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EDITORIAL

Withdrawing interferon-α from psychiatric patients: clinical care or unjustifiable stigma?

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IFN-α is an effective therapy for chronic viral hepatitis C and today still represents an effective first-line treatment. Unfortunately, its use is associated with a number of side-effects, including psychiatric problems like depression, mania, psychosis, delirium and other cognitive disturbances. Clinicians have been concerned about the risks of worsening of pre-existent psychiatric disorders and of precipitating suicidal attempts in psychiatric patients. The presence of a mental illness is, therefore, often deemed to be a contraindication to the use of antiviral treatment. However, this amounts to stigmatization and discrimination, as it basically implies withholding a life-saving medical treatment because of a psychiatric diagnosis. Is this clinically and socially acceptable? With novel treatments now entering clinical practice as adjuvant to IFN-α, it is particularly important to make a statement now, to ensure that psychiatric patients are not left behind. The aim of this editorial is to critically discuss this notion, by reviewing the few studies ($n=14$) that have indeed administered IFN-α to patients with a pre-existing psychiatric disorder. We find evidence that these patients have rates of treatment adherence and sustained virological response similar to those of non-psychiatric patients, and that their IFN-α-induced psychiatric symptoms respond successfully to clinical management. We conclude that there is no support to withdrawing IFN-α therapy from psychiatric patients.

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Introduction

Hepatitis C virus (HCV) infection is a major health problem affecting approximately 170 million people worldwide and 4 million of people in the USA (Asnis & De La Garza, 2006). Up to 85% of HCV-infected individuals may develop chronic hepatitis C, a disease associated with serious clinical complications, including cirrhosis of the liver and hepatocellular carcinoma. Chronic hepatitis C is the leading cause of liver transplantation in the developed world. It is estimated that there are approximately 5 million carriers of HCV in Europe, 70–80% of whom are likely to develop a chronic infection. In the UK, around 216 000 individuals are chronically infected with hepatitis C; and, as in all countries, the major risk factor for infection is injecting drug use (HPA, 2011). Therefore, it is easy to understand the importance of using appropriate antiviral treatments to successfully induce a viral remission, in order to reduce the morbidity and mortality associated with chronic hepatitis C.

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First-line treatment consists of a combination therapy with pegylated IFN-α (pegIFN-α) plus ribavirin. In pegIFN-α, polyethylene glycol is added to make IFN-α's half-life longer, thus allowing once-weekly administration. This combination therapy can reach a sustained viral eradication in 45–95% of patients, according to viral genotype, viral load and treatment adherence. Novel protease inhibitor antiviral drugs will soon enter clinical care, and promise to increase considerably the rate of viral eradication; but they will be added to IFN-α – not be a substitute for it.

IFN-α neuropsychiatric side-effects

Unfortunately, the use of IFN-α is associated with numerous side-effects, both medical and neuropsychiatric. Among the first, there are flu-like symptoms, including fever, chills, malaise, tachycardia, headache, arthralgias and myalgias, occurring in more than 30% of patients, usually at the beginning of the therapy. Neuropsychiatric side-effects are also common, and there are reports of a variety of symptoms, including depressive syndromes, manic and psychotic episodes, and delirium. In a previous review (Quelhas & Lopes, 2009), prospective studies (that excluded patients with a lifetime history of psychiatric disorders) report an incidence of IFN-α-induced

