

Managing the neuropsychiatric complications of hepatitis C treatment

Interferon- α is the mainstay of hepatitis C treatment and has been linked to several neuropsychiatric complications, including depression, anxiety, mania, psychosis and cognitive changes. This article reviews the management of neuropsychiatric adverse effects and the risks of interferon- α treatment to psychiatric patients.

Hepatitis C virus (HCV), formerly known as non-hepatitis A and non-hepatitis B virus, was first isolated in 1989. This flaviviridae virus is predominantly transmitted through intravenous drug use, with an estimated 170 million people worldwide and at least 250 000 individuals in the UK currently infected (World Health Organization, 1997). Once infected, approximately 55–85% of individuals will develop chronic HCV, which is the leading reason for liver transplantation (Strader et al, 2004). Treatment of HCV consists of interferon-alpha (IFN- α) with oral ribavirin for 24 weeks in genotypes 2 and 3, and 48 weeks in genotypes 1, 4, 5 and 6. Advances in HCV antiviral therapy, specifically weekly subcutaneous pegylated IFN- α (peg-IFN- α) in combination with daily ribavirin, has led to increased treatment response rates of at least 50% in patients with genotype 1 and 80–90% in patients with genotypes 2 or 3 (Hadziyannis et al, 2004; Strader et al, 2004).

Despite the improved treatment outcomes with peg-IFN- α , psychiatric complications, most commonly

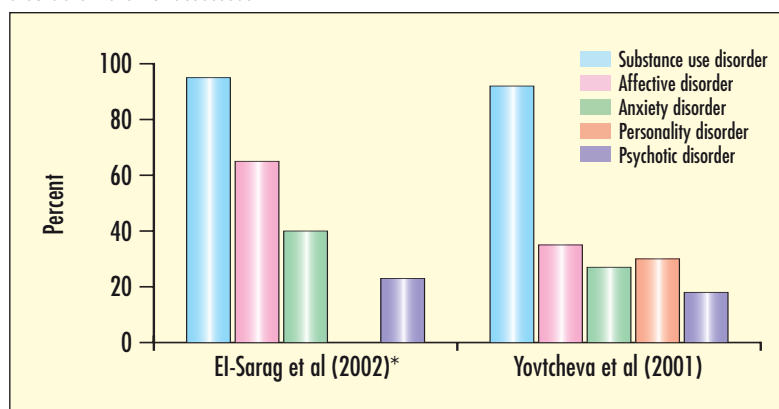
depression, continue to plague HCV treatment. Moreover, psychiatric sequelae of antiviral therapy can result in dose reduction or discontinuation of IFN- α treatment and compromise the effectiveness of HCV treatment. This article will summarize key psychiatric complications of IFN- α treatment in HCV and provide clinicians with a treatment approach to these adverse effects. For the purpose of this review, the term 'depression' will refer to major depression caused by IFN- α , as opposed to non-specific depressive symptoms.

Treating hepatitis C in patients with mental illness

Several studies report a higher incidence of psychiatric disorders in patients diagnosed with HCV (Yovtcheva et al, 2001; El-Sarag et al, 2002); psychiatric co-morbidity is often the rule rather than the exception in HCV (Figure 1). Intravenous drug use is the primary mode of transmission of the HCV virus, and substance use disorders and depression are the most common psychiatric diagnoses in this population. Therefore, initial assessments of HCV patients should include a screen for co-morbid psychiatric disorders, past psychiatric treatment and the presence of substance use disorders. Patients with a suspected psychiatric disorder or complicated psychiatric history may benefit from a referral to a psychiatrist for further assessment and treatment recommendations before starting IFN- α therapy.

Historically, the high rates of psychiatric co-morbidity in HCV patients have raised concerns about potential treatment non-compliance, reduction in HCV treatment response and higher rates of IFN- α discontinuation. These assumptions resulted in a large number of patients being excluded from HCV treatment because they had a history of mental illness (Rifai et al, 2006). However, studies evaluating treatment response in patients suffering from mental illness, including substance use disorders, demonstrate comparable sustained virological response (SVR) rates (defined by the absence of detectable HCV RNA in the serum at 6 months post-treatment) and treatment adherence to controls (Van Thiel et al, 1995; Schaefer et al, 2003). Moreover, increased adverse effects in psychiatric patients are likely limited to a specific subset of patients suffering from post-traumatic stress disorder and concurrent substance use disorder.

