Review Article

# Interferon-Induced Psychosis as a "Psychiatric Contraindication" to Hepatitis C Treatment: A Review and Case-Based Discussion

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**Background:** *Hepatitis C (HCV) infection is a major cause of liver disease, cirrhosis, and hepatocellular carcinoma. Interferon-based treatments have the potential to decrease the burden of disease, but are complicated by side effects, including neuropsychiatric symptoms.* **Objective:** *The authors described a case of interferon-induced psychosis as a framework to review the literature and discuss the decision to pursue antiviral treatment in psychiatrically ill patients with hepatitis C.* **Method:** *The authors followed a patient with chronic HCV who received interferon and ribavirin and who developed hallucinations ultimately requiring psychiatric hospitalization.* **Results:** *Despite treatment with various neuroleptics, the psychosis resolved only when the interferon/ribavirin were discontinued.* **Conclusion:** *Psychiatric illness should not rule out the possibility of interferon-based therapy, but it calls for close integration of psychiatric and medical care and individualized decision-making based on the biological and psychosocial circumstances of each case.* (Psychosomatics 2010; 51:1–7)

Acute infection with the hepatitis C virus (HCV) leads to chronic HCV infection in 75% to 85% of cases, and 10% to 20% of patients with chronic infection develop cirrhosis over a period of 20 to 30 years.[1] Since approximately 2% of the population in the United States has evidence of infection, a large number of persons are at risk for liver failure, hepatocellular carcinoma, and death.[2] Interferon-based treatments can lead to improvement in liver function, decreased histologic inflammation, and diminished hepatitis C viral levels or even a sustained virological response (defined as absence of viral RNA in the serum 6 months after completion of interferon therapy). The achieved sustained virological responses range from 20% to 80%, depending on the treatment regimen and patient characteristics.[3,4] Successful treatment leads to improved quality of life[5,6] and reduces the risk of progression to cirrhosis and liver failure.[7]

The current standard treatment for chronic hepatitis C is pegylated interferon alpha (peg-interferon) in combination with ribavirin.[4] The substantial side effects of interferon, however, complicate treatment. A majority of patients receiving an interferon-based therapy experience side effects, including fatigue, muscle aches, influenza-like symptoms, gastrointestinal disturbances, hematologic abnormalities, and neuropsychiatric symptoms.[4,8,9] Side effects are generally proportionate to treatment dose and duration and have been noted with all types of interferon

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treatment. Intolerability caused by neuropsychiatric side effects, in particular, leads to discontinuation of interferon in up to 13% of cases.[10]

The most common neuropsychiatric side effects are fatigue and depressive symptoms, although a variety of other clinical symptoms have been noted. Approximately 20% to 40% of chronic hepatitis C patients treated with interferon suffer from symptoms of depression, often necessitating discontinuation of treatment.[11,12] Suicidal thoughts and actions have also been reported.[13–15] Other neuropsychiatric side effects include panic and anxiety, emotional lability, irritability, anger, aggression, hypomania and mania, and confusion and disorientation.[16–19]

Although rare, psychosis (with hallucinations and delusions) is a possible complication of interferon-based treatment regimens for hepatitis C. Psychosis occurs, according to the package insert for peg-interferon alfa-2b (PegIntron™ powder for injection [Schering Corp.; Kenilworth, NJ]) with a frequency of ≤1%. In a retrospective study of 943 Japanese patients receiving interferon for chronic hepatitis C, Hosoda and colleagues[20] identified 4 patients (0.4 percent) who developed psychosis, including auditory hallucinations and persecutory delusions. All 4 patients prematurely terminated interferon treatment. Psychotic symptoms resolved within 3 months with antipsychotic medications and interferon discontinuation. The authors noted psychosis to have occurred predominantly in the context of mood symptoms. In a larger survey of 11,241 patients with chronic hepatitis C receiving interferon alpha treatment in Italy, Fattovich and colleagues[21] noted 10 cases of treatment-emergent psychosis (0.09 percent), which also resolved with termination of interferon treatment and appropriate psychotropic medications.

In a case series, Hoffman and colleagues[22] described four cases of interferon-induced psychosis in patients co-infected with hepatitis C and HIV and receiving antiviral therapy for chronic hepatitis C. These patients had enrolled in a multicenter trial to assess the safety and efficacy of daily (versus 3-times-per-week) interferon and ribavirin treatment in patients co-infected with hepatitis C and HIV (N=180).[23] Hoffman and colleagues reported that 4 of the 6 patients enrolled at their trial site developed psychosis. None of these patients had had previous psychotic episodes. They experienced auditory and visual hallucinations, along with persecutory delusions, that resolved with antipsychotic medications and discontinuation of interferon therapy.

