Patients with Chronic Hepatitis C Undergoing Watchful Waiting: Exploring Trajectories of Illness Uncertainty and Fatigue

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Abstract

We identified trajectories of illness uncertainty in chronic hepatitis C patients and examined their association with fatigue levels during 12 months of disease monitoring without treatment (watchful waiting). Sixty-two men and 63 women completed uncertainty and fatigue measures. Groups were formed by uncertainty scores (high, medium, low) at baseline. Baseline fatigue levels were higher in the high uncertainty group than in the medium and low groups. Over time, uncertainty levels did not change. Fatigue levels in the low uncertainty group remained constant, increased in the medium, and decreased in the high groups. Findings suggest that uncertainty and fatigue do not remit spontaneously. Being aware of this may help nurses identify those patients needing support for these two concerns.

Keywords

fatigue; uncertainty; chronic illness; gastrointestinal system
Hepatitis C Virus (HCV), the most common blood-borne infection in the U.S., affects at least 3.2 million individuals, with more than 19,000 new cases of infection occurring each year (Centers for Disease Control and Prevention [CDC], 2008). Further, up to 85% of those with acute HCV develop chronic hepatitis C (CHC), and the CDC has projected a fourfold increase in the number of individuals with CHC between 1990 and 2015 (Kim, 2002). Many CHC patients are potential candidates for treatment with combination peginterferon alfa and ribavirin therapy, and approximately 50% of patients who receive this treatment have a sustained response, with long-term viral eradication (Rossi & Wright, 2003). However, the benefits of therapy are less clear for those with mild disease and co-morbid illnesses and for older patients (National Institutes of Health, 2002).

Further, treatment has been associated with a multitude of side effects such as depression (Fried, 2002), which can be severe and limit treatment. Because of these side effects, approximately 15% of patients discontinue therapy (Jacobson et al., 2007). Other patients fail to achieve a sustained viral response or relapse after treatment (Ghany, Strader, Thomas, & Seeff, 2009), and up to 30% of patients may be advised to forego therapy (Ghany et al., 2003; Herrine, Rossi, & Navorro, 2006). Still other patients may defer treatment hoping that new and improved therapies will have fewer side effects (Bailey, Wallace, & Mishel, 2007). Thus, currently approximately 50% of CHC patients are not undergoing active treatment but instead are watching, waiting, and monitoring their disease. This strategy known as watchful waiting is also referred to as observation, expectant management, active monitoring, or deferred treatment.

Both uncertainty and fatigue are common among CHC patients during watchful waiting, but very little is known about how these potentially debilitating issues may be related in CHC patients. The purpose of this study was to identify trajectories of uncertainty and fatigue in patients with CHC and to explore relationships among these trajectories over a 12-month period of watchful waiting.

Many CHC patients undergoing watchful waiting experience illness uncertainty similar to that experienced by individuals with other chronic or life-threatening diseases (Bailey et al., 2007). Illness uncertainty is defined as the inability to find meaning for illness-related events (Mishel, 1988). That is, the person cannot assign definite value to objects or events and/or is unable to accurately predict outcomes because sufficient cues are lacking. Uncertainty develops if the patient cannot formulate a cognitive schema for illness events (Mishel, 1988). In CHC, illness uncertainty appears to stem from a general lack of knowledge about the disease and from the unpredictable disease trajectory and prognosis (Glacken, Kernohan, & Coates, 2001; Teague, Hepworth & Krug, 1999). In other illnesses, age, education, and race/ethnicity also have been linked to illness uncertainty, along with co-morbidities (Germino et al., 1998; Gil et al., 2004; Mishel, 1997b). The rationale for studying education, age, and race/ethnicity as factors influencing uncertainty lies in the knowledge and experience that are likely to be embedded in older age, higher education, and minority race/ethnicity.

