Published in final edited form as:

Curr Hepat Rep. 2010 April 6; 9(2): 113–118. doi:10.1007/s11901-010-0035-5.

Management of Psychiatric Disease in Hepatitis C Treatment Candidates

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Abstract

Depression and other influences on mental health can impact antiviral response rates during chronic hepatitis C treatment, the quality of life for these patients, and the risk for adverse outcomes such as suicide. Enhanced treatment outcomes for patients who are receiving interferon- α requires 1) addressing preexisting mental health problems, 2) alleviating psychiatric conditions that emerge during treatment, and 3) prediction and prevention of these conditions. Accumulating evidence indicates that these three goals are feasible. Collaborative involvement of psychiatric management may often be critical in this regard.

Keywords

Depression; Interferon; Treatment; Prevention; Screening

Introduction

Treatment of chronic hepatitis C virus (HCV) typically consists of interferon- α (IFN- α) in combination with ribavirin. Untreated HCV may lead to cirrhosis, hepatocellular carcinoma, or liver failure. However, pegylated IFN- α may enter the central nervous system [1•], potentially influencing neurotransmitter and neuronal function [2,3]. Depression caused by IFN- α can lead to discontinuation of treatment, lower quality of life, and occasionally suicide [4].

In addition to major depressive disorder (MDD), potential psychiatric problems emerging during IFN- α treatment include irritability and labile anger, severe fatigue, mania, psychosis, and cognitive slowing and delirium. Complicating these various problems, preexisting psychiatric disorders are often prevalent in those with HCV infection [5], and the preexisting disorders often go unrecognized [6]. Therefore, optimal HCV treatment often requires better screening, treatment, and stabilization of any preexisting psychiatric disorders prior to and during IFN- α -based therapy; accurate diagnosis and treatment of psychiatric disorders newly emerging during IFN- α therapy; and enhanced prediction and prevention of mood disorders that may result from IFN- α therapy.

Preexisting Psychiatric Disorders

Many HCV patients already have at least one preexisting psychiatric disorder. These patients are sometimes excluded from starting IFN- α -based treatment [7] or can have poor outcomes when treatment is initiated [8]. Therefore, a complete psychiatric assessment prior to initiating IFN- α is warranted in any patient screened to potentially have a psychiatric diagnosis. This assessment should include ensuring that alcohol use is minimized (ideally, sustained sobriety prior to treatment); other types of drug abuse or dependence are in remission (this includes being effectively managed with methadone); mood disorders are remitted; anxiety disorders are remitted or stabilized; and psychotic disorders are adequately treated. The suggested time span for “effectively stabilized treatment” is typically at least 3 to 6 months prior to initiating IFN- α -based therapy [9].

If preexisting psychiatric conditions are diagnosed and have not been adequately treated prior to initiating therapy, then further psychiatric involvement will be critical to successfully completing therapy. In addition to pharmacologic therapies, providers should consider whether family, vocational, and social supports can be more optimally employed. Furthermore, the pretreatment assessment should determine financial concerns, coping styles (eg, avoidance), or beliefs that could affect adherence to IFN- α therapy. Barriers to adherence for psychiatric care may be an important indicator that adherence to IFN- α therapy will be problematic. Addressing these barriers is therefore important.

Ongoing alcohol abuse is of particular concern because it can affect depression risk, treatment efficacy, and adherence. Less is known about preexisting anxiety disorders such as post-traumatic stress disorder, social anxiety disorder, and other miscellaneous disorders. However, treatment should attempt to mitigate the potential impact of these disorders on adherence. Regardless, multiple studies have found that if preexisting psychiatric disorders are effectively and stably managed, then IFN- α -based treatment outcomes can be similar to those observed in patients without psychiatric disorders [10]. Therefore, every attempt should be made to accomplish this goal prior to initiating IFN- α treatment.

