Managing the neuropsychiatric side effects of interferon-based therapy for hepatitis C

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ABSTRACT

Neuropsychiatric side effects are common with interferon-based therapy for chronic hepatitis C, and their prompt recognition and management is essential to effective patient care. Depression induced by interferon has been a significant cause of early treatment discontinuation in clinical trials. The need to monitor for and treat interferon-induced depression is well established, but whether to use antidepressants prophylactically remains controversial. Nonetheless, clinicians should maintain a low threshold for antidepressant therapy. Other significant neuropsychiatric side effects include anxiety, hypomania or mania, fatigue, and cognitive dysfunction. These can be additional sources of patient distress during interferon therapy and require appropriate intervention through patient education, psychotropic medications, support, and behavioral techniques.

Despite recent gains in the efficacy of antiviral regimens for the treatment of chronic hepatitis C, the tolerability of these regimens continues to be a significant problem. Neuropsychiatric side effects, such as depression, anxiety, mania, and fatigue, are especially common with regimens that include interferon alfa or pegylated interferon alfa, and they contribute to the morbidity and mortality associated with these therapies for hepatitis C. Prompt recognition and management of these side effects is necessary to optimize patient safety and enhance treatment tolerability.

This article reviews the manifestations and management of depression and other neuropsychiatric side effects of interferon-based therapy, with the goal of helping physicians who treat patients with hepatitis C improve their overall patient management.

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COMORBID PSYCHIATRIC AND SUBSTANCE ABUSE DISORDERS ARE COMMON WITH HEPATITIS C

Any discussion of the neuropsychiatric side effects of interferon therapy (which refers throughout this article to regimens including either conventional interferon alfa or pegylated interferon alfa) must consider the specific patient factors frequently associated with hepatitis C. Because illicit injection-drug use is a primary risk factor for infection with the hepatitis C virus, patients with hepatitis C often have a history of substance abuse. These patients also frequently have accompanying psychiatric illnesses, such as major depression, posttraumatic stress disorder, and personality disorders.

Because serious neuropsychiatric side effects (eg, severe depression, psychosis) have occurred in interferon-treated hepatitis C patients without a prior history of mental illness or substance abuse, concerns arose about the safety of interferon therapy in those with preexisting psychopathology. These concerns led to recommendations not to prescribe interferon to this patient group, despite their high rates of hepatitis C.[1–3] Fortunately, recent experiences have shown that many of these patients can tolerate interferon therapy safely, without undue worsening of their psychiatric or substance abuse disorders.[4–8] As a result, current recommendations call for patients to be considered on a case-by-case basis.[9–11] For many patients, close monitoring during interferon therapy and good coordination of care among hepatologists, mental health

providers, and addiction specialists can yield successful treatment.

DEPRESSION IN INTERFERON-TREATED PATIENTS

When and how depression manifests

Depressive symptoms that arise during interferon therapy for hepatitis C have been a significant cause of premature treatment discontinuation in clinical trials. The precise prevalence of depression in interferon-treated patients with hepatitis C is unknown, owing to an abundance of confounding factors in clinical studies, such as differences in the diagnostic criteria and screening tools used to diagnose depression, whether or not preexisting depression has been present, and differences in the patient groups studied. Given these variations, the reported frequency of depression in interferon-treated patients with hepatitis C has ranged from 0% to 44%.

Risk factors for interferon-induced depression include the use of higher interferon doses, longer treatment duration, and the presence of subclinical depressive symptoms.[12,13] Most often, depressive symptoms begin to develop within the first 12 weeks of interferon treatment and reach clinical significance in as little as 2 weeks.[13] Because the incidence of depression is highest early in the course of therapy, patients should be monitored closely early in therapy using clinical interview and screening tools such as the Beck Depression Inventory (BDI), the Center for Epidemiologic Studies Depression Scale (CES-D), the Hamilton Depression Rating Scale (HAM-D), and the Montgomery-Asberg Depression Rating Scale (MADRS). In fact, the CES-D was validated for use among patients with chronic hepatitis C.[14]

Interferon-induced depression is considered a substance-induced mood disorder.[15] Its symptoms are the same as those of major depression and include mood disturbance, apathy, anhedonia, fatigue, insomnia, anorexia, sexual dysfunction, and cognitive impairment. Suicidal ideation may be present but tends to be relatively infrequent. The accompanying mood disturbance may be described as feeling sad or "blue," but it may also consist of marked irritability. Because irritability also occurs with interferon-induced hypomania and mania, particular care is needed to distinguish which problem is present since antidepressants aggravate hypomanic and manic symptoms.

