Psychological Medicine, 2005, **35**, 433–441. © 2004 Cambridge University Press
DOI: 10.1017/S0033291704003526 Printed in the United Kingdom

Early increase in vegetative symptoms predicts IFN-α-induced cognitive-depressive changes

M. C. WICHERS[1]*, G. H. KOEK[2], G. ROBAEYS[3], A. J. PRAAMSTRA[1] AND M. MAES[1]

[1] *Department of Psychiatry and Neuropsychology, Maastricht University, The Netherlands*; [2] *Department of Internal Medicine, Academic Hospital Maastricht (AZM), The Netherlands*; [3] *Department of Internal Medicine, Ziekenhuis Oost Limburg (ZOL), Genk, Belgium*

ABSTRACT

Background. The vegetative symptoms of depression resemble the symptoms of malaise associated with activation of the inflammatory response system (IRS), and can be regarded as an expression of a central motivational state that resets the organism's priorities to promote recovery from infection. Early vegetative symptoms, however, may also contribute to the high rates of depression seen later in the course of immune activation. We hypothesized that the onset of vegetative-depressive symptoms early in the treatment with the pro-inflammatory cytokine IFN-α in chronic hepatitis C patients would increase the risk for subsequent depressive cognitions.

Method. Sixteen patients eligible for IFN-α treatment and free of psychiatric disorders were recruited. The DSM-IV, the Multidimensional Fatigue Inventory, and the Montgomery–Asberg Depression Rating Scale (MADRS) were administered at baseline and 1, 2, 4, 8, 12 and 24 weeks after treatment was initiated. Cognitive-depressive and vegetative-depressive symptom clusters were constructed.

Results. Fatigue and depression scores increased significantly during IFN-α treatment. Depression scores were highest at week 8 of treatment. First week increase in vegetative-depressive symptom score predicted cognitive-depressive symptom score at week 8 and at week 24.

Conclusions. During IFN-α treatment, vegetative symptoms of depression appear earlier than, and are predictive of, their cognitive counterparts. This finding suggests that low mood state may in part be driven by the increase in early vegetative-depressive symptoms in the course of IFN-α-induced immune activation.

INTRODUCTION

Administration of interferon-alpha (IFN-α), a cytokine demonstrating major antiviral and immunomodulatory effects, has been used effectively as treatment for a variety of chronic viral infections and malignant disorders, including chronic hepatitis C. Despite its potential therapeutic benefits, administration of IFN-α frequently induces psychiatric pathology such as severe fatigue and depressive symptoms. Recent clinical studies have shown that approximately 16–45% of patients treated with IFN-α developed depressive symptoms during the course of therapy (Musselman *et al.* 2001; Bonaccorso *et al.* 2002*b*; Hauser *et al.* 2002; Dieperink *et al.* 2003). Prevalences of neuropsychiatric side-effects due to IFN-α treatment differ greatly between studies, but most variation may be explained by differences in the methodology used. Thus, neuropsychiatric side-effects appear to be dose-related, duration of therapy varies between studies, different assessment scales were used and sometimes prevalences were based only on subjective patient reports (Schaefer *et al.* 2002; Van Gool *et al.* 2003). Finally, co-administration

* Address for correspondence: Dr M. C. Wichers, Department of Psychiatry and Neuropsychology, Maastricht University, PO Box 616 (PAR 45), 6200 MD Maastricht, The Netherlands.
(Email: m.wichers@sp.unimaas.nl)

https://doi.org/10.1017/S0033291704003526 Published online by Cambridge University Press

of IFN-α with ribavirin or administration of IFN-α in pegylated (PEG) form are associated with different prevalences of neuropsychiatric side-effects than standard IFN-α administration (Keating & Curran, 2003). However, most studies agree on the fact that fatigue, irritability and depression are very troublesome side-effects of IFN-α treatment which may require dose reduction or even discontinuation (Dusheiko, 1997; Dalakas *et al*. 1998; Licinio *et al*. 1998).

