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The importance of fatigue cognitions in chronic hepatitis C infection ☆

Dora Zalai [a,*], Morris Sherman [b], Kelly McShane [a], Colin M. Shapiro [c,d], Colleen E. Carney [a]

[a] Dept. of Psychology, Ryerson University, Toronto, Canada
[b] Dept. of Gastroenterology, University Health Network, University of Toronto, Toronto, Canada
[c] Dept. of Psychiatry, University Health Network, University of Toronto, Toronto, Canada
[d] Dept. of Ophthalmology, University Health Network, University of Toronto, Toronto, Canada

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ABSTRACT

Chronic Hepatitis C virus (HCV) infection is a source of significant public health burden worldwide. Fatigue is a cardinal patient reported consequence of the disease. HCV infection associated fatigue leads to significant impairment in the quality of life and day-to-day functioning. Despite its clinical significance, the factors that contribute to adverse impact of fatigue in HCV infection are largely unknown.

Objectives: This study evaluated the contributions of insomnia, depression symptoms, and fatigue-specific cognitions to fatigue-related functional impairment.

Methods: Fatigue, insomnia, depression symptoms, as well as fatigue cognitions were assessed in participants (36% females; age > 18 years, N = 115) with chronic HCV infection at a tertiary hepatitis clinic.

Results: Sixty percent of participants reported clinically significant fatigue (Fatigue Severity Index FSS ≥ 4). Comorbidities and fatigue perceptions accounted for 61% of the variation of fatigue. Fatigue perceptions were the main predictors of adverse fatigue outcomes ($B = .114$, 95% CI = .054–.154). Patients with clinically significant fatigue were four-times more likely than less fatigued patients to believe that the main cause of their fatigue was the infection.

Conclusion: Patients' beliefs about their fatigue were the main predictors of adverse fatigue outcomes. These results suggest that fatigue associated with chronic hepatitis C infection can be conceptualized using a cognitive behavioral approach. This was the first study to evaluate the role of both comorbid mood/sleep and cognitive predictors of fatigue in a single model. Integrating the findings into existing treatment strategies could improve patient reported outcomes in chronic hepatitis C infection.

Introduction

Hepatitis C virus (HCV) causes chronic, insidious liver infection in 130–170 million individuals around the world [1]. The screening of transfusion blood has resulted in a significant decline in the rate of new infections in North America and Europe, but chronic HCV infection has been, and is predicted to remain, the leading cause of liver transplantation on these continents [2]. Although anti-viral treatment is available, its impact is restricted because: (1) the majority of individuals with chronic HCV infection are not aware of their infection, therefore do not seek anti-viral treatment; (2) patients with mild liver disease may not be offered treatment; (3) treatment adherence may be limited as a result of psychiatric comorbidities; and (4) not all patients show sustained treatment response to the currently available antiviral agents [3]. Therefore, a significant proportion of those infected live with a slowly progressing liver disease for years or decades. For these individuals, symptoms that impact quality of life and every day functioning are of the key disease-related concerns.

Fatigue is among the leading patient-reported symptoms in chronic HCV infection [4,5]. In qualitative studies, patients described fatigue as the most concerning symptom of their illness and in quantitative reports fatigue was the second most common patient-reported outcome measure of the infection [5]. In the presence of persistent fatigue, increased effort is required to maintain important social roles and activities. Therefore, fatigue has an impact both on subjective well-being and on everyday functioning. Previous research has failed to detect a relationship between disease markers (e.g. virus load and liver disease severity) and fatigue in chronic hepatitis C infection [6–8]. This evidence suggests that factors other than the disease per se give rise to the "lived experience" of fatigue in the context of chronic HCV infection. Despite fatigue being ubiquitous and a significant concern for patients with chronic HCV infection, the secondary factors that may contribute to chronic fatigue in this condition are largely unexplored. In order to advance the study of fatigue in chronic HCV infection, one should rely

Abbreviations: HCV, chronic hepatitis C virus.

☆ This study was conducted at the University Health Network, University of Toronto, Toronto, Canada.

* Corresponding author at: Department of Psychology, Ryerson University, 350 Victoria Street, Toronto M5B 2K3, ON, Canada. Tel.: +1 416 836 6250; fax: +1 647 349 4228.
E-mail address: dora.zalai@psych.ryerson.ca (D. Zalai).

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on evidence-based fatigue models that can be systematically tested and adapted to hepatitis C -related fatigue.

Theoretical models of fatigue in the medically ill posit that disease-related (primary) biological factors give rise to physiological fatigue that is maintained and amplified by secondary factors associated with the disease, including depression and sleep problems [9]. A parallel line of research, conceived in the cognitive–behavioral tradition, has shown that patients' beliefs about their illness and fatigue predict chronic fatigue independently of the characteristics (e.g. severity, course and activity) of the underlying disease [10–17]. The importance of fatigue cognitions is also supported by the fact that change of fatigue-specific beliefs mediates the therapeutic effect of cognitive behavioral therapy for fatigue in multiple sclerosis and chronic fatigue syndrome [14,15,18].