Figure 1. Prevalence of psychiatric disorders in untreated hepatitis C patients. *Personality disorders were not assessed.



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ders (Ho et al, 2001). As a result of these studies, treatment guidelines were amended and currently list uncontrolled major depression as the only absolute psychiatric contraindication to IFN- α treatment (Strader et al, 2004). As a result, a greater proportion of HCV patients are receiving immunotherapy and the potential for neuropsychiatric adverse events has further emerged as a growing concern.

IFN- α -induced depression

The prevalence of IFN- α -induced depression in HCV patients ranges from 10–40%, with more rigorous studies reporting an estimated prevalence of between 20 and 30% (Dieperink et al, 2000; Bonaccorso et al, 2002a; Horikawa et al, 2003). Horikawa et al (2003) followed 99 patients starting IFN- α immunotherapy for hepatitis C and found a 23.2% incidence of major depressive episodes using structured psychiatric interviews. Nearly 75% of patients in this study developed a major depressive episode within the first 8 weeks of treatment. In one prospective study of 55 HCV patients, peak suicidal ideation also occurred at week 8 of IFN- α treatment (Dieperink et al, 2004). Furthermore, no completed suicides were observed over the 24-week study period, although completed suicides related to IFN- α have been reported anecdotally in the literature (Janssen et al, 1994). Therefore, suicide risk should be assessed before initiating immunotherapy in addition to screening for depression.

Given the risk of depression during IFN- α therapy, identification of high-risk patients and appropriate monitoring strategies has remained a research focus in this area. Multiple studies have evaluated potential risk factors and found that elevated baseline depressive symptoms were a robust predictor of IFN- α -induced depression in HCV patients (Bonaccorso et al, 2002b; Dieperink et al, 2003; Raison et al, 2005). Psychiatric co-morbidity, history of psychiatric illness, increased IFN- α dose, longer IFN- α treatment duration and increased ribavirin dose are also listed as additional risk factors, although further research is required to evaluate their exact strength (Schaefer et al, 2002; Dieperink et al, 2003; Raison et al, 2005). While age and gender have been noted to be risk factors for depression in the general population, these trends have not been observed in treated HCV patients. In cases where analysis of risks and benefits for IFN- α therapy are complex, a referral to a psychiatrist for further evaluation and potential reduction in depression risk factors is warranted.

Mechanism of IFN- α -induced depression

While several proposed mechanisms for IFN- α -induced depression are cited in the literature, much of the evidence supports IFN- α associated changes in the serotonin system (Figure 2) (Bonaccorso et al, 2002b; Capuron et al, 2003; Wichers et al, 2005). Studies have reported reductions in both tryptophan and plasma sero-

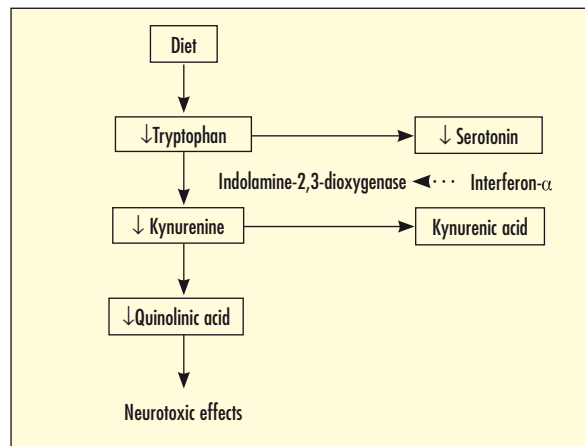


Figure 2. Proposed mechanism for interferon- α -induced depression.

tonin concentrations following IFN- α administration, both of which were correlated with increased Montgomery-Asberg depression rating scale (MADRS) scores (Bonaccorso et al, 2002b; Capuron et al, 2003). It is thought that IFN- α increases indolamine-2,3-dioxygenase (IDO) activity (an enzyme converting tryptophan to kynurenine), resulting in increased kynurenine and reduced serum serotonin (5-hydroxytryptamine (5-HT)) levels (Bonaccorso et al, 2002b). Furthermore, prophylactic treatment paroxetine appears to attenuate tryptophan depletion following IFN- α exposure (Capuron et al, 2003).

