Brain, Behavior, & Immunity - Health 2 (2020) 100035

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

Full Length Article

Somatic pain associated with initiation of interferon-alpha (IFN-α) plus ribavirin (RBV) therapy in chronic HCV patients: A prospective study

Chih Ying Lin [a,f], Ta-Wei Guu [b,f], Hsueh-Chou Lai [a,c], Cheng-Yuan Peng [a,c], Jill Yi-Ju Chiang [f], Hui-Ting Chen [f], Tsai-Chung Li [a,d], Shing-Yu Yang [a,d], Kuan-Pin Su [a,e,f], Jane Pei-Chen Chang [a,e,f,*]

[a] School of Medicine, China Medical University (CMU), Taichung, Taiwan
[b] Department Psychiatry, CMU Beigang Hospital, Yunlin, Taiwan
[c] Departement of Hepatogastroenterology, China Medial University Hospital, Taichung, Taiwan
[d] China Medical University Graduate Institute of Biostatistics, Taiwan
[e] Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
[f] Mind-Body Interface Lab (MBI-Lab) and Department of Psychiatry, CMUH, Taichung, Taiwan

ARTICLE INFO

Keywords:
Somatic pain
IFN-α
Major depressive disorder

ABSTRACT

Objective: This study is aimed to investigate the association between interferon-alpha (IFN-α) plus ribavirin (RBV) treatment and emergence of somatic pain symptoms in patients with hepatitis C virus (HCV) over a 24-week treatment.

Method: In this prospective cohort study, 297 patients with HCV were evaluated at baseline and 2nd, 4th, 8th, 12th, 16th, 20th, and 24th week with structured Mini-International Neuropsychiatric Interview for Major Depressive Disorder (MDD) diagnosis and the Neurotoxicity Rating Scale (NRS) for somatic symptoms.

Results: Eighty-seven out of the 297 patients (29%) developed IFN-α induced depression and had significantly higher somatic pain symptoms as early as the 2nd week and at all the assessment time points ($p < .001$). Most depressed patients perceived greatest somatic pain at the 8th week of treatment. Moreover, NRS somatic pain scores after initial therapy strongly correlated with NRS somatic pain scores at all other assessment time points ($p < .001$).

Conclusion: IFN-α therapy induce significant somatic pain as early as the 2nd week of treatment in HCV patients who later developed MDD. Thus, initial NRS somatic pain score after initiation of IFN-α treatment may serve as a reference for the susceptibility of the individual to IFN-α induced depression.

1. Introduction

The multiplicity and unexplained nature of somatic symptoms were strongly associated with depression (Bekhuis et al., 2015; Kroenke, 2003; Schaefert et al., 2013; Zhu et al., 2012). Previous literature suggested that depressive episode that predominates with somatic symptoms is the most common form of depression (Jones and Hall, 1963; Tylee and Gandhi, 2005). Somatic symptoms consist of painful and non-painful symptoms. Painful symptoms classically include multiple diffuse pain, arthralgia and backaches; whereas, fatigue, general weakness and poor appetite are typical non-painful symptoms (Khan et al., 2003; Kroenke and Price, 1993; Tylee and Gandhi, 2005).

Somatic pain symptoms also positively predicted the occurrence of depression (Bair et al., 2003; Gerber et al., 1992). In Asian population, somatic pain symptoms are frequent in depression. Moreover, the severity of somatic pain symptoms in particular correlated with less remission and treatment response rates in depressed patients (Novick et al., 2013). Concordantly, various literature revealed that the severity and frequency of somatic pain symptoms often lead to substantial functional impairment of the individual with an increase duration, severity and recurrence of depressive episodes (Bekhuis et al., 2016; Creed et al., 2012; Fishbain, 1999; Kapfhammer, 2006; Kroenke, 2003; Ohayon and Schatzberg, 2003; Tylee and Gandhi, 2005; Von Korff and Simon, 1996). Therefore, somatic pain symptoms had shown prognostic value in treating patients with depression.

In the past, interferon-alpha, as a pro-inflammatory cytokine, had

* Corresponding author. Department of Psychiatry, China Medical University Hospital, No. 2 Yu-Der Road, Taichung, 404, Taiwan.
E-mail address: peko80@gmail.com (J.P.-C. Chang).

https://doi.org/10.1016/j.bbih.2019.100035
Received 5 December 2019; Received in revised form 21 December 2019; Accepted 28 December 2019
Available online 3 January 2020

contributed to our understanding of how cytokine administration induces sickness behaviors and depression. For instance, interferon-alpha induced the occurrence of somatic symptoms, such as fatigue, insomnia, headaches, arthralgia and anorexia in patients with hepatitis C virus infection (HCV) (Denicoff et al., 1987; Fontana et al., 2002; Kirkwood et al., 1996; Schaefer et al., 2002; Su, 2009; Valentine et al., 1998; Yates and Gleason, 1998). In fact, depressive episodes were frequently observed in HCV patients receiving interferon-alpha (IFN-α) therapy with a prevalence rate of 15–40% (Raison et al., 2005a, 2005b; Schaefer et al., 2012; Su, 2015).

Recently, literature reported the development of painful and non-painful somatic symptoms in HCV patients after receiving IFN-α therapy (Chang et al., 2017; Hsiao et al., 2016; Huckans et al., 2015; Loftis et al., 2013). For instance, Huckans et al. revealed worsening of depression, anxiety, fatigue and somatic pain symptoms in HCV patients within the three-month course of IFN-α therapy (Huckans et al., 2015). However, the underlying mechanism of how IFN-α induce somatic symptoms is not known. Moreover, previous longitudinal studies on the somatic symptoms and depression induced by IFN-α encompass relatively small sample size (n = 32-33) (Huckans et al., 2015; Loftis et al., 2013). Therefore, generalization of their research findings was limited. Nevertheless, the prospective cohort of HCV patients receiving interferon therapy is an ideal model for studying and elucidating the causal relationship between pro-inflammatory cytokines (in this case interferon therapy), somatic pain symptoms, and depression.

To understand the effect of pro-inflammatory cytokine on the occurrence of somatic pain symptoms and depression, we aimed to investigate the relationship of somatic pain symptoms and the emergence of depression in patients with HCV receiving IFN-α therapy, in a prospective 24-week study.