Table 1. *Summary of studies on psychiatric patients taking interferon-α*

Study	No. of patients	Diagnosis	IFN-α dose	Outcome of therapy with IFN-α
Dieperink *et al*. 2003	55 patients with hepatitis, of which 42 treated with IFN-α. Prospective study	11 patients with psychiatric diagnosis	3 MU of IFN-α three times/week and ribavirin 1000–1200 mg/day for 24 weeks	Patients with psychiatric diagnosis scored higher on all rating scales at baseline and became more symptomatic during treatment Of the 31 (74%) patients not in psychiatric care at baseline, 15 (48%) required treatment for neuropsychiatric symptoms, and 7 (23%) met criteria for major depression during INF therapy. The control group of 13 untreated subjects showed little change over the 24-week period.
Dieperink *et al*. 2008	16 Prospective study	16 patients with PTSD, 5 received IFN, 11 did not receive treatment	1.5 μg/kg pegIFN-α-2b once a week plus ribavirin, for 12 or 24 weeks.	Depressive scores significantly increased among the 5 patients treated with IFN, but no significant differences in PTSD scores were found compared with 11 control patients.
Evon *et al*. 2009	394 Prospective study	47 patients with depression according to CES-D	Combination of pegIFN-α and ribavirin	Patients with pre-existent depression were more likely to have psychiatric adverse events or start new antidepressants (45& *v*.28%) and to have had early treatment discontinuation (38% *v*.13%) Sustained virological response rates were similar (38% *v*. 40%) to those of participants without baseline depression.
Ho *et al*. 2001	33 Retrospective study	19 patients with previous psychiatric diagnosis	5 MU of IFN-α three times/week for 6 months, followed by a tapering dose for additional 6 months	Of the patients with pre-existing psychiatric diagnoses, 13/19 (68%) developed major adverse events requiring intervention or discontinuation of therapy 4/14 (29%) patients without psychiatric diagnoses developed major adverse events In the psychiatric group, 6/19 (32%) developed major neuropsychiatric side-effects compared to 2/14 patients (14%) in the non-psychiatric group Patients with and without psychiatric diagnoses had equivalent virological responses to therapy
Huckans *et al*. 2010	60 Retrospective chart review	30 patients with schizophrenia, 30 controls	PegIFN-α-2a or -2b or non-pegIFN for 24 or 48 weeks	For all genotypes considered, the patients with schizophrenia were not more likely than controls to discontinue therapy early for psychiatric symptoms Patients with schizophrenia seemed to be able to complete and respond to antiviral therapy for chronic hepatitis C at rates comparable to those of controls
Lang *et al*. 2010	1860 Cohort study	403 patients with pre-existing psychiatric disorders	Combination of pegIFN-α and ribavirin	Strict adherence was similar in psychiatric and non-psychiatric patients (35% *v*. 39%) as was the rate of sustained virological response (52% *v*. 51%) The rate of mental adverse events was higher in psychiatric patients (78% *v*. 57%)
Lim *et al*. 2010	165 Retrospective study	33 patients with positive PHQ-9 for mood disorders, 132 controls with negative PHQ	Combination of pegIFN-α and ribavirin	41 (30%) of the control patients had adverse psychiatric events. Psychiatric events occurred in 8 (36%) of 22 patients with positive PHQ but negative MDQ; 8 (73%) of 11 with positive PHQ and positive MDQ had psychiatric adverse events The overall sustained viral response rate was 58% and not statistically significant among groups
Mulder *et al*. 2000	63 Prospective study	47% of total patients with pre-existing major depression	3 MU of IFN-α, three times a week for 6 months.	No significant rise in psychiatric symptoms among patients on IFN-α compared to baseline. A lifetime history of major depression did not predict the onset or worsening of mood symptoms, although such patients had higher mean depression scores throughout their treatment. None of the patients made a suicidal attempt

