Hepatitis C and interferon: Watch for hostility, impulsivity

Manic side effects may emerge with antiviral treatment

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Pegylated interferon-alpha with ribavirin is the most effective therapy for chronic hepatitis C infection,[1,2] but psychiatric patients often discontinue IFN-alpha because of its mood side effects.[3] Most studies describe depressive states, although manic symptoms—irritability, aggression, anger, hostility, emotional lability, anxiety, panic attacks, and insomnia—also have been reported.[4-6]

To help you manage adverse mood changes and prevent IFN-alpha treatment discontinuation in patients with hepatitis C, this article:

- reviews studies of patients with a history mood disorders who were treated with IFN-alpha
- explains how to recognize and treat IFN-alpha-induced mood disturbances when antidepressants are contraindicated.

PSYCHIATRIC PATIENTS AND IFN THERAPY

Chronic hepatitis C infection is common among psychiatric patients. Routine screening among 1,556 patients admitted to a U.S. public psychiatric hospital across 3 years identified 133 patients (8.5%) who were positive for hepatitis C virus.[7]

Patients with psychopathologic symptoms before starting IFN therapy may suffer more-severe adverse psychiatric effects during treatment than those without psychopathology.[8] In fact, mood disorders were considered an absolute contraindication to IFN therapy until recently.

Now that the National Institutes of Health (NIH) has recommended extending hepatitis C research and treatment to psychiatric patients, IFN-alpha-induced mental illness could become more common in clinical practice. Before the 2002 NIH consensus statement, patients with mental illness and substance use disorders—who represent >50% of candidates who need IFN therapy—were excluded from research protocols.

Safely using IFN. Some reports and studies suggest that patients with past or existing psychiatric disorders can be treated safely and effectively with IFN-alpha.

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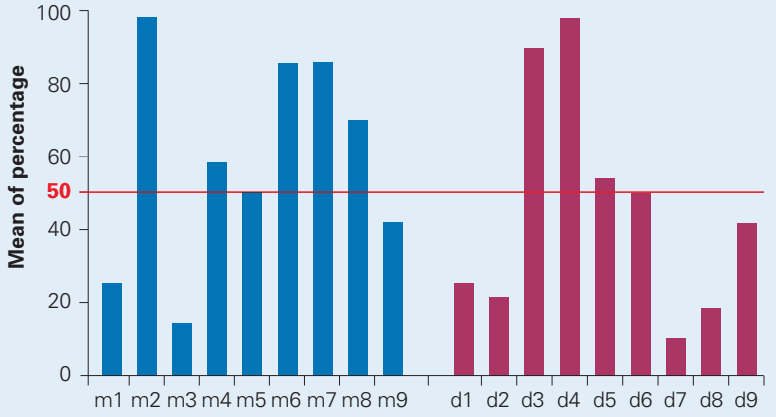
Figure 1

Mood symptoms identified in 24 patients after 12 weeks of IFN-alpha treatment



Manic/hypomanic symptoms
m1: elevated moods
m2: irritability
m3: self-esteem
m4: insomnia
m5: talkativeness
m6: racing thoughts
m7: distractibility
m8: agitation
m9: pleasurable activities

Depressive symptoms
d1: depressed mood
d2: anhedonia
d3: weight loss
d4: insomnia or hypersomnia
d5: psychomotor disturbances
d6: fatigue
d7: guilt
d8: reduced concentration
d9: thoughts of death

IFN: Interferon
Source: Reference 12

In a prospective open-label study, 29 of 31 patients with co-existing chronic hepatitis C and psychiatric illness completed 6 months of IFN therapy, 5 million units (MU) three times/week or 5 MU daily. Patients continued maintenance psychotropics during IFN treatment, and a psychiatrist monitored psychiatric symptoms.

Psychiatric illness worsened in four patients, and two discontinued IFN treatment. Serum alanine aminotransferase returned to normal in 22 patients (71%), and hepatitis C virus RNA cleared from the sera of 15 (48%).[9]

Another prospective study of 50 patients treated with IFN for chronic hepatitis found that those with a pre-existing mood or anxiety disorder were not more likely than others to discontinue IFN therapy.[10]

Unique to hepatitis therapy? IFN-induced mood disturbances are probably different in patients with chronic hepatitis C than in those receiving IFN for other diseases because of differences in regimens and effects of the underlying pathologies. For example, prescribing a preventative antidepressant before starting IFN treatment might help cancer patients but not patients with hepatitis C.[11]

This distinction could be particularly important when giving IFN-alpha to patients who are vulnerable to psychiatric illness with impulsive features. To emphasize this point, we describe clinical features and treatment response in patients with hepatitis C who were treated in our department.