Expanding on these findings, Wichers and colleagues have proposed a neurotoxic model for IFN- α -induced depression by demonstrating a positive correlation between the production of quinolinic acid (a neurotoxic metabolite of kynurenine) and MADRS scores (Wichers et al, 2005). Further evidence for serotonin dysregulation has been derived from an animal study showing IFN- α -induced up-regulation of 5-HT transporter messenger RNA in rats, resulting in increased 5-HT reuptake (Morikawa et al, 1998).

Management of IFN- α -induced depression

Management of IFN- α -induced depression begins with screening for baseline depressive symptoms before initiating immunotherapy. The initial assessment should incorporate the use of standardized depression rating scales, such as the MADRS, Hamilton depression rating scale (HAM-D), Beck depression inventory (BDI) or the Centre for Epidemiological Studies depression scale (CES-D), to evaluate baseline depressive psychopathology and the presence of major depression. When HCV patients receiving IFN- α therapy report symptoms of depression, clinicians should be cognizant of additional IFN- α -related adverse effects, such as anaemia or hypothyroidism, which may cause or exacerbate depressive symptoms. Before starting immunotherapy, HCV patients with baseline depressive symptoms or an elevated risk for developing IFN- α -induced depression should be treated with antidepressants using one of two

Table 1. Prophylactic treatment of interferon- α -induced depression in hepatitis C patients

Study	Description	Duration (weeks)	n	Measures	Treatment	Results
Shaefer et al (2005)	Open-label prospective controlled trial	24	36	DSM IV	Citalopram 20 mg/day +/- augmentation with mirtazapine 30–60 mg/day	Reduced incidence of major depressive episode in prophylactic group (14%) compared to psychiatric disorder (64%) and control groups (55%)
Kraus et al (2005a)	Open-label prospective controlled trial*	~38–40	17	HADS	Paroxetine 20 mg/day (n=6) Citalopram 20 mg/day (n=2)	Significant reduction in HADS
Dieperink et al (2003)	Open-label prospective trial	24	55	HAM-D, BDI, Zung, IDD, MFI, PANAS, POMS, SFHS	Sertraline 50 mg/day initiated (Mean doses not reported)	Drop-out rates did not differ between prophylactic and no psychiatric treatment groups No difference in major depressive episode between prophylactic group and untreated hepatitis C controls

*Past history of interferon- α -induced major depressive episode in prophylactic group. BDI = Beck depression inventory; DSM IV = indicates clinical examination as per major depressive episode criteria; HADS = hospital anxiety and depression scale; IDD = inventory to diagnose depression; MFI = multidimensional fatigue inventory; POMS = the profile of mood states; PANAS = the positive and negative affect scale; SFHS = short-form health survey quality of life scale.

approaches: prophylactic antidepressant treatment (starting antidepressant before initiation of IFN- α); or symptomatic antidepressant treatment (initiating antidepressant treatment once or if significant depressive symptoms emerge). All published studies and case series for treating IFN- α -induced depression in HCV patients using prophylactic and symptomatic approaches are summarized in *Tables 1* and *2*. Both treatment strategies are acceptable, however, the efficacy and indication for each approach requires further elaboration.

Currently, no randomized controlled trials in HCV patients evaluating prophylactic antidepressant therapy for IFN- α -induced depression have been published. The only randomized controlled trial evaluating prophylactic antidepressant treatment for IFN- α -induced depression was conducted in patients treated for melanoma (Musselman et al, 2001). In this seminal study, Musselman et al demonstrated the efficacy of prophylactic paroxet-

ine treatment (mean dose = 31 mg/day) for IFN- α -induced depression in 40 melanoma patients treated with IFN- α and showed a significant reduction in HAM-D scores after 2 weeks of treatment. Re-analysis of the data from this study suggested that prophylactic treatment was most effective for the mood and cognitive changes associated with depression as opposed to neurovegetative and somatic symptoms (Capuron et al, 2002). Caution is needed when extrapolating these findings to patients with HCV, as higher IFN- α doses are used in melanoma treatment.

