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Psychiatric Clearance for Patients Started on Interferon-Alpha-Based Therapies

Francis E. Lotrich, M.D., Ph.D.
Western Psychiatric Institute and Clinic, Pittsburgh

Newly Emergent Depression During IFN-α Therapy

Increasingly, psychiatrists are asked to provide "psychiatric clearance" for patients who are to be treated with a regimen that includes recombinant preparations of interferon-alpha (IFN-α), often in combination with other antiviral medications. The most common use for IFN-α is in the treatment of chronic hepatitis C, which affects about 2% of the general U.S. population and about 20% of people with severe mental illness (1). Each year, more people in the United States die from hepatitis C complications, such as severe cirrhosis and hepatocellular cancer, than from HIV. IFN-α is also used, in combination with other medications, to treat some cancers, such as metastatic melanoma.

This recombinant inflammatory cytokine has been associated with adverse effects on mental health, worse quality of life, increased risk for suicide, and treatment discontinuation. Most patients develop some fatigue and loss of appetite during treatment, which can be severe but is usually tolerable. However, 10%–40% additionally develop a full depressive disorder syndrome that can include suicidal ideation, amotivation, social withdrawal, guilt, anhedonia, irritability, anxiety, and crying (2–8). Untreated depression is a major contributor to dosage reductions or treatment discontinuations and consequent risk for viral relapse (9–11). Additionally, many patients with hepatitis C already have preexisting mental health disorders (12) that often go unrecognized (13). Such disorders can adversely affect a person's ability to tolerate a 24- to 48-week course of antiviral IFN-α therapy.

In addition to depression during IFN-α treatment, many patients (up to 25%) may develop anger and irritability (14–17), which can be independent of depression. These symptoms can occasionally be serious enough to result in road rage, spousal discord, and problems at work. Another common side effect of IFN-α is severe fatigue. Less commonly, mania, delirium, and psychosis can occur. Monitoring for these various psychiatric side effects, as well as distinguishing among these distinct conditions, is one role for the psychiatrist. Also, coadministered medications such as telaprevir and boceprevir (antiviral protease inhibitors) can inhibit cytochrome P450 (CYP) 3A4, resulting in increased blood levels of many psychiatric medications. A knowledge of psychopharmacology and potential medication interactions is thus also important. Finally, IFN-α treatment commonly has mild side effects such as nausea and malaise and occasionally is complicated by severe hematologic

Address correspondence to Dr. Lotrich (lotrichfe@upmc.edu).

abnormalities. Both sustained adherence and psychosocial stability are necessary, even in patients who do not develop frank neuropsychiatric syndromes.

Treating Depression and Other Syndromes During IFN-α Therapy

Most patients (75%–85%) who develop emergent depression during IFN-α therapy respond well to selective serotonin reuptake inhibitors (SSRIs) (18–20), with resolution of most symptoms (other than fatigue) within 4–8 weeks. When SSRIs are not an option, case reports support the use of other classes of antidepressants as well as ECT. Some medications, such as nefazodone and duloxetine, have been associated with rare instances of liver toxicity and are therefore not typically first-line choices. Dosage selection should be guided by awareness that concurrent use of protease inhibitors can increase blood levels of medications that are metabolized by CYP 3A4. The concurrent use of protease inhibitors with IFN-α and ribavirin, sometimes referred to as “triple therapy,” can result in a number of medication interactions. Thus, the psychiatrist should be informed about the concurrent antiviral medications that are used to augment IFN-α.

Effectively treating depression with medications in this medical population benefits from developing a trusting therapeutic alliance and providing psychoeducation, both of which are often critical for adherence. When effective, antidepressants should be continued throughout treatment and for at least a few months after completion of IFN-α treatment (21). The vast majority of the time, any newly emergent depression wanes and then ultimately remits within weeks (and occasionally a few months) after IFN-α is discontinued. However, there have been possible cases where the incident depressive episode became chronic and unremitting long after IFN-α discontinuation. Another rare syndrome that has been reported involves the development of manic symptoms when IFN-α is stopped. Also, the clinician should be alert to changes in medication blood levels that result from discontinuing the CYP 3A4 inhibitors at the conclusion of IFN-α therapy. For example, clonazepam levels can increase during triple therapy and then precipitously drop when therapy is completed, resulting in rebound anxiety and insomnia.