Also, a number of individual case reports have documented treatment-emergent psychosis in individuals receiving interferon for chronic hepatitis C.[24,25] The case-based literature suggests that psychosis can occur at any time during the treatment course, ranging from within 2 weeks after initiation of treatment[26,27] to as late as days after treatment has been completed.[28] The same literature also shows that psychosis resolved in most,[29–37] but not all,[38–41] cases after termination of interferon treatment and/or treatment with psychotropic medications (predominantly antipsychotics and antidepressants). Some cases of prolonged psychosis responded to ECT.[42,43]

In this article, we present a case of psychosis induced by interferon treatment for chronic hepatitis C in a patient with a very complex psychiatric history that included past intravenous drug use, depression, posttraumatic stress disorder (PTSD), and borderline personality disorder. Her psychosis resolved with discontinuation of interferon and initiation of an antipsychotic, but re-occurred when interferon was restarted, in spite of ongoing antipsychotic treatment. In our discussion, we will ask this question: For whom should we decide to withhold interferon-based treatment in the face of psychiatric contraindications, given interferon's potential to change the natural history of HCV infection?

## Case Report

"Ms. S" was a 44-year-old, single, white woman with a past psychiatric history of non-psychotic major depressive disorder, opiate and alcohol dependence, and posttraumatic stress disorder, who had acquired genotype 1a HCV from a period of intravenous heroin use in her 20s. Borderline personality disorder had also been diagnosed, and she had episodes of self-harm and suicidality, leading to many psychiatric hospital admissions. For the past 4 years, however, she had been in remission from substance use and had not required any hospitalization. She had two previous episodes of psychosis: one distant LSD-induced episode and one episode when she received interferon 2 years ago. During the LSD-induced psychotic episode, she stabbed herself in the foot with a knife in response to religious delusions; the injury required hospitalization and multiple surgeries. The interferon-induced psychotic episode was characterized by persecutory delusions and confusion, leading to termination of this treatment after 8 weeks, with subsequent resolution of psychosis. Notably, her viral load in this brief treatment course fell from >700,000 IU/mL to 43,200 IU/mL, raising the possibility that she might achieve early virologic response (>2 log

drop, or undetectable viral load at 12 weeks), which would suggest a chance for sustained virologic response.[44] Her only current active medical condition was diabetes type II, for which she took metformin.

At Ms. S's request, her gastroenterology team reinitiated interferon treatment for asymptomatic hepatitis C, given her psychosocial stability (she was in stable recovery and attending a day program; she adhered to psychiatric medications and follow-up with her psychiatrist and therapist). Before re-treatment, her viral load had again risen to >700,000 IU/mL. Work-up before her initial interferon course 2 years earlier revealed no evidence of liver failure (liver ultrasound without cirrhosis or hepatocellular carcinoma; liver biopsy consistent with chronic HCV, including hepatic activity index of 4/18, fibrosis stage 1/6, interface hepatitis 1/4, and portal inflammation 2/4). Her liver function tests (LFTs) were slightly elevated (ALT 50 U/L, AST 38 U/L, AlkP 115 U/L, TB 0.6 mg/dL), although consistent with her previous results for many years. Notably, Ms. S's seeking this re-treatment with interferon was triggered by the death of a friend from end-stage liver disease secondary to hepatitis C. Her treatment team considered the risks and benefits of interferon treatment with her and supported her choice to pursue this course, although she was at overall low risk for complications from HCV infection, and treatment may not have been recommended without her independently expressing this preference.

Within 12 weeks of treatment with pegylated interferon alpha$_{2a}$ (180 mcg weekly) and ribavirin (400 mg bid), the patient developed auditory, visual, and tactile hallucinations: she saw an angel with wings, feathers, and breathing movements in the room with her and felt this angel touch her on the shoulders. This angel issued commands, including instructions to Ms. S to end her life by jumping off a cliff into the ocean and to ignore her treatment team during her hospitalization. She also saw ancient religious symbols in the tiles on the floor and felt it was her job to interpret these signals in order to protect civilization. In spite of these symptoms, she expressed an ongoing desire to continue interferon treatment and received her 18th weekly injection. Although her outpatient psychiatrist started dual therapy with aripiprazole (2 mg daily) and risperidone (0.5 mg daily on as-needed basis for anxiety related to psychotic symptoms), her psychiatric status deteriorated, and she was admitted to the hospital shortly after her 18th interferon treatment.

