Mood Alterations During Interferon-Alfa Therapy in Patients With Chronic Hepatitis C: Evidence for an Overlap Between Manic/Hypomanic and Depressive Symptoms

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Background: Psychiatric side effects are common during interferon-alfa (IFN-alfa) therapy and often responsible for early treatment discontinuation, thus limiting its therapeutic potential. Depression is considered the hallmark of these side effects. However, irritability, anger/hostility, and manic/hypomanic episodes have also been reported, suggesting that these symptoms are important features of IFN-alfa–induced neuropsychiatric side effects.

Objective: The aim of this prospective study was to use item-by-item analysis to thoroughly characterize neuropsychiatric symptoms occurring during early IFN-alfa therapy in a large cohort of patients with chronic hepatitis C.

Method: Ninety-three previously IFN-alfa–naive patients treated with pegylated IFN-alfa plus ribavirin for chronic hepatitis C were studied. Neuropsychiatric assessments were conducted before initiation and after weeks 4 and 12 of antiviral therapy. They included the Mini-International Neuropsychiatric Interview, the 10-item Montgomery-Asberg Depression Rating Scale, the State-Trait Anxiety Inventory, and the Brief Fatigue Inventory.

Results: Psychiatric events occurred in 30 patients (32%). They consisted of mood disorders in all cases: mania in 3 cases (10%), irritable hypomania in 15 cases (50%), and depressive mixed states in 12 cases (40%). Neurovegetative symptoms appeared within 4 weeks in most patients. In patients who developed mood disorders, sadness and depressive thoughts were present but minimal in severity. In contrast, inner tension and anxiety symptoms increased significantly over time only in these patients.

Conclusions: Our results suggest that IFN-alfa–induced mood disorders are common and consist of an overlap between depressive and manic symptoms rather than a mere depression. The impact of such findings on therapeutic management should be investigated.

(J Clin Psychiatry 2005;66:1050–1057)

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The authors report no financial affiliations or other relationships relevant to the subject of this article.

The authors wish to acknowledge Mattew Armitage for translation support and Patrick Champbenoit, M.D., Guillaume Sauvé, M.D., Juliette Foucher, M.D., and Pierre-Henri Bernard, M.D., for support in participant recruitment.

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Hepatitis C virus (HCV) is a major public health problem, with over 170 million people infected worldwide.[1] HCV is the leading cause of chronic liver disease and the main indication for liver transplantation in the Western world. The most effective and available treatment for chronic hepatitis C (CHC) is currently the combination of pegylated interferon-alfa (IFN-alfa) and ribavirin. This results in sustained viral clearance in more than 55% of cases.[2,3] However, IFN-alfa induces significant neuropsychiatric effects, which are often responsible for early discontinuation of antiviral treatment, thus limiting its therapeutic potential.[4–6] Depression is currently considered the hallmark of IFN-alfa–induced neuropsychiatric side effects,[7–9] which mainly occur within the first 12 weeks of therapy. Depression can lead to potentially serious complications such as attempted or completed suicides.[4,10,11] Reported incidence rates of IFN-alfa–induced depression range from 0% to 44%.[4] Several methodological shortcomings might account for this substantial variation between published studies, including bias in patient selection, study designs (retrospective studies, small sample sizes, heterogeneous treatment schedules), and lack of sensitivity of diagnostic tools (subjective report of psy-

chiatric disorders rather than objective criterion-based instruments). In addition, it is difficult to determine exactly how many individuals actually suffer from IFN-alfa–induced depression because of the different definitions and methods used to define depression.[12] Finally, irritability, anxiety, and manic episodes have also been reported during IFN-alfa therapy,[2,3,13–18] suggesting that these symptoms are also important neuropsychiatric side effects of IFN-alfa.

The aim of this prospective study was to use item-by-item analysis to thoroughly characterize the occurrence of neuropsychiatric symptoms during the first 12 weeks of IFN-alfa therapy in a large series of patients with CHC.