2. Methods

2.1. Study sample

This is a 24-week prospective cohort study conducted in Liver Center of the China Medical University Hospital in Taiwan. Patients with chronic HCV were recruited by two hepatologists during clinical service between the year of 2009 to 2014. Informed consents were obtained from all patients before their enrollment, and this study was approved by the China Medical University Hospital Institutional Review Board.

Three hundred and seventy-two HCV patients were initially recruited and received combinatory antiviral therapy (Regime: 1.5 μg of peg IFN-α-2beta per kilogram of body weight subcutaneously once weekly, and 600–800 mg of ribavirin daily) for 24 weeks. Exclusion criteria included having liver disease other than HCV and those who withdrawn from study due to personal reasons. To evaluate the effect of IFN based regime on the emergence of depression, we excluded patients with a diagnosis of depression before the anti-viral therapy administration to avoid possible confounding factors. Patients with mental disorder other than depression were also excluded. Seventy-five patients out of the 372 recruits were excluded, and 297 patients (79.8%) completed the 24-week study.

2.2. Assessments

Patients were assessed with the structured Mini-International Neuropsychiatric Interview (MINI) for confirmation of Major Depressive Disorder (MDD) (Sheehan et al., 1998) and with Neurotoxicity Rating Scale (NRS) for somatic symptoms at baseline and at the 2nd, 4th, 8th, 12th, 16th, 20th and 24th week. Both MINI and NRS were administrated by qualified psychiatrists.

2.3. Measure

2.3.1. Mini-International Neuropsychiatric Interview (MINI)

MINI is a brief structured diagnostic interview for making diagnoses of psychiatric disorders including MDD and was designed to be compatible with international diagnostic criteria, including DSM-IV and ICD-10 (Sheehan et al., 1998). The interview comprising of 17 modules with closed ended questions takes 15 min to administer, and serves as a short but accurate interview for clinical trials and epidemiology studies. Moreover, its application in clinical assessment of depression and anxiety disorder is well received by practitioners and patients (Pettersson et al., 2018). In terms of reliability and validity, MINI had shown good concordance with the structured Clinical Interview for DSM-III-R(SCID) (Sheehan et al., 1997) and Composite International Diagnostic Interview(CIDI) (Lecrubier et al., 1997). The information of translation, validation and instruction of Taiwanese version of MINI can be accessed on the website of Taiwanese Society of Psychiatry (http://www.sop.org.tw/).

2.3.2. Neurotoxicity rating scale (NRS)

NRS is a self-administrated questionnaire for evaluation of cytokine therapy related neuropsychiatric symptoms and were recognized as a valid tool to evaluate psychiatric and physical symptoms (Li et al., 2016; Loftis et al., 2013; Valentine et al., 1995). Additionally, NRS had been used to qualify the intensity of somatic symptoms in HCV population receiving IFN based therapy and the items regarding somatic symptoms of NRS corresponded to that of Beck Depression Inventory, Second Edition (BDI-II) (Loftis et al., 2013). Items of the NRS questionnaire include three parts: checklists for general symptoms, non-painful somatic symptoms and painful somatic symptoms. In our study, only items representing somatic pain symptoms were selected. Items 18, 19 and 20, which respectively stand for generalized pain, arthralgia and other pain, were used for analysis in our study. Each item is rated from 0 to 10 on a visual analog scale, and the sum of the selected items ranges from 0 to 30. A higher score indicates the patient perceive greater somatic pain symptoms.

2.4. Statistical analyses

Demographic and group comparisons of patients with and without newly diagnosed depressive episodes during IFN-α therapy were evaluated with *t*-test or chi-square test where appropriate. Baseline characteristics were presented as frequency (percentage) for categorical variable and mean ± standard deviation (SD) for continuous variable. Analysis of covariance (ANCOVA) was applied to adjust for the baseline NRS somatic pain score.

A two-way ANOVA with depression as independent factor, time as dependent factor, and interaction of depression and time was conducted to examine the effect of time on the variations of NRS somatic pain scores throughout the course of therapy between depression (Dep group) and non-depression (non-Dep) groups. For missing data, we apply last observation carried forward and linear interpolation. All statistical significance tests used two tailed with p value $< .05$. All statistical analysis was conducted with Statistical Analysis System (SAS) version 9.4 for windows.

3. Results

Eighty-seven out of the 297 patients (29%) were diagnosed with MDD throughout the IFN-α treatment course (Dep group). Fifty-seven out of the 87 depressed patients (65.5%) were diagnosed with MDD within the first 8 weeks. Moreover, the majority of depressed patients [31 out of the 87 depressed patients (35.6%)] were in fact diagnosed with MDD on the 8th week. On the other hand, the non-Dep group composed of 210 participants (71%) and had never developed depression after 24 weeks of treatment. In comparison, Dep group was significantly older in age ($p = .007$), received less education ($p = .018$), and involved more females ($p = .002$) than non-Dep group. Also, individuals were more inclined to have a past history of depression ($p < .001$) and reported a higher baseline NRS somatic pain scores ($p = .0003$) (Table 1). Moreover,

women reported a higher NRS somatic pain score, and the gender differences of the NRS somatic pain score were significant throughout the 24 weeks (Appendix Table A.1).

After initiation of IFN-α therapy, Dep group had a higher somatic pain score at week 2 ($p < .001$), week 4 ($p < .001$), week 8 ($p < .001$), week 12 ($p < .001$), week 16 ($p < .001$), week 20 ($p < .001$), week 24 ($p < .001$) (Table 1). For the first 8 weeks, there was a greater increment in NRS somatic pain scores in the Dep group; and the somatic pain scores reached a peak at the 8th week in Dep group. For the remaining treatment course, NRS somatic pain scores of both Dep and non-Dep group gradually declined. Meanwhile, the NRS somatic pain scores of the final week in both Dep and non-Dep group continued to be higher than their baseline NRS somatic pain scores (Appendix Fig. A.1).

We have noted a baseline NRS somatic pain score difference between the Dep and non-Dep group; thus, analysis of covariance (ANCOVA) were applied for adjusting baseline difference. After ANCOVA adjustment, Dep group still perceive more somatic pain symptoms than their counterparts for all the assessed periods (Table 2). The results from two-way ANOVA revealed a significant interaction between the effects of time and depression status on the NRS somatic pain scores, $F(7, 2065) = 3.61$, $p = .0007$ (Appendix Table A.2). Post hoc analysis revealed that for all assessed periods, Dep group perceived greater somatic pain symptoms than Non-Dep group ($p < .001$).