The prevalence of fatigue in CHC ranges from 53–92% (Lang et al., 2006; Poynard et al., 2002; Stefanova-Petrova et al., 2007). It is one of the most troubling symptoms of CHC and is characterized by lethargy and a lack of energy. It does not respond to usual restorative techniques and negatively affects patients’ activities of daily living, dramatically decreasing their quality of life (QOL; Glacken, Coates, Kernohan, & Hegarty, 2003; Groessl et al., 2008; Kallman et al., 2007). Despite its prevalence, Seaman, Paterson, Vallis, Hirsch, and Peltekian (2009), who reviewed the literature on fatigue among untreated CHC patients, concluded that there is no widely accepted definition of CHC-related fatigue, and the factors...
associated with fatigue in patients with CHC are not clear, making its management difficult at best.

While we know that certain mood states, such as depression, anger, anxiety, and hostility, are associated with CHC-related fatigue (e.g., Hilsabeck, Hassanein, & Perry, 2005; Lang et al., 2006; McDonald, Jayasuriya, Bindley, Gonsalvez, & Gluseska, 2002), to our knowledge there are no studies of the relationship between illness uncertainty and CHC-related fatigue. Dealing with illness uncertainty is itself fatiguing as patients constantly evaluate new symptoms, fearing that they may indicate disease progression. In turn, fatigue may exacerbate uncertainty because of its lack of predictability. Yet little is known about how the trajectories of fatigue and uncertainty may be entwined over time during watchful waiting, and previous finding have indicated that in other illnesses trajectories may increase, decrease, or remain stable over time (e.g., Taylor, Ezell, Kuchibhatla, Ostbye, & Clipp, 2008).

Exploring the relationship between fatigue and illness uncertainty and ways in which this relationship changes over time may provide useful knowledge for developing interventions to manage both illness uncertainty and fatigue. Therefore this exploratory study was designed to identify the trajectory of illness uncertainty in patients with chronic hepatitis C (CHC) and its demographic and illness-related correlates, and to explore the association of fatigue and illness uncertainty trajectories over a 12-month period of watchful waiting. We used the trajectory perspective of Clipp, Elder, George, and Pieper (1998), which considers a typological or health pattern approach to change in illness over time, and Mishel’s uncertainty in illness theory (Mishel, 1988, 1990), according to which uncertainty in chronic illness results from the unpredictability of symptoms such as fatigue, continual concerns about exacerbation, and an unknown future.

The research questions were:

1. What is the trajectory of illness uncertainty among CHC patients undergoing watchful waiting over a 12-month period?

2. What demographic and illness-related characteristics are associated with different trajectories of illness uncertainty over time?

3. How are illness uncertainty trajectories related to levels of fatigue?

Method

Design

This study was part of a larger longitudinal study of CHC-related illness uncertainty, symptoms, and quality of life in patients who were monitoring their disease through a watchful waiting protocol consisting of regularly scheduled clinic appointments with their healthcare provider and laboratory testing. Convenience sampling was used to recruit participants from the gastroenterology clinic of a tertiary care medical center in a southeastern state; data were collected from 2006 to 2008. After approval by the university Committee for the Protection of Human Subjects, a nurse or research assistant met with eligible patients following their scheduled clinic appointments to explain the study and answer questions. Patients who wanted more time to think about participating were given a number to call, or if requested, the study staff member called them at home. We obtained informed written consent from all patients who agreed to participate in the study.
Participants

Patients included in the study were men and women over the age of 21 who had been diagnosed with CHC, were not receiving active treatment, had a telephone or access to a telephone, read and spoke English, and resided in the state. Patients co-infected with HIV were excluded because they could have been in active treatment for that disease and unable to differentiate the uncertainties involved in the two illnesses. Pregnant women also were excluded. A total of 135 individuals were invited to enroll in the study; 125 (93%) agreed to participate and provided complete baseline data. At 6 months 111 participants provided data to our interviewer during a telephone call, and at 12 months 100 participants provided data in the same manner. Potential participants who declined did so because they were unable to schedule time for an interview or were concerned about confidentiality. Participants included 62 men and 63 women who identified themselves as Caucasian, African-American, Latino, Asian American, American Indian, or of mixed race. Their ages ranged from 27–78 yrs (M=53, SD=9.4); years of education ranged from 7–22 yrs (M=14, SD=2.7). The number of co-morbidities reported by participants ranged from 0–13 with a mean of 4.1. The participants reported that they had been living with their disease an average of 6.9 years (SD=5.2). Demographic data for the sample by uncertainty group are shown in Table 1.