METHOD

Patients

All patients with CHC (defined as detectable hepatitis C antibodies and HCV RNA in serum) eligible for antiviral treatment (1.5 μg/kg subcutaneous pegylated IFN-alfa-2b once a week plus 800 to 1200 mg of oral ribavirin per day) seen in our center between November 2001 and May 2003 were enrolled. Exclusion criteria were as follows: age over 75 years, previous antiviral treatment with IFN, current antidepressant treatment, previous or current malignancy, decompensated cirrhosis, human immunodeficiency virus coinfection, current psychotic or manic disorders, severe intellectual impairment, and inability to communicate in French. The study design was approved by a local ethics committee, and all patients gave written informed consent.

Neuropsychiatric Assessment

Patients were prospectively assessed before starting antiviral therapy (baseline) and were assessed after 4 and 12 weeks of treatment. Past and current psychiatric disorders were diagnosed using the Mini-International Neuropsychiatric Interview (MINI),[19] Version 5, an abbreviated, structured psychiatric interview that uses decision tree logic to assess the major adult Axis I disorders in the DSM-IV.[20] This interview investigates all the symptoms listed in the DSM-IV criteria for 15 major Axis I disorders, 1 Axis II disorder, and suicidality. Its diagnostic algorithms are consistent with DSM-IV diagnostic algorithms. Severity of depressive symptoms was assessed using the Montgomery-Asberg Depression Rating Scale (MADRS),[21] a 10-item semistructured standard depressive state examination. This scale includes 4 affective items (apparent sadness, expressed sadness, inner tension, anhedonia), 4 neurovegetative items (sleep disturbance, loss of appetite, lack of concentration, lassitude), and 2 cognitive items (pessimistic thoughts, suicidal thoughts). The score for each item varies from 0 to 6. Total scores range from 0 (no depressive symptoms) to 60 (severe depressive symptoms). Anxiety was assessed using the state version of the State-Trait Anxiety Inventory (STAI),[22] a 20-item standardized self-report scale. The score for each item varies from 1 to 4. Total scores range from 20 (low anxiety level) to 80 (high anxiety level). Both the trait and state versions have been validated in French.[22,23] Fatigue was assessed using the BFI (Brief Fatigue Inventory),[24] a 10-point self-report scale ranging from 1 (no fatigue) to 10 (extreme fatigue).

Table 1. Baseline Characteristics of the Study Population (N = 98)

Characteristic	Value
Age, mean ± SD, y	46 ± 12
Gender, N	
Men	51
Women	47
Routes of CHC transmission, N (%)	
Blood transfusion	36 (37)
Intravenous drug use	27 (27)
Other[a]	35 (36)
Psychiatric disorders at baseline (MINI), N (%)	
Major depressive disorder	4 (4)
Past psychiatric disorders (MINI lifetime), N (%)	
Major depressive disorder	34 (35)
Drug abuse/dependence	27 (28)
Generalized anxiety disorder	19 (19)
Alcohol abuse/dependence	14 (14)
Agoraphobia	11 (11)
Panic disorder	10 (10)
Manic/hypomanic episode	5 (5)
Antisocial personality disorder	5 (5)
Eating disorder	3 (3)
Social phobia	2 (2)

[a]Includes invasive medical and nonmedical acts; unknown routes of transmission with or without suspected medical causes.
Abbreviations: CHC = chronic hepatitis C, MINI = Mini-International Neuropsychiatric Interview.

Statistical Analyses

At baseline, categorical variables were assessed using Pearson's χ^2 test, and continuous variables were assessed using 1-way analysis of variance (ANOVA). A p value $< .05$ was considered significant. Patients were divided into 3 groups according to the occurrence of mood disorders during antiviral therapy and according to the type of mood disorders: patients without mood disorders, patients with depressive mixed states, and patients with mania/hypomania. Mixed-design ANOVA (groups × repeated measures) was used to compare changes between the 3 groups in MADRS, STAI, and BFI scores from baseline to week 12. Post hoc comparisons were carried out using the Scheffé test of significance.