Etiology of interferon-induced depression

Various theories have been advanced about the etiology of interferon-induced depression, but the exact mechanism remains unclear. Interferon is known to alter production of secondary cytokines, which in turn affects the central nervous system. In particular, increases in levels of the cytokines IL-6 and IL-8 have been linked to the development of interferon-induced anxiety and depressive symptoms.[16] Secondary cytokines, which are also thought to affect the serotonergic system, are an area of interest because of their clear influence on psychiatric disorders. Animal studies have revealed reductions in serotonin and tryptophan levels in the brain following interferon exposure, while other studies have detected increases in serotonin reuptake mechanisms.[16] Interferon also leads to depletion of tryptophan stores, the primary precursor of serotonin.[17] Anxiety, depression, and cognitive disturbances associated with interferon therapy have been correlated with these reductions in tryptophan levels.[17]

Beyond influences on the serotonergic system, interferon also has effects on the hypothalamic-pituitary-adrenal (HPA) axis. Changes in the HPA axis have been linked to mood disorders and recently have been reported with interferon-induced depression.[18] Patients who developed interferon-induced depression produced significantly elevated levels of cortisol and ACTH in response to initial doses of interferon, which suggests that there is an underlying vulnerability of the HPA axis in these individuals.[18]

Therapeutic strategies: To prevent or to treat?

While the importance of diagnosing and treating interferon-induced depression has been recognized, when to start antidepressant therapy is still debatable. Some studies support the prophylactic use of antidepressants for all patients receiving interferon for hepatitis C because of the frequency of interferon-induced depression.[12,19] Most notably, one trial demonstrated a significant difference in the rate of depression among patients who received the selective serotonin reuptake inhibitor (SSRI) paroxetine prophylactically and those who did not.[12] Others have raised concerns about potential risks associated with antidepressant therapy, including retinal and gastrointestinal hemorrhage and stimulation of secondary mania.[13,20] Instead, they recommend frequent monitoring of patients who are receiving interferon and prompt initiation of antidepressants once signs and symptoms of major depression arise.

Arguments can be made for either of these approaches, but further clinical studies are necessary. At this point, clinicians should maintain a low threshold for antidepressant therapy. Evidence of subclinical depression at the beginning of interferon therapy requires serious consideration of antidepres-

sants, given the increased risk of developing full-blown interferon-induced depression. Further decisions about early antidepressant use should take into account the patient's coping skills, support systems, and level of life stressors (eg, job setting, family duties, presence or absence of substance abuse) to determine whether mild mood symptoms from interferon therapy would be tolerable. Patients should be educated about the risks and benefits of prophylactic antidepressant therapy to allow them to play an active role in the decision whether to start medications.

SSRIs: The most-studied therapy option

Data on the treatment of interferon-induced depression has focused on SSRIs **(Table 1)**, partly because of their ease of use and overall tolerability. More important has been the evidence suggesting that serotonin and tryptophan depletion may be the cause of interferon-induced mood disturbances. Sertraline, citalopram, fluoxetine, and paroxetine have all been reported to be effective in treating depression in interferon recipients,[21–27] and the latter two agents have also been given as prophylaxis for interferon-induced depression.[12,28] Besides their utility as antidepressants, SSRIs also have demonstrated efficacy against symptoms of anxiety as well as a modest impact on alcohol consumption.[29] Not all interferon-induced neuropsychiatric symptoms respond equally to SSRI therapy, however, as anorexia and fatigue were noted in one study to be less responsive to paroxetine than were depression, anxiety, cognitive dysfunction, and pain.[30]

Although SSRIs are generally considered safe, a recent report and a literature review have suggested that patients receiving both interferon and an SSRI may have an increased risk of retinal and gastrointestinal hemorrhage as well as cotton-wool spots.[13,20] Since SSRIs can affect platelet function, concerns about their use in patients with hepatitis C who may have a tendency to bleed are not unfounded.

Evaluating other therapy options

Although experience in treating interferon-induced depression has focused on SSRIs, other antidepressants **(Table 1)** offer comparable efficacy and may be more helpful when certain interferon-related side effects are present.

Bupropion, for example, is a norepinephrine and dopamine reuptake inhibitor with activating qualities that may reduce the fatigue, psychomotor slowing, and cognitive impairment associated with interferon therapy. Bupropion also offers benefits for smoking cessation, which may be a consideration since tobacco use may hasten liver fibrosis in hepatitis C.[31] A small risk of seizures with bupropion use must also be taken into account, however, since interferon also can induce seizures.

Mirtazapine enhances both serotonergic and norepinephrine transmission, and it provides a more rapid onset of action than most antidepressants. Because of its antihistaminergic activity, mirtazapine tends to cause sedation as well as appetite increase and weight gain. These side effects can prove beneficial, however, when interferon-related insomnia and anorexia trouble patients. In rare cases, mirtazapine has been linked to agranulocytosis and severe neutropenia.[32]

Venlafaxine is a serotonin and norepinephrine reuptake inhibitor that may also offer a more rapid onset of action than most antidepressants. Its overall side-effect profile is similar to that of the SSRIs, though hypertension is an additional possibility. There have also been a limited number of case reports of hepatotoxicity.