Additionally, various other neuropsychiatric side effects need to be distinguished from depression, as they often require different interventions. Most patients (>50%) develop some worsening of fatigue during treatment. Incapacitating fatigue (independent of depression) can sometimes be alleviated by addressing newly emergent medical conditions, such as anemia and hypothyroidism. In fact, clinically significant anemia can occur in 25%–50% of patients. This anemia is often the result of ribavirin treatment and may require reduction of the ribavirin dosage and/or erythropoietin treatment. Thyroid dysfunction develops in about 20%, although progression to more chronic hypothyroidism occurs in only 1%–2%. Fatigue may also be related to basal ganglia alterations and impaired dopaminergic function (22). Unfortunately, the complete resolution of fatigue is uncommon, but small open-label treatment trials have found mild benefits from modafinil (23) and methylphenidate (24).

Poor sleep quality and insomnia occur to some degree in the majority of patients (>50%) treated with IFN-α. Ribavirin treatment may contribute to this side effect. Nonpharmacologic treatments for insomnia potentially include behavioral therapies that

target sleep hygiene, stimulus control, sleep education, and relaxation techniques. Medications include sedating antidepressants such as mirtazapine, trazodone, and amitriptyline. Antihistamines (particularly in the setting of comorbid pruritus) can be useful, as can benzodiazepine receptor agonists for patients who are at low risk for drug abuse.

Interferon-induced mania, which is relatively uncommon in patients without a history of preexisting bipolar disorder, may respond to antipsychotics, gabapentin (25), or lithium (26). The treatment of emergent irritability, in the absence of other manic symptoms, has been less studied. Irritability can take the form of labile anger, with temporary and short-lived periods of mood dysregulation. It is often mild and can be effectively managed with behavioral therapy. When mild and coexistent with major depression and insomnia, it may improve with successful treatment of the depression and insomnia. It can occasionally be clinically severe, however, and may require mood-stabilizing medications.

Psychosis, which is treated with antipsychotics, occurs in less than 0.1% of patients (27). It is more typical in the presence of comorbid medical disorders such as HIV (28). Often, IFN-α will have to be temporarily discontinued while antipsychotic medications are initiated. Most patients (>50%) will endorse some slight slowing of cognitive processing and reaction times (29), and delirium sometimes occurs, particularly during high-dose intravenous IFN-α administration (30). Dosage reduction or discontinuation is often required in this situation.

Diagnosing these disorders requires educating the patient (and often the patient's family) about the symptoms of depression and irritability during the evaluation for psychiatric clearance. Because there is no blood test for these neuropsychiatric conditions, patients need to be explicitly instructed to self-monitor and be comfortable with freely reporting new symptoms. Some clinics may also regularly use self-report depression questionnaires to screen for depression. Ultimately, however, when the chief complaint is being grouchy and not wanting to get off the couch, a diagnostic interview is often required to clarify the differential diagnosis.

Preventing Depression

Prophylactic treatment with an SSRI has been proposed before beginning IFN-α treatment, and this appears to cut the incidence of emergent depression approximately in half (6, 7). However, because most patients will not develop a major depressive episode, the risks and potential benefits of starting an SSRI (which can include serious concerns such as retinopathy) should be discussed with the patient. Subsyndromal depression symptoms are major risk factor for developing major depression once IFN-α is initiated. Therefore, mildly depressed patients may be an important subgroup to specifically target for prophylactic SSRI treatment (31).

In addition to SSRIs, there are other approaches to potentially minimize the likelihood of depression. Poor sleep quality can increase the risk for subsequent depression (15, 32) and may be a target for increasing resilience. Unfortunately, it is not yet known which aspect of insomnia is most critical to treat. Benzodiazepine receptor agonists may decrease restlessness and increase sleep time but at the cost of decreasing slow-wave sleep. Nonetheless, attempting to address sleep problems may become an important element of

pre-IFN-α treatment. Low levels of omega-3 fatty acids may be another feasible dietary target for improving resilience (33), because the ratio of omega-3 and omega-6 fatty acids is associated with vulnerability. Exercise can modify interleukin-6 (IL-6) levels (34, 35), and elevated IL-6 is predictive of emergent depression during IFN-α treatment (32, 36). Psychosocial interventions to improve resilience include addressing social isolation and neuroticism (16), which have been associated with vulnerability. Thus, based on these observed risk factors for vulnerability, all patients should be strongly encouraged to sleep well, eat well, exercise, and socialize.

