Hepatitis C and interferon: Watch for hostility, impulsivity

Manic side effects may emerge with antiviral treatment

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

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 of 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.

Patients with psychopathologic symptoms before starting IFN therapy may suffer more severe adverse psychiatric effects during treatment than those without psychopathology. 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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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%).

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. Unicidal 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.

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. 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-

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<table>
<thead>
<tr>
<th>Manic/hypomanic symptoms</th>
<th>Depressive symptoms</th>
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<tbody>
<tr>
<td>m1: elevated moods</td>
<td>d1: depressed mood</td>
</tr>
<tr>
<td>m2: irritability</td>
<td>d2: anhedonia</td>
</tr>
<tr>
<td>m3: self-esteem</td>
<td>d3: weight loss</td>
</tr>
<tr>
<td>m4: insomnia</td>
<td>d4: insomnia or hypersomnia</td>
</tr>
<tr>
<td>m5: talkativeness</td>
<td>d5: psychomotor disturbances</td>
</tr>
<tr>
<td>m6: racing thoughts</td>
<td>d6: fatigue</td>
</tr>
<tr>
<td>m7: distractibility</td>
<td>d7: guilt</td>
</tr>
<tr>
<td>m8: agitation</td>
<td>d8: reduced concentration</td>
</tr>
<tr>
<td>m9: pleasurable activities</td>
<td>d9: thoughts of death</td>
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IFN: Interferon
Source: Reference 12

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Figure 1: Mood symptoms identified in 24 patients after 12 weeks of IFN-alpha treatment

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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). 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. Most felt extremely impulsive and feared losing control. Two faced legal difficulties, and one was in prison.

The patients’ mean Montgomery-Åsberg 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 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.

**DISCUSSION**

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

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**Table**

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

<table>
<thead>
<tr>
<th>5 manic symptoms (% of patients)</th>
<th>3 depressive symptoms (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritability (100%)</td>
<td>Insomnia or hypersomnia (100%)</td>
</tr>
<tr>
<td>Racing thoughts (87%)</td>
<td>Poor appetite or weight loss (92%)</td>
</tr>
<tr>
<td>Distractibility (87%)</td>
<td>Psychomotor agitation or retardation (54%)</td>
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<tr>
<td>Insomnia (58%)</td>
<td></td>
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<tr>
<td>Agitation (70%)</td>
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IFN: Interferon
Source: Reference 12

**Low to moderate antipsychotic doses enabled 23 of 24 patients to continue antiviral therapy**
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 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 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. By contrast, atypical antipsychotics have been shown to improve bipolar depression.
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

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-

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.