The link between immune activation and depressive symptoms has been documented extensively. Major depression is accompanied by an activation of the inflammatory response system (Maes, 1995). Furthermore, acute infectious illness (Meijer *et al*. 1988) and upper respiratory tract infections (Hall & Smith, 1996), as well as chronic inflammatory diseases (Minden & Schiffer, 1990; Foley *et al*. 1992; Parker *et al*. 1992; Pincus *et al*. 1996; Elsehety & Bertorini, 1997) have been associated with depressive symptoms. Furthermore, cytokines can enter the brain by crossing the blood–brain barrier (BBB) via transport mechanisms, through areas where the BBB is absent and they can transmit signals to the brain via the vagus nerve. Also, they can activate the brain vasculature to cause release of signalling molecules within the brain parenchyma (Blatteis, 2000). The fact that cytokines are able to communicate with the central nervous system (CNS) to influence behaviour (Besedovsky & del Rey, 1996), supports the possibility of their role as contributors to psychopathology, including mood disorders.

Cytokines produced in response to infection endogenously produce behavioural changes similar to those produced by the exogenous administration of IFN-α. These behavioural changes include fever, experience of weakness, fatigue, hypersomnia, depressed activity, decreased appetite and loss of interest in social activities, and result in a state of general malaise. Instead of regarding these behaviours as the result of the debilitation process that occurs during infection, it has been argued that they are actually part of a natural homeostatic reaction the body uses to fight infection. Sickness behaviour (Dunn & Swiergiel, 1998; Kelley *et al*. 2003) can be regarded as an expression of a central motivational state that resets the organism's priorities to promote recovery from infection (Hart, 1988). This behavioural response to infection is triggered by the pro-inflammatory cytokines that are produced by activated immune cells [mainly interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)-α].

Observable behavioural symptoms of depression, or vegetative symptoms, resemble those seen in the malaise state after infection. Traditionally, in depression, symptoms of malaise have been interpreted as secondary to the mood change in major depressive disorder (MDD). However, Charlton (2000) argues that MDD is the behavioural response to a physical illness, a syndrome in which low mood is the product of malaise. In contrast to animals, humans may interpret their lack of energy, lack of motivation, etc. as a moral failure, leading to cognitive symptoms such as feeling of guilt, unworthiness and irritability. Eventually, the depressive cognitive style becomes habitual and it may persist even after resolution of the hyperimmune state that originally caused the sickness behaviour (Charlton, 2000). Clearly, in order to unravel the temporal order and direction of effects as described by this theory, longitudinal studies are essential. Although there is an extensive literature describing the effects of IFN-α on behaviour, most studies only examined a short period of time; while cognitive symptoms of depression may sometimes develop after a few weeks of treatment they often also develop after longer periods. Furthermore, according to the malaise theory of Charlton it can be hypothesized that symptoms of malaise may be linked prospectively to the development of the cognitive expression of depression.

The present study, therefore, focused on the differentiation between vegetative and cognitive symptoms of depression and on the predictive value of vegetative-depressive symptoms on the cognitive expression of depression. In addition, the possibility exists that pure fatigue, one major symptom within this cluster of vegetative-depressive symptoms that is highly increased by IFN-α (Bonaccorso *et al*. 2002*a*), is solely responsible for later cognitive-depressive changes (Charlton, 2000). To our knowledge, only one recent study assessed fatigue during IFN-α treatment using a structured questionnaire (Dieperink *et al*. 2003). Furthermore, little is known about factors that may predict IFN-α induced psychopathology. For a better insight

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into possible predictive factors longitudinal and systematical research is needed with dissection of the cognitive- and vegetative-depressive symptom cluster.

The following describes a prospective study of chronic hepatitis C patients undergoing IFN-α treatment. We hypothesized that: (i) symptoms of depression would increase over time during treatment; (ii) that vegetative-depressive symptoms would arise before, and would be predictive of, cognitive-depressive symptoms.

