Depression During Pegylated Interferon-Alpha Plus Ribavirin Therapy: Prevalence and Prediction

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Background: Interferon-alpha (IFN-alpha) plus ribavirin is used to treat hepatitis C virus (HCV) infection and is associated with a high rate of depression. Newer, pegylated preparations of IFN-alpha have a longer half-life, require once-per-week dosing, and may be associated with reduced neuropsychiatric burden. Limited data exist on depression during pegylated IFN-alpha therapy.

Method: Depressive symptoms were assessed using the Zung Self-Rating Depression Scale (SDS) in 162 HCV-infected patients at baseline and after 4, 8, 12, and 24 weeks of treatment with pegylated IFN alpha-2b (PEG IFN) plus weight-based (N = 86) versus standard dose (N = 76) ribavirin. Data were collected from March 2001 to April 2003.

Results: Compared with baseline, mean SDS index scores were significantly increased by week 4 and remained elevated throughout the study. Thirty-nine percent of the sample experienced moderate to severe depressive symptoms (SDS index score ≥ 60) at some point during PEG IFN/ribavirin therapy. Baseline depression scores significantly predicted severity of depressive symptoms during PEG IFN/ribavirin treatment (simple regression analysis: $Y = 0.55X + 32.7$, $p < .0001$). In addition, assignment to weight-based ribavirin treatment and history of depression were associated with increased likelihood of developing moderate to severe depressive symptoms (odds ratio [OR] = 2.7, 95% CI = 1.3 to 5.6, $p < .01$, and OR = 3.3, 95% CI = 1.3 to 8.1, $p < .01$, respectively).

Conclusions: Development of moderate to severe depressive symptoms occurred frequently during PEG IFN/ribavirin treatment and was predicted by baseline depression scores and higher doses of ribavirin. History of major depressive disorder was also a significant predictive factor, but only through association with elevated baseline depression status. All of these factors can be evaluated and addressed to limit neuropsychiatric morbidity during HCV treatment.

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Interferon-alpha (IFN-alpha) is a cytokine released early in viral infection that has both antiviral and antiproliferative activities.[1] Accordingly, IFN-alpha is currently used for treatment of viral infections and certain cancers. In combination with the antiviral agent ribavirin, IFN-alpha is the only U.S. Food and Drug Administration–approved treatment of hepatitis C, which afflicts 4 to 5 million people in the United States and is the leading cause of liver failure requiring transplantation.[2–4] Although a successful antiviral strategy, IFN-alpha treatment has been repeatedly shown to induce significant symptoms of depression in 20% to 50% of patients.[5–9] Combined with fatigue, these symptoms represent a primary cause of poor compliance and/or treatment discontinuation.[10,11] Given recent data demonstrating the seminal importance of adherence in achieving viral clearance,[12] increasing attention is being paid to IFN-alpha–induced neuropsychiatric side effects as potentially manageable impediments to achieving sustained viral response during hepatitis C virus (HCV) treatment.

Recent advances in the treatment of HCV include the development of pegylated preparations of IFN-alpha-2a

and -2b. Pegylation extends medication half-life and appears to increase rates of sustained viral response while offering the convenience of once-per-week dosing.[13,14] Recent data also suggest that pegylated interferons may be associated with decreased self-reported rates of neuropsychiatric side effects, including depression, when compared with older preparations.[13–15] However, prospective evaluations of the prevalence and time course of depressive symptoms utilizing validated screening tools specific for depression during treatment with pegylated IFN-alpha have yet to be reported. Of relevance in this regard, rates of depression during therapy with non-pegylated forms of IFN-alpha have typically been higher in studies that have monitored psychiatric symptoms prospectively and have used validated assessment instruments.[16]

In view of the association between neuropsychiatric side effects and poor treatment outcome,[7,11,15] it is important to identify factors that may increase the risk for developing depression during IFN-alpha therapy. Studies with non-pegylated preparations of IFN-alpha have indicated that the presence of depressive and/or anxiety symptoms immediately prior to IFN-alpha treatment initiation appears to play a role.[7,9,17–20] In terms of risk factors inherent to treatment itself, the risk of developing depression has been found to increase with increasing dosage and duration of IFN-alpha therapy.[6] Interestingly, some indirect evidence suggests that ribavirin may also contribute to depressive symptoms in patients with HCV, both alone[21] and in combination with IFN-alpha.[22]

The present study was designed to prospectively evaluate the prevalence and severity of depressive symptoms in patients receiving pegylated IFN alpha-2b (PEG IFN) and ribavirin for the treatment of HCV. In addition, premorbid (i.e., history of depression or substance abuse) and treatment-specific (i.e., dosage of ribavirin) risk factors for the development of depression during treatment with PEG IFN plus ribavirin were examined.