Next, we carried out a correlation analysis of the NRS somatic pain scores of all the assessed periods. In Dep group, NRS somatic pain score of the 2nd week have a strong correlation with the 4th week [$r(85) = .869$, $p < .001$] and a moderation correlation were observed between the 2nd week and the 24th week (or final week) [$r(85) = .689$, $p < .001$] (Table 3). Similar correlations were identified in non-Dep group as well (Appendix Table A.3). Meanwhile, NRS somatic pain score of the 2nd week positively correlates with that of the following treatment course, including the peak of NRS somatic pain score at the 8th week and the 24th week in both Dep and non-Dep group ($p < .001$) (Table 3 and Appendix Table A.3).

Table 1
Demographic data.

	Depressed (n = 87)	Non-Depressed (n = 210)	*p* value
Age, years (mean ± SD)	52 ± 9.25	49.46 ± 11.46	.007**
Gender			.002**
Female, *n* (%)	51(58.62%)	81(38.57%)	
Education (years)	8.54 ± 3.36	9.80 ± 4.41	.018*
Marriage, *n* (%)			.098
Married	66(75.86%)	178(84.76%)	
Single/divorced	21(24.1%)	32(15.24%)	
Previous depression history (%)	12(13.79%)	3(1.43%)	< .001***
NRS scores (mean ± SD)			
Baseline	5.84 ± 7.72	2.53 ± 4.12	.0003***
Week 02	7.22 ± 7.34	2.90 ± 4.10	< .001***
Week 04	7.90 ± 7.26	2.95 ± 4.02	< .001***
Week 08	8.29 ± 7.24	3.04 ± 3.79	< .001***
Week 12	8.11 ± 7.05	3.01 ± 3.98	< .001***
Week 16	7.52 ± 6.46	3.02 ± 4.27	< .001***
Week 20	6.83 ± 6.52	2.94 ± 4.24	< .001***
Week 24	6.48 ± 6.86	2.76 ± 4.06	< .001***

N, number; NRS, neurotoxicity rating scale; NRS somatic pain score, sum of the items 18, 19 and 20 of the NRS, which stand for generalized pain, arthralgia and other pain, respectively; SD, standard deviation. *indicates a statistical significance of $p < .05$. **indicates a statistical significance of $p < .01$. ***indicates a statistical significance of $p < .001$.

4. Discussion

This is the first study to evaluate the natural course of somatic pain symptoms in HCV patients receiving 24 weeks of IFN-α therapy. This was more inclusive than previous studies (Chang et al., 2017; Huckans et al., 2015) in terms of sample size, duration of treatment course and was more focused on the longitudinal course of somatic pain symptoms in Asian population with HCV infections. For stance, our previous study only assessed somatic pain symptoms during the first 2 weeks of IFN-α therapy, while longitudinal study by Loftis et al. (2013) only evaluated somatic symptoms within 16 weeks, and did not include somatic pain symptoms in evaluation. In addition, we enrolled a larger sample size than previous longitudinal studies (Huckans et al., 2015; Loftis et al., 2013).

The major finding of our study is that IFN-α therapy induced somatic symptoms occurred early in those who later developed depression, as early as the 2nd week, during the treatment period (Appendix Fig. A.1). The early presentation of somatic pain in depression is compatible with previous studies (Capuron et al., 2002; Chang et al., 2017), and corresponds with the common clinical phenomenon where some patients present solely with somatic symptoms before being diagnosed with MDD (Bair et al., 2003; Kapfhammer, 2006; Tamayo et al., 2005). Although the weekly changes in NRS scores in many instances do not seemed to be particularly robust for either the Dep group or the non-Dep group, we continues to see the differences between the Dep group or the non-Dep group. This further implied that the Dep group had more somatic symptoms than non-Dep group even before they were diagnosed with depression. Additionally, our study also showed HCV patients who had more somatic pain symptoms as early as the 2nd week reported more painful symptoms at the 8th week and for the remaining treatment course (Table 3 and Appendix Table A.3). Our results supported that somatic pain symptoms may precede the development of depressive symptoms after IFN-α therapy (Capuron et al., 2002) and are associated with depression and other mood disorders (Gerber et al., 1992; Kroenke et al., 1994). Interestingly, depressed patients were observed to have a reduced pain threshold and thus aberrant perception of pain (Adler-Neal et al., 2019; Adler and Gattaz, 1993; Lautenbacher and Krieg, 1994). Similarly, we found that Dep group reported more somatic pain symptoms than their counterparts. In addition, severe pain symptoms have been correlated with prolonged duration of depression and higher risk of suicide in literature (Fishbain, 1999; Kapfhammer, 2006; Kroenke and Price, 1993; Ohayon and Schatzberg, 2003; Tylee and Gandhi, 2005; Von Korff and Simon, 1996). To address the side effects of IFN-α, various randomized control trials had adopted prophylactic anti-depressive therapy with serotonin reuptake inhibitors (SSRIs) and paroxetine. There are mixed results (Diez-Quevedo et al., 2011; Raison et al., 2007), but recent meta-analysis supports the use of SSRIs in reducing incidence of interferon induced depression (Udina et al., 2014). Of note, though, the pre-emptive use of anti-depressants would expose the patients to unnecessary side effects of anti-depressants and increase likelihood of drug interaction with medication for systemic disease or with other anti-viral therapy. Therefore, screening patients in the early phase of IFN-α regimen would assist physicians in deciding the individual risk to depression and the proper timing of intervention. Our study support using somatic pain symptoms as an indicator of one's susceptibility to later onset depression, as we have revealed nature course of somatic pain symptoms in HCV patients and the relation of somatic pain symptoms with IFN-α associated depression.