MATERIALS AND METHOD

Subjects

Twenty-one patients with chronic active hepatitis C infection, aged 25–57 years and eligible for IFN-α treatment, were recruited. Chronic hepatitis C was defined as: antibodies to HCV positive, HCV-RNA positive and elevated transaminases at least once in the previous 6 months.

Patients had a complete medical history, physical examination and laboratory blood check before study entry. In addition, an ultrasound of the upper abdomen, an ECG, and a pregnancy test (in women of childbearing potential) was carried out. A liver biopsy was performed in most patients.

Excluded were patients currently meeting criteria of Axis I psychiatric disorders as defined by DSM-IV or patients currently on antidepressant medication. In addition, patients who had co-infections such as hepatitis B virus or human immunodeficiency virus, or patients with a diagnosis of uncontrolled neurological, cardiovascular, endocrine, haematological, hepatic or renal disease, or patients with insufficient knowledge of the Dutch language were excluded. Patients were recruited from the Academic Hospital Maastricht (AZM) in The Netherlands and from the Ziekenhuis Oost Limburg (ZOL) in Belgium. All patients received some form of IFN-α treatment and ribavirin. One patient received IFN-α 2b (intron A), 3×3 mega units (MU) weekly throughout the study period. Nine patients received intron A for the first 12 days of treatment (10 MU daily for the first 6 days and 5 MU daily after day 6). After the first 12 days, they received a weekly injection of 80–180 μg PEG IFN-α 2b. Six patients began directly with weekly injections of 80–180 μg PEG IFN-α 2b. Ribavirin (1000–1200 mg/d) was administered orally in all patients, depending on body weight.

The study was approved by the standing Medical Ethics Committee of Maastricht University, and carried out in accordance with the Declaration of Helsinki (Hong Kong Modification, 1989). Written informed consent was obtained from each subject prior to participation.

Assessments

Patients were assessed regularly during the first 24 weeks after starting IFN-α treatment. All questionnaires were administered before and 1, 2, 4, 8, 12 and 24 weeks after starting treatment. The presence of depressive symptoms was assessed by the 17-item Hamilton Depression Rating Scale (HAMD; Hamilton, 1967) and the Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979). Fatigue was assessed by the Multidimensional Fatigue Inventory (MFI), which is a self-report instrument consisting of five scales measuring general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue (Smets *et al.* 1995). To determine the presence of any Axis I psychiatric disorder, the Mini International Neuropsychiatric Interview for DSM-IV Axis I Disorders, Version 5.0 was administered (Sheehan *et al.* 1998). In addition, at each assessment patients were first asked to describe what side-effects they had experienced since the last visit.

Statistical analysis

Two separate dimensions of depressive symptoms, one representing cognitive-depressive and one representing vegetative-depressive symptoms were constructed out of both the HAMD and the MADRS questionnaires. The cognitive-depressive symptom cluster was constructed by calculating the sum of the HAMD item scores concerning depressed mood, feelings of guilt, suicidal thoughts and tension/worry. In addition, the sum was obtained from the HAMD item scores concerning difficulty with falling asleep, sleeping during the night, early awakening, reduced motivation, psychomotor retardation, reduced appetite and decreased energy and libido, to construct the vegetative-depressive symptom cluster. For the MADRS, the same

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procedure was followed. Scores of the items concerning reported sadness, tension/irritability, feelings of guilt/inferiority and suicidal thoughts were summed to construct the cognitive-depressive symptom cluster and scores of the items concerning observed sadness, sleep problems, reduced appetite, decreased energy and interest in social activities were summed together to construct the vegetative-depressive symptom cluster. Furthermore, the five dimensions of the MFI fatigue were highly and significantly correlated with each other. Therefore, the sum of all five MFI fatigue dimensions was used in further analyses.