METHOD

Patients

Subjects were recruited from the southeastern United States region of a multicenter, randomized clinical trial (the WIN-R trial: Evaluation of Weight-Based Dosing With PEG-Intron/Rebetol, Schering-Plough) of fixed-dose (800 mg/day) versus weight-based (< 65 kg: 800 mg/day; 65 to 85 kg: 1000 mg/day; > 85 to 105 kg: 1200 mg/day; > 105 to 125 kg: 1400 mg/day) ribavirin in combination with PEG IFN alpha-2b (1.5 μg/kg once weekly). One hundred sixty-two patients volunteered to participate and completed at least 1 psychiatric evaluation during PEG IFN/ribavirin therapy. Subjects were treated in community gastroenterology clinics and at a local academic medical center (Emory University, Atlanta, Ga.). All subjects had chronic HCV infection with compensated liver disease. Exclusion criteria included prior IFN-alpha therapy, pregnancy, autoimmune disorder, or any cause for liver disease other than HCV. Subjects with a history of substance abuse were required to be abstinent for at least 6 months prior to study entry. Psychiatric exclusion criteria (as determined by the treating gastroenterologist) included preexisting severe depression, psychosis, and suicidal ideation and/or attempt. Severe depression was further defined as any depression that required hospitalization or electroconvulsive therapy or any depression that resulted in prolonged absence from work or significant disruption of daily functions. After complete description of the study to the subjects, written informed consent was obtained. The study was approved by the Emory University School of Medicine Institutional Review Board. Data were collected from March 2001 to April 2003.

Design

The study utilized a prospective cohort design. Subjects were evaluated at baseline and following 4, 8, 12, and 24 weeks of PEG IFN/ribavirin treatment. At each assessment, trained clinicians (blinded to standard vs. weight-based ribavirin dose assignment) contacted the subjects by phone and monitored completion of the Zung Self-Rating Depression Scale (SDS).[23] The baseline assessment of depression and substance abuse history was conducted over the phone by trained interviewers using the appropriate modules from the Structured Clinical Interview for DSM-IV (SCID).[24] Concomitant medications, including antidepressants, and continuing use of PEG IFN and ribavirin were also reviewed. Antidepressant administration was dictated by the clinical judgment of treating physicians and was not controlled by study protocol. Information on dose reduction of PEG IFN and/or ribavirin was obtained from medical records of treating physicians.

Assessment of Depression

Symptoms of depression were assessed using the 20-item SDS.[23] Each item is rated 1 to 4, with higher scores representing greater symptom severity (or less severity for negatively phrased questions). Following standard procedure for the SDS, raw scores were converted to a 100-point scale (SDS index) in which < 50 = normal mood, 50 to 59 = mild depression, 60 to 69 = moderate to marked depression, and ≥ 70 = severe depression.[23] The SDS index has been widely used to evaluate depressive symptoms in medically ill patients[25] and has been used to measure depressive symptoms in patients receiving non-pegylated preparations of IFN-alpha.[26] History of depression (and substance abuse) was determined at baseline by completion of the depression and substance abuse modules of the Structured Clinical Interview for DSM-IV.[24]

Table 1. Characteristics of 162 Study Participants

Characteristic	Value
Age, y	
Mean (SD)	45.0 (6.7)
Range	18–70
Baseline SDS index score	
Mean (SD)	41.9 (9.9)
Range	25–69
Male, N (%)	94 (58.0)
White, N (%)	142 (87.7)
Education, high school graduate, N (%)	83 (51.2)
Genotype 1 viral strain, N (%)	125 (77.2)
Weight-based ribavirin dosage, N (%)	86 (53.1)
History of major depressive disorder, N (%)	31 (19.1)
History of substance abuse, N (%)	90 (55.6)

Abbreviation: SDS = Zung Self-Rating Depression Scale.