Pariante *et al*. 1999	50 Prospective study	16 patients with current psychiatric diagnosis	6–10 MU of IFN-α, three times a week for 12 months	10 (41%) patients in the case group and 10 (38%) patients in the control group interrupted the therapy. However, there was no evidence that psychiatric cases were more likely than controls to interrupt the therapy because of psychiatric adverse effects 11 patients (6 cases, 5 controls) developed psychiatric adverse effects (5 major depression, 3 depression not otherwise specified, 1 anxiety disorder, 2 severe dysphoria). 3 patients interrupted the therapy (1 case and 2 controls) because of the psychiatric adverse effects
Pariante *et al*. 2002	60 Prospective study	25 patients with psychiatric diagnosis, 35 controls	6–10 MU of IFN-α three times a week for 12 months	After adjusting for the baseline values, there was no evidence that patients with a pre-existing psychiatric diagnosis and patients with no psychiatric diagnosis had different maximal scores on the psychopathological rating scales No significant difference between groups in incidence of psychiatric side-effects 3 out 25 psychiatric patients required antidepressant treatment during IFN-α therapy. 7 out of 35 controls required antidepressant treatment
Schaefer *et al*. 2003	81 Prospective study	16 patients with psychiatric disorders, 21 on methadone substitution treatment, 21 former drug users, 23 controls	3 MU of IFN-α-2a 3 times weekly plus ribavirin	No significant differences between groups were detected with respect to IFN-α related development of depression during treatment. No patient in the psychiatric group had to discontinue treatment because of psychiatric deterioration but significantly more of them received antidepressant treatment Sustained virological response was 37% overall and did not differ significantly between the subgroups
Schaefer *et al*. 2005	36 Prospective, open label study	14 patients with psychiatric illness (group A) treated with citalopram, 11 patients with psychiatric illness, not treated with antidepressant (group B), 11 patients with no psychiatric illness (group C)	PegIFN-α-2b plus ribavirin for 24 weeks	Major depressive symptoms, diagnosed with DSM-IV criteria, developed in 14% of group A, 64% of group B and 55% of group C. IFN-α-induced depression in psychiatric risk patients can be improved by use of antidepressant medication
Schaefer *et al*. 2007	70 Prospective study	22 patients with psychiatric diagnosis (10 with affective disorder, 6 schizophrenia, 6 personality disorder), 17 controls, 18 methadone substitution treatment, 13 former drug users	IFN-α-2b (1.5 μg/kg a week) *or* IFN-α-2a (180 μg/week) plus ribavirin for 24 or 48 weeks	Psychiatric patients were not at increased risk of worsening depression or psychosis during antiviral treatment compared to controls. Taking into account that baseline depression and psychotic symptom scores of those in the psychiatric risk groups were higher than those of the controls, no significant differences were detected during treatment. Sustained virological response was achieved in: 58.6% of all patients, 58.8% of controls, 50% of patients with a psychiatric diagnosis, and 72.2% of patients on methadone substitution treatment Only virus genotype was found to significantly influence sustained virological response rate
Van Thiel *et al*. 1995	31 Prospective, open label study	31 patients with chronic HCV and psychiatric illness	5 MU of IFN-α, three times/week for 6 months ($n=17$) or 5 MU daily for 6 months ($n=14$)	29 out of 31 patients completed the 6 months therapy. 15 (48%) patients achieved sustained virological response Only 4 patients experienced a worsening of the psychiatric symptoms and 2 had to stop the therapy because of that

CESD, Center for Epidemiologic Studies Depression Scale; IFN, interferon; PHQ, Physician Health Questionnaire; PTSD, post-traumatic stress disorder; MDQ, Mood Disorders Questionnaire; MU, million units.

neuropsychiatric symptoms of 12–41%, while studies without this exclusion criterion report an incidence of 17–58%. Depression appears to be the most common side-effect in patients with chronic hepatitis C, and the incidence of major depressive episodes (MDEs), diagnosed according to DSM-IV-TR criteria, generally ranges from 12% to 42% (Quelhas & Lopes, 2009). The incidence of mania during IFN-α treatment is unknown; however, several cases have been reported, including cases of mania emerging spontaneously after IFN-α-induced depression and/or after withdrawal of IFN-α, and reports of 'switches' from depression to mania during antidepressant therapy (Quelhas & Lopes, 2009). Cognitive side-effects, especially memory disturbances and concentration problems, have also been found in 10–20% of patients receiving IFN-α, with the risk of cognitive decline possibly being higher with a larger cumulative dose of IFN-α and a longer duration of treatment. There are a few case reports of psychotic episodes induced by IFN-α therapy (Quelhas & Lopes, 2009).

Worsening of psychiatric symptoms in IFN-α therapy

Generally, patients with chronic hepatitis C tend to have a significant history of psychopathology (Yovtcheva *et al*. 2001), which has been considered by some authors as a significant cause for treatment withdrawal, due to the theoretical risk of worsening of psychiatric symptomatology induced by IFN-α treatment. In particular, concerns have been raised about worsening or exacerbation of depression or of suicidal ideation, as well as of psychotic symptoms in patients suffering from bipolar disorder and psychotic illnesses. As recently as in the 2012 Recommendations from the USA National Hepatitis C Program Office, it is prescribed that 'uncontrolled depression or active suicidal ideation is an absolute contraindication to IFN-based therapies' (Yee *et al*. 2012). While we agree with the accepted clinical practice that patients with active psychopathology should be assessed and supported before starting IFN-α, the wording of the recommendation undoubtedly confirms the degree of anxiety by which medical professionals see psychiatric patients in this context. As we have argued already 10 years ago (Pariante *et al*. 2002), withholding IFN-α inappropriately, especially from members of a stigmatized class, raises questions about fairness and discrimination.