The data were analysed with the STATA computer program, version 7 (StataCorp, 2001). Since the two depression rating scales were highly correlated ($r=0{\cdot}72$) only results of the MADRS are shown, with the exception, for methodological reasons, of some analyses (see below). The MADRS was chosen as the main outcome because it has been used frequently to assess IFN-α-induced depressive symptoms and therefore allows comparison with earlier studies in which this scale was used.

Because repeated measurements within the same person were used, the observations cannot be considered independent statistically. Therefore, multilevel random regression models were fitted, using the XTREG procedure in STATA (StataCorp, 2001). This takes into account the fact that level 1 units (level of individual observations) were clustered into level 2 units (levels of the subjects). Effect sizes of explanatory variables were expressed as regression coefficients (β) from the multilevel models. All analyses were corrected for the following *a priori* hypothesized confounders: age, sex, smoking, hospital centre, use of benzodiazepine medication, use of marijuana during the study and mode of acquisition of infection.

Multilevel regression models were then used to assess the effect of time on the total MADRS score, the MADRS vegetative-depressive symptom score, the MADRS cognitive-depressive symptom score and the total MFI score. The effects of increase in fatigue and vegetative-depressive symptoms within the first week of treatment on cognitive-depressive symptoms at weeks 8 and 24 were assessed using standard (unilevel) regression analysis. These analyses were corrected for baseline cognitive-depressive symptoms score. In order to prevent bias due to inter-item correlations between items of the same scale, HAMD cognitive-depressive symptoms were regressed on MADRS vegetative-depressive symptoms.

All regression analyses were performed again without subjects whose IFN-α dose had been reduced during the course of treatment, in order to examine if the magnitude of depression scores was biased by any reduction in dose.

RESULTS

Subject characteristics

Twenty-one patients were included in the study. Four patients dropped out during the study period due to problems unrelated to psychiatric side-effects. In addition, one patient was left out of the analyses because of insufficient data. The final study sample consisted of 16 patients, 12 men and 4 women. Their mean age was $42 \pm 7{\cdot}7$ years. In 7 out of 16 patients, a temporary dose reduction or discontinuation of treatment was necessary due to severe side-effects. Eleven patients (68%) reported lifetime drug dependence – these were patients who had acquired the virus by intravenous drug use (IVDU). Seven out of the 16 patients (44%) received low-dosage benzodiazepines (varying between 10 and 40 mg/day) during the study and seven out of 16 patients were using some form of drugs: five were regular users of marijuana. Of these five individuals one used heroin on a regular basis. Two other individuals were on methadone substitution. Their drug habit was stable throughout the study period. Five out of 16 (31%) patients, four men and one woman, fulfilled the criteria for MDD at some point during the study period. One of the patients developed a panic disorder after 2 weeks of treatment. There were no large or statistically significant differences between patients who did and did not develop MDD with respect to age ($T=0{\cdot}7$, $p=0{\cdot}49$), history of suicide attempts ($\chi^2=0{\cdot}26$, $p=0{\cdot}6$), family history of psychiatric disorders ($\chi^2=0{\cdot}37$, $p=0{\cdot}5$) past diagnosis of a psychiatric disorder ($\chi^2=0{\cdot}87, p=0{\cdot}4$), acquiring the virus by IVDU ($\chi^2=0{\cdot}26, p=0{\cdot}6$), continuing drug habit ($\chi^2=0{\cdot}78$, $p=0{\cdot}4$) during the study. Similarly, none of the scores on fatigue, depression or irritability differed between the

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Table 1. *Clinical characteristics of hepatitis C patients undergoing interferon-α therapy*