RESULTS

Participants

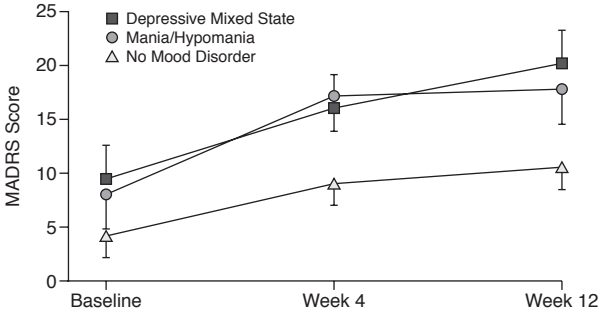
Ninety-eight patients fulfilled the inclusion criteria. Their characteristics are shown in Table 1. There were 51 men and 47 women, with a mean ± SD age of 46 ± 12 years. Thirty-six (37%) were infected through blood trans-

Table 2. Risk Factors for the Occurrence of Mood Disorders During the First 12 Weeks of Interferon-Alfa Therapy (N=93)

Variable	Patients With Mood Disorders, N = 30	Patients Without Mood Disorders, N = 63	p Value[a]
Age, mean ± SD, y	42.5 ± 10.7	47.8 ± 12.7	NS
Gender, N (%)			
Men	15 (50)	34 (54)	
Women	15 (50)	29 (46)	NS
Routes of CHC transmission, N (%)			
Blood transfusion	8 (26)	26 (41)	
Intravenous drug use	14 (48)	11 (18)	< .02
Other	8 (26)	26 (41)	
Past alcohol abuse/dependence (MINI lifetime), N (%)			
No	24 (80)	56 (89)	
Yes	6 (20)	7 (11)	NS
Past psychiatric disorders (MINI lifetime), N (%)			
No	11 (37)	44 (70)	
Yes	19 (63)	19 (30)	< .003
MADRS score, mean ± SD	8.9 ± 7.3	4.0 ± 3.6	< .001
STAI score, mean ± SD	40.1 ± 13.1	30.0 ± 9.1	< .001

[a]Differences were calculated using Pearson's χ^2 for categorical variables and 1-way analysis of variance for continuous variables.
Abbreviations: CHC = chronic hepatitis C, MADRS = Montgomery-Asberg Depression Rating Scale, MINI = Mini-International Neuropsychiatric Interview, NS = nonsignificant, STAI = State-Trait Anxiety Inventory.

Figure 1. Mean Montgomery-Asberg Depression Rating Scale (MADRS) Scores in Patients With Mood Disorders (depressive mixed state, mania/hypomania) and in Patients Without Mood Disorders During the First 12 Weeks of Interferon-Alfa Therapy[a]



[a]The error bars represent upper and lower bounds of 95% confidence intervals.

fusion, whereas 27 (27%) were infected through intravenous drug use. According to the MINI lifetime item, 34 patients (35%) had a history of major depressive disorder, and 19 (19%) suffered from generalized anxiety disorder. Four patients (4%) met the DSM-IV criteria for major depressive disorder at baseline. These 4 patients and another patient, who was lost to follow-up during the first 12 weeks, were excluded from further analysis.

Incidence, Time Course, and Characterization of IFN-Alfa–Induced Psychiatric Disorders

Thirty patients (32%) developed IFN-alfa–induced psychiatric disorders, 6 (20%) before week 4 and 24 (80%) thereafter. These disorders consisted in all cases of mood disorders according to the DSM-IV criteria.

Eighteen patients (60%) met the criteria for irritable manic/hypomanic episodes. Three of the 18 reported euphoria, inflated self-esteem, increase in goal-directed activity, decreased need for sleep, and excessive involvement in pleasurable activities with severe consequences (e.g., spending money, antisocial behavior) and were diagnosed as manic. The remaining 15 patients reported irritable mood, racing thoughts, distractibility, transient psychomotor agitation, and insomnia and were diagnosed as hypomanic. None of the 15 presented with excessive involvement in pleasurable activities.