Measures

Illness uncertainty was measured with the Mishel Uncertainty in Illness Scale (MUIS-A; Mishel, 1981). The MUIS-A scale has 33 items, each scored from 1 (strongly disagree) to 5 (strongly agree); total scores range from 33–165. Participants respond to the items to describe how they are feeling today; items were re-worded for this study to be specific to watchful waiting. Mishel (1997a) reported Cronbach’s alpha of .87 for the total scale, indicating a high level of internal consistency; the scale has been used with chronically ill patients suffering from multiple sclerosis, cystic fibrosis, and end-stage renal disease (Mishel, 1997a). In this study, Cronbach’s alpha for the MUIS-A was .90 (see Bailey et al., 2009, for MUIS-A sample items). Although the MUIS-A includes four subscales or factors, each representing a distinct dimension of uncertainty (ambiguity, complexity, inconsistency, unpredictability), we used the entire scale scores only for this analysis.

Fatigue was measured with the Revised Piper Fatigue Scale (RPFS), which is composed of 22 items; participants are asked to respond to these items in terms of how they are feeling now, with responses ranging from 0–10 (Piper et al., 1998). Four dimensions of fatigue are measured: behavioral/severity, affective meaning, sensory, and cognitive/mood. The RPFS is scored by summing the scores on all items and dividing the total by 22, which keeps the total score on a 0 to 10 numeric scale. Five open-ended questions are included for participants to provide information on symptom distress not captured in the quantitative ratings; those qualitative data are not included in the score. Concurrent validity has been established by significant correlations with the Profile of Mood States (POMS; McNair, Lorr, & Droppelman, 1971). Piper et al. (1998) reported Cronbach’s alpha of .97 for the scale; in this study, the value was .99. Although there are subscales to the RPFS, we used the entire scale scores for the analysis. Piper provides scores delineating different categories of fatigue (0 = none, 1–3 = mild, 4–6 = moderate, 7–10 = high), but we used the scale scores as a continuous variable so that we could examine how levels of fatigue correlated with uncertainty.

Procedures

After giving informed consent, participants completed a questionnaire in the clinic or by telephone at a convenient time, usually within 3 days of initial contact. They answered questions about their gender, age, race, and educational level and provided basic illness information, co-morbidities, and the reason for adopting watchful waiting. Participants were
called on the telephone by a study research assistant at 6 and 12 months to complete the time 2 and time 3 questionnaires, which contained questions about their illness. They completed the MUIS-A and RPFS at baseline, 6, and 12 months.

Analysis

The primary goal of this study was to explore the association between illness uncertainty (IU), as measured by the MUIS-A, and fatigue, as measured by the RPFS, controlling for demographic and illness-related variables. To identify the number and type of distinct trajectories of uncertainty we used Latent Class Trajectory Analysis (LCTA). The LCTA models are more appropriate than standard growth trajectory models (e.g., mixed models) when it cannot be assumed that all sample members change in the same direction (Andruff, Carraro, Thompson, Gaudreau, & Louvet, 2009; Nagin & Tremblay, 2005). The LCTA is based on the statistical models of Heckman and Singer (1984) and Rindskopf (1990), and was performed using the Latent GOLD® software (Vermundt & Magidson, 2005). A minimum of 100 cases is required to use this analytic technique (Nagin & Tremblay, 2005).

With LCTA, we were able to test empirically how many distinct classes of trajectories were present in the data, assign respondents to trajectory classes based on membership probabilities, and estimate the relationship of membership in a particular trajectory class to other variables in the design (Land, McCall & Nagin, 1996; Nagin, 1999). With Latent GOLD, these relationships are assessed using a multinomial logistic model with class membership dependent (Vermundt & Magidson, 2005). Our sample size (N=125) provided 80% power to detect standardized effect sizes of about .35 (p<.05, 2-tailed) in analyses involving the relationships among uncertainty, fatigue, and other variables of interest (Cohen, 1988). As a result, our significance tests were conservative, and we were unable to detect small effects. This is taken into account in the interpretation of the findings.