Our study identified a significant effect of time and depression on variation of somatic pain symptoms throughout all assessed periods by two-way ANOVA analysis. In Appendix Fig. A.1, not only did patients in Dep group perceived more somatic pain symptoms, but the 8th week appeared to be a critical period in treatment course as it is when most HCV patients were diagnosed with MDD and when their NRS somatic pain scores peaked. The peak of somatic pain scores at 8th week may imply the cumulative result of stress response to chronic pain and contributed to the higher incidence of depressive episodes in the first 8 weeks of our study. Similarly, previous literature also reported a higher depression incidence in the first 8 weeks in HCV patients receiving IFN-α therapy (Choi et al., 2017; Horikawa et al., 2003; Malaguarnera et al., 2001). Moreover, previous literature revealed a positive predictive effect

Table 2
Adjusted Means of Neurotoxicity Rating Scale of Dep and Non-Dep group.

	Depressed	Non-Depressed	Effect size of	*p* value
	(n = 94)	(n = 253)	ANCOVA	
Age, years (mean ± SD)	52 ± 9.25	49.46 ± 11.46	-	.007**
Gender			-	.002**
Female (%)	51(58.62%)	81(38.57%)	-	
Education (years)	8.54 ± 3.36	9.80 ± 4.41	-	.018*
Marriage, *n* (%)				.098
Married	66(75.86%)	178(84.76%)	-	
Single/divorced	21(24.1%)	32(15.24%)	-	
Previous depression history(%)	12(13.79%)	3(1.43%)	-	< .001***
NRS scores (Adjusted mean ± SE)				
Week 02	5.43 ± 0.36	3.64 ± 0.23	0.29	< .001***
Week 04	6.39 ± 0.42	3.58 ± 0.27	0.35	< .001***
Week 08	6.96 ± 0.44	3.59 ± 0.28	0.41	< .001***
Week 12	6.71 ± 0.43	3.59 ± 0.27	0.37	< .001***
Week 16	6.50 ± 0.49	3.44 ± 0.31	0.29	< .001***
Week 20	5.7 ± 0.47	3.40 ± 0.30	0.25	< .001***
Week 24	5.35 ± 0.47	3.23 ± 0.30	0.26	.0002***

N, number; NRS, neurotoxicity rating scale; NRS somatic pain score, sum of the items 18, 19 and 20 of the NRS, which stand for generalized pain, arthralgia and other pain, respectively; SE, standard error. *indicates a statistical significance of $p < .05$. **indicates a statistical significance of $p < .01$. ***indicates a statistical significance of $p < .001$.

of somatic pain, especially non-specific musculoskeletal complaints, on the occurrence of depression (Gerber et al., 1992). On the other hand, we observed a decline in the intensity of somatic pain symptoms after the 8th week (Appendix Fig. A.1). We speculate this decline was due to tolerance to side effects of IFN-α therapy. Interestingly, previous studies (Adinolfi et al., 2017; Huckans et al., 2015) has observed improved depressive and somatic symptoms after the termination of IFN-α, particularly in patients who achieved viral clearance. It was suggested that IFN-α as a pro-inflammatory cytokine, contributes to peripheral immune activation and is pertinent with psychiatric symptoms. Upon viral clearance, there's a restoration of dysfunctional immune system and an improvement of mood disorders (Huckans et al., 2015). Despite there was a decline in NRS levels after the 8th week, Dep group still perceived a greater intensity of somatic pain symptoms in the final week than the non-Dep group (Appendix Fig. A.1). This raise the question as to the extent of restoring immune dysregulation upon viral clearance. However, our study design has prevented us from elucidating the effect of IFN-α on immune dysregulation and the variety in intensity in somatic pain. Future study is warranted. In addition, we also observed that pain scores were higher at baseline in the group that became depressed when compared with the non-Dep group. This may imply that one's vulnerability to pain may increase the risk for IFN-α therapy induced depression.

Of note, women perceived more somatic pain symptoms than men, and were more vulnerable to IFN-α induced depression (Appendix Table A.1). The gender dependency theory of depression has been proposed to result from a specific phenotype referred as "somatic depression," which is more prevalent among women (Silverstein et al., 2013). Somatic depression among women was correlated with somatic symptoms of insomnia, loss of appetite and headache (Silverstein et al., 2013). Literature has attributed prevalence of somatic pain symptoms to the high prevalence of anxiety in women, and their tendency to report stress and somatic complaints in clinical settings (Jackson et al., 2003). In our study, woman perceive higher levels of somatic pain, which might be attributed to their vulnerability to somatic depression and expressive nature in reporting pain symptoms.

The strength of our study encompasses a large sample size and is comprehensive in study duration by including the entire 24 weeks of Interferon-alpha regimen. Our study has several limitations. Firstly, we could not analyze the positive predictive value of NRS somatic pain score in patients who later developed depression because there's no consensus on the specific thresholds for rating mild to severe somatic symptoms. We could only interpret higher scores as having more somatic pain symptoms in a qualitative manner. However, the use of NRS in assessing somatic complaints had been verified by previous literatures (Li et al., 2016; Loftis et al., 2013; Valentine et al., 1995). Moreover, concordant with recent study (Su et al., 2019) applying NRS in assessment, our study concluded that IFN-induced depression was pertinent with more somatic symptoms, and pain in particular. Interestingly, this aberrant perception of pain was noted to have an early occurrence, which warrants early interventions. Secondly, because of ethical concerns we did not have control group that received placebo treatments for HCV infection. Lastly, aside from interferon based regime, there has been a recent introduction of direct-acting antivirals (DAA), which was effective and safe in treating HCV patients. However, the high cost of DAA has restricted its use to patients with advanced liver disease in resource limited regions (Feld, 2014). Moreover, research suggested that co-administrating of IFN-α with multiple DAAs in chronic hepatitis is necessary for multiple drug resistant patients (Aronsohn and Jensen, 2014). Given that IFN could serve as the main therapy or as an adjunct to DAA or even as the salvage therapy in managing multidrug resistant HCV infection, the effect of IFN on depression remains essential in clinical practice.

5. Conclusion

IFN-α therapy induces significant somatic pain symptoms as early as the 2nd week of treatment in HCV patients who later developed MDD. This study further demonstrated the 8th week as a critical time point, since the incidence of MDD is the highest and the MDD patients perceived the greatest somatic pain symptoms. Moreover, the initial NRS somatic

Table 3
Correlation between different weeks of NRS somatic pain score in dep group.