Evidence for prophylactic antidepressant treatment exclusively in HCV patients receiving immunotherapy, has been restricted to open-label controlled studies (*Table 1*). Schaefer et al (2005) demonstrated benefits in a 24-week open-label trial involving pre-treatment with citalopram 20 mg/day and augmentation with mirtazapine (for refractory cases) in 14 patients receiving IFN- α .

Table 2. Symptomatic treatment of interferon- α -induced depression in hepatitis C patients

Study	Description	Study duration (weeks)	n	Evaluation of depression	Treatment	Results
Kraus et al (2002)	Open-label prospective uncontrolled trial*	52	14	DSM-IV HADS	Paroxetine 20 mg/day	11/14 patients completed interferon- α therapy
Hauser et al (2002)	Open-label prospective uncontrolled trial	26–52	13	BDI SCID-I	Citalopram 20–60 mg/day	9/11 achieved response Mean time to response = 5.4 weeks
Horikawa et al (2003)	Open label prospective uncontrolled trial	36	22	HAM-D DSM-IV	Sulpiride 150 mg/day	Sulpiride: 13/17 had remission No treatment: 2/5 had remission†
Scalori et al (2005)	Open uncontrolled prospective trial	12	11	MMPI depression scale	Paroxetine Sertraline (doses not reported)	Successful treatment of depression or severe irritability in all 11 cases
Schramm et al (2000)	Case series	N/A	10	Self-report	Sertraline 50 mg/day	7/10 patients reported 'marked improvement'
Maddock et al (2004)	Case series	52	5	DSM-III-R CGI	Paroxetine 20–40 mg/day Amisulpride 50–150 mg/day Levosulpiride 50 mg/day	2 of 2 had good response 1 of 2 had good response No reduction in CGI

*Sub-sample from 121 patients in study; † Difference failed to achieve significance. BDI = Beck depression inventory; CGI = clinical global improvement; DSM IV = indicates clinical examination as per major depressive episode criteria; HADS = hospital anxiety depression scale; HAM-D = Hamilton depression rating scale; MMPI = Minnesota multiphasic personality inventory; SCID-I = structured clinical interview for DSM-IV axis I disorders.

Antidepressant pre-treatment resulted in at least a 40% decrease in the incidence of IFN- α -induced major depressive episodes compared to the two control groups – an untreated group with psychiatric disorders and an untreated group without a psychiatric history. A smaller open-label controlled study evaluated the efficacy of prophylactic paroxetine or citalopram in HCV patients with a history of IFN- α -induced depression and subsequent antiviral discontinuation (Kraus et al, 2005). In this study, prophylactic antidepressant treatment resulted in significantly lower depressive scores during peg-IFN- α re-treatment. Therefore, antidepressant pre-treatment can be beneficial in HCV patients at risk for IFN- α -induced depression or with prior episodes.

Although prophylactic antidepressant treatment can reduce the incidence of IFN- α -induced depression, many HCV patients do not develop depression during their course of antiviral therapy. In fact, a prospective controlled study evaluating prophylactic sertraline (50 mg/day) in high-risk patients (HAM-D>20) and three comparison groups found that only 48% of patients without psychiatric care at baseline developed IFN- α -induced depression (Dieperink et al, 2003). Furthermore, reported prevalence rates for depression suggest that nearly 75% of treated HCV patients do not experience severe depressive symptoms (Horikawa et al, 2003). Broad-based prophylactic therapy would unnecessarily expose a large number of patients to antidepressant medications, which carry their own side effect risks, and result in IFN- α discontinuation. Therefore, prophylactic antidepressant treatment in treated HCV patients should be reserved for patients scoring greater than 10 on the BDI (Dieperink et al, 2003). In patients with BDI scores between 6 and 10, antidepressant therapy may be of benefit if multiple risk factors for IFN- α -induced depression are identified in the patient's history.

The alternative for patients who are at lower risk or who are opposed to prophylactic antidepressant treatment is a symptomatic treatment approach. *Table 2* highlights the current literature for symptomatic antidepressant in HCV patients. The results of studies suggest that IFN- α -induced depression responds well to antidepressant therapy, mainly selective serotonin-reuptake inhibitors (SSRIs). Medication tolerance was not a significant issue for patients receiving antidepressant therapy in these studies.