Psychiatric Disorders Emerging During IFN- α Therapy

About 15% to 40% of patients who are prospectively followed with psychiatric assessments are noted to develop major depressive disorder (MDD) during the first several weeks of IFN- α therapy (IFN-MDD) [11]. Therefore, regular screening for IFN-MDD during the first 3 to 4 months of IFN- α therapy is recommended, because this is the period of highest risk. However, MDD can occur any time during IFN- α -based therapy, and thus continued monitoring for MDD symptoms throughout therapy is important. To guide treatment of IFN-MDD once it is diagnosed, one published double-blind randomized placebo-controlled trial (RCT) compared citalopram and placebo in 29 hepatitis C patients, and demonstrated efficacy for this selective serotonin reuptake inhibitor (SSRI) [12•]. Several other open-label prospective studies note similar efficacy and tolerance for either citalopram or escitalopram [13,14]. Of 105 subjects treated with SSRIs in case reports or open-label trials [15], more than 80% responded well to treatment, with either a 50% reduction in symptoms or clinical remission of the depression.

In addition to SSRIs, limited case reports of other antidepressants indicate that these may also be used successfully, as well as electroconvulsive therapy [15,16]. Further study is clearly required. A variety of antidepressant agents are available (Table 1). Regardless of choice, effective antidepressant use requires accurate and timely diagnosis of MDD and prompt initiation of treatment. Screening options include the routine use of self-report questionnaires or simply inquiring about depressed mood and anhedonia at all visits. Positive screens should be quickly followed by a more complete diagnostic assessment. The

current recommendation is to initiate treatment with an antidepressant as soon as IFN-MDD is diagnosed. Also, potential risks of using antidepressants in this population should be reviewed with the patient and monitored [17]. These risks includes the rare occurrence of mania or hypomania, and a rare, but possible, increased risk of hemorrhage, including retinal hemorrhage.

Fatigue is another prevalent side effect that can be incapacitating during IFN- α -based therapy. Fatigue may be distinct from IFN-MDD, and less responsive to antidepressant treatment [18]. It has been hypothesized that fatigue may be related to basal ganglia alterations and decreased dopaminergic function [19]. Open-label treatment with modafinil, a medication used to increase alertness in patients with narcolepsy, in 11 patients resulted in only very minimal improvements in self-rated fatigue [20]. However, a combination of methylphenidate and exercise was effective in 12 patients, as compared to historic controls [21]. Nonetheless, very little is known about the effective resolution of fatigue symptoms in this population, other than the targeted treatment of anemia and hypothyroidism when these are diagnosed.

In addition to IFN-MDD and fatigue, a syndrome comprised of labile anger, irritability, and/or hostility has been reported [22–25]; this syndrome affects up to 25% of patients receiving IFN- α therapy and appears to be distinct from depression. Less is known about effectively treating labile anger, and whether it would respond to antidepressants and/or mood stabilizers; further study is indicated. Labile anger requires distinction from dysphoric mania or IFN-MDD [16,22]. In fact, several case reports of actual frank mania have been published [26•]. IFN-induced mania may respond to antipsychotics, gabapentin [27], and/or lithium [28]. Whether these medications may help with labile anger has not been examined.

Poor sleep quality and insomnia often complicate treatment, and may also contribute to worsened depression, irritability, and/or fatigue. Treatment selection for insomnia should be guided by knowledge of the patient's drug abuse history and concurrent sedating medications (eg, methadone). When available, nonpharmacologic treatments can be effective and include cognitive-behavioral therapies that target sleep hygiene, stimulus control, sleep education, sleep restriction, and relaxation techniques. In patients with comorbid depression, antidepressants with sedating properties (eg, mirtazapine) may be effective. For some, antihistamines (eg, hydroxyzine) may be useful for sleep difficulties and pruritus. In patients with lower risk for drug abuse, benzodiazepines (eg, temazepam and lorazepam) can be effective for acute treatment, particularly in the setting of anxiety, although dependence can occur with more chronic use. Both benzodiazepines have intermediate half lives and are primarily excreted via glucuronidation. Other benzodiazepine receptor agonists (eg, zolpidem, zaleplon, and eszopiclone) may have less abuse potential and can also be effective. Antihistaminergic antidepressants (eg, trazodone) may also be useful, but this medication has been associated with rare cases of hepatotoxicity and more commonly with dizziness and daytime sedation. Whether melatonin or melatonin receptor agonists would be effective in this population is not known, although these have minimal abuse potential and limited side effects.