The studies on fatigue-specific cognitions and behaviors have been largely related to cancer, multiple sclerosis and chronic fatigue syndrome hitherto. Although the above theories have not been tested in patients with HCV infection, the association of depression with fatigue has been established in patients with HCV treated at tertiary liver clinics [8, 19–21]. However, the relative contribution of depression to fatigue even in this selected patient population is unclear, since the studies conducted thus far have not included other, theoretically important "secondary" factors (e.g. sleep problems and fatigue-cognitions) concurrently in the assessments and in the statistical models. With respect to sleep, limited evidence indicates that 60–70% of patients with chronic HCV infection report sleep problems, but the prevalence of specific sleep disorders and the contribution of compromised sleep to fatigue in HCV are unknown. Hepatitis C related fatigue has not been studied from the cognitive behavioral perspective. Qualitative studies have been a rich source of information vis-à-vis patients' subjective perception of the illness. However, a quantitative evaluation of these illness cognitions in relation to fatigue has been very limited [22].

Given that: (1) a large number of individuals with HCV infection do not require/receive antiviral treatment; and (3) mood, sleep, and non-adaptive cognitions are amenable to therapeutic interventions, evaluating the possible contribution of these factors to HCV-related fatigue is imperative.

The objective of the current study was to evaluate the "secondary fatigue" and cognitive models in chronic HCV infection. Specifically, we set out to evaluate the contribution of depression, insomnia, as well as fatigue perceptions to clinically significant (functionally disabling) fatigue in patients with chronic HCV infection. Our hypothesis was that depression symptoms, clinical insomnia, and fatigue-perceptions predict the functional impact of fatigue above and beyond the severity of the liver disease and the presence other medical comorbidities.

Method

Participants

A consecutive sample of English speaking participants (N = 132, age > 18 years) diagnosed with chronic hepatitis C infection was recruited at the Toronto General Hospital Liver Clinic, Toronto, Canada. All participants were anti-HCV positive as verified by ELISA II or III, and confirmed by RIBA II or III, or by PCR for HCV RNA. Only individuals who had not received antiviral treatment within 6 weeks of enrolment were recruited; this period was determined based on the pharmacological properties of the standard antiviral medications and was to avoid the presence of treatment-related fatigue. Two individuals were excluded from the study, because they did not meet inclusion criteria. Fifteen participants who did not return the questionnaires were excluded from the analysis. This yielded a response rate of 87%. The final sample included 115 participants (Table 1). This sample size was adequate to detect a medium size effect with .8 power based on an a-priori power analysis.

Procedures

The patients' hepatologist identified potential participants based on the inclusion criteria and assessed patients' interest in participating. After consenting to participate, participants completed the questionnaires at the clinic after their appointment or took the questionnaires home and mailed them to the researchers within 10 days. The most recent measure of disease severity was retrieved from the participants' electronic medical records. Comorbid conditions (for example cardiovascular disorders, history of cancer, chronic pain conditions, chronic kidney disease, autoimmune disorders, and a history of substance use); history of previous anti-HCV treatment; and demographic data were obtained from self-reports and subsequently verified in the hospital medical records.

Measures

The outcome measure was the *Fatigue Severity Scale* (FSS) [23]. The FSS is a nine- item questionnaire assessing the functional impact of fatigue on multiple life domains using scales from 1 (*strongly disagree*) to 7 (*strongly agree*). The fatigue score is the mean score of the 9 items. Clinically significant fatigue is defined as score equal or above four. The FSS showed excellent psychometric properties (internal consistency $\alpha = .94$; test–retest reliability = .82, convergent validity with SF-36 vitality subscale $r = -0.76$) in a multi-center clinical trial in chronic HCV infection [24]. It has been suggested that FSS is used as a patient reported-outcome measure in chronic HCV infection [5].

The *Insomnia Severity Index* (ISI) is a seven item questionnaire developed for the clinical assessment of insomnia and recommended for use in insomnia research [25]. Traditionally, a total score of above 14 indicates clinically significant, moderate or severe insomnia. The ISI has adequate internal consistency ($\alpha = .77$) and good convergent validity compared with sleep diary; and with sleep onset latency on polysomnography [26].

The *Depression Anxiety Stress Scale-21* (DASS-21) is a 21 item scale evaluating depression, anxiety, and stress [27,28]. Respondents rate how they felt over the past week from zero (*did not apply to me at all*) to three (*applied to me very much, or most of the time*). The scale shows good construct validity: the correlation between the depression subscale and the Beck Depression Inventory (BDI) was .79; the correlation between the anxiety subscale and the Beck Anxiety Inventory (BAI) was .85 and the correlation between the stress scale and BDI, State-

Table 1
Participant characteristics.

Demographics	
Age (years) (mean ± SD)	56 ± 10
Gender (female) (%)	36.5
Marital status (married) (%)	57
Hepatitis related data	
Time since diagnosis (years) (median (IQR))	13 (5–20)
Fibrosis stage (%)	
F0	9.8
F1	17.9
F2	8.9
F3	18.8
F4	44.6
Antiviral treatment (received)	50.40
Laboratory data	
Serum total bilirubin (umol/L) (median (IQR))	11 (8–18)
Serum gamma-glutamyl transpeptidase (U/L) (median (IQR)	65 (35–154)
Serum albumin (g/L) (mean ± SD)	38 ± 4
Blood hemoglobin (g/L) (mean ± SD)	147 ± 19
Serum platelet (×10 eg/L) (median (IQR)	178 (129–226)
Number of comorbid medical conditions (mean, range)	2 (0–9)