, Gumnick JF, Manatunga AK, Penna S, Goodkin RS, Greiner K, Nemeroff CB, Miller AH: Paroxetine for the prevention of depression induced by high-dose interferon alfa. N Engl J Med 2001; 344:961–966
66. Dobmeier M, Frick E, Frank S, Franke C, Wolfersdorf M: Schizophrenic psychosis: a contraindication for treatment of hepatitis C with interferon alpha? Pharmacopsychiatry 2000; 33:72–74
67. Kim WR: The burden of hepatitis C in the United States. Hepatology 2002; 36(5, suppl 1):S30–S34