An Exploration of Depressive Symptoms in Hepatitis C Patients Taking Interferon-alpha: Increase in Sickness Behaviors but not Negative Cognitions

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Objective: The most investigated adverse event associated with interferon-alpha (IFN- α) treatment is depressed mood, with many studies finding a significant increase in depression scale scores from baseline to treatment. This paper is concerned with exploring discrete categories of depressive symptoms (somatic, behavioral, negative cognitions and depressed mood) in order to explore the behavioral syndrome associated with IFN- α . **Methods:** Thirty-five Hepatitis C patients due to commence IFN- α treatment were assessed using the Structured Clinical Interview (SCID), and the 24-item Hamilton Depression Inventory (HAM-D) at 0 and 8 weeks. **Results:** Somatic symptoms comprised the significant majority of scores across all weeks for patients taking IFN- α . Patients who developed a depression had significantly more somatic and mood symptoms at Week 8 than those patients who did not develop a depression. **Conclusions:** These exploratory results indicate that the increase in raw depression scores is due to an increase in somatic and mood symptoms, rather than negative cognitions. However, this increase does not correspond to a proportional increase in a particular subscale. These results also indicate that development of an IFN- α -induced depression is due to mood symptoms rather than negative cognitions. (J CLIN EXP HEPATOL 2012;2:218–223)

The currently preferred treatment for the Hepatitis C Virus (HCV) is the pro-inflammatory cytokine Interferon-alpha (IFN- α). This drug works by inhibiting the rate at which viral cells proliferate, 'interfering' with replication of the HCV virus and inducing a general increase in immune system functioning.¹ These generally beneficial biological effects are often accompanied by psychiatric, behavioral and physical side-effects such as flu-like symptoms, fatigue, insomnia, depressed mood and irritability.^{2–4} Sickness behavior is the general term given to this collection of symptoms. Sickness behaviors represent an alteration in the motivational state of an organism so that they can preferentially respond to infections.^{5–7} In other words, the organism will have depressed functioning of mood, activity and metabolism so that all of its energy is put into fighting illness.

A diagnosis of Major Depressive Disorder (MDD) requires the presence of at least 5 of 9 characteristics which

consist of mood symptoms, behavioral symptoms, relationship symptoms, somatic symptoms, negative cognitions and perception symptoms.⁸ Many of the symptoms of MDD are also the features of sickness behaviors,^{9,10} with the main difference between these two syndromes being the presence of negative cognitions such as hopelessness, helplessness and worthlessness in MDD but not sickness behavior. The observation that sickness behaviors overlap considerably with symptoms of MDD has led to considerable interest in trying to understand the behavioral syndrome that accompanies IFN- α therapy.

Previous studies have shown that between up to 42% of patients who commence IFN- α therapy develop a clinically diagnosed MDD¹¹ and most patients show a significant increase in depression scale scores from baseline to treatment.^{12–15} However, many of the studies that find an increased prevalence of depression in people taking IFN- α use depression scales rather than a formal diagnostic interview. A formal diagnostic interview allows the interviewer to derive which symptoms are due to depression and which are due to sickness. However, depression scales are often high in somatic/physical items and as IFN- α is a drug that induces sickness behavior, many patients taking this drug could score highly on these scales because they are sick, rather than depressed.¹⁶

Should it be the case that sickness behaviors comprise the majority of the increase in depressive symptoms it is

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Abbreviations: IFN- α : Interferon-alpha; SCID: Structured clinical interview; HAM-D: Hamilton depression inventory; HCV: Hepatitis C virus; MDD: Major depressive disorder; PEG: pegylated; SCID: statistical manual for psychiatric disorders; PAEs: Psychiatric adverse events

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possible that IFN- α induces a specific behavioral syndrome that overlaps significantly with MDD, but is a distinct syndrome. This finding would have substantial clinical importance as clinicians would be able to inform their patients that the somatic symptoms and depressed mood they may experience are caused by being sick rather than having a mental illness.

The aim of this study is to better understand the IFN- α -induced increase in depression scale scores by breaking down the 24-item HAM-D into HAM-D symptom categories that measure the raw scores and proportions of the total depression score explained by distinct HAM-D symptom categories (somatic, behavioral, negative cognitions and depressed mood).