Risk Factors for Depression

Previous studies have identified a number of risk factors that may be relevant to the development of depressive symptoms in at-risk populations, including age, gender, and history of depression and/or substance abuse, as well as baseline depression status.[5,8,9,17,19,27–30] Recent data indicate that ribavirin may be an additional risk factor for developing depression during HCV treatment.[22,30] Because patients were randomly assigned to receive standard (800 mg/day) versus weight-based (800–1400 mg/day) ribavirin, group assignment (standard vs. weight-based) was evaluated as a depression risk factor, controlling independently for dose reduction of ribavirin and/or PEG IFN.

Statistical Analysis

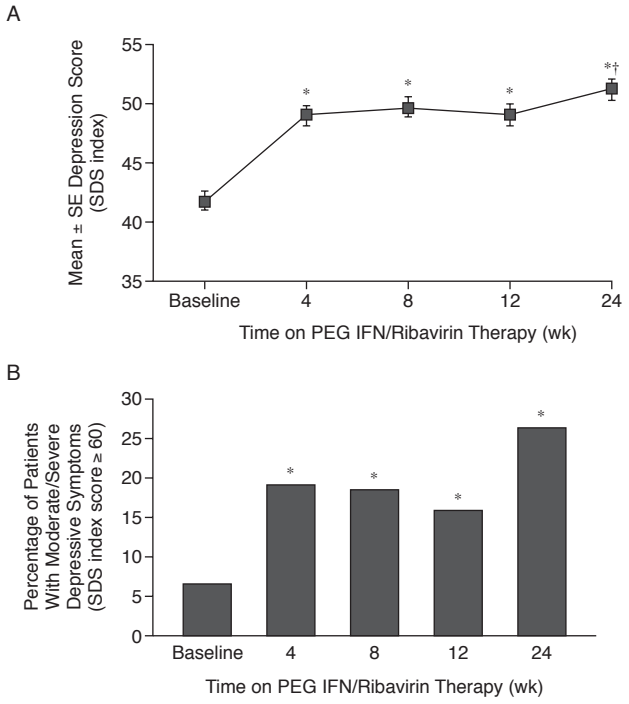
Data were analyzed using the SAS statistical package (SAS Institute, Inc.; Cary, N.C.). Changes in SDS index scores as a function of time were assessed using repeated-measures analysis of variance employing mixed linear modeling with contrasts to compare specific time points during IFN-alpha/ribavirin therapy.[31] The percentage of subjects experiencing moderate to severe depressive symptoms (SDS index score ≥ 60) before and during PEG IFN/ribavirin therapy was evaluated using the trend test of Cochran-Armitage.[32] Simple linear regression analysis and the Bravais-Pearson product moment correlation coefficient were used to assess the relationship between baseline SDS index scores and maximal depression scores during PEG IFN/ribavirin treatment. Finally, an unconditional logistic regression was used to test the association between relevant predictive factors and the development of moderate to severe depression (SDS index score ≥ 60) during PEG IFN/ribavirin therapy. To ensure that all patients had an equal opportunity to reach this threshold depression score, only patients who completed all 24 weeks of the study were included in this analysis (N = 140). Age (categorized as < or ≥ 45 years—based on a median split), gender, history of alcohol or drug abuse, history of major depressive disorder, dose of ribavirin, antidepressant usage, and PEG IFN or ribavirin dosage reduction were initially entered into the model. Stepwise, backward elimination (with $p < .05$ as the criterion of elimination) was used to remove nonsignificant factors. For purposes of the regression analysis, antidepressant usage was defined as any self-reported use of an antidepressant for at least 2 consecutive weeks. Because antidepressant treatment was not controlled by study protocol, antidepressant usage was not further categorized regarding therapeutic adequacy. To specifically evaluate the contribution of antidepressant usage and ribavirin/PEG IFN dose reduction to the development of moderate to severe depressive symptoms during treatment, antidepressant usage and dose reduction of ribavirin and/or PEG IFN were considered in the regression analysis only if they occurred before the subject reached an SDS index score of ≥ 60. Adjusted odds ratios (ORs) and corresponding Wald confidence intervals were calculated using regression coefficients. The Hosmer-Lemeshow goodness-of-fit test was used to evaluate adequacy of the model.[33] All tests of significance were 2-sided with an alpha level of .05.