The emergence of psychosis has also been observed, albeit rarely. Psychosis typically occurs in less than 0.1% of subjects [29], and may be particularly of concern in patients with other comorbid disorders such as HIV [30]. For this rare side effect, case-control studies report that antipsychotic medications may be useful [30]. Cognitive processing and reaction times may also be slowed by IFN- α [31], particularly in those with other comorbidities. However, because most cases of severe cognitive disruption and delirium have been described in the setting of high-dose intravenous IFN- α use [26•], dose reduction or discontinuation is currently the most effective treatment for this adverse effect.

In summary, IFN-MDD often responds well to treatment with an antidepressant, and SSRIs have been the most widely studied for this indication. Nonetheless, selection of a specific medication should be guided by prior treatment history, patient preference, side-effect profile, and potential interactions with other medications (Table 1) [15,16]. Furthermore, because the risk for depression relapse remains high immediately following the discontinuation of IFN- α treatment [32], any antidepressant used successfully to treat IFN-MDD should be continued for a period after the completion of IFN- α therapy. Although there is minimal evidence base to guide when discontinuation should occur, this period should be a minimum of 3 to 6 months after IFN- α treatment. Moreover, IFN-MDD must be distinguished from other syndromes, including fatigue, labile anger, mania, cognitive slowing, and psychosis, because these may be less responsive to antidepressant treatment alone.

There is a paucity of clinical evidence regarding treatment of syndromes other than IFN-MDD; however, consideration may be given to stimulants for fatigue, mood stabilizers for both labile anger and mania, lowered IFN- α dose for cognitive slowing, and antipsychotics for IFN-induced psychosis. However, if any treatment is chosen for these symptoms, the rationale, potential side effects and risks, and the limited evidence base should be clearly discussed with the patient. For these reasons, prompt consultation with a psychiatrist is often important for clarifying the psychiatric diagnosis, selecting a treatment, and educating the patient about treatment expectations.

Prevention of IFN-MDD

Because IFN-MDD is so common and disabling, prophylactic use of SSRIs prior to beginning the IFN- α therapy has been considered [33]. However, the two small published RCT studies for HCV did not find evidence for prevention of IFN-MDD [34•,35•]. Thus, limited evidence exists to support starting all patients on an antidepressant prior to initiating IFN- α therapy. Nonetheless, in the open-label trials of patients who had prior history of affective disorder, only 9% developed IFN-MDD while taking SSRIs [33]. Thus, it is possible that pretreatment with SSRIs may be useful in a specific subgroup of patients (ie, those with a history of MDD).

Post-hoc exploratory analyses of the RCT data also indicated that treating sub-threshold symptoms of depression in patients may have prevented the progression to fully diagnosable IFN-MDD in this subset [35•]. This observation is also consistent with the often-repeated finding that pretreatment baseline depression-rating scale scores are predictive of subsequent IFN-MDD. Therefore, it is plausible that treating sub-threshold depression and/or treating patients with past histories of recurrent MDD may prevent further progression to IFN-MDD. As above, the rationale, potential side effects and risks, and the limited evidence base should be clearly discussed with the patient.

Future Prediction of IFN-MDD

Most patients do not develop IFN-MDD, and preventive measures would be unnecessary in these individuals. Several biologic and demographic predictors of increased risk for IFN-MDD have been observed. As alluded to above, a history of MDD and/or elevated pretreatment depressive symptoms increases the chance that the patient will subsequently develop IFN-MDD, but the odds are still less than 50% [16,17,33]. Evidence for other risk factors includes variation in serotonergic genes [36–38], in the interleukin-6 (IL-6) gene [37], in pretreatment IL-6 levels [39], in pretreatment sleep quality [22], a hyperactive stress response in the hypothalamic-pituitary-adrenal axis [40], social isolation, and the personality trait of neuroticism [36]. Less evidence exists for a consistent relationship between IFN-MDD risk and age, gender, or history of drug and alcohol abuse.