Following standard practice (Nylund, Asparouhov, & Muthén, 2007), we began with a one class model (in which all participants have the same uncertainty trajectory), added classes in successive models, and used the Bayesian Information Criterion to determine the optimal number of classes. Demographic and illness-related variables thought to be associated with illness uncertainty were then added to the LCTA model to assess their association with trajectory class membership. The five covariates used were age, education level, number of co-morbid conditions (all expressed as a continuous metric), race (white vs. nonwhite), and gender.

Mixed models (SAS PROC MIXED; SAS Institute, Inc., 1992) were used to assess the association between illness uncertainty trajectory class and fatigue over three time points. Covariates of interest consisted of the same five used in the LCTA analysis: age, education level, number of co-morbidities, race, and gender.

Results

In response to the first research question, What is the trajectory of illness uncertainty among CHC patients undergoing watchful waiting over a 12-month period? latent class trajectory analysis identified three distinct illness uncertainty (IU) groups. These groups differed on baseline uncertainty, as indicated by baseline means on IU shown in Table 1. The three groups were labeled Low, Medium, and High. The LCTA also showed that mean uncertainty levels in each group did not change over time (within-group trajectories were horizontal). The second research question sought to identify the demographic and illness-related characteristics associated with different trajectories of illness uncertainty over time. Two of the five covariates examined (education and number of co-morbid conditions) were significantly related to uncertainty group membership. The means in Table 1 give the
direction, magnitude, and significance of covariate associations with uncertainty group membership.

To address the third research question, How are illness uncertainty trajectories related to levels of fatigue? we used longitudinal mixed modeling (Singer & Willett, 2003) to determine the effects of uncertainty group membership on baseline fatigue and change in fatigue over time. Education, gender, age, race, and number of co-morbidities were included in the analyses as controls. Results are given in Table 2. The overall illness uncertainty group effect was significant indicating the presence of significant group differences at baseline. The intercept gives the predicted mean for baseline fatigue among those in the high illness uncertainty group. Baseline fatigue was significantly lower in the medium illness uncertainty group and in the low illness uncertainty group than in the high illness uncertainty group. A significant illness uncertainty group by time interaction was present indicating differences in the trajectory of fatigue across the three uncertainty groups. The coefficient for time in Table 2 gives the effect of time on fatigue in the high uncertainty group and shows a modest but significant linear decline in fatigue. The time*medium IU term was significant and positive, indicating that the trajectory of change was significantly more positive in this group than in the high uncertainty group. The effect of time in the medium uncertainty group can be calculated as (−.45+.81=.36). Additional analyses indicated that that this effect (.36) differed significantly from zero. The p-value for time by low uncertainty was not significant, indicating that the trajectory of change in this group did not differ from that in the high uncertainty group. Further analyses showed that the fatigue slope in the low illness uncertainty group did not differ from zero and thus fatigue did not change over time. Number of co-morbidities was positively related to fatigue.

Thus illness uncertainty groups reported different levels of fatigue at baseline and over time; fatigue in the low uncertainty group remained constant, while fatigue increased in the medium uncertainty group and decreased in the high uncertainty group. These changes were relatively small, however, and the three groups maintained their relative rankings on fatigue throughout the observation period. This can be seen in Figure 1, which shows that fatigue increased over time in the medium illness uncertainty group, but was still lower than fatigue in the high uncertainty group at 12 months.

Discussion

We report descriptive data on the trajectories of illness uncertainty and fatigue in CHC patients and the relationship between illness uncertainty and this symptom over a 12-month period of watchful waiting. Using LCTA, we identified three distinct trajectory groups of illness uncertainty (low, medium, and high) based on uncertainty scores and a related typology of demographic and illness characteristics. This emerging typology may help clinicians working with this population quickly identify patients with heightened illness uncertainty using the demographic variable older age and the illness characteristic number of co-morbid health conditions as a guide.

The three groups’ levels of uncertainty remained essentially unchanged through the 12 months of follow-up. This finding is similar to the findings of Gil et al. (2006) in their uncertainty management intervention study of breast cancer survivors (M = 64 yrs) who were 5–9 years post-treatment for their disease. In that study, control participants’ levels of illness uncertainty remained unchanged. These two groups of patients, those with chronic hepatitis C undergoing watchful waiting and women 5–9 years post-treatment for breast cancer, are similar in that they both are