METHODS

Participants

Thirty-nine patients due to start treatment with IFN- α were recruited from the Hepatology Unit at St. James's Hospital, Dublin. Thirty-five participants were followed up to Week 8; one patient presented with MDD at baseline, one discontinued treatment at Week 4 due to intolerance of side-effects of treatment, one did not return for their Week 8 visit, and one patient had their start date changed for medical reasons. Data for a total of 35 patients was therefore analyzed (mean age 37.8 ± 1.4 , 63% male, 86% ex-intravenous drug-users). All patients were taking 180 μ g pegylated (PEG)-IFN- α -2b subcutaneously once per week, with a weight-based dose of Ribavirin (800–1200 mg) once per day. Exclusion criteria included being aged below 16 or above 65; having used illicit substances in the last 6 months; having a significant psychiatric or medical co-morbidity.

Patients were split into those groups who did and did not develop a depression, with two patients who developed a hypomanic episode excluded from these analyses.

Informed Consent and Institutional Review Board (IRB) Approval

This study was approved by the Trinity College Dublin Psychology Ethics Committee and the St. James' Hospital Ethics Committee. All patients gave their informed consent prior to study enrollment.

Procedures

The Structured Clinical Interview for the Diagnostic and Statistical Manual for Psychiatric Disorders (SCID) was used to diagnose depression. Depression severity was assessed using a 24-item HAM-D which comprises all items from the 21-item inventory plus an additional 3 items that measure the negative cognitions hopelessness, helplessness and worthlessness. The 24-item of the HAM-D was used due to the large number of items it encompasses,

allowing different aspects of the depressive syndrome to be explored in greater detail.

Analysis

Normality was checked using the Shapiro-Wilks test, and parametric tests then used to assess data (with adjusted degrees of freedom, where appropriate). Independent sample *t*-tests, one-way ANOVAs, repeated-measures ANOVAs and paired *t*-tests were used. For statistically-significant ANOVAs, Bonferroni post-hoc comparisons were run to determine the source of significant differences. For categorical data, Chi-squared analyses were preferred.

Breakdown of Hamilton Depression Inventory

The HAM-D was broken down into four categories based on Carr and McNulty⁸: Mood symptoms (mood, motivation, anxiety-psychic); Behavior symptoms (psychomotor agitation, psychomotor retardation); Somatic symptoms (appetite, fatigue, appetite, libido, early insomnia, middle insomnia, late insomnia, anxiety-somatic, hypochondriasis, diurnal variation); Negative cognitions (guilt, suicide, insight, depersonalization, paranoia, compulsiveness, helplessness, hopelessness, worthlessness). These four HAM-D symptom categories were then compared from week-to-week using repeated-measures ANOVA to see if there was an overall effect of week on each category, and then a one-way ANOVA was used to assess whether there was a significant difference in the proportion/raw score of symptoms explained by a particular category. Proportions for each HAM-D symptom category were assessed by calculating the percentage of the participants' total score which was explained by depressed mood symptoms, behavior symptoms, somatic symptoms and negative cognitions.

RESULTS

Psychiatric Adverse Events

Crosstabulation analysis demonstrated a significant increase in the frequency of psychiatric adverse events (PAEs) when assessed with the SCID from Week 0 (no PAE's) to Week 8 ($\chi^2(1, N = 70) = 11.67, p < 0.01$). By Week 8 two participants (6%) met the criteria for a major depressive episode and six (17%) were experiencing a minor depression; these two groups were combined for further analysis.

Hamilton Depression Inventory Raw Scores

There was an overall effect of week on HAM-D scores ($t(34) = -5.57, p < 0.01$), with a significant increase in scores from Week 0 (8.2 ± 1.35) to Week 8 (15 ± 1.27).

There was an overall effect of HAM-D symptom category on raw scores at Week 0 ($F(2.10, 69.43) 23.38$,

$p < 0.001$). The significant majority of symptoms were somatic symptoms, when compared to mood, behavior, and negative cognitions; there was also a significant difference between mood and behavior (see Table 1).