IFN-ALPHA-INDUCED MOODS

In our prospective study of 93 patients, 30 (32%) developed IFN-alpha-induced mood disorders during the first 12 weeks of treatment.[12] Contrary to previous studies focusing on depression, most of our patients had a mix of manic/hypomanic and depressive symptoms. Twenty-four (13 women and 11 men, mean age 43) accepted referral to a psychiatrist specializing in mood disorders to characterize their symptoms.

Mood characteristics. Using DSM-IV criteria, the psychiatrist determined that IFN-alpha induced both manic/hypomanic and depressive symptoms in many patients, and the manic/hypomanic fea-

continued on page 75

continued from page 72

tures predominated. Five manic symptoms and three depressive symptoms were present in >50% of patients (*Figure 1, page 72, and Table*).

Three patients presented with a manic episode, 15 with hypomania with prevalent irritability and dysphoric features, and 6 with a mixed depressive state (major depressive episode with at least 3 hypomania symptoms).[13] Four patients (17%) suffered a relapse of alcohol or cannabis abuse.

Nearly all (84%) reported paroxysmal anxiety, and all had emotional hyperreactivity that the psychiatrist described as a main symptom of a manic or mixed state.[14] Most felt extremely impulsive and feared losing control. Two faced legal difficulties, and one was in prison.

The patients' mean Montgomery-Åsburg Depression Rating Scale (MADRS) score was 16.12 (±1.6), indicating a mild to moderate depressive state. The highest-scoring items were inner tension, reduced sleep, reduced appetite, and lassitude (*Figure 2, page 76*).

Their mean Bech-Rafaelsen Mania Scale[15] score was 14.33 (±1.3), indicating hypomanic or moderate manic symptoms. Hostility was by far the predominant manic symptom (mean score 3.2/4). Other manic symptom scores ranged from 0.2/4 to 2.1/4 (*Figure 3, page 77*).

Treatment. Given the predominance of manic/hypomanic symptoms, we treated the 24 patients with low-to-moderate dosages of an atypical antipsychotic (amisulpride, 100 to 600 mg/d). This medication—not available in the United States—would be similar to using risperidone, 1 to 6 mg/d. Low-dose benzodiazepines (clonazepam or alprazolam) were added as needed to manage insomnia.

Antipsychotic treatment enabled 23 of 24 patients (96%) to continue antiviral therapy.

Five patients had received selective serotonin reuptake inhibitors (SSRIs) for 1 to 4 weeks before referral to the psychiatrist. Antidepressants worsened their mood symptoms, which included impulsivity, agitation, and insomnia. Emotional hyper-reactivity, irritability, hostility, and impulsiveness improved in all 5 patients within 1 to 2 weeks of stopping SSRIs and starting the atypical antipsychotic.

Low to moderate antipsychotic doses enabled 23 of 24 patients to continue antiviral therapy

Table

Most-prevalent IFN-induced mood symptoms in 24 patients treated for hepatitis C

5 manic symptoms (% of patients)	3 depressive symptoms (% of patients)
Irritability (100%)	Insomnia or hypersomnia (100%)
Racing thoughts (87%)	Poor appetite or weight loss (92%)
Distractibility (87%)	Psychomotor agitation or retardation (54%)
Insomnia (58%)	
Agitation (70%)	

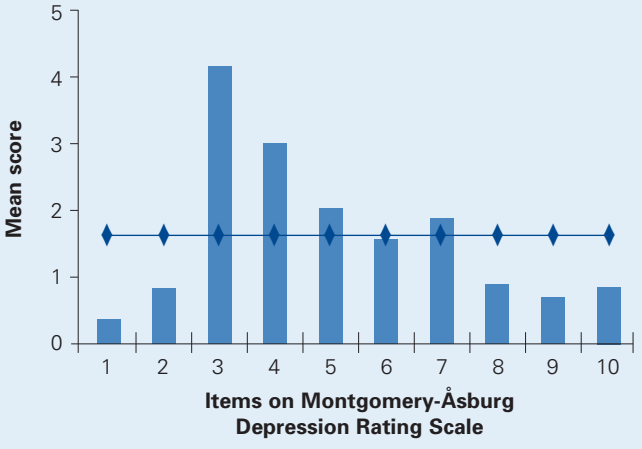
IFN: Interferon
Source: Reference 12

DISCUSSION

Accurately characterizing IFN-induced mood states confirmed our published data showing a mix of manic/hypomanic and depressive symp-

Figure 2

Depressive symptoms in 24 patients with IFN-induced mood disorder



1: apparent sadness
2: reported sadness
3: inner tension
4: reduced sleep
5: reduced appetite
6: concentration difficulties
7: lassitude
8: inability to feel
9: pessimistic thoughts
10: suicidal thoughts

IFN: Interferon
Source: Reference 12

toms in psychiatric patients treated for chronic hepatitis C. Irritability and hostility were the two most prominent symptoms.