Regardless of the antidepressant treatment approach, regular follow up and monitoring of depressive symptoms is essential. All high-risk individuals with HCV require routine follow up every 2 weeks for at least the first 3 months of IFN- α treatment and monthly thereafter, because of the aforementioned risk of depression during the initial months of antiviral therapy. Both close monitoring and appropriate use of prophylactic antidepressant therapy can result in improved IFN- α completion rates during HCV treatment (Kraus et al, 2005).

Selecting an antidepressant for IFN- α -induced depression

As outlined in *Tables 1* and *2*, pharmacotherapy of IFN- α -induced depression has primarily involved SSRIs, particularly citalopram and paroxetine. Both citalopram and escitalopram are tolerated well by untreated HCV patients and have minimal drug interactions (Gleason et al, 2004, 2005). Despite demonstrated benefits in treating HCV patients with IFN- α -induced depression, paroxetine carries an increased risk of withdrawal side effects upon discontinuation (Kraus et al, 2002). Mirtazapine should be used cautiously because of its added risk of neutropenia, which is a significant adverse effect of IFN- α and a cause for dose reduction or discontinuation of immunotherapy. Bupropion has the propensity to lower seizure threshold and requires careful dose titration when used with IFN- α because of rare risks of seizures with high dose immunotherapy. Lastly, the association between SSRIs and gastrointestinal bleeding poses a significant concern in HCV patients with a history of oesophageal varices or receiving concurrent non-steroidal anti-inflammatory medications (Weinrieb et al, 2003).

Consideration of pharmacological profile can also be helpful in choosing an antidepressant for IFN- α -induced depression. Clinicians should be cognizant of possible adverse effects to medication when treating depressed HCV patients with antidepressant agents, as choice of an agent based on its pharmacological profile may prove beneficial in reducing side effects and managing symptoms. In addition to antidepressants, agents such as D2-antagonists have shown benefits in treating cases of IFN- α -induced depression but remain limited to small uncontrolled trials and have not been replicated (Horikawa et al, 2003). However, combined treatment with antipsychotic and antidepressant medications is warranted in severe cases of IFN- α -induced depression with psychotic features, with favourable treatment outcomes reported anecdotally (Sockalingam and Balderson, 2005). Although large studies evaluating adjunctive psychotherapy, such as cognitive behavioural therapy, and lifestyle modifications are lacking, these interventions can be beneficial augmentation strategies in some HCV patients failing to respond to antidepressant treatment.

IFN- α -induced depression generally responds to antidepressant therapy within the first 4 weeks of treatment (Kraus et al, 2002). Response rates as high as 78% have been reported, although these estimates are likely inflated secondary to the uncontrolled nature of the studies (Kraus et al, 2002). In depressed HCV patients, timely antidepressant therapy can often preclude the need for IFN- α dose reduction or discontinuation (Schramm et al, 2000; Kraus et al, 2005). However, if patients develop severe IFN- α -induced depression or have a poor treatment response to antidepressant therapy, IFN- α discontinuation may be required.

Anxiety and IFN- α treatment

Anxiety symptoms are also associated with IFN- α treatment of HCV, with one prospective study showing increased anxiety symptoms from 13% pre-treatment to 26% following initiation of IFN- α therapy (Kraus et al, 2003). Although no robust associations exist between IFN- α and specific anxiety disorders, IFN- α -induced anxiety has been successfully treated with antidepressants and benzodiazepines (Maddock et al, 2004). Of the benzodiazepines, lorazepam, oxazepam and temazepam are preferred in HCV patients because of their ability to bypass phase I hepatic metabolism and their exclusive use of glucuronidation. As in depression, cognitive behavioural therapy can be beneficial in treating IFN- α -induced anxiety, particularly as an augmentation to pharmacotherapy (Farber et al, 2005).