At Week 8 there was a similar result ($F(2.50, 82.42) 106.80, p < 0.001$) with somatic and mood symptoms again comprising the significant majority of scores (see Table 1).

Between weeks there was a significant week by HAM-D symptom category interaction ($F(2.10, 70.25) 26.37, p < 0.001$). There was a significant increase from Week 0 (8.2 ± 1.35) to Week 8 (15 ± 1.27) in raw scores for all HAM-D symptom categories except negative cognitions.

Hamilton Depression Inventory Proportion Scores

There was an overall difference in proportions at Week 0 ($F(1.87, 63.56) 41.67, p < 0.001$); there were significantly somatic symptoms than mood symptoms, behavior symptoms, and negative cognitions; there was also a significant difference between mood and behavior (Figure 1).

For proportions there was also a significant overall effect of HAM-D symptom category at Week 8 ($F(1.9, 64.68) 131.12, p < 0.01$); again due to the majority of symptoms being somatic and mood symptoms (Figure 1).

Despite the significant difference observed within weeks, when HAM-D symptom categories were compared between weeks, there was no overall significant effect of treatment ($F(1.78, 60.28) 1.51, P = 0.2$) (Figure 2).

Comparison Between-groups at Week 8 (Depressed and Non-depressed)

Hamilton Depression Inventory Raw Scores

Both the group who developed no psychiatric adverse events (Non-PAE) ($t(25) 3.95, p < 0.01$) and depressed ($t(8) 4.22, p < 0.01$) groups showed a significant increase in overall HAM-D scores from Week 0 to Week 8. Between-groups there was no difference at Week 0 ($t(13.91) 0.83, P = 0.8$),

Figure 1 Within week variance for proportion of symptoms explained by HAM-D symptom category. The significant majority of symptoms were somatic symptoms at Week 0 and Week 8 (** $p < 0.01$), and to a lesser extent depressed mood symptoms but only when compared to behavior symptoms (* $p < 0.05$; ** $p < 0.01$). Week 0: somatic symptoms ($M = 52.55, SD = 4.6$); mood symptoms ($M = 14.82, SD = 2.1$); behavior symptoms ($M = 5.55, SD = 1.7$); negative cognitions ($M = 15.94, SD = 2.9$). Week 8: somatic symptoms ($M = 59.29, SD = 2.5$); mood symptoms ($M = 19.18, SD = 1.5$); behavior symptoms ($M = 8.75, SD = 1$); negative cognitions ($M = 12.78, SD = 1.9$).

however there was a difference at Week 8 ($t(31) 2.91, p < 0.01$) (Table 1).

For the Non-PAE group there was an overall effect of HAM-D symptom category on the symptom breakdown ($F(2.26, 54.21) 67.66, p < 0.001$). There were significant differences between the somatic HAM-D symptom category and all other HAM-D symptom categories.

This group was then assessed for the effect of week on HAM-D symptom category scores. There was a significant week by HAM-D symptom category interaction ($F(3, 22.90) 13.51, p < 0.001$). Post-hoc analyses showed that there was a significant increase in behavior and mood symptoms from Week 0 to Week 8 (Table 1).

For the Depressed group there was also an overall effect of HAM-D symptom category on the symptom breakdown ($F(2.46, 17.21) 75.40, p < 0.001$). At Week 8 there were significantly more somatic symptoms compared to all HAM-D symptom categories, and significantly more mood

Table 1 Within-and-between-groups' differences in raw scores.