RESULTS

One hundred sixty-two patients volunteered to participate in the study and completed at least 1 psychiatric assessment during PEG IFN/ribavirin treatment. Demographic and clinical data for the study sample are presented in Table 1. Men comprised 58% of the sample, and 88% of patients were non-Hispanic white. Mean age was 45.0 years (SD = 6.7; range, 18–70 years). Consistent with patterns of HCV infection in the United States,[3] 77% of patients were infected with genotype 1 viral strain. Seventy-six patients (47%) were randomly assigned to receive standard ribavirin dosing (800 mg/day), and 86 patients (53%) received weight-based dosing (800–1400 mg/day). Thirty-one patients (19%) endorsed a history of at least 1 prior episode of major depressive disorder, and 90 (56%) were positive for a history of substance abuse (substance abuse disorder in remission). At baseline, 2 patients met criteria for current major depressive disorder, and no patients met criteria for current drug or alcohol abuse. Due to the lack of patients with active depression or substance abuse, neither condition was included as a predictive factor in the statistical analyses.

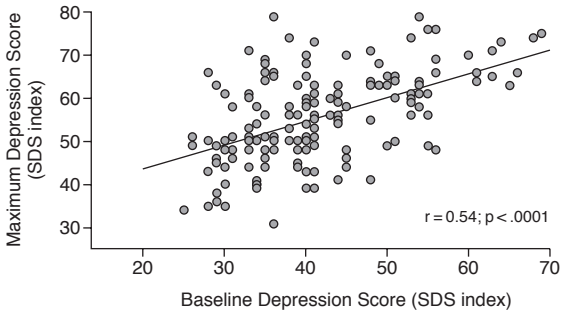
The mean SDS index score for the study population at baseline was 41.9 (SD = 9.9). This score is similar to the mean score reported for the U.S. population as a whole[34] and is consistent with some,[18,27,35,36] but not all,[26,37,38] previous reports of depressive symptoms in patients with HCV not receiving IFN-alpha/ribavirin therapy. Of note, patients with a history of depression exhibited significantly higher mean baseline SDS index scores compared with patients without a depression history (48.7 [SD = 10.9] vs. 40.3 [SD = 9.0], $t = 4.5$, $p < .0001$). Finally, 47

Figure 1. Depression Scores (A) and Percentage of Patients Experiencing Moderate to Severe Depressive Symptoms (B) Among Patients With HCV Receiving PEG IFN/Ribavirin Therapy[a]



[a]Depressive symptoms were assessed using the SDS. Numbers of patients included at each assessment point were as follows: baseline, N = 162; week 4, N = 162; week 8, N = 156; week 12, N = 150; week 24, N = 140.
*Significantly different from baseline ($p < .05$).
†Significantly different from other time points ($p < .05$).
Abbreviations: HCV = hepatitis C virus, PEG IFN = pegylated interferon alpha-2b, SDS = Zung Self-Rating Depression Scale.

Figure 2. Relationship Between Baseline and Maximum Depression Scores During PEG IFN/Ribavirin Treatment in 162 Patients With HCV[a]



[a]Depressive symptoms were assessed using the SDS. The baseline depression score for each patient was plotted along with the maximum depression score reached at any point during PEG IFN/ribavirin therapy. Linear regression analysis revealed a significant linear relationship ($Y = 0.55X + 32.7$, $p < .0001$) between baseline (X) and maximum (Y) depression scores that allowed prediction of severity of depressive symptoms during PEG IFN/ribavirin therapy based on the baseline depression score.
Abbreviations: HCV = hepatitis C virus, PEG IFN = pegylated interferon alpha-2b, SDS = Zung Self-Rating Depression Scale.

patients (29%) were receiving an antidepressant at baseline, and an additional 36 patients (22%) started taking an antidepressant during PEG IFN/ribavirin treatment.

Twenty-two patients discontinued the study prior to week 24. Eleven patients withdrew consent or were lost to follow-up. Six patients discontinued due to IFN-alpha–related behavioral symptoms (e.g., depression/anxiety/fatigue), and 5 patients discontinued due to medical complications. There were no statistically significant differences between patients who dropped out and study completers in terms of age, gender, baseline SDS score, history of major depressive disorder, or history of substance abuse (data not shown).