At the time of admission, Ms. S's next scheduled interferon dose was withheld while ribavirin was continued, with an undetectable hepatitis C viral load (<600 IU/mL) and stably elevated liver function tests (ALT 28 U/L, AST 33 U/L, AlkP 136 U/L, TB 0.5 mg/dL). Initial treatment included discontinuation of aripiprazole, in favor of a trial of risperidone monotherapy that was titrated up to 2 mg/day. After 4 days, however, Ms. S developed risperidone-induced muscle stiffness, leading to its discontinuation and a change to aripiprazole monotherapy that was subsequently increased to 20 mg/day. After 1 week of hospitalization (and 4 days of aripiprazole treatment), Ms. S's psychosis had completely resolved.

Since the patient expressed ongoing interest in continuing interferon therapy, the treatment team, after a review of risks and benefits and in consultation with the gastroenterology department, agreed to restarting interferon in an inpatient hospital setting and with ongoing co-administered aripiprazole. After 8 days of aripiprazole therapy, Ms. S received her 19th interferon injection; 2 days later, her psychotic symptoms returned; she experienced auditory and visual hallucinations similar to her initial presentation, and she reported feeling as if all sounds were distorted. Also, she had significant confusion and disorientation, at one point wandering into another patient's room, unable to find her own bed. Her symptoms persisted throughout the day without fluctuation. She was awake, alert, and attentive to interviews with her team. Her confusion was perhaps exacerbated by pain medications related to a dental procedure and benztropine for akathisia, which developed after 9 days of aripiprazole (at which time her dose was lowered to 10 mg/day).

## RESULTS

Interferon was again withheld, and, 8 days later, Ms. S's mental status again returned to baseline, with resolution of her hallucinations, confusion, and disorientation.

Ms. S reached the independent conclusion that she would be unable to continue interferon therapy, and ribavirin was also discontinued. After a 26-day stay, she was discharged from the hospital at her baseline mental status, continuing on aripiprazole at 10 mg/day. Follow-up from her primary-care physician 1 week later confirmed the absence of any ongoing psychosis. In the end, her HCV viral load again became detectable, given that she had received only 19 of the recommended 48 doses of interferon treatment.

## DISCUSSION

Our case adds to the literature on psychosis as a rare complication of interferon-based treatments. Our patient, "Ms. S," who had a complex premorbid psychiatric history and past episodes of drug- and interferon-induced psychosis, developed clear-cut psychosis within a few months after interferon treatment was initiated. Psychosis could not be controlled in spite of antipsychotic use in an inpatient setting; only cessation of interferon led to the remission of the psychosis. Our patient did not have a history of chronic psychotic illness. Her psychotic episodes appear to be separate reactions to LSD and interferon, resolving after removal of the inciting agent. In her final interferon trial, the patient's combination of confusion, disorientation, and hallucinations raise the possibility of delirium, possibly worsened by concurrent use of pain medications and benztropine. However, there was no fluctuation in mental status or alteration in consciousness or attention, arguing against delirium in favor of a straightforward psychotic reaction.

Were we too aggressive in pursuing treatment with interferon in this particular patient with previous interferon-induced psychosis? Although we may not have spontaneously recommended antiviral treatment in light of her low risk for HCV complications (mild histologic disease) and low likelihood of response (high HCV viral load and genotype 1a infection), we reinitiated interferon in response to the patient's independent requests and psychosocial stability, after having thoroughly discussed the risks and benefits with her.

Physicians may be hesitant to treat patients with psychiatric illness with interferon, because of the possibility of higher risks of neuropsychiatric adverse reactions or unmasking of underlying symptoms,[45,46] along with concerns about decision-making capacity to engage in treatment.[47,48] In past studies, current or previous psychosis has been cited as a contraindication to the treatment of chronic hepatitis C with interferon.[49–52] A risk–benefit model to determine which individual patients should receive interferon treatment has been proposed, based on available evidence weighing likelihood of viral clearance and risks of psychiatric side effects.[53,54] However, debate over eligibility continues.[55–58] Individualized decision-making has been recognized as a goal in patients with active substance abuse and comorbid hepatitis C.[59,60]