	Total ($n=16$)	MDD ($n=5$)	Non-MDD ($n=11$)
Age, years (S.D.) …	42 (7·7)	44 (5·2)	41 (8·6)
Gender			
Female	4	1	3
Male	12	4	8
Cigarette smoking (%)	7 (44%)	3 (60%)	4 (36%)
Aquisition virus			
Blood transfusion	2	0	2
IVDU	11	3	8
Unknown	3	2	1
Substance use during study (%)			
No substance use	9 (56%)	2 (40%)	7 (64%)
Marijuana smoking	4 (25%)	1 (20%)	3 (27%)
Methadone	2 (13%)	1 (20%)	1 (9%)
Heroin (and marijuana)	1 (6%)	1 (20%)	0 (0%)
Benzodiazepine medication during study (%)	4 (25%)	1 (20%)	3 (22%)
Family history of psychiatric illness (%)	2 (13%)	1 (20%)	1 (9%)
Diagnose in past of psychiatric illness (%)	3 (19%)	1 (20%)	2 (18%)
Past suicide attempt (%)	4 (25%)	2 (40%)	2 (18%)
Past use of antidepressants (%)	3 (19%)	1 (20%)	2 (18%)

MDD, Major depressive disorder; IVDU, intravenous drug use.

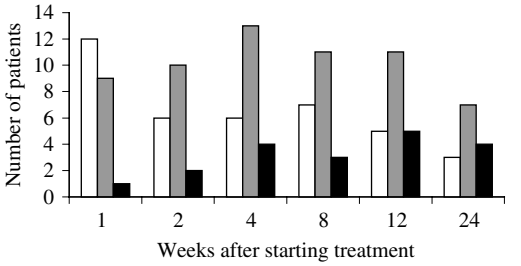


FIG. 1. Number of patients reporting flu-like symptoms (□), fatigue (▨) and/or a depressive feeling (■), for each time-point after starting treatment.

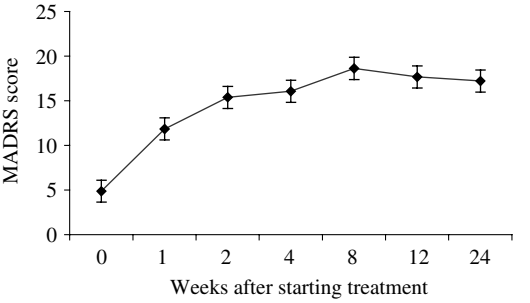


FIG. 2. MADRS scores from baseline until the 24th week of IFN-α treatment.

MDD and the non-MDD group at baseline (for means and proportions see Table 1).

Self-reported side-effects

All but one patient experienced flu-like symptoms at some point during the study period, and all but one reported fatigue. High percentages of reported 'irritability' and 'depressive feeling' were found, 75% and 63% respectively. Depressed appetite was reported in 63%, problems with concentrating in 50% and symptoms of panic/anxiety (as defined by at least one of the following: feeling like fainting, dizziness, chest ache, palpitations) in 25%. Flu-like symptoms (see Fig. 1) were mostly reported in the first weeks of treatment, while the highest frequency of patients reporting a depressed feeling was at week 12. Fatigue symptoms tended to be reported during the whole study period with a peak at 4 weeks after initiation of treatment.

Total depression score during IFN-α treatment

The MADRS depression score showed a significant increase during IFN-α treatment (effect time: $\beta=0{\cdot}32$, $p=0{\cdot}000$), with an immediate sharp increase in depressive symptoms until week 8, followed by a flattening of the line and a small but non-significant decline in score at weeks 12 and 24 (Fig. 2, Table 2). However, the analysis performed without subjects with dose reductions showed that the highest difference with baseline occurred at week 24 ($\beta=14{\cdot}7$, $p=0{\cdot}000$) and not at week 8 ($\beta=14{\cdot}0$, $p=0{\cdot}000$) and effect sizes were increased. Marijuana use

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Table 2. *Multilevel regression analyses indicating differences on each dimension for each time point, compared to baseline, using the regression coefficient (β)*

Dimension	Weeks … 1 β	2 β	4 β	8 β	12 β	24 β
Total MFI score	14·5***	21·6***	19·2***	21·0***	16·4***	15·0***
Total MADRS score	6·97*	10·5***	11·2***	13·8***	12·8***	12·3***
Vegetative-depressive symptom score	5·22***	6·58***	6·81***	8·63***	8·87***	7·91***
Cognitive-depressive symptom score	0·17	0·94	1·44*	1·38*	1·04	1·38*

MFI, Multidimensional Fatigue Inventory; MADRS, Montgomery–Asberg Depression Rating Scale.
* $p<0·05$, *** $p<0·001$.

showed no significant effect on MADRS score nor did difference in IFN-α treatment (intron A followed by PEG IFN-α compared to immediate PEG IFN-α treatment), although the group starting with intron A showed slightly lower depression scores.