Nefazodone, a serotonergic reuptake inhibitor and receptor antagonist, is an additional option for managing depression and anxiety. Because of its association with cases of acute hepatic failure, however, it is an unlikely choice for patients with chronic hepatitis C.

Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) are no longer first-line choices for treating depression or anxiety because of their side effects and potential for serious drug interactions. For patients with interferon-induced cognitive impairment, the anticholinergic effects of tricyclic antidepressants may cause further disturbances in cognitive function. MAOIs require a special diet along with avoidance of various medications. Additionally, while suicidal behavior tends to be infrequent in patients with interferon-induced depression, tricyclic antidepressants and MAOIs are more lethal in overdose than other antidepressants.

Psychostimulants such as methylphenidate or dextroamphetamine may offer an alternative approach for interferon-induced depression. Both of these psychostimulants have been used extensively in treating depression in the medically ill and in cases of treatment-refractory depression. Their onset of action is rapid, with improvements noted in as little as a few days to a week. Psychostimulants also offer benefits for reducing interferon-induced fatigue and cognitive dysfunction, as discussed below. Contraindications to the use of psychostimulants include a history of psychosis, tic disorders, uncontrolled hypertension, and tachycardia. Patients whose depression is accompanied by symptoms of anxiety may be unable to tolerate the

TABLE 1
Commonly used antidepressants and mood stabilizers that may help manage interferon-induced neuropsychiatric effects

Drug	Daily dosage (initial to maximum)	Comments
Antidepressants		
Selective serotonin reuptake inhibitors (SSRIs)		• General SSRI side effects include nausea, headache, jitteriness, sexual dysfunction, hyponatremia, reduced platelet function • Paroxetine can produce a discontinuation syndrome, so it should be tapered gradually
Citalopram (Celexa)	10–60 mg	
Escitalopram (Lexapro)	10–20 mg	
Fluoxetine (Prozac and others)	5–80 mg	
Fluvoxamine (Luvox and others)	25–250 mg	
Paroxetine (Paxil)	10–60 mg	
Paroxetine, controlled-release (Paxil CR)	12.5–62.5 mg	
Sertraline (Zoloft)	25–200 mg	
Bupropion, sustained-release (Wellbutrin SR)	100–400 mg	• Can be used for nicotine dependence • May lower seizure threshold • Not indicated for anxiety disorders
Mirtazapine (Remeron)	15–45 mg	• Antihistaminergic effects can counteract interferon-induced insomnia and anorexia
Venlafaxine (Effexor)	37.5–225 mg	• May increase blood pressure (dose-related) • Cases of hepatotoxicity reported
Psychostimulants		• Psychostimulants can also be helpful for fatigue or cognitive dysfunction • Psychostimulants have addictive potential
Methylphenidate	5–60 mg	
Dextroamphetamine	5–40 mg	
Mood stabilizers		
Valproate	250–3,000 mg	• Requires blood level monitoring
Lithium	150–1,200 mg	• Requires blood level monitoring
Carbamazepine	200–1,600 mg	• Requires blood level monitoring • May foster bone marrow suppression
Olanzapine (Zyprexa)	5–20 mg	• May foster glucose intolerance and hyperlipidemia

activating effects of these medications. Use of the psychostimulant pemoline is contraindicated for patients with hepatitis C because of the risk of hepatotoxicity.

ANXIETY: MANY SIMILARITIES WITH DEPRESSION

Symptoms of anxiety develop in approximately 10% to 20% of patients receiving interferon,[33] but it is unclear whether they are simply part of the presentation of interferon-induced depression or a separate phenomenon. Nonetheless, anxiety tends to develop shortly after interferon is started, and episodes of anxiety become more frequent and severe over time. The etiology of these anxiety symptoms appears to be similar to that of interferon-induced depression, as changes are noted in levels of serotonin, tryptophan, and cytokines.[16–18]

Interferon-induced anxiety has been reported to respond to serotonergic antidepressants, but other antidepressants may also be effective. Benzodiazepines are another treatment option, offering more rapid anxiolysis. However, use of benzodiazepines in patients with a history of substance abuse requires caution, owing to their addictive potential. Gabapentin, an antiepileptic agent that is not metabolized in the liver, has also demonstrated some anxiolytic properties and may be an additional choice for treatment of interferon-induced anxiety.[34]

MANIA AND HYPOMANIA: GENERALLY A CAUSE FOR STOPPING INTERFERON

Interferon-induced mania and its milder presentation, hypomania, have been reported in a limited number of cases. In these cases, patients demonstrate excess energy, pressured speech, racing thoughts, marked distractibility, and increased goal-directed activity. When frankly manic, patients may also have paranoid or grandiose delusions and visual or auditory hallucinations. Accompanying mood disturbances include euphoria, expansiveness, irritability, and hostility. Hypomania and mania may develop a few weeks to several months after interferon therapy has

been initiated. Mania has also emerged following abrupt discontinuation of interferon or after a significant dose reduction. The etiology of interferon-induced mania remains unclear, but it may be related to dopamine hyperactivity or frontal cortical dysfunction. Less frequently, cases of interferon-induced psychosis have also been reported, although several included mood disturbances that suggested severe depression or mania.