Several additional biological risk factors for depression during IFN-α therapy have been identified that may lead to targeted prophylactic interventions. These include a past history of major depression and/or elevated pretreatment depressive symptoms (7, 37); variation in serotonergic genes (36, 38, 39), in the interleukin-6 (IL-6) gene (36), and in phospholipase A2 and cyclooxygenase 2 genes (40); a hyperactive stress response in the hypothalamic-pituitary-adrenal axis (41); low brain-derived neurotropic factor (BDNF) levels and the BDNF gene (42); the TNF-α gene (17); and elevated sensitivity to activating the p38 mitogen-activated protein kinase (43).

Depression's Biology

Although the mechanism by which IFN-α causes depression is not known, a number of systems have been implicated. IFN-α administration can influence both frontal lobe and anterior cingulate function (44, 45), the basal ganglia (46), dopaminergic activity (47), serotonergic activity (48–51), glutamatergic systems (51, 52), including via increases in kynurenine and quinolinic acid, BDNF (42), mitogen-associated protein kinases (43), and circadian rhythms through effects on CLOCK gene expression (53). Thus, there is a plethora of pathways that plausibly mediate the various neuropsychiatric effects of IFN-α, and any combination of these pathways is likely to play a role in the development of depression. It can sometimes be helpful for patients to understand that the symptoms that emerge during IFN-α treatment have these various biological underpinnings. This education can often be part of the psychiatric clearance. Moreover, delineating the intracellular pathways and subsequent alterations in neurocircuitry will likely be important for understanding inflammatory cytokine-associated depression in general.

Elements of a Psychiatric Clearance for IFN-α Treatment

Because of the importance of both preexisting psychiatric conditions and the high rate of newly emergent diagnoses such as depression, a pretreatment psychiatric collaboration is often requested to identify and treat preexisting psychiatric disorders, address barriers to adherence, educate the patient, and ensure good communication among the treatment team.

Identify, diagnose, and treat preexisting psychiatric disorders

Many hepatitis C patients have a preexisting psychiatric disorder, which can potentially result in poor outcomes (54). Ideally, any preexisting mental illness should be stably managed for 6 months before starting IFN-α, although the exact length of time is a clinical judgment (55). Patients with severe mental health disorders such as schizophrenia should be

adherent with effective medications and therapy appointments. Ideally, preexisting mood disorders should be in remission before IFN-α is started. It is now known that most patients with preexisting psychiatric disorders or symptoms can do well with IFN-α treatment (56–59) if their symptoms are stably treated at baseline and closely monitored so that newly emergent symptoms can be addressed. As noted above, even preexisting subsyndromal depression symptoms are an important risk factor and may be amenable to antidepressant treatment. The benefits and risks of addressing these symptoms with an antidepressant should be discussed.

Importantly, alcohol use should be minimized, with sobriety as an important goal (55). Alcohol not only increases the risk for progression to cirrhosis in patients with hepatitis C, but it also may prevent the efficacy of antiviral therapies. Multidisciplinary teams can sometimes be effective in treating patients who have not managed to obtain 6 months of sobriety and who are at high risk for relapse to alcohol use (60) but for whom it is clinically important to start IFN-α as soon as possible. For patients who continue to drink, these considerations should be a clear part of the consent for IFN-α therapy. There is some evidence that many patients who continue to drink, as long as adherence with IFN-α treatment is maintained, can have a response comparable to that of nondrinkers (61). Likewise, patients who are actively and stably managed in methadone programs can tolerate IFN-α treatment as well as nonpsychiatric patients (62).

Address any barriers to adherence with the antiviral regimen

This starts with an assessment of family, social, and vocational supports, as well as coping styles and beliefs about mental illness. Establishing a therapeutic alliance with the patient is important for both timely and accurate reporting of neuropsychiatric symptoms and successful adherence with pharmacologic interventions. In collaboration with the hepatologist (and depending on the patient's individual risk for disease progression), consider delaying treatment until major social barriers can be effectively addressed.