Group	Week	Mood	Behavior	Somatic	Negative cognitions
All participants ($n = 35$)	0	1.60 ± 0.36	0.57 ± 0.16	4.06 ± 0.57	1.71 ± 0.42
	8	3.06 ± 0.33	1.34 ± 0.17	8.26 ± 0.58	2.34 ± 0.44
Non-depressed ($n = 25$)	0	1.52 ± 0.44	0.57 ± 0.20	3.75 ± 0.74 (ww**)	1.80 ± 0.53
	8	2.32 ± 0.83 (ww** with behavior only)	1.20 ± 0.27 (wb*)	7.20 ± 0.98 (ww***) (wb***)	1.88 ± 0.74
Depressed ($n = 8$)	0	1.88 ± 0.33	0.64 ± 0.21	4.08 ± 0.67 (ww* with behavior only)	1.13 ± 0.49
	8	5.13 ± 0.52 (ww* except somatic) (wb**) (b**)	1.75 ± 0.16 (wb*)	10.88 ± 0.55 (ww***) (wb**) (b***)	2.63 ± 0.80

Table showing all data for HAM-D symptom categories across weeks and groups. Data is shown as the mean score for each group $\pm$ standard errors of the mean. Significant differences are indicated in parentheses and are preceded by the following analysis identifiers; Within-group and week significantly higher score (ww); Within-group and between week increase in score (wb); Between-groups and within-week significantly higher score (b). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Figure 2 Between week variance for proportion of symptoms explained by HAM-D symptom category. There was no significant difference in the proportion of symptoms explained by each HAM-D symptom category from Week 0 to Week 8. Somatic symptoms (Week 0: $M = 52.55$, $SD = 4.6$; Week 8: $M = 59.29$, $SD = 2.5$). Mood symptoms (Week 0: $M = 14.82$, $SD = 2.1$; Week 8: $M = 19.18$, $SD = 1.5$). Behavior symptoms (Week 0: $M = 5.55$, $SD = 1.7$; Week 8: $M = 8.75$, $SD = 1$). Negative cognitions (Week 0: $M = 15.94$, $SD = 2.9$; Week 8: $M = 12.78$, $SD = 1.9$).

symptoms than behavior symptoms and negative cognitions. The Depressed group also showed a significant effect of week on HAM-D symptom category scores ($F(3, 29.43) 16.56$, $p < 0.001$). Post-hoc analyses showed significant differences between all HAM-D symptom categories other than negative cognitions.

Between-group analysis showed the Depressed group had significantly more mood and somatic symptoms than the Non-PAE group at Week 8 (Table 1).

Hamilton Depression Inventory Proportion Scores

For the Non-PAE group: there was an overall effect of HAM-D symptom category on the symptom breakdown ($F(1.84, 44.22) 94.3$, $p < 0.001$), which was significant between the somatic HAM-D symptom category, and the HAM-D symptom categories of mood, behavior and negative cognitions. There was also a difference between depressed mood and behavior (Figure 3).

For the Depressed group there was also an overall effect of HAM-D symptom category on the symptom breakdown ($F(3, 21) 56.4$, $p < 0.01$), which was significant when the somatic and mood HAM-D symptom categories were compared to one another. However, the HAM-D showed an overall effect of group between the Non-PAE and Depressed group for the mood HAM-D symptom category ($F(1, 32) 5.4$, $p < 0.05$) (Figure 3).

When the two groups were then assessed for effect of week on each of the HAM-D symptom categories it was found that there was no significant difference in any of the HAM-D symptom categories for either the depressed ($F(3, 21) 0.41$, $P = 0.7$), or Non-PAE group ($F(3, 72) 2.05$, $P = 0.1$).

DISCUSSION

These results demonstrate that IFN- α causes a significant increase in clinically diagnosable depression and a general

Figure 3 Comparison of patients taking IFN- α who developed depression with those who experienced no depression (Week 8 only). When the groups were examined individually, both groups had the majority of symptoms explained by somatic symptoms. However, for the Depressed group significantly more of their symptoms were explained by somatic symptoms and depressed mood symptoms. * $p < 0.05$; ** $p < 0.01$. The two groups had a similar proportion of symptoms explained by the somatic, behavior, and negative cognition HAM-D symptom categories. However, the Depressed group had significantly more of their symptoms explained by depressed mood symptoms ($a = p < 0.05$) than the depressed. Non-PAE group: somatic symptoms ($M = 61.74$, $SD = 3.2$); mood symptoms ($M = 17.4$, $SD = 1.8$); behavior symptoms ($M = 8.99$, $SD = 1.3$); negative cognitions ($M = 11.87$, $SD = 2.1$). Depressed group: somatic symptoms ($M = 54.6$, $SD = 3.1$); mood symptoms ($M = 25.1$, $SD = 1.5$); behavior symptoms ($M = 8.85$, $SD = 1.06$); negative cognitions ($M = 11.48$, $SD = 3.2$).