As shown in Figure 1A, there was a significant main effect of time on mean SDS index scores ($F = 40.29$, $df = 4,161$; $p < .001$). Multiple pairwise comparisons of specific time points during the study revealed that depression scores were significantly elevated over baseline by week 4 (week 4 vs. baseline, $t = 9.46$, $df = 161$, $p < .001$) and remained increased through the 24th week of PEG IFN/ribavirin treatment, at which time mean depression scores were the highest (week 24 vs. week 4, $t = 3.33$, $df = 161$, $p < .01$; week 24 vs. week 8, $t = 2.26$, $df = 161$, $p < .05$; week 24 vs. week 12, $t = 3.54$, $df = 161$, $p < .001$). Of note, the point prevalence of moderate to severe depression (SDS index score ≥ 60) also significantly increased over the course of PEG IFN/ribavirin therapy (Cochran-Armitage Test, $z = 3.8$, $p < .001$) (Figure 1B). Whereas 11 (6.8%) of 162 patients exhibited symptoms consistent with moderate to severe depression at baseline, 37 (26.4%) of the 140 patients remaining at week 24 had an SDS index score ≥ 60. Over the entire 24-week treatment period, 38.9% of patients exhibited moderate to severe depressive symptoms during at least 1 assessment. Prevalence rates for mild depressive symptoms, defined as an SDS index score ≥ 50, also increased significantly during treatment, from 24.7% at baseline to a maximum of 55.7% at 24 weeks (Cochran-Armitage Test, $z = 4.2$, $p < .001$). Seventy-two percent of patients had an SDS index score ≥ 50 during at least 1 assessment over the study period.

Based on previous results from our group and others, we examined the relationship between baseline depressive symptoms and the maximal depression score during PEG IFN plus ribavirin treatment. As shown in Figure 2, baseline depression scores were highly predictive of the maximal depression score during PEG IFN plus ribavirin treatment (simple regression analysis; $Y = 0.55X + 32.7$, $p < .0001$ for slope; $R = 0.54$, $p < .0001$).

To evaluate the contribution of other relevant factors to the development of moderate to severe depressive symp-

toms (SDS index score ≥ 60), logistic regression analysis was performed in patients who completed all 24 weeks of the study (N = 140) (see Method). Given the impact of baseline depression scores on the development of depression during PEG IFN/ribavirin treatment, logistic regression was initially conducted controlling for baseline SDS index score. Backward stepwise elimination was used to remove nonsignificant factors from the model. Only ribavirin dose assignment significantly predicted the development of moderate to severe depressive symptoms when baseline SDS index score was controlled for. Patients who received weight-based dosing of ribavirin (800–1400 mg/day) were significantly more likely to develop moderate to severe depressive symptoms compared with patients who received standard dosing (800 mg/day) (OR = 2.4, 95% CI = 1.1 to 5.4, $p < .05$). Consistent with this finding, the mean SDS index score across the 24-week treatment period was significantly higher in the group randomly assigned to weight-based ribavirin versus the group receiving standard dose therapy (51.5 [SD = 9.3] vs. 46.8 [SD = 8.2], respectively, $t = 3.1$, $p < .01$). Patients randomly assigned to weight-based ribavirin began the study taking more ribavirin (mean starting dose = 13.5 mg/kg) than patients randomly assigned to standard dose therapy (mean starting dose = 9.8 mg/kg). Of note, somatic symptoms on the SDS scale (including sleep difficulties, altered appetite, weight loss, constipation, palpitations, and fatigue) were not significantly increased in patients receiving weight-based versus standard dose ribavirin (data not shown).

Factors that did not predict the development of depression during PEG IFN plus ribavirin treatment when controlling for baseline SDS index score included gender, age, viral genotype, history of substance abuse, history of depression, antidepressant use, or the need for dose reductions of either PEG IFN or ribavirin. Of the 140 patients considered in the logistic regression analysis, 19.3% (N = 27) required reduction in the dosage of PEG IFN, and 21.4% (N = 30) required reduction in ribavirin for a period of at least 1 week. Although history of major depressive disorder was eliminated from the regression model described above, patients with a depression history exhibited a significantly higher rate of moderate to severe depressive symptoms (SDS index score ≥ 60) during PEG IFN/ribavirin treatment than patients with no history of depression (64.5% vs. 32.8%, respectively; $\chi^2 = 10.6$, $df = 1$, $p < .005$). As previously mentioned, baseline depression scores were also higher in patients with a depression history, indicating that the increased rate of moderate to severe depressive symptoms in patients with a history of depression occurred through an association with elevated baseline depression status. Indeed, when logistic regression analysis was repeated without controlling for baseline SDS index score (using backward stepwise elimination of nonsignificant factors as noted above), a history of major depressive disorder emerged as a significant predictor of moderate to severe depression during PEG IFN/ribavirin therapy (OR = 3.3, 95% CI = 1.3 to 8.1, $p < .01$). As in the previous regression analysis, assignment to weight-based ribavirin remained a significant predictive factor in the model (OR = 2.7, 95% CI = 1.3 to 5.6, $p < .01$).