	Baseline Week 0	2nd week	4th week	8th week	12th week	16th week	20th week	24th week
		r						
NRS of Baseline	1							
NRS of 2nd week	.863***	1	-	-	-	-	-	-
NRS of 4th week	.693***	.869***	1	-	-	-	-	-
NRS of 8th week	.635***	.717***	.786***	1	-	-	-	-
NRS of 12th week	.612***	.742***	.759***	.856***	1	-	-	-
NRS of 16th week	.462***	.569***	.595***	.668***	.753***	1	-	-
NRS of 20th week	.581***	.656***	.645***	.716***	.764***	.868***	1	-
NRS of 24th week	.549***	.689***	.690***	.693***	.809***	.855***	.933***	1

NRS, neurotoxicity rating scale; NRS somatic pain score, sum of the items 18, 19 and 20 of the NRS, which stand for generalized pain, arthralgia and other pain, respectively; Dep, Depression group; SD, standard deviation. *r,* Pearson coefficient. *** indicates a statistical significance of $p < .001$

pain score before treatment may be used as a reference value to predict the susceptibility of the individual to depression. Intervention strategies for early-onset somatic symptoms in HCV patients receiving IFN-α therapy may prevent the later onset of depression.

Contributors

KPS and JPC created the concept, designed the study, and received the research funding. JPC undertook the interpretation of results, prepare and revised the manuscript. CYL perform the literature search and prepared the manuscript. HCl, TWG CYP, YJJC, HTC performed the clinical assessments, helped with subject enrollment, and conducted the study. TCL and SYY supervised and performed the statistical analysis. All the authors have approved the final manuscript and take responsibility for the integrity and accuracy of this study.

Declaration of competing interest

None.

Acknowledgments and Role of Funding Source

The authors of this work were supported by the following grants: MOST 106-2314-B-039-027-MY3; 106-2314-B-038-049; 106-2314-B-039-031; 106-2314-B-039-035; 105-2918-I-039-001; 104-2314-B-039-022-MY2, and 104-2314-B-039-050-MY3 from the Ministry of Science and Technology, Taiwan; NHRI-EX106-10528NI from the National Health Research Institutes, Taiwan; and CRS-106-063, DMR-107-202, DMR-107-204, DMR-107-091, DRM-107-097, DRM-108-091 and Chinese Medicine Research Center from the China Medical University, Taiwan.

Appendix

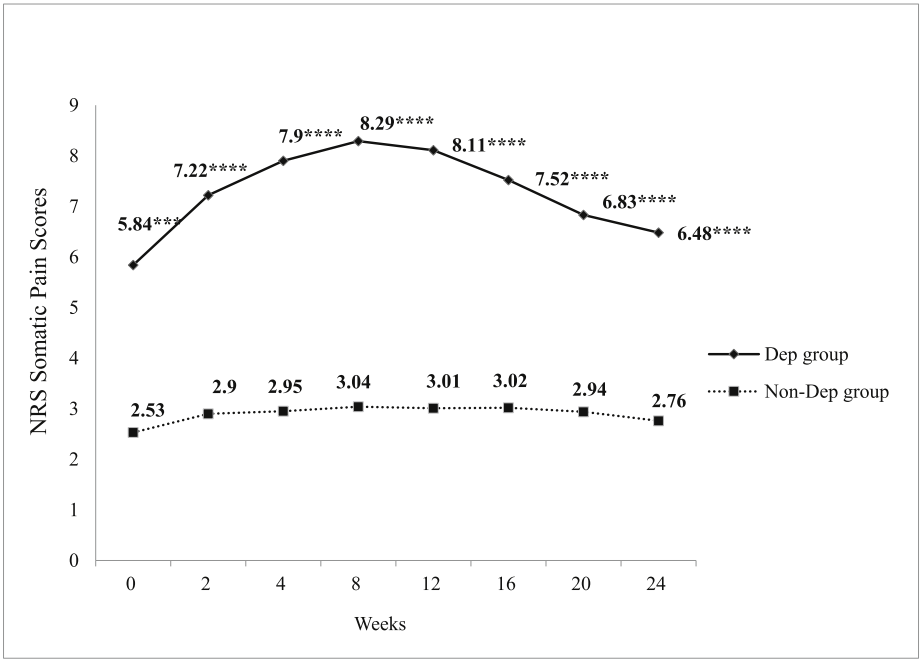

Fig. A.1. NRS pain score in Dep group (solid line) and non-Dep group (dotted line).
Dep group, patients with IFN-α induced depression; N, number; Non-Dep, patients without IFN-α induced depression; NRS, neurotoxicity rating scale; NRS somatic pain score, sum of the items 18, 19 and 20 of the NRS, which stand for generalized pain, arthralgia and other pain, respectively. The overall tests of two-way ANOVA: $F(1, 295) = 62.08$, $p < .001$ for depression effect; $F(7, 2065) = 7.44$, $p < .001$ for time effect; and $F(7, 2065) = 3.61$, $p < .001$ for interaction of time and depression; ***indicates a statistical significance of $p < .001$ from post hoc tests of ANOVA.

Table A.1
Gender Differences in Somatic pain associated with depression

	Male (n = 165)	Female (n = 132)	*p* value
Age, years (mean ± SD)	48.88 ± 10.86	51.84 ± 10.77	.020*
Education (years)	10.30 ± 3.57	8.33 ± 4.59	< .001***
Marriage, *n*			.006**
Married (%)	145 (87.9%)	99 (75%)	
Single/divorced (%)	20 (12.1%)	33 (25%)	
Previous Depression history (%)	4 (2.4%)	11 (8.3%)	.041*
Depression during Interferon therapy	36 (21.8%)	51(38.6%)	.002**
Baseline NRS scores (mean ± SD)	2.66 ± 4.82	4.55 ± 6.34	.005**
Week 02	3.15 ± 4.65	5.43 ± 6.41	.0007***
Week 04	3.15 ± 4.39	5.96 ± 6.58	< .001***
Week 08	3.57 ± 4.50	5.83 ± 6.48	.0008***

(*continued on next column*)

Table A.1 (*continued*)

	Male (n = 165)	Female (n = 132)	*p* value
Week 12	3.58 ± 4.53	5.67 ± 6.48	.0019**
Week 16	3.55 ± 4.65	5.32 ± 6.10	.0062**
Week 20	3.24 ± 4.51	5.12 ± 6.02	.0031**
Week 24	2.96 ± 4.27	4.95 ± 6.22	.0019**

NRS, neurotoxicity rating scale; NRS somatic pain score, sum of the items 18, 19 and 20 of the NRS, which stand for generalized pain, arthralgia and other pain, respectively; SD, standard deviation. *indicates a statistical significance of $p < .05$. **indicates a statistical significance of $p < .01$. ***indicates a statistical significance of $p < .001$.