Finally, 12 patients (40%) met the criteria for major depressive disorder but also presented with hypomanic symptoms (irritability, racing thoughts, psychomotor agitation, and aggressive behaviors) and thus were diagnosed as exhibiting "depressive mixed states," according to the phraseology of Akiskal et al.[25,26]

Risk Factors for the Occurrence of IFN-Alfa–Induced Mood Disorders

Risk factors for the occurrence of mood disorders are shown in Table 2. They included past history of psychiatric disorders ($p < .003$), infection through intravenous drug use ($p < .02$), and baseline elevated MADRS ($p < .001$) and STAI ($p < .001$) scores. No relationship between the nature of psychiatric disorders (depressive mixed states and mania/hypomania) and those factors could be found.

MADRS Global Score Analysis

MADRS scores increased significantly between baseline and week 12 ($p < .001$) (Figure 1). MADRS scores were significantly higher in patients with mood disorders (depressive mixed states or mania/hypomania) than in those without mood disorders at all time points ($p < .001$). The interaction effect was significant ($F = 2.88$, $df = 4,180$; $p < .03$). Post hoc tests revealed that mean ± SD MADRS scores increased significantly between week 4 and week 12 in patients with depressive mixed states (week 4: 16.1 ± 6.3, week 12: 21.3 ± 9.6; $p < .03$) but not in patients with mania/hypomania (week 4: 18.0 ± 6.3, week 12: 19.0 ± 4.5; $p > .05$) nor in patients without mood disorders (week 4: 9.2 ± 6.3, week 12: 10.4 ± 6.7; $p > .05$). However, no significant differences in MADRS scores were observed between patients with depressive mixed states and those with mania/hypomania at any time points ($p > .05$).

MADRS Item-by-Item Analysis

To distinguish patients who developed depressive mixed states and manic/hypomanic episodes from those

who did not, we performed 2-way ANOVA (3 × 3; groups: depressive mixed states, mania/hypomania, no mood disorder × time: baseline, week 4, and week 12) with each of the 10 MADRS items as the dependent variable (Figure 2). Apparent sadness (Figure 2A), expressed sadness (Figure 2B), inner tension (Figure 2C), all 4 neurovegetative items (sleep disturbance, loss of appetite, lack of concentration, and lassitude; Figures 2D–G, respectively) and anhedonia (Figure 2H), increased significantly between baseline and week 12 ($p < .001$), whereas pessimistic thoughts (Figure 2I) and suicidal thoughts (Figure 2J) did not. Patients with mood disorders had significantly higher scores for all MADRS items than those without mood disorders ($p < .01$). Apparent sadness (Figure 2A), expressed sadness (Figure 2B), and inner tension (Figure 2C) showed significant interaction effects. Post hoc tests revealed that apparent and expressed sadness scores increased significantly between baseline, week 4, and week 12 in patients with depressive mixed states but not in patients with mania/hypomania or in patients without mood disorders. Inner tension scores increased significantly between baseline, week 4, and week 12 in all patients with mood disorders ($p < .001$) but not in patients without mood disorders ($p > .05$).

State Anxiety Analysis

STAI scores increased significantly between baseline and week 12 ($p < .001$) (Figure 3). STAI scores were significantly higher in patients with mood disorders (depressive mixed states or mania/hypomania) than in patients without mood disorders at all time points ($p < .001$). The interaction effect was significant ($F = 2.49$, $df = 4$, 180; $p < .05$). Post hoc tests revealed that mean ± SD STAI scores increased significantly between baseline, week 4, and week 12 in patients with depressive mixed states (baseline: 39.7 ± 11.4, week 4: 45.1 ± 13.5, and week 12: 54.3 ± 12.0; $p < .001$) and in patients with mania/hypomania (baseline: 40.4 ± 14.4, week 4: 43.9 ± 13.5, and week 12: 48.0 ± 9.7; $p < .02$) but not in those without mood disorders (baseline: 30.0 ± 9.0, week 4: 32.0 ± 10.8, and week 12: 33.2 ± 10.5; $p > .05$). However, no significant differences in STAI scores were observed between patients with depressive mixed states and those with mania/hypomania at any time point ($p > .05$).