Vegetative-depressive and cognitive-depressive symptom score during IFN-α treatment

Fatigue score and vegetative-depressive symptom score were significantly increased at all time points during IFN-α treatment, compared to baseline (Table 2). Vegetative-depressive symptoms increased rapidly. After 1 week of treatment three patients showed increases in scores between 50% and 100%. Another three patients showed increases between 100% and 300% and the scores of six patients were increased by more than 300%. Only four patients showed no increase in vegetative-depressive symptoms in the first week.

Cognitive-depressive symptoms were only significantly increased compared with baseline at weeks 4, 8 and 24 (Table 2). At week 12, difference with baseline was of comparable effect size but did not reach statistical significance according to conventional alpha ($\beta=1·04$, $p=0·07$). However, when subjects with dose reductions were excluded from the analyses, the increase at week 12 was significant and effect sizes for weeks 8, 12 and 24 were increased ($\beta=1·4$, $p=0·05$; $\beta=1·7$, $p=0·03$; $\beta=1·7$, $p=0·03$ respectively).

Impact of early increase in physical fatigue and vegetative-depressive symptoms on later cognitive-depressive symptoms

A first-week increase in fatigue score had no impact on cognitive-depressive symptoms at weeks 8 or 24. However, a first-week increase in MADRS vegetative-depressive symptoms, corrected for baseline HAMD cognitive-depressive symptoms, displayed a strong impact on HAMD cognitive-depressive symptoms at week 8 ($\beta=0·46$, $p=0·02$) and week 24 ($\beta=0·43$, $p=0·005$). Analyses were similarly significant when using, inversely, MADRS cognitive-depressive symptom score and HAMD vegetative-depressive symptom score (results not shown).

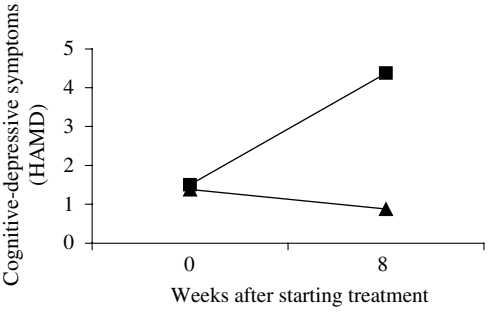


FIG. 3. Increase in cognitive-depressive symptoms (HAMD) during IFN-α treatment for low (–▲–) and high (–■–) first-week increase in vegetative-depressive symptoms (MADRS).

Furthermore, when subjects were differentiated into those having a low or high increase in MADRS vegetative-depressive symptom score in the first week according to a medium split of the distribution, a significant interaction was found between 'time' and 'high or low increase in first-week vegetative-depressive symptoms' in the model of cognitive-depressive symptoms ($\beta=3·34$, $p=0·003$), indicating that subjects with a high first-week increase in vegetative-depressive symptoms had a significantly higher increase in cognitive-depressive symptom score from baseline to week 8, compared to subjects with a low first-week vegetative-depressive symptom increase (Fig. 3).

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DISCUSSION

IFN-α treatment significantly increased symptoms of fatigue, and vegetative and cognitive symptoms of depression. Thirty-one per cent of the patients fulfilled the criteria for MDD at least once during the study period. Depression scores showed an initial sharp increase which attenuated approximately after 8 weeks of treatment. Furthermore, a first-week increase in vegetative-depressive symptoms was predictive of cognitive-depressive symptoms at weeks 8 and 24.