Recent reports have demonstrated the successful ability to treat psychiatrically-ill patients (including patients with a chronic psychotic illness or PTSD) with interferon for chronic hepatitis C.[61] In a prospective controlled trial of 70 patients, Schaefer et al.[62] demonstrated successful interferon-based treatment for chronic hepatitis C in patients with a variety of premorbid psychiatric conditions, including affective, personality, and psychotic disorders. Patients with psychiatric illness, including 10 patients with a history of psychotic disorder, had sustained virological response at the same rate as control subjects. None of the patients with a psychotic disorder experienced an exacerbation of their psychotic symptoms (e.g., hallucinations or delusions). This research, built upon a previous prospective controlled trial of 81 patients, in which Schaefer et al.[63] showed that patients with psychiatric illness (including six patients with a history of a psychotic illness who completed the trial without any exacerbation in illness) were able to receive interferon for treatment of chronic hepatitis C with similar rates of side effects and drop-outs as control subjects. Similarly, Van Thiel et al.[64] enrolled 31 consecutive patients with chronic hepatitis C and psychiatric comorbidity into a prospective study of interferon-alpha treatment; the sample included 13 patients with schizophrenia. Of the entire group, 29 patients completed the study, with 15 patients (48%) clearing hepatitis C virus from their serum. The two patients who discontinued treatment experienced worsening mania.

Adding further support, a number of case reports have demonstrated successful treatment of hepatitis C with interferon in patients with chronic psychotic illness, without exacerbation of the underlying illness.[65,66] Liukkonen et al.[67] reported successful treatment of hepatitis C with interferon in a patient receiving clozapine for chronic psychotic illness, without any psychiatric decompensation or treatment-ending agranulocytosis.

In support of its tolerability in patients with psychotic disorders, interferon has been investigated in small studies as a treatment for schizophrenia.[68,69] Results showed some improved symptoms and decreased doses of co-administered antipsychotics.

Optimization of psychiatric treatment regimens and active involvement with psychiatrists before interferon treatment may improve the likelihood of treatment adherence and success. Unfortunately, in contrast to depression, where both prophylactic and symptom-based treatment with antidepressants has been shown to reduce the rate and severity of interferon-induced depression in patients with HCV,[70–73] no studies guide clinicians as to the value of prophylactic or symptom-based antipsychotics in patients with interferon-induced psychosis. Another unanswered

question in the literature is whether a previous episode of interferon-induced psychosis predicts another incident. In our case, the patient had a previous episode of interferon-induced psychosis, and a longer period of prophylactic antipsychotic before the initiation of interferon might have been tried. During the interferon trial leading to hospitalization, the outpatient psychiatrist could have tried higher doses of antipsychotic in response to emerging psychotic symptoms. Similarly, longer pre-treatment with aripiprazole, which takes several weeks to reach steady state, could have been considered before retrying interferon in the hospital. Future studies aimed at understanding the mechanisms of interferon-induced psychosis may be helpful for predicting complications and guiding specific psychiatric treatments. Registry of interferon-induced psychosis cases may be a first step toward increasing our knowledge-base.

Close integration of psychiatric and medical care has been shown to increase the likelihood that patients with psychiatric illness and chronic hepatitis C may start interferon treatment with improved subsequent adherence to therapy.[74] Large-scale implementations are possible: the VA system has developed and implemented an effective screening and treatment model for psychiatrically ill patients with hepatitis C. A study of 293,445 VA patients across the United States found those with schizophrenia (1.6 percent of the total) to receive interferon treatment at nearly the same rates as other patients (11.9 percent versus 13.9 percent, a non-statistically significant difference).[75] Practical hurdles remain: Freudenreich and colleagues[76] screened 98 outpatients with schizophrenia who attended a clozapine clinic for hepatitis C. None of the 8 patients found to have hepatitis C had received antiviral therapy 2 years after screening. In these cases, reasons for non-treatment were mostly related to patients' refusal and not following up with referrals.

Overall, gastroenterologists and psychiatrists are gaining increased experience in treating psychiatrically ill patients with interferon. The exact rates of interferon-induced side effects in the treatment of psychiatric populations are not known, and they are not necessarily higher than for other populations. Close collaboration between medical and psychiatric treatment teams, as in our described case, can assure that previously excluded patient populations have access to interferon treatment.

## CONCLUSIONS

Neuropsychiatric side effects have been recognized as a valid cause for withholding or discontinuing interferon treatment, especially in patients with preexisting psychiatric disorders. We believe that a psychiatric history should not automatically disqualify a patient from receiving interferon therapy, even if the previous psychiatric history is complex. Instead, attempts should be made to offer treatment under the safest possible circumstances, which usually will mean an interdisciplinary effort and frequent patient contact. Issues of safety related to psychosis should be clearly and explicitly discussed with the patient, and patients with previous psychosis should be warned about the possibility of its reemergence, including the potential for prolonged psychosis and the need for hospitalization. In summary, our case report emphasizes that the decision to utilize interferon-based treatments in psychiatrically ill patients with HCV should be highly collaborative and individualized, considering biological and psychosocial factors, risks and benefits, and patient preferences.

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