These findings differ from those of investigations that identified depressive symptoms as the hallmark of IFN's psychiatric side effects.[6] Our data were thoroughly characterized according to DSM-IV-TR criteria, two mood-rating scales, and a psychiatrist experienced in mood disorders.

Why is mania missed? One possible explanation for these different findings is that IFN-alpha-induced fatigue and flu-like symptoms could be misinterpreted as depressive symptoms. Also, most researchers have used depression rating scales—but not mania scales—and have not considered other psychiatric diagnostics.[16]

Self-report questionnaires for evaluating depression also take into account somatic side effects, resulting in higher rating scores. Moreover, few studies have included clinical psychiatric interviews and even fewer diagnostic confirmation by a psychiatrist.

Finally, clinical experience indicates that patients who present with both manic/hypomanic and depressive symptoms are more likely to complain about depression than about manic symptoms. Therefore, clinicians may miss manic symptoms if they don't actively seek them.

Irritability and hostility. Previous studies have described irritability, mood lability, and anger/hostility as frequent symptoms[4,5] but failed to consider them as possible manifestations of mania or hypomania. Many of our patients reported irritability severe enough to interfere with their work, social, and family relationships.

Hostility was the symptom with the highest score on the Bech-Rafaelsen Mania Scale. This objective evidence suggests that investigating the consequences to patients of increased irritability, impulsivity, or hostility might reveal some frightening behavior.

How to treat these patients. Considerable evidence from characterizing IFN-induced side effects in patients with hepatitis C points to a syndrome of depressive and manic/hypomanic symptoms[13,17-19] that does not fulfill criteria for a mixed state. This disorder is not described in DSM-IV-TR and, unfortunately, usually is misdiagnosed as a depressive state.

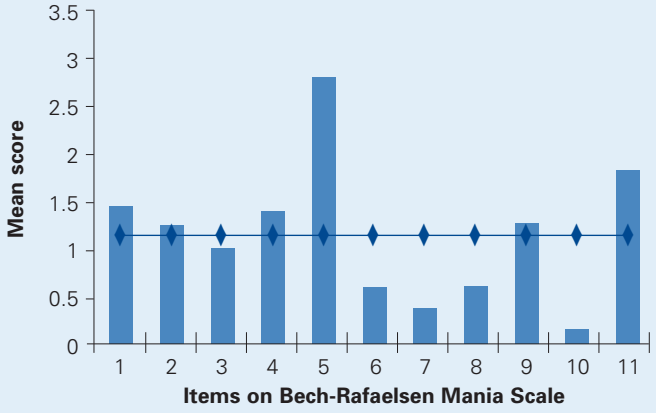
Antidepressants can worsen depression by causing agitation and impulsivity and can increase risk of suicide.[17,18,20] By contrast, atypical antipsychotics have been shown to improve bipolar depression.[21,22]

We used an atypical antipsychotic to treat patients with prevalent manic or hypomanic symptoms and those who did not respond to SSRIs. Their IFN-induced mood disorders improved rapidly on low dosages of amisulpride, and antiviral therapy discontinuation rates were low (1/24; 4%). By comparison, other studies have reported antiviral treatment discontinuation rates of 30% to 40% in patients taking antidepressants.[23,24]

The atypical antipsychotic did not improve our patients' fatigue and other neurovegetative symptoms, but antidepressants likewise do not improve these symptoms.[8]

Figure 3

Manic symptoms in 24 patients with IFN-induced mood disorder



1: motor activity
2: pressure of speech
3: flight of thoughts
4: noise level of speech
5: hostility and irritability
6: elevated mood
7: self-esteem
8: social contact
9: sleep disturbances
10: sexual activity
11: social activities, distractibility

IFN: Interferon
Source: Reference 12

RECOMMENDATIONS

This study leads us to warn clinicians that antidepressants can worsen IFN-alpha-induced mood disorders and to recommend that antipsychotics be considered:

- at least before you decide to discontinue a hepatitis C patient's IFN-alpha therapy
- or in patients with high irritability and hostility.

To determine whether to use an antidepressant or antimanic agent as first-line treatment, carefully diagnose the patient's symptoms as a manic/hypomanic state, depressive mixed state, or depression. Successful IFN therapy requires:

- psychological support
- medication for psychiatric adverse effects
- collaboration between the psychiatrist and hepatologist.

IFN-alpha-induced mood disorders are triggered exogenously, do not correspond to typical features of any classic psychiatric disorder, and require further study. IFN-induced impulsivity and hostility also need to be better characterized, particularly as more patients with pre-existing psychiatric disorders are treated for hepatitis C.

References

1. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus rib-

Bottom Line

Psychiatric symptoms in IFN-treated patients with hepatitis C do not match DSM-IV-TR criteria. To determine first-line treatment—an antidepressant or antimanic agent—look for mania/hypomania, mixed states, or depression. IFN-induced impulsivity and hostility may increase risk for dangerous behavior or suicide attempts.