The evidence

The aim of this editorial is to discuss the existing literature with regard to the administration of IFN-α therapy in patients with chronic hepatitis C and a current psychiatric illness. Studies were identified by using the PubMed database, cross-searching for 'Interferon-α', 'psychiatric symptoms' and 'chronic hepatitis C'. Further references were obtained from bibliographies of the reviewed articles. Fourteen studies were considered eligible, and are summarized in Table 1, with details of the findings. Overall, most studies did *not* find a significantly higher risk of IFN-α-induced neuropsychiatric toxicity in patients with a psychiatric diagnosis, once the higher baseline psychopathology was taken into account. Interestingly, patients with severe mental illnesses, such as schizophrenia, seem also to be resilient during IFN-α. Furthermore, no higher suicidal risk was recorded in these patients. Of particular relevance, and consistently across all studies, is the fact that the rates of completion of therapy and sustained virological response are comparable between psychiatric and non-psychiatric patients.

Conclusions

Our analysis of the relatively scant literature highlights that patients with a psychiatric illness have rates of treatment adherence and sustained virological response similar to those of non-psychiatric patients. Moreover, the majority of the studies do not show a significantly higher neurotoxicity of IFN-α therapy in these patients; and even in those studies that find a greater incidence of psychiatric adverse events, psychiatric patients are able to successfully complete the therapy. The lack of an increased risk of suicide in psychiatric patients is also consistent with a recent review on this topic (Sockalingam *et al*. 2011), which also found that the evidence for an increased suicide risk during IFN-α is largely anecdotal. In most cases, a combination of psychotropic and psychosocial interventions can be used to both prevent worsening of existing symptoms and to manage patients who show a reactivation of psychiatric problems. In fact, there is reasonably good evidence in favour of use of antidepressants, for both prophylaxis and treatment of anxiety and depressive symptoms induced by IFN-α (Baraldi *et al*. 2012). In addition, the early involvement of a multidisciplinary therapeutic approach, such as the assessment and follow-up with liaison psychiatrists and psychologists (Neri *et al*. 2010), or an interdisciplinary nurse-managed treatment programme, can be used to support patients with pre-existent psychiatric problems undergoing IFN-α therapy (Gardenier *et al*. 2011). It should be noted that it is important not to underestimate the fact that patients with no psychiatric history have virtually the same risk of developing IFN-α-induced side-effects, and as

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such they may suffer even more from the lack of management programmes and prophylactic strategies. In summary, while we support the notion of assertive psychosocial and pharmacological prevention in these patients, we find no evidence that patients with a pre-existing psychiatric disorder should not be treated with interferon-α; and withdrawal of such treatment should be considered as discrimination.

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Declaration of Interest

None.

References

Asnis GM, De La Garza R (2006). Interferon-induced depression in chronic hepatitis C: a review of its prevalence, risk factors, biology and treatment approaches. *Journal of Clinical Gastroenterology* **40**, 322–335.

Baraldi S, Hepgul N, Mondelli V, Pariante CM (2012). Symptomatic treatment of interferon-α-induced depression in hepatitis C: a systematic review. *Journal of Clinical Psychopharmacology* **32**, 531–543.

Dieperink E, Ho SB, Thuras P, Willenbring ML (2003). A prospective study of neuropsychiatric symptoms associated with interferon-alpha-2b and ribavirin therapy for patients with chronic hepatitis C. *Psychosomatics* **44**, 104–112.

Dieperink E, Leskela J, Dieperink ME, Evans B, Thuras P, Ho SB (2008). The effect of pegylated interferon-alpha2b and ribavirin on posttraumatic stress disorder symptoms. *Psychosomatics* **49**, 225–229.

Evon DM, Ramcharran D, Belle SH, Terrault NA, Fontana RJ, Fried MW (2009). Virahep-C Study Group. Prospective analysis of depression during peginterferon and ribavirin therapy of chronic hepatitis C: results of the Virahep-C study. *American Journal of Gastroenterology* **104**, 2949–2958.

Gardenier D, Wisnivesky J, McGinn LK, Kronish IM, McGinn TG (2011). Hepatitis C treatment completion in individuals with psychiatric comorbidity and depression. *Gastroenterology Nursing* **34**, 102–106.

Ho SB, Nguyen H, Tetrick LL, Opitz GA, Basara ML, Dieperink E (2001). Influence of psychiatric diagnoses on interferon-alpha treatment for chronic hepatitis C in a veteran population. *American Journal of Gastroenterology* **96**, 157–164.

HPA (2011). Hepatitis C in the UK, Report. Health Protection Agency, London.