Educate the patient about the symptoms of depression and their personal risk

Emergent depression can occur at any time during therapy, but it typically develops within the first 2 or 3 months of IFN-α treatment (11, 63–66). When appropriate, also provide the patient with education on the rationale and risks of prophylactic treatment to prevent depression.

Ensure prompt and open communication between the psychiatrist and hepatologist

This includes completion of the consent process for release of information. Ensure that regular patient monitoring will be feasible, with more frequency for particularly high-risk patients. Thus, an initial communication to the treating hepatologist that these four steps have occurred can be considered the definition of psychiatric clearance.

Conclusions

For Ms. A, the patient in the vignette, her fears regarding medications were discussed, and she initiated both citalopram and amitriptyline at night. Within 1 month, she was feeling

motivated and less depressed. Within 2 months, she was sleeping well and her depression was in complete remission. She subsequently developed ocular pain, dizziness, and vision changes. She was soon diagnosed with posterior scleritis. The possibility that this unusual syndrome was secondary to the SSRI was reviewed, but rather than discontinue the patient's antidepressant, the scleritis was successfully treated with prednisone. Despite this new medical complication, Ms. A's depression remained in remission through the remainder of treatment (other than some ongoing fatigue), her viral count remained undetectable, and she remained abstinent from alcohol. Several months after successful completion of her antiviral therapy, she elected to discontinue both the citalopram and the amitriptyline. She has remained in remission from both hepatitis C and depression.

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A middle-aged woman with chronic hepatitis C is referred for psychiatric clearance before starting antiviral therapy

"Ms. A" is a 56-year-old, married homemaker with chronic hepatitis C who was recommended for treatment with interferon-alpha (IFN-α) after her liver biopsy demonstrated a fibrotic score of 4/6. Because she had a history of excessive alcohol use, she was referred for psychiatric clearance before starting antiviral therapy. From the age of 21, Ms. A drank most days of the week, sometimes until she passed out asleep. She had a history of driving under the influence, of multiple attempts to stop drinking (resulting in mild agitation and insomnia but no other withdrawal problems), and of frequently feeling hung over. At age 55, she was diagnosed with hepatitis C during routine screening of liver function tests by her primary care physician. Her physician strongly recommended that she stop drinking, and a few months later, she successfully did so. Her only withdrawal symptom was insomnia. Other than a few experiments with marijuana and psychedelics in the early 1970s and past abuse of methaqualone to help sleep, no other drug use was noted.

At her initial psychiatric evaluation, Ms. A had already been completely abstinent from alcohol for 5 months. She did have a sense of being a failure in life, with poor self-esteem; however, she denied most other depression symptoms. Her Montgomery-Åsberg Depression Rating Scale (MADRS) score was 4 (minimal depressive symptoms). She endorsed having had one episode, 10 years earlier, in which she had notably low mood, anhedonia, weight loss, fatigue, passive death wish, insomnia, and an increased sense of being guilty. This resolved in about 1 year without treatment. There was no history of anxious, psychotic, or manic episodes. Her marriage of 30 years was stable, her 26-year-old son was now independent, and she volunteered several days a week delivering food to the elderly. She was recently started on metformin for fatty liver and occasionally took ibuprofen for carpal tunnel syndrome pain. Her only other medications were daily multivitamin, iron, and vitamin E supplements. Because of her past history of alcohol abuse, she was reluctant to start any medications for occasional insomnia.

After a 6-month waiting period for financial reasons, Ms. A was started on a 6-month course of weekly subcutaneous pegylated interferon-α2A injections (180 μg), daily ribavirin (1200 mg), and daily telepravir (2250 mg). Within 1 month, her viral levels were undetectable. However, she soon had worsening fatigue along with pancytopenia. Her hemoglobin level went from 14.9 to 6.9. She was given two units of packed red blood cells and an injection of epoetin alpha, and her ribavirin was briefly held. Her anemia and fatigue improved, but by week 8 of treatment, she reported increased depression and suicidal ideation. Her hepatologist prescribed citalopram (20 mg) and a small dose of amitriptyline (10 mg) for sleep. She was fearful of taking these medications, however, and did not start them. She was referred for a psychiatric reevaluation. By that time, her MADRS score was 19 (consistent with moderate depression) with increased suicidal ideation.