Table A.2
Effect of Depression on NRS Somatic Pain Scores through Treatment Course

	df	Type III Sum of Squares	Mean Square	*F*	*P* value
Depression	1	9438.51968	9438.51968	62.08	<.001***
Time(Weeks)	7	436.16817	62.30974	7.44	<.001***
Time*Depression Interaction	7	211.64643	30.23520	3.61	.0007***
Error of Time*Depression	2065	17283.14696	8.36956		

Two-way ANOVA was run on a sample of 297 participants to examine the effect of time and depression on NRS somatic pain scores. The results of two-way ANOVA: $F(1, 295) = 62.08$, $p < .001$ for depression effect; $F(7, 2065) = 7.44$, $p < .001$ for time effect; and $F(7, 2065) = 3.61$, $p < .001$ for interaction of time and depression; ***indicates a statistical significance of $p < .001$ from post hoc tests of ANOVA.

Table A.3
Correlation Between Different Weeks of NRS Somatic Pain Score in Non-Dep Group

	Baseline Week 0	2nd week	4th week	8th week	12th week	16th week	20th week	24th week
		r						
NRS of Baseline	-							
NRS of 2nd week	.686***	-	-	-	-	-	-	-
NRS of 4th week	.651***	.695***	-	-	-	-	-	-
NRS of 8th week	.571***	.600***	.777***	-	-	-	-	-
NRS of 12th week	.677***	.593***	.719***	.780***	-	-	-	-
NRS of 16th week	.483***	.508***	.572***	.680***	.717***	-	-	-
NRS of 20th week	.453***	.502***	.600***	.671***	.718***	.794***	-	-
NRS of 24th week	.483***	.474***	.600***	.711***	.742***	.797***	.896***	-

NRS, neurotoxicity rating scale; NRS somatic pain score, sum of the items 18, 19 and 20 of the NRS, which stand for generalized pain, arthralgia and other pain, respectively; Non-Dep group, non-depression group; SD, standard deviation. *r,* Pearson coefficient. *** indicates a statistical significance of $p < .001$.

References

Adinolfi, L.E., Nevola, R., Rinaldi, L., Romano, C., Giordano, M., 2017. Chronic hepatitis C virus infection and depression. Clin. Liver Dis. 21, 517–534. https://doi.org/10.1016/j.cld.2017.03.007.

Adler-Neal, A.L., Emerson, N.M., Farris, S.R., Jung, Y., Coghill, R.C., Zeidan, F., 2019. Brain moderators supporting the relationship between depressive mood and pain. Pain 160, 2028–2035. https://doi.org/10.1097/j.pain.0000000000001595.

Adler, G., Gattaz, W.F., 1993. Pain perception threshold in major depression. Biol. Psychiatry 34, 687–689.

Aronsohn, A., Jensen, D., 2014. Interferon-combination strategies for the treatment of chronic hepatitis C. Semin. Liver Dis. 34, 30–36. https://doi.org/10.1055/s-0034-1371008.

Bair, M.J., Robinson, R.L., Katon, W., Kroenke, K., 2003. Depression and pain comorbidity: a literature review. Arch. Intern. Med. 163, 2433–2445. https://doi.org/10.1001/archinte.163.20.2433.

Bekhuis, E., Boschloo, L., Rosmalen, J.G., de Boer, M.K., Schoevers, R.A., 2016. The impact of somatic symptoms on the course of major depressive disorder. J. Affect. Disord. 205, 112–118. https://doi.org/10.1016/j.jad.2016.06.030.

Bekhuis, E., Boschloo, L., Rosmalen, J.G., Schoevers, R.A., 2015. Differential associations of specific depressive and anxiety disorders with somatic symptoms. J. Psychosom. Res. 78, 116–122. https://doi.org/10.1016/j.jpsychores.2014.11.007.

Capuron, L., Gumnick, J.F., Musselman, D.L., Lawson, D.H., Reemsnyder, A., Nemeroff, C.B., Miller, A.H., 2002. Neurobehavioral effects of interferon-alpha in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. Neuropsychopharmacology 26, 643–652. https://doi.org/10.1016/s0893-133x(01)00407-9 official publication of the American College of Neuropsychopharmacology.

Chang, J.P., Lai, H.C., Yang, H.T., Su, W.P., Peng, C.Y., Galecki, P., Walczewska, A., Pariante, C.M., Su, K.P., 2017. Polyunsaturated fatty acids levels and initial presentation of somatic symptoms induced by interferon-alpha therapy in patients with chronic hepatitis C viral infection. Nutr. Neurosci. 20, 291–296. https://doi.org/10.1080/1028415x.2015.1123378.

Choi, J.S., Kim, W., Sohn, B.K., Lee, J.Y., Jung, H.Y., Oh, S., Joo, S.K., Kim, H.Y., Jung, Y.J., 2017. Association of changes in mood status and psychosocial well-being with depression during interferon-based treatment for hepatitis C. Psychiatr. Investig. 14, 314–324. https://doi.org/10.4306/pi.2017.14.3.314.

Creed, F.H., Davies, I., Jackson, J., Littlewood, A., Chew-Graham, C., Tomenson, B., Macfarlane, G., Barsky, A., Katon, W., McBeth, J., 2012. The epidemiology of multiple somatic symptoms. J. Psychosom. Res. 72, 311–317. https://doi.org/10.1016/j.jpsychores.2012.01.009.

Denicoff, K.D., Rubinow, D.R., Papa, M.Z., Simpson, C., Seipp, C.A., Lotze, M.T., Chang, A.E., Rosenstein, D., Rosenberg, S.A., 1987. The neuropsychiatric effects of treatment with interleukin-2 and lymphokine-activated killer cells. Ann. Intern. Med. 107, 293–300.