Fatigue Analysis

A significant increase in fatigue scores was observed between baseline and week 12 ($p < .001$) (Figure 4). Fatigue scores were significantly higher in patients with mood disorders than in patients without mood disorders at all time points ($p < .001$). The interaction effect was not significant ($p > .05$). No significant differences in BFI scores were observed between patients with depressive mixed states and those with mania/hypomania at any time point ($p > .05$).

DISCUSSION

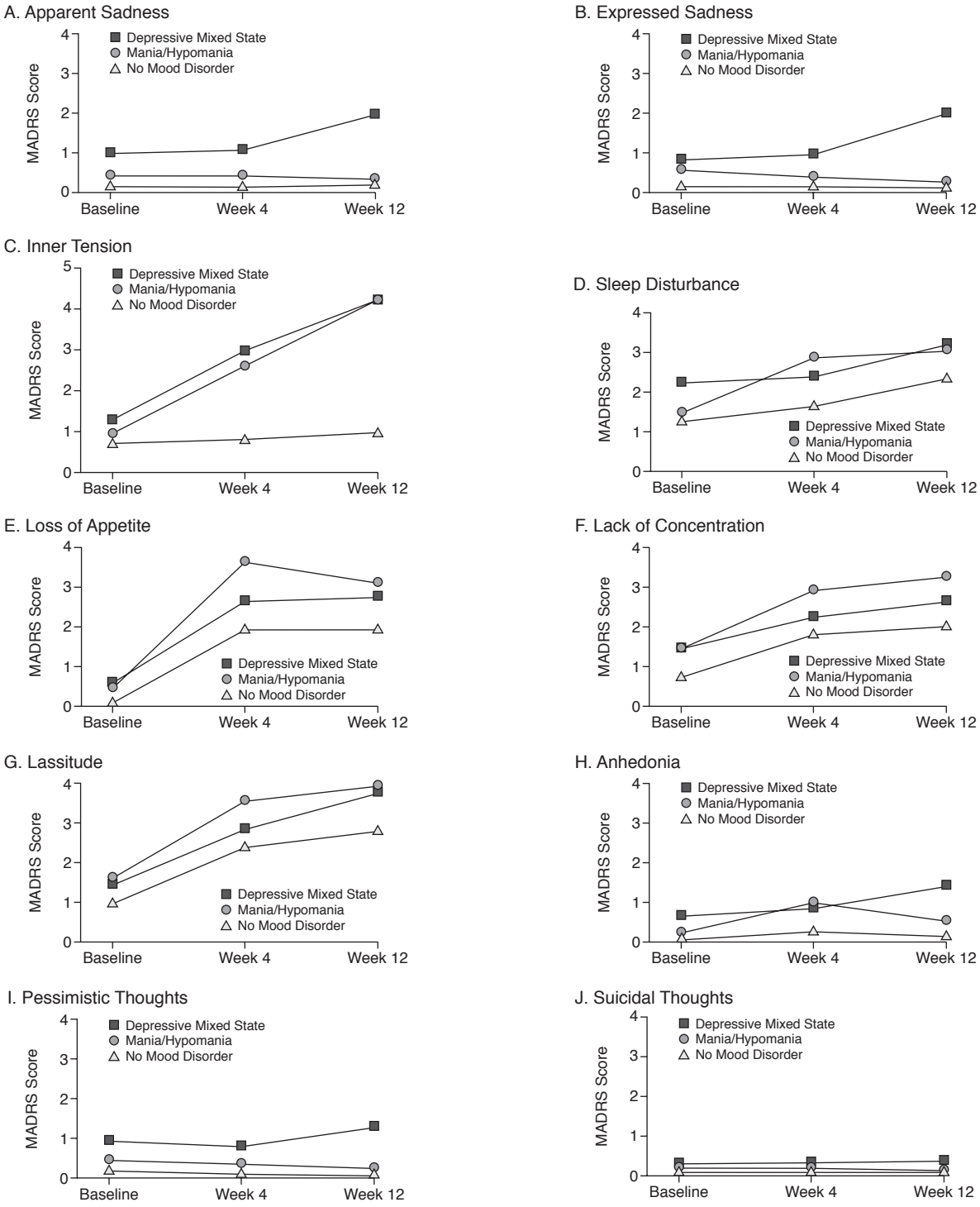
This prospective study, conducted in a large cohort of patients with CHC currently receiving a standard treatment course of pegylated IFN-alfa and ribavirin, confirms the high prevalence (32%) of IFN-alfa–induced mood disorders,[7–9,27–30] a finding consistent with the results of recent studies.[7,9,31] However, our results regarding the nature of these disorders differ substantially from those in previous studies[4,6] identifying depression as the hallmark of IFN-alfa–induced neuropsychiatric side effects and provide new insight into the characterization of these disorders.