Huckans M, Mitchell A, Ruimy S, Loftis J, Hauser P (2010). Antiviral therapy completion and response rates among hepatitis C patients with and without schizophrenia. *Schizophrenia Bulletin* **36**, 165–172.

Lang JP, Melin P, Ouzan D, Rotily M, Fontanges T, Marcellin P, Chousterman M, Cacoub P; CheObs Study Group (2010). Pegylated interferon-alpha2b plus ribavirin therapy in patients with hepatitis C and psychiatric disorders: results of a cohort study. *Antiviral Therapy* **15**, 599–606.

Lim C, Olson J, Zaman A, Phelps J, Ingram KD (2010). Prevalence and impact of manic traits in depressed patients initiating interferon therapy for chronic hepatitis C infection. *Journal of Clinical Gastroenterology* **44**, 141–146.

Mulder RT, Ang M, Chapman B, Ross A, Stevens IF, Edgar C (2000). Interferon treatment is not associated with a worsening of psychiatric symptoms in patients with hepatitis C. *Journal of Gastroenterology and Hepatology* **15**, 300–303.

Neri S, Bertino G, Petralia A, Giancarlo C, Rizzotto A, Calvagno GS, Mauceri B, Abate G, Boemi P, Di Pino A, Ignaccolo L, Vadala' G, Misseri M, Maiorca D, Mastrosimone G, Judica A, Palermo F (2010). A multidisciplinary therapeutic approach for reducing the risk of psychiatric side-effects in patients with chronic hepatitis C treated with pegylated Interferon alpha and ribavirin. *Journal of Clinical Gastroenterology* **44**, 210–217.

Pariante CM, Landau S, Carpiniello B; Cagliari Group (2002). Interferon alpha-induced adverse effects in patients with a psychiatric diagnosis. *New England Journal of Medicine* **347**, 148–149.

Pariante CM, Orrù MG, Baita A, Farci MG, Carpiniello B (1999). Treatment with interferon alpha in patients with chronic hepatitis and mood or anxiety disorders. *Lancet* **354**, 131–132.

Quelhas R, Lopes A (2009). Psychiatric problems in patients infected with hepatitis C before and during antiviral treatment with interferon-alpha: a review. *Journal of Psychiatric Practice* **15**, 262–281.

Schaefer M, Hinzpeter A, Mohmand A, Janssen G, Pich M, Schwaiger M, Sarkar R, Friebe A, Heinz A, Kluschke M, Ziemer M, Gutsche J, Weich V, Halangk J, Berg T (2007). Hepatitis C treatment in 'difficult-to-treat' psychiatric patients with pegylated interferon-alpha and ribavirin: response and psychiatric side effects. *Hepatology* **46**, 991–998.

Schaefer M, Schmidt F, Folwaczny C, Lorenz R, Martin G, Schindlbeck N, Heldwein W, Soyka M, Grunze H, Koenig A, Loeschke K (2003). Adherence and mental side-effects during hepatitis C treatment with interferon alpha and ribavirin in psychiatric risk groups. *Hepatology* **37**, 443–451.

Schaefer M, Schwaiger M, Garkisch AS, Pich M, Hinzpeter A, Uebelhack R, Heinz A, van Boemmel F, Berg T (2005). Prevention of interferon-alpha associated depression in psychiatric risk patients with chronic hepatitis C. *Journal of Hepatology* **42**, 793–798.

Sockalingam S, Links PS, Abbey SE (2011). Suicide risk in hepatitis C and during interferon-alpha therapy: a review and clinical update. *Journal of Viral Hepatitis* **18**, 153–160.

Van Thiel DH, Friedlander L, Molloy PJ, Fagiuoli S, Kania RJ, Caraceni P (1995). Interferon-alpha can be used successfully in patients with hepatitis C virus-positive chronic hepatitis who have a psychiatric illness. *European Journal of Gastroenterology and Hepatology* **7**, 165–168.

Yee HS, Chang MF, Pocha C, Lim J, Ross D, Morgan TR, Monto A; Department of Veterans Affairs Hepatitis C Resource Center Program; National Hepatitis C Program Office (2012). Update on the management and treatment of hepatitis C virus infection: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office. *American Journal of Gastroenterology* **107**, 669–689.

Yovtcheva SP, Rifai MA, Moles JK, Van Der Linden BJ (2001). Psychiatric comorbidity among hepatitis-C-positive patients. *Psychosomatics* **42**, 411–415.