increase in depression scale scores. These findings back up previous research which consistently show that IFN- α induces an increase in depression symptomatology and MDD.¹¹⁻¹⁵

In order to explore the behavioral syndrome that occurs in people taking IFN- α the HAM-D was broken down into four distinct symptom categories (mood, behavior, somatic and negative cognitions). When the HAM-D was broken down into these categories it was found that from Week 0 to 8 there was a difference in raw scores for mood, somatic and behavior symptoms but no difference in any of the proportions investigated. The fact that there was a significant increase in raw scores that was not backed up by a significant increase in any proportions suggests that IFN- α exacerbated symptoms already present, enhancing the primarily somatic baseline state. This suggests that in this sample the significant majority of depression scores for HCV and concurrent treatment with IFN- α were due to items that measure symptoms of sickness behavior.

Further analysis showed that an IFN- α -induced depression comprised of significantly more depressed mood symptoms (but not negative cognitions) than those who did not develop depression. At Week 8 the majority of the Non-PAE groups score comprised of somatic symptoms, however, for the Depressed group the majority of symptoms were made up of somatic symptoms and depressed mood. Depressed mood and somatic symptoms are key components of sickness behavior,⁶ which provides

further support for the idea that the depression observed in these patients could be an extreme form of sickness behavior.

The Depressed group was then investigated in more detail in order to see whether there was any increase in any of the HAM-D symptom categories from Baseline to Week 8 of treatment. Data from Week 8 showed that there was a significant difference in raw scores for all HAM-D symptom categories except negative cognitions but that there was no proportional difference in any of the HAM-D symptom categories, consistent with what was found in the Non-PAE group.

Interestingly, IFN- α did not cause a significant increase in raw scores for negative cognitions for any group (depressed or non-depressed). Negative cognitions are a key part of the depressive syndrome,⁸ but are not a feature of sickness behavior.^{9,10} The fact that IFN- α did not increase negative cognitions in this sample indicates that the behavioral syndrome we observed is due to sickness behaviors and could be different to an idiopathic depression. Support for this idea comes from the work of Pasquini et al¹⁷ who found that an IFN- α -induced depression comprised significantly less negative cognitions than a primary depression. However, work from Capuron et al¹⁸ found that the two types of depression were similar. Further work comparing these two types of depression is needed to clarify this issue.

Furthermore, the results indicate the care that needs to be taken by healthcare providers when diagnosing depression in a population that are experiencing sickness behaviors. Using diagnostic clinical interviews allows the healthcare provider to determine which symptoms are experienced due to depression and which are experienced due to sickness. However, using a cut-off on a depression scale does not allow for this, and it is possible that a cut-off score could be reached through sickness behaviors rather than a depression.

Limitations of this study include the fact that only mild-to-moderate depression was observed, possibly explaining the lack of negative cognitions observed. Also the number of participants in this study was low, meaning results should be interpreted with caution, and further work looking at these associations in a larger number of participants is necessitated.

These data suggest that the IFN- α -induced behavioral syndrome consists mainly of somatic symptoms. It also suggests concurrent depression will lead to additional symptoms of depressed mood. All symptoms observed in all groups are core features of sickness behavior. The fact that there was no change in the proportion of symptoms despite a significant increase in raw scores from Week 0 to Week 8 indicates that IFN- α exacerbates symptoms present at baseline, the majority of which are somatic. These results are clinically significant as they suggest that the increase in depression scores observed during IFN-

α therapy is primarily due to sickness behaviors. Should the results from this article be backed up by future research there will be important implications for those patients due to commence IFN- α therapy. Furthermore, healthcare providers will be able to explain that the depressed mood patients may experience is due to sickness and their body acting to conserve energy so that all their energy can be put into fighting HCV rather than the development of MDD.

CONFLICTS OF INTEREST

All authors have none to declare.

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