Regardless, the clinical importance of these predictors will require ongoing and future examination. They are not currently a routine element of the pretreatment assessment. However, of these potential risk factors, poor sleep quality may be one that is readily modifiable [33], and thus worth further examination. The hazard ratio for IFN-MDD in patients having very poor sleep quality was greater than four [22]. Whether treating insomnia can prevent IFNMDD remains to be tested. Nonetheless, treatment of sleep disorders and insomnia may be beneficial for the patient, whether doing so prevents IFN-MDD or not. Thus, preexisting sleep disorders should be a recommended element of pretreatment assessment and treatment.

The Role of Psychiatric Collaboration

Not all patients will require a psychiatrist's involvement. During the initial pretreatment work-up, all HCV patients who are being considered for IFN- α therapy should be briefly screened for past histories of any psychiatric disorders, past and current mental health treatments, current depressive symptoms (eg, using a questionnaire such as the Physician Depression Questionnaire-9 [PDQ-9], the Beck Depression Inventory-II, or the Hospital Anxiety and Depression Scale), and current sleep quality. For general screening purposes, the PDQ-9 has only nine questions; these items directly correspond to symptoms diagnostic of MDD including sleep, and it is available for free. HCV patients who are found to have absolutely no evidence of mental health problems at screening can be educated regarding the potential psychiatric effects of IFN- α therapy, and then closely followed during treatment. For these individuals, a complete pretreatment psychiatric assessment is probably not necessary, although continued screening for IFN-MDD should occur regularly during the first 3 to 4 months of IFN- α therapy. Although this is the period of highest risk, monitoring should continue throughout therapy.

However, if basic screening does indicate a potential problem, then further psychiatric assessment is warranted. When requested, this "psychiatric clearance" to initiate IFN- α therapy should include:

- 1) assessing whether there are any psychiatric disorders and whether they have been stably managed for the past 3 to 6 months,
- 2) assessing any barriers to adherence with either psychiatric or IFN- α treatment,
- 3) assessing the level of current depressive symptoms and considering prophylactic treatment if the patient does have subsyndromal depression,
- 4) educating the patient and family about their individual risk for developing IFN-MDD during IFN- α treatment, the symptoms of IFN-MDD, and the plan (should IFNMDD develop),
- 5) assessing the strength of family, social, and vocational supports,
- 6) ensuring that prompt communication is possible between the psychiatrist and hepatologist, typically involving signed informed consent to communicate should the need arise, and
- 7) ensuring that regular follow-up is available and feasible, with more frequency for particularly high-risk patients.

A consultation request from the hepatologist for psychiatric clearance may consider specifying that each of these needs be individually addressed, whether for patients currently undergoing mental health care or those who have never been treated. As a result of this initial assessment, some patients may require further or more intensive treatment, initiation of a new treatment, closer monitoring with more frequent appointments, further education,

addressing barriers to treatment adherence, and/or deferring IFN- α therapy. However, this clinical decision is best accomplished by collaboration between the hepatologist and psychiatrist, and should be influenced by the status of the patient's liver disease and the presence of other comorbid medical illness, as well as the individual requirements of specific patients.

Conclusions

By addressing both preexisting and emerging psychiatric problems in HCV patients, chances are enhanced for a better antiviral treatment outcome, minimized psychiatric suffering, and a better quality of life. Treatment algorithms for this purpose have been implemented at some comprehensive HCV treatment centers [9,16]. One unifying theme of these algorithms is the need for screening and then a more complete pretreatment psychiatric evaluation in many patients, followed by ongoing psychiatric monitoring during IFN- α treatment, prompt initiation and adjustment of antidepressant treatments, and continuing bidirectional communication between the hepatologist and psychiatrist. When this collaboration transpires, the majority of patients with preexisting psychiatric concerns can be effectively treated with IFN- α [17], most cases of emergent IFN-MDD can be effectively remedied [15], and the future prediction and personalized prevention of IFN-MDD may soon be possible [33].