IFN- α -induced mania

Mania is a recognized complication of IFN- α noted in the literature (Onyike et al, 2004). Irritability is more common than euphoria among patients developing IFN- α -induced mania (as in bipolar disorder, in general) and should be distinguished from depression (Constant et al, 2005). Estimates of manic symptoms in treated HCV patients vary depending on the criteria used to define mania, although prevalence rates as high as 18% were reported in one prospective study (Constant et al, 2005). Moreover, the use of standardized rating scales, such as the Young mania rating scale, can assist with the diagnosis of IFN- α -induced mania in certain cases. Although manic or hypomanic symptoms can emerge at any time during therapy, IFN- α withdrawal or dose reduction have been associated with IFN- α -induced mania (Shuto et al, 1997). According to Shuto and colleagues, long-term IFN- α treatment results in decreased dopamine levels in the brain, with a rebound surge in dopamine levels following withdrawal or reduction in IFN- α dose possibly precipitating a manic episode. However, further studies are required to evaluate this hypothesis.

Antipsychotic medications are the mainstay of IFN- α -induced mania treatment, largely because of the presence of psychotic symptoms with mania in reported cases. In one case study of IFN- α -induced mania, symptoms were treated with haloperidol 5 mg daily acutely followed by

lithium 300 mg twice daily for maintenance therapy (Onyike et al, 2004). Valproic acid, a mood stabilizer used to treat acute mania, has only been associated with minimal liver enzyme elevation in HCV patients treated for epilepsy and may be a viable alternative provided liver enzymes are closely monitored (Felker et al, 2003). Carbamazepine and oxcarbazepine should be avoided as a result of their increased risk of agranulocytosis when used in combination with IFN- α .

IFN- α -induced psychosis

IFN- α -induced psychosis is a relatively uncommon complication of HCV antiviral treatment, occurring in approximately 0.01–0.04% of HCV-treated patients (Fattovich et al, 1996; Hosoda et al, 2000). Both studies were limited by their retrospective design and likely reflect referral rates, thus underestimating the actual incidence of IFN- α -induced psychosis. Furthermore, these studies demonstrated a tendency for psychotic symptoms to emerge late into the course of IFN- α treatment. Discontinuation of IFN- α treatment in combination with either a conventional or novel antipsychotic treatment resulted in remission of psychotic symptoms but cases of persistent IFN- α -induced psychosis have been reported in the literature (Telio et al, 2006). Among available antipsychotic agents, clinicians should avoid concomitant use of clozapine with IFN- α because of added risks of agranulocytosis.

IFN- α -induced cognitive changes

Evidence regarding cognitive impairments associated with HCV treatment remains inconclusive (Bonaccorso et al, 2002a). Delirium can occur during the acute phase of IFN- α therapy but remains quite rare in HCV treated patients. Proposed risk factors for cognitive sequelae during IFN- α therapy include pre-existing brain injury and a history of substance abuse, although larger studies are required to replicate these findings (Renault et al, 1987). If neurocognitive complications occur during HCV treatment, a thorough cognitive assessment and formal neuropsychological evaluation should be considered in order to clarify the patient's cognitive deficits.

Conclusions

Psychiatric illness plays an intricate role in the treatment of HCV and should be a component of the risk–benefit analysis for IFN- α treatment. IFN- α -induced depression is the most common adverse effect of HCV treatment, but a range of neuropsychiatric complications has been identified. Given these adverse effects, patients being considered for immunotherapy require evaluation and education on the potential psychiatric complications associated with IFN- α . Although the evidence is lacking to make clear treatment recommendations, several open-label studies have demonstrated benefits with prophylactic antidepressant treatment for high-risk HCV patients undergoing IFN- α treatment. Less rigorous evidence

KEY POINTS

- Hepatitis C can be treated successfully in patients with pre-existing mental illness.
- Neuropsychiatric symptoms, most notably depression, are common adverse effects during interferon- α therapy for hepatitis C.
- Interferon- α -induced depression can be successfully treated for hepatitis C using prophylactic antidepressant therapy in high-risk patients.
- Other psychiatric complications of hepatitis C antiviral therapy include anxiety, mania, psychosis and cognitive changes.
- Treatment outcomes for hepatitis C can be enhanced with regular screening and timely management of interferon- α -induced psychiatric symptoms.

exists for the management of IFN- α -induced anxiety, mania, psychosis and cognitive impairment. Therefore, psychiatric evaluation should be incorporated into the treatment of HCV to reduce neuropsychiatric adverse effects and optimize IFN- α treatment outcomes. **BJHM**

Conflict of interest: none.

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