In general, the management of hypomania or mania requires discontinuation of interferon, prompt psychiatric referral, and initiation of mood stabilizers **(Table 1)**. Lithium, carbamazepine, and valproate are effective mood stabilizers that require careful monitoring of drug levels. With lithium, stable levels are difficult to maintain if fluid imbalance (ie, edema, ascites) or renal dysfunction is present. Potential side effects and drug toxicities must also be considered with these agents. Lithium-induced hypothyroidism and carbamazepine-induced neutropenia or thrombocytopenia may be a greater concern for patients already at risk for these side effects with interferon therapy. While valproate has raised fears about the risk of drug-induced hepatotoxicity, the recent literature suggests that safe use may be possible for patients with chronic hepatitis C.[35]

Atypical antipsychotic agents are newer mood stabilizers that are likely to be the first choice for interferon-induced mania because of their ease of use, effectiveness, and tolerability. Unlike standard mood stabilizers, these agents do not require monitoring of serum drug levels and their dosing levels may be changed rapidly. Olanzapine has been the most studied of the atypical antipsychotics and has proven beneficial in treating manic episodes in patients with bipolar disorder at doses from 5 to 20 mg/d.[36] Quetiapine, risperidone, and ziprasidone are other atypical agents that can be used. Olanzapine is associated with an increased risk of glucose intolerance, which is a potential concern for patients with hepatitis C, since they have a higher than normal incidence of type 2 diabetes. On the other hand, the increased appetite and weight gain that are associated with olanzapine use may counteract interferon-related anorexia.

An alternative option for mood stabilization is gabapentin, given in doses from 900 to 1,800 mg/d. Successful control of interferon-induced mania was achieved at this dose range in a small series of patients with melanoma who received interferon alfa.[34] Besides providing mood stabilization, gabapentin was also believed to provide benefits as both an anxiolytic and a hypnotic.[34]

FATIGUE: THE MOST COMMON SIDE EFFECT

Fatigue is the most common and troubling side effect of interferon because of its ability to interfere with daily functioning. Managing fatigue requires a multifaceted approach to address the loss of both physical and mental energy. Patient education about interferon-induced fatigue should alert patients to this complication and provide potential coping techniques (eg, flexible work hours, reassigning household responsibilities). Appropriate nutrition and rest should be encouraged. Nonpharmacologic techniques that are beneficial for cancer-related fatigue, such as energy conservation, moderate exercise, and restorative therapy, can be incorporated.

Beyond the use of recombinant human erythropoietin and thyroid hormone supplements, psychotropic medications offer additional options for treating fatigue. The psychostimulants methylphenidate (15 to 60 mg/d) and dextroamphetamine (10 to 40 mg/d) can be given in divided doses in the morning and at noontime.[37,38] Both have been effective against fatigue related to cancer, HIV infection, and multiple sclerosis, but they must be used cautiously in patients with a history of substance abuse. Modafinil, a novel wake-promoting agent, has been helpful for treating fatigue in patients with multiple sclerosis. Small trials used doses of 100 to 300 mg/d and demonstrated good tolerability.[39,40] Results from another trial suggest that carnitine supplementation (2 g/d) may reduce interferon-related fatigue in patients with hepatitis C.[41] Carnitine's mechanism of action against fatigue is unknown but may be related to its effects on cellular energy metabolism.[41]

COGNITIVE DYSFUNCTION

Cognitive dysfunction is a less frequent side effect of interferon therapy, and studies have demonstrated changes suggestive of frontosubcortical impairment. Motor coordination, psychomotor speed, verbal memory, and executive function may be affected, though symptoms normally abate once interferon is stopped.

Interventions to reduce interferon-induced cognitive impairment are limited. Behavioral techniques used in early dementia, such as daily calendars and note-taking, may be helpful. Psychostimulants have improved cognitive function in patients with brain tumors or HIV infection by raising the level of alertness and enhancing attention and concentration.[42] The opioid antagonist naltrexone has been used in a few cancer patients to reduce

interferon-induced neuropsychiatric symptoms; although some patients demonstrated improved cognitive function, tolerability was often a problem.[43] Additionally, a risk of hepatotoxicity reduces naltrexone's appeal for use in patients with hepatitis C.

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