Diez-Quevedo, C., Masnou, H., Planas, R., Castellvi, P., Gimenez, D., Morillas, R.M., Martin-Santos, R., Navines, R., Sola, R., Giner, P., Ardevol, M., Costa, J., Diago, M., Pretel, J., 2011. Prophylactic treatment with escitalopram of pegylated interferon alfa-2a-induced depression in hepatitis C: a 12-week, randomized, double-blind, placebo-controlled trial. J. Clin. Psychiatry 72, 522–528. https://doi.org/10.4088/JCP.09m05282blu.

Feld, J.J., 2014. The beginning of the end: what is the future of interferon therapy for chronic hepatitis C? Antivir. Res. 105, 32–38. https://doi.org/10.1016/j.antiviral.2014.02.005.

Fishbain, D.A., 1999. The association of chronic pain and suicide. Semin. Clin. Neuropsychiatry 4, 221–227 doi: 10.153/SCNP00400221.

Fontana, R.J., Hussain, K.B., Schwartz, S.M., Moyer, C.A., Su, G.L., Lok, A.S., 2002. Emotional distress in chronic hepatitis C patients not receiving antiviral therapy. J. Hepatol. 36, 401–407.

Gerber, P.D., Barrett, J.E., Barrett, J.A., Oxman, T.E., Manheimer, E., Smith, R., Whiting, R.D., 1992. The relationship of presenting physical complaints to depressive symptoms in primary care patients. J. Gen. Intern. Med. 7, 170–173.

Horikawa, N., Yamazaki, T., Izumi, N., Uchihara, M., 2003. Incidence and clinical course of major depression in patients with chronic hepatitis type C undergoing interferon-alpha therapy: a prospective study. Gen. Hosp. Psychiatry 25, 34–38.

Hsiao, P.J., Hsieh, P.F., Chou, E.C., Lai, H.C., Peng, C.Y., Su, K.P., 2016. Anti-viral therapy and decreased sexual desire in patients with chronic hepatitis C. PLoS One 11, e0160450. https://doi.org/10.1371/journal.pone.0160450.

Huckans, M., Fuller, B., Wheaton, V., Jaehnert, S., Ellis, C., Kolessar, M., Kriz, D., Anderson, J.R., Berggren, K., Olavarria, H., Sasaki, A.W., Chang, M., Flora, K.D., Loftis, J.M., 2015. A longitudinal study evaluating the effects of interferon-alpha therapy on cognitive and psychiatric function in adults with chronic hepatitis C. J. Psychosom. Res. 78, 184–192. https://doi.org/10.1016/j.jpsychores.2014.07.020.

Jackson, J.L., Chamberlin, J., Kroenke, K., 2003. Gender and symptoms in primary care practices. Psychosomatics 44, 359–366. https://doi.org/10.1176/appi.psy.44.5.359.

Jones, D., Hall, S.B., 1963. Significance of somatic complaints in patients suffering from psychotic depression. Acta Psychother. Psychosom. 11, 193–199.

Kapfhammer, H.-P., 2006. Somatic symptoms in depression. Dialogues Clin. Neurosci. 8, 227–239.

Khan, A.A., Khan, A., Harezlak, J., Tu, W., Kroenke, K., 2003. Somatic symptoms in primary care: etiology and outcome. Psychosomatics 44, 471–478. https://doi.org/10.1176/appi.psy.44.6.471.

Kirkwood, J.M., Strawderman, M.H., Ernstoff, M.S., Smith, T.J., Borden, E.C., Blum, R.H., 1996. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group Trial EST 1684. J. Clin. Oncol. 14, 7–17. https://doi.org/10.1200/jco.1996.14.1.7.

Kroenke, K., 2003. Patients presenting with somatic complaints: epidemiology, psychiatric comorbidity and management. Int. J. Methods Psychiatr. Res. 12, 34–43.

Kroenke, K., Price, R.K., 1993. Symptoms in the community: prevalence, classification, and psychiatric comorbidity. Arch. Intern. Med. 153, 2474–2480. https://doi.org/10.1001/archinte.1993.00410210102011.

Kroenke, K., Spitzer, R.L., Williams, J.B., Linzer, M., Hahn, S.R., deGruy 3rd, F.V., Brody, D., 1994. Physical symptoms in primary care. Predictors of psychiatric disorders and functional impairment. Arch. Fam. Med. 3, 774–779.

Lautenbacher, S., Krieg, J.C., 1994. Pain perception in psychiatric disorders: a review of the literature. J. Psychiatr. Res. 28, 109–122.

Lecrubier, Y., Sheehan, D.V., Weiller, E., Amorim, P., Bonora, I., Harnett Sheehan, K., Janavs, J., Dunbar, G.C., 1997. The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. Eur. Psychiatry 12, 224–231. https://doi.org/10.1016/S0924-9338(97)83296-8.

Li, M., Kouzmina, E., McCusker, M., Rodin, D., Boutros, P.C., Paige, C.J., Rodin, G., 2016. Pro- and anti-inflammatory cytokine associations with major depression in cancer patients. Psycho Oncol. https://doi.org/10.1002/pon.4316.

Loftis, J.M., Patterson, A.L., Wilhelm, C.J., McNett, H., Morasco, B.J., Huckans, M., Morgan, T., Saperstein, S., Asghar, A., Hauser, P., 2013. Vulnerability to somatic symptoms of depression during interferon-alpha therapy for hepatitis C: a 16-week prospective study. J. Psychosom. Res. 74, 57–63. https://doi.org/10.1016/j.jpsychores.2012.10.012.

Malaguarnera, M., Laurino, A., Di Fazio, I., Pistone, G., Castorina, M., Guccione, N., Rampello, L., 2001. Neuropsychiatric effects and type of IFN-alpha in chronic hepatitis C. J. Interferon Cytokine Res. 21, 273–278. https://doi.org/10.1089/107999001300177457.

Novick, D., Montgomery, W., Aguado, J., Kadziola, Z., Peng, X., Brugnoli, R., Haro, J.M., 2013. Which somatic symptoms are associated with an unfavorable course in Asian patients with major depressive disorder? J. Affect. Disord. 149, 182–188. https://doi.org/10.1016/j.jad.2013.01.020.