Although psychiatric events recorded in our study consisted of mood disorders in all cases, 18 (60%) of 30 patients did not meet the usual DSM-IV criteria for major depressive disorder but rather those for irritable manic/hypomanic episodes. Indeed, 15 patients reported irritable mood, racing thoughts, distractibility, transient psychomotor agitation, and insomnia and were diagnosed as hypomanic. However, despite presenting these hypomanic symptoms, patients exhibited severe fatigue as evidenced by high BFI scores (Figure 4), a symptom that is not a criterion for the diagnosis of hypomania. Three patients reported only the typical euphoric/expansive characteristics of mania/hypomania: euphoria, inflated self-esteem, increase in goal-directed activity, decreased need for sleep, and excessive involvement in pleasurable activities with severe consequences (e.g., spending money, antisocial behaviors), and not fatigue and anhedonia, as reported by the 15 previous patients. Additionally, the remaining 12 patients (40%) meeting criteria for major depressive disorder also exhibited irritable hypomanic symptoms and severe fatigue and thus were classified as having depressive mixed states.

Although these disorders are not described in the current classification of mental illnesses, an extensive literature gives many arguments for their existence.[26,32–38] The results of the present study highlight the difficulties of classifying IFN-induced psychiatric disorders, suggesting that they may not fit into the usual DSM-IV diagnostic categories. Indeed, concomitant fatigue and anhedonia are not present in patients with typical manic/hypomanic episodes. However, in the case of patients treated with IFN, the presence of fatigue is likely related to the flu-like syndrome, observed in nearly all patients particularly during the first month of therapy. In keeping with this, our results show that fatigue scores increased significantly only between baseline and week 4, whereas inner tension and anxiety increased significantly between baseline, week 4, and week 12.

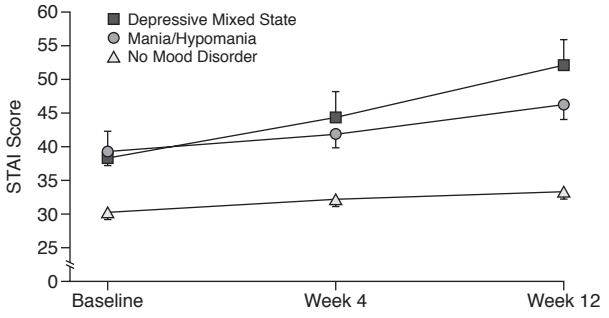
In the present study, patients were screened systematically at regular intervals for the occurrence of psychiatric disorders using validated tools such as the MINI and MADRS. As previously reported,[9] global MADRS

Figure 2. Analysis of Variance F Ratios and p Values for Each Montgomery-Asberg Depression Rating Scale (MADRS) Item[a]