DISCUSSION

The data demonstrate that treatment with PEG IFN plus ribavirin is associated with a significant increase in depressive symptoms. Depressive symptoms were apparent as early as 4 weeks following treatment initiation and peaked at week 24, suggesting that the adverse neuropsychiatric effects of PEG IFN/ribavirin escalate as a function of treatment duration (as has been observed with older interferon preparations).[16] The development of moderate to severe depressive symptoms during PEG IFN/ribavirin therapy was predicted by baseline depression scores and was associated with a history of depression and ribavirin dosage.

Thirty-nine percent of the patients in our study endorsed moderate to severe depressive symptoms (i.e., an SDS index score ≥ 60) at some point during the first 24 weeks of treatment. These results are similar to those of a large multicenter trial by Manns and colleagues[13] in which rates of self-reported depression were 29% for patients assigned to lower-dose PEG IFN (1.5 μg/kg once weekly for 4 weeks, then 0.5 μg/kg) and 31% for higher-dose PEG IFN (1.5 μg/kg per week), the dose used in the current study. Of note, Manns et al. assessed depression as a single item as part of a general side effect screening process and followed patients for 48 weeks.[13]

Several risk factors for developing depressive symptoms during PEG IFN/ribavirin treatment were identified in this study, including baseline SDS index score, history of depression, and ribavirin dosage assignment. A review of the available literature suggests that pretreatment mood disturbance, even when subsyndromal, is the most reliable predictor of developing both depressive symptoms and major depressive disorder during therapy with IFN-alpha, with or without concomitant ribavirin.[7,9,17–19] Results from the current study support the centrality of baseline mood status as a risk factor. Indeed, based on the linear relationship between initial depression scores and maximal depression scores, the resulting regression equation ($Y = 0.55X + 32.72$, $p < .0001$) indicates that patients with mild depression (SDS index score ~50) or greater at baseline are highly likely to progress to depressive symptoms in the moderate to severe range during PEG IFN/ribavirin therapy.

These data provide a relevant clinical "yardstick" by which to assess risk and suggest that patients presenting for IFN-alpha therapy with mild to moderate depressive

symptoms (as assessed by any depression rating scale) should be cautioned regarding the potential neuropsychiatric risks and should be considered for pretreatment with an antidepressant. Indeed, antidepressant pretreatment has been found to effectively reduce the development of depression in patients receiving high-dose IFN-alpha for malignant melanoma,[7] and preliminary data in psychiatric patients with hepatitis C suggest that antidepressant pretreatment may also reduce the risk of becoming depressed during IFN-alpha/ribavirin therapy.[39]

A large body of data supports the notion that a history of major depressive disorder is a significant risk factor for the subsequent development of depression.[40] Nevertheless, there are conflicting reports on whether a history of depression is a risk factor for depression during IFN-alpha treatment.[8,16,19,30,41] In the current study, a history of major depressive disorder was predictive of treatment-emergent depressive symptoms only when baseline depression scores were not included in the analysis. These data indicate that a history of major depressive disorder contributes to the risk of developing depressive symptoms during PEG IFN/ribavirin therapy through an association with elevated baseline depression status. Indeed, baseline depression scores were significantly elevated in patients with a history of major depressive disorder. These findings are consistent with previous work indicating that patients with a depression history often exhibit persisting subsyndromal mood symptoms even when not experiencing an episode of illness.[42]

Taken together, the results indicate that mood status immediately prior to commencing PEG IFN/ribavirin therapy is more relevant than past mood disturbance for identifying at-risk patients. Nonetheless, a history of major depressive disorder should alert the clinician to a careful evaluation of current mood status. It should be noted, however, that history of major depressive disorder (and substance abuse) were evaluated using a phone-based SCID interview. Although studies suggest that phone-administered SCID assessments are valid,[43,44] we appreciate the possibility that face-to-face assessments may have improved the reliability of the information obtained.