Ohayon, M.M., Schatzberg, A.F., 2003. Using chronic pain to predict depressive morbidity in the general population. Arch. Gen. Psychiatr. 60, 39–47.

Pettersson, A., Modin, S., Wahlström, R., Af Winklerfelt Hammarberg, S., Krakau, I., 2018. The Mini-International Neuropsychiatric Interview is useful and well accepted as part of the clinical assessment for depression and anxiety in primary care: a mixed-methods study. BMC Fam. Pract. 19 https://doi.org/10.1186/s12875-017-0674-5, 19-19.

Raison, C.L., Borisov, A.S., Broadwell, S.D., Capuron, L., Woolwine, B.J., Jacobson, I.M., Nemeroff, C.B., Miller, A.H., 2005a. Depression during pegylated interferon-alpha plus ribavirin therapy: prevalence and prediction. J. Clin. Psychiatry 66, 41–48.

Raison, C.L., Demetrashvili, M., Capuron, L., Miller, A.H., 2005b. Neuropsychiatric adverse effects of interferon-alpha: recognition and management. CNS Drugs 19, 105–123.

Raison, C.L., Woolwine, B.J., Demetrashvili, M.F., Borisov, A.S., Weinreib, R., Staab, J.P., Zajecka, J.M., Bruno, C.J., Henderson, M.A., Reinus, J.F., Evans, D.L., Asnis, G.M., Miller, A.H., 2007. Paroxetine for prevention of depressive symptoms induced by interferon-alpha and ribavirin for hepatitis C. Aliment. Pharmacol. Ther. 25, 1163–1174. https://doi.org/10.1111/j.1365-2036.2007.03316.x.

Schaefer, M., Capuron, L., Friebe, A., Diez-Quevedo, C., Robaeys, G., Neri, S., Foster, G.R., Kautz, A., Forton, D., Pariante, C.M., 2012. Hepatitis C infection, antiviral treatment and mental health: a European expert consensus statement. J. Hepatol. 57, 1379–1390. https://doi.org/10.1016/j.jhep.2012.07.037.

Schaefer, M., Engelbrecht, M.A., Gut, O., Fiebich, B.L., Bauer, J., Schmidt, F., Grunze, H., Lieb, K., 2002. Interferon alpha (IFNalpha) and psychiatric syndromes: a review. Prog. Neuropsychopharmacol. Biol. Psychiatry 26, 731–746.

Schaefert, R., Höner, C., Salm, F., Wirsching, M., Leonhart, R., Yang, J., Wei, J., Lu, W., Larisch, A., Fritzsche, K., 2013. Psychological and behavioral variables associated with the somatic symptom severity of general hospital outpatients in China. Gen. Hosp. Psychiatry 35, 297–303. https://doi.org/10.1016/j.genhosppsych.2012.11.001.

Sheehan, D.V., Lecrubier, Y., Harnett Sheehan, K., Janavs, J., Weiller, E., Keskiner, A., Schinka, J., Knapp, E., Sheehan, M.F., Dunbar, G.C., 1997. The validity of the Mini international neuropsychiatric interview (MINI) according to the SCID-P and its reliability. Eur. Psychiatry 12, 232–241. https://doi.org/10.1016/S0924-9338(97)83297-X.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59 (Suppl. 20), 22–33 quiz 34-57.

Silverstein, B., Edwards, T., Gamma, A., Ajdacic-Gross, V., Rossler, W., Angst, J., 2013. The role played by depression associated with somatic symptomatology in accounting for the gender difference in the prevalence of depression. Soc. Psychiatry Psychiatr. Epidemiol. 48, 257–263. https://doi.org/10.1007/s00127-012-0540-7.

Su, K.P., 2009. Biological mechanism of antidepressant effect of omega-3 fatty acids: how does fish oil act as a 'mind-body interface'? Neurosignals 17, 144–152. https://doi.org/10.1159/000198167.

Su, K.P., 2015. Nutrition, psychoneuroimmunology and depression: the therapeutic implications of omega-3 fatty acids in interferon-alpha-induced depression. Biomedicine 5, 21. https://doi.org/10.7603/s40681-015-0021-x.

Su, K.P., Lai, H.C., Peng, C.Y., Su, W.P., Chang, J.P., Pariante, C.M., 2019. Interferon-alpha-induced depression: comparisons between early- and late-onset subgroups and with patients with major depressive disorder. Brain Behav. Immun. 80, 512–518. https://doi.org/10.1016/j.bbi.2019.04.032.

Tamayo, J.M., Roman, K., Fumero, J.J., Rivas, M., 2005. The level of recognition of physical symptoms in patients with a major depression episode in the outpatient psychiatric practice in Puerto Rico: an observational study. BMC Psychiatry 5, 28. https://doi.org/10.1186/1471-244x-5-28.

Tylee, A., Gandhi, P., 2005. The importance of somatic symptoms in depression in primary care. Prim. Care Companion J. Clin. Psychiatry 7, 167–176.

Udina, M., Hidalgo, D., Navines, R., Forns, X., Sola, R., Farre, M., Capuron, L., Vieta, E., Martin-Santos, R., 2014. Prophylactic antidepressant treatment of interferon-induced depression in chronic hepatitis C: a systematic review and meta-analysis. J. Clin. Psychiatry 75, e1113–1121. https://doi.org/10.4088/JCP.13r08800.

Valentine, A.D., Meyers, C.A., Kling, M.A., Richelson, E., Hauser, P., 1998. Mood and cognitive side effects of interferon-alpha therapy. Semin. Oncol. 25, 39–47.

Valentine, A.D., Meyers, C.A., Talpaz, M., 1995. Treatment of neurotoxic side effects of interferon-alpha with naltrexone. Canc. Invest. 13, 561–566.

Von Korff, M., Simon, G., 1996. The relationship between pain and depression. Br. J. Psychiatry Suppl, 101–108.

Yates, W.R., Gleason, O., 1998. Hepatitis C and depression. Depress. Anxiety 7, 188–193.

Zhu, C., Ou, L., Geng, Q., Zhang, M., Ye, R., Chen, J., Jiang, W., 2012. Association of somatic symptoms with depression and anxiety in clinical patients of general hospitals in Guangzhou, China. Gen. Hosp. Psychiatry 34, 113–120. https://doi.org/10.1016/j.genhosppsych.2011.09.005.