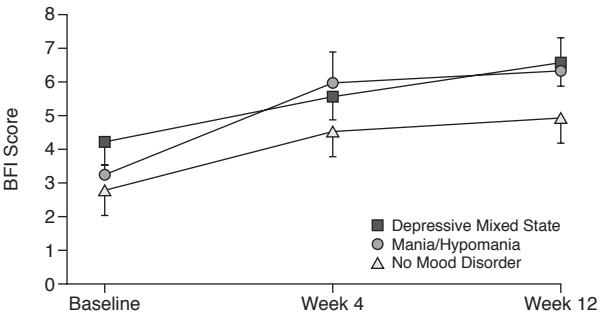
[a]**Apparent sadness (A):** $F_{group} = 32.15$, df = 2,90; $p < .001$. $F_{time} = 4.21$, df = 2,180; $p < .02$. $F_{group \times time} = 4.03$, df = 4,180; $p < .004$. **Expressed sadness (B):** $F_{group} = 39.42$, df = 2,90; $p < .001$. $F_{time} = 4.41$, df = 2,180; $p < .002$. $F_{group \times time} = 6.51$, df = 4,180; $p < .001$. **Inner tension (C):** $F_{group} = 60.02$, df = 2,90; $p < .001$. $F_{time} = 64.82$, df = 2,180; $p < .001$. $F_{group \times time} = 19.06$, df = 4,180; $p < .001$. **Sleep disturbance (D):** $F_{group} = 3.92$, df = 2,90; $p < .03$. $F_{time} = 5.97$, df = 2,180; $p < .004$. $F_{group \times time}$ = NS, df = 4,190. **Loss of appetite (E):** $F_{group} = 8.49$, df = 2,90; $p < .001$. $F_{time} = 47.95$, df = 2,180; $p < .001$. $F_{group \times time}$ = NS, df = 4,180. **Lack of concentration (F):** $F_{group} = 5.51$, df = 2,90; $p < .006$. $F_{time} = 18.63$, df = 2,180; $p < .001$. $F_{group \times time}$ = NS, df = 4,180. **Lassitude (G):** $F_{group} = 6.71$, df = 2,90; $p < .002$. $F_{time} = 42.28$, df = 2,180; $p < .001$. $F_{group \times time}$ = NS, df = 4,180. **Anhedonia (H):** $F_{group} = 18.02$, df = 2,90; $p < .001$. $F_{time} = 4.77$, df = 2,180; $p < .01$. $F_{group \times time}$ = NS, df = 4,180. **Pessimistic thoughts (I):** $F_{group} = 29.7$, df = 2,90; $p < .001$. F_{time} = NS, df = 2,180. $F_{group \times time}$ = NS, df = 4,180. **Suicidal thoughts (J):** $F_{group} = 9.08$, df = 2,90; $p < .0003$. F_{time} = NS, df = 2,180. $F_{group \times time}$ = NS, df = 4,180.
Abbreviation: NS = nonsignificant.

Figure 3. Mean State-Trait Anxiety Inventory (STAI) Scores in Patients With Mood Disorders (depressive mixed state, mania/hypomania) and in Patients Without Mood Disorders During the First 12 Weeks of Interferon-Alfa Therapy[a]



[a]The error bars represent upper and lower bounds of 95% confidence intervals.

Figure 4. Mean Brief Fatigue Inventory (BFI) Scores in Patients With Mood Disorders (depressive mixed state, mania/hypomania) and in Patients Without Mood Disorders During the First 12 Weeks of Interferon-Alfa Therapy[a]



[a]The error bars represent upper and lower bounds of 95% confidence intervals.

scores increased significantly during the first 12 weeks of IFN therapy, with significantly higher scores in patients who developed mood disorders than in those who did not (Figure 1). Interestingly, the strategy of examining each MADRS item individually allowed us to better characterize the features that distinguish patients who developed mood disorders from those who did not. Neurovegetative symptoms that appeared within the first 4 weeks accounted for the increase in MADRS score in all patients (Figure 2D–G). These symptoms, together with anhedonia, belong to a nonspecific response to stress triggered by cytokine (e.g., IFN) release, known as the "sickness behavior."[39,40] As the symptoms of sickness behavior and depressive states are identical, the incidence of depression may have been overestimated in studies in which the diagnosis of depression was not based on DSM-IV criteria.