Related resources

- Lauer GM, Walker BD. Hepatitis C virus infection. *N Engl J Med* 2001;345(1):41-52.
- Onyike CU, Bonner JO, Lyketsos CG, Treisman GJ. Mania during treatment of chronic hepatitis C with pegylated interferon and ribavirin. *Am J Psychiatry* 2004;161:3.

DRUG BRAND NAMES

Alprazolam • Xanax
Amisulpride • (not available in the United States)
Clonazepam • Klonopin
Risperidone • Risperdal

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avirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001;358:958-65.

2. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002;347:975-82.
3. Zdilar D, Franco-Bronson K, Buchler N, et al. Hepatitis C, interferon alfa, and depression. *Hepatology* 2000;31:1207-11.
4. Schaefer M, Engelbrecht MA, Gut O, et al. Interferon alpha (INF-alpha) and psychiatric syndromes: a review. *Prog Neuropsychopharmacol Biol Psychiatry* 2002;26:731-46.
5. Trask PC, Esper P, Riba M, Redman B. Psychiatric side effects of interferon therapy: prevalence, proposed mechanisms, and future directions. *J Clin Oncol* 2000;18:2316-26
6. Kraus MR, Schäfer A, Faler H, et al. Psychiatric symptoms in patients with chronic hepatitis C receiving interferon alfa-2B therapy. *J Clin Psychiatry* 2003;64:6.
7. Dinwiddie SH, Shicker L, Newman T. Prevalence of hepatitis C among psychiatric patients in the public sector. *Am J Psychiatry* 2003;160(1):172-4.
8. Capuron L, Gummick JF, Musselman DL, et al. Neurobehavioral effects of interferon-alpha in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. *Neuropsychopharmacology* 2002;26:643-52.
9. Van Thiel DH, Friedlander L, Molloy PJ, et al. 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(2):165-8.
10. Pariante CM, Landau S, Carpiniello B. Interferon alfa-induced adverse effects in patients with a psychiatric diagnosis. *N Engl J Med* 2002;347(2):148-9.
11. Musselman DL, Lawson DH, Gumnick JF, et al. Paroxetine for the prevention of depression induced by high-dose interferon-alfa. *N Engl J Med* 2001;344(13):961-6.
12. Constant A, Castera L, Dantzer R, et al. Mood alterations during interferon-alfa therapy in patients with chronic hepatitis C: evidence for an overlap between manic/hypomanic and depressive symptoms, *J Clin Psychiatry* 2005;66;8:1050-7.
13. Benazzi F. Major depressive episodes with hypomanic symptoms are common among depressed outpatients. *Comprehensive Psychiatry* 2001;42(2):139-43,
14. Henry C, Swendsen J, Van Den Bulke D, et al. Emotional hyperreactivity as the fundamental mood characteristic of manic and mixed states. *Eur Psychiat* 2003;18:124-8.
15. Bech P, Rafaelsen OJ, Kramp P, Bolwig TG. The mania rating scale: scale construction and inter-observer agreement. *Neuropharmacology* 1978;17:430-1.
16. Castera L, Constant A, Henry C, et al. Incidence, risk factors and treatment of mood disorders associated with peginterferon and ribavirin therapy in patients with chronic hepatitis C: results of a prospective study (abstract). *Hepatology* 2003;38 (suppl.1):735A.
17. Koukopoulos A, Koukopoulos A. Agitated depression as a mixed state and the problem of melancholia. Bipolarity: beyond classic mania. *Psychiatr Clin North Am* 1999;22(3):564-74.
18. Benazzi F, Koukopoulos A, Akiskal HS. Toward a validation of a new definition of agitated depression as a bipolar mixed state (mixed depression). *European Psychiatry* 2004;19:85-90.
19. Suppes T, Mintz J, McElroy SL, et al. Mixed hypomania in 908 patients with bipolar disorder evaluated prospectively in the Stanley Foundation Bipolar Treatment Network. A sex-specific phenomenon. *Arch Gen Psychiatry* 2005;62:1089-96.
20. Henry C, Demotes-Mainard J. Avoiding drug-induced switching in patients with bipolar depression. *Drug Safety* 2003;26:337-51.
21. Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry* 2003;60(11):1079-88.
22. Calabrese JR, Keck PE Jr, MacFadden W, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression, *Am J Psychiatry* 2005; 162(7):1351-60.
23. Kraus MR, Schafer A, Faller H, et al. Paroxetine for the treatment of interferon-alpha-induced depression in chronic hepatitis C. *Aliment Pharmacol Ther* 2002;16:1091-9.
24. Hauser P, Khosla J, Aurora H, et al. A prospective study of the incidence and open-label treatment of interferon-induced major depressive disorder in patients with hepatitis C. *Mol Psychiatry* 2002;7:942-7.