The percentage of patients developing an MDD during IFN-α treatment in our sample and the finding that after 8 weeks most depressive symptoms have come to expression is comparable to results found in other recent studies (Capuron *et al*. 2002; Hauser *et al*. 2002; Dieperink *et al*. 2003; Horikawa *et al*. 2003; Schaefer *et al*. 2003). Similarly to our findings, Capuron *et al*. (2002), who also distinguished vegetative-depressive symptoms (labelled 'neurovegetative symptoms') from cognitive-depressive symptoms (labelled as 'depressive symptoms'), also found an immediate and lasting increase in neurovegetative symptoms compared to baseline, while the cognitive-depressive symptoms were not significantly different from baseline until week 8 of treatment. Our study contrasts with the study of Dieperink *et al*. (2003) in which an association was reported between baseline and IFN-α-induced depressive symptoms.

In the present study, based on a longitudinal design and dimensional analyses, different time patterns among emerging symptoms could be distinguished. The whole cluster of vegetative-depressive symptoms emerging in the first week of treatment, i.e. reductions in sleep, motivation, appetite, energy, libido, social interest and slowness of movement and speech, appeared to be important in predicting cognitive-depressive symptoms at weeks 8 and 24. This finding supports Charlton's theory that cognitive symptoms of depression follow from a feeling of malaise, which arises in response to infection to reset the organism's priorities and is triggered by a set of pro-inflammatory cytokines.

According to this theory, increase in pro-inflammatory cytokines causes a behavioural state of malaise which itself induces cognitive complaints and mood change. However, our results may also be consistent with the idea that the pro-inflammatory cytokines that produce the vegetative-depressive symptoms, also affect other biological systems, in a dose-dependent manner, which then may result in a state of increased vulnerability to depressed mood. As pro-inflammatory cytokines, mainly IL-1 and IL-6 (John & Buckingham, 2003), are potent activators of the hypothalamic–pituitary–adrenal (HPA) axis, it is not unreasonable to assume that they are involved in the HPA axis hyperactivity that is associated with MDD (Checkley, 1996). In addition, other possible mechanisms by which cytokines may induce MDD may be considered. The pro-inflammatory cytokine IFN-γ induces the kynurenine pathway by induction of the enzyme indoleamine-2,3 dioxygenase (IDO), which converts tryptophan (Trp), the precursor of serotonin (5-HT), to kynurenine and other metabolites, some of which have neurotoxic properties (Wirleitner *et al*. 2003). Depletion of peripheral Trp, which lowers the availability of Trp to the brain, leads to decreased central 5-HT synthesis, a neurotransmitter that is considered important in the aetiology of depression (Graeff *et al*. 1996). Moreover, the production of neurotoxic substances along the kynurenine pathway may be involved in the development of neuropsychiatric disorders (Stone, 2001).

This study has some limitations. No control group was used in this study. As mentioned in the Introduction, inclusion of a control group in these kind of studies, such as untreated hepatitis C patients, is a major challenge. First, it implies asking patients to postpone the start of their treatment which is not justifiable ethically. Second, a double-blind research design would be impossible to implement, since effects of IFN-α compared to placebo treatment would be so obvious that patients and interviewers would be unblinded from the start. However, in a within-subject design a control group is not strictly necessary, because subjects function as their own controls using their own baseline measurements.

Another limitation is the relatively small sample size and the inclusion of patients having experienced past drug addiction. This may limit the extrapolation to populations other than

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hepatitis C patients. Furthermore, occurrence of depressive symptoms may have been influenced by differences in form of IFN-α treatment and current drug use. The rate of drug use during the study was 60% in patients who developed MDD, compared to only 36% in patients who remained free of MDD (Table 1). Although not significant, this finding suggests that current drug use may function as a risk factor. Further studies should examine the effects of treatment form and drug use on depressive symptoms.

ACKNOWLEDGEMENTS

We thank Jim van Os for extensive comments on earlier drafts of this paper.

DECLARATION OF INTEREST

None.

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