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Table 1

Antidepressants^a

	Comments regarding clinical use
SSRIs	Given their safety profile, SSRIs are typically recommended as first-line antidepressants. Occasionally, SSRIs can have mild side effects (eg, sedation, akathisia, nausea, loose stools, headaches) during first week of treatment. Effects on sexual function are occasionally longer lasting. Induction of mania is a rare side effect. Concomitant use of other serotonergic agents (eg, tramadol or St. John's Wort) can result in serotonin syndrome.
Citalopram	Minimal p450 interactions. Citalopram has the largest evidence base for treating MDD during IFN- α -based therapy. Typical dose, 20 mg/d.
Escitalopram	A specific stereoisomer of citalopram. Minimal p450 interactions. Typical dose, 10 mg/d. Not yet available in generic form.
Sertraline	Minimal p450 interactions. Dose range, 50–200 mg/d.
Fluoxetine	Very long half-life. Notable p450 2D6 inhibition. Some inhibition of 1A2, 3A4. Typical dose, 20 mg/d.
Paroxetine	Notable p450 2D6 inhibition. Mild anticholinergic side effects and occasionally slightly sedating when first initiating. Typical dose, 20 mg/d. May become an SNRI at higher doses.
Fluvoxamine	Notable p450 1A2 interactions. Also inhibits 2D6, 3A4, 2C19. Dose range, 25–100 mg/d.
SNRIs	Only sporadic case reports exist for this class of medications in treating MDD during IFN- α -based therapy.
Venlafaxine	Occasional slight increase in blood pressure. Typical dose range, 75–300 mg/d. May be more serotonin selective at lower doses.
Desvenlafaxine	Active metabolite of venlafaxine. Typical dose range, 100–200 mg/d.
Duloxetine	Rare cases of liver toxicity complicate use in HCV patients. Typical dose, 60 or 120 mg/d.
DNRI	
Bupropion	Can be slightly activating rather than sedating. Comes in sustained-release and extended-release formulations. Typical dose range, 100–300 mg. Minimal sexual side effects.
Mixed-Receptor	
Mirtazapine	Serotonin receptor 3 antagonism may be useful for alleviating nausea. Can be sedating; has been associated with weight gain. No sexual side effects. Rare case reports of neutropenia. Typical dose range, 15–60 mg/d.
Nefazodone	Sporadic cases of liver toxicity. No sexual side effects. Can be sedating, helpful with insomnia.
TCAs	All TCAs have the potential for cardiac toxicity following overdose.
Nortriptyline	Similar to SNRIs. Some anticholinergic side effects. Typical dose, 75 to 150 mg/d.
Imipramine	Sedating. Anticholinergic side effects.
D2/5HT2 agents	
Risperidone Paliperidone Olanzapine Quetiapine Ziprasidone Aripiprazole	No evidence base for use in patients on IFN- α . None are approved as sole agents for the treatment of unipolar MDD. Some are approved for augmentation to treat depression with psychosis or to treat bipolar depression. This class can variably have effects on lipids and glucose regulation, in addition to weight gain.

DNRI dopamine/norepinephrine reuptake inhibitor; FDA Food and Drug Administration; HCV hepatitis C virus; IFN interferon; MDD major depressive disorder; SNRI serotonin/norepinephrine reuptake inhibitor; SSRI selective serotonin reuptake inhibitor; TCA tricyclic antidepressant

^aThe list includes SSRIs approved for use in the United States, SNRIs, DNRI, and two representative TCAs. The rationale for use and any potential side effects or expected interactions should be discussed prior to initiating antidepressant treatment. This is *not* an all-inclusive list of medications that have been used to treat MDD. Lithium, monoamine oxidase inhibitors, electroconvulsive therapy, and vagal nerve stimulation have also received FDA approval for treating depression. In addition to medications that act on the dopamine 2 and serotonin 2 receptors (D2/5HT2), there have been depression treatment trials of a variety of other medicinal products not on this list, but they are not currently FDA approved