Among the 10 items analyzed, only inner tension (Figure 2C) increased significantly over time in all patients who developed mood disorders (either depressive mixed states or manic/hypomanic episode) as compared with those who did not. Similarly, state anxiety increased significantly over time only in patients with mood disorders (Figure 3). These results suggest that both of these symptoms, which are closely related to irritability,[41,42] are key components of IFN-alfa–induced mood disorders. So far, most studies have focused mainly on depressive symptoms rather than assessing a wider range of potential side effects. However, in clinical practice, patients with CHC treated with IFN-alfa often report increased impatience, irritability, and hostility. Indeed, in 2 pivotal studies including more than 2000 patients treated with pegylated IFN plus ribavirin for CHC, irritability was reported in 24%[2] and 35%[3] of patients, a prevalence similar to that of depression (22% and 31%, respectively). Kraus et al.[43] have also recently reported a significant increase in anger/hostility scores during IFN-alfa therapy in HCV-infected patients. Finally, cases of mania and bipolar syndromes have been reported in patients treated with IFN for melanoma.[18]

The strategy of examining each MADRS item individually also allowed us to better characterize the features that distinguish patients with depressive mixed states from those with manic/hypomanic episodes and to show their specific patterns. Indeed, apparent and expressed sadness increased significantly over time only in patients with depressive mixed states (Figure 2A–B). In these patients, however, depressed thoughts were minimal in severity and did not become significantly worse over time (Figure 2I–J). This may represent a major distinction between typical clinical depression and IFN-alfa–induced depressive mixed states.

The mechanisms underlying IFN-alfa–induced mood disorders remain poorly understood. There are many pathways by which IFN-alfa may cause neuropsychiatric complications, including the induction of proinflammatory cytokines,[44,45] activation of the hypothalamic-pituitary-adrenal axis,[46] and depletion of tryptophan[47] resulting in lower serotonin (5-HT) function. Our results are consistent with this last biological hypothesis, as irritability and aggressive behavior are considered to be symptoms related to lowered central 5-HT function.[48–51] Further studies are needed to confirm this hypothesis.

The existence of risk factors for the occurrence of IFN-induced mood disorders remains debated.[7,29,31,52,53] In the present study, past history of psychiatric disorders, infection through intravenous drug use, and elevated MADRS and STAI baseline scores were risk factors for the occurrence of mood disorders. However, no relationship between the type of mood disorders (i.e., depressive mixed states or mania/hypomania) and past history of psychiatric disorders could be found.

Our findings not only are of diagnostic relevance but also may have important therapeutic implications for clinicians managing patients with CHC. Antidepressants, particularly selective serotonin reuptake inhibitors, are currently the recommended treatment of IFN-alfa–induced mood disorders.[7,54] However, despite the use of these antidepressants, antiviral treatment discontinuation has been reported in a significant proportion of patients.[7,54] In addition, antimanic therapy has been successfully used in some patients.[18] Finally, antidepressant therapy may worsen underdiagnosed manic/hypomanic states. Accordingly, distinction between manic/hypomanic states and depressive mixed states is of critical importance, given that where one draws the line between irritable depression and irritable mania will dictate whether antidepressants or antimanic agents should be employed as first-line therapy. This important issue requires further investigation.

In conclusion, our findings suggest that IFN-alfa–induced mood disorders are common in patients with CHC and consist of an overlap between depressive and manic/hypomanic symptoms rather than a mere depression. Item-by-item analysis highlighted the key role of irritability in these disorders, suggesting that they are complex and multidimensional and that they may not fit into the usual DSM-IV diagnostic categories. The impact of such findings on therapeutic management deserves further investigation.

Drug name: ribavirin (Rebetol and others).

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