A somewhat surprising finding in the current study was the association of weight-based dosing of ribavirin with an increased risk of an SDS index score ≥ 60 and higher mean SDS index scores across the 24 weeks of treatment, which suggests that higher doses of ribavirin increase the depressive burden associated with IFN-alpha therapy. The current study is the first to directly examine the potential depressogenic effects of ribavirin, and, given the nature of the study design, the opportunity to observe severity of depressive symptoms in patients randomly assigned to 2 different dosing strategies of ribavirin while maintaining a standardized dose of IFN-alpha was unique. Nevertheless, the finding that weight-based ribavirin therapy significantly increased the risk for developing depressive symptoms is consistent with past observations.[21,22] Ribavirin has been reported to be associated with increased depression when used as a single agent for HCV.[21] More recently, a study that prospectively evaluated the development of depression in patients receiving IFN-alpha with and without ribavirin found that rates of depression were increased in patients receiving combined interferon-alpha/ribavirin treatment.[22] Taken together, these findings highlight the potential contribution of ribavirin to a depressive syndrome that has previously been ascribed exclusively to IFN-alpha. Of note, weight-based ribavirin dosing was not associated with increased somatic symptoms including appetite disturbances, weight loss, and fatigue, suggesting that the effects of ribavirin on behavior may not primarily derive from asthenia secondary to reduced blood hemoglobin concentrations and/or poor oral intake. Nevertheless, without data on hemoglobin concentrations and a more systematic evaluation of oral intake, these findings remain open to further investigation.

Consistent with prior studies,[8,9,19,22,45] a history of substance abuse did not predict the development of depressive symptoms during PEG IFN/ribavirin therapy. The replicability of this finding across the majority of studies suggests that abstinent patients with a history of drug or alcohol abuse or dependence represent viable candidates for IFN-alpha therapy. As has been noted in many,[5,8,22,29] but not all,[27,30] past studies, gender also did not emerge as a predictor for developing depressive symptoms during PEG IFN/ribavirin therapy. This finding suggests that, in contradistinction to idiopathic major depressive disorder,[46] mood disturbance in the context of cytokine therapy may be as common in males as females.

Antidepressants have been observed to ameliorate IFN-alpha–induced mood symptoms.[7,8,47] However, antidepressant usage in the current study was not sufficiently well controlled to evaluate the impact of antidepressant treatment on symptom development. Nevertheless, it is important to note that a high percentage (50.7%) of patients were treated with antidepressants before and during the study period, suggesting that levels of depressive symptoms might have been even higher in the absence of antidepressant therapy and that subsyndromal depressive symptoms warranted antidepressant treatment. Similar results were found by Dieperink and colleagues,[9] who reported that although 23% of their cohort met DSM-IV criteria for major depressive disorder, 48% required psychiatric intervention during IFN alpha/ribavirin therapy.

Regarding the limitations of the current study, all patients received treatment with PEG IFN/ribavirin; hence, a control population of HCV-seropositive patients was not available. Therefore, it is possible that the significant increase in depressive symptoms noted during the study might have resulted from random variations in mood across time. However, this seems unlikely given the repeated observation that the prevalence of depression in

HCV-seropositive patients does not change, or decreases, across time when such individuals are included as control subjects in trials of IFN-alpha.[26,48,49] A second limitation relates to the psychiatric exclusion criteria and how they were applied. Given the nonspecialist status of treating gastroenterologists and the lack of more stringent psychiatric exclusion criteria, it is likely that psychiatric exclusions were somewhat variable across sites. Nevertheless, the fact that baseline depression scores in the study population as a whole approached those seen in the general population, in conjunction with the relatively small number of patients with moderate to severe depression at baseline, suggests that some appropriate screening occurred. Such screening would serve to limit the participation of potentially vulnerable psychiatric patients in the study and therefore could contribute to an underestimation of the neuropsychiatric impact of PEG IFN/ribavirin.

Drug names: pegylated interferon alpha-2b (PEG-Intron), ribavirin (Rebetol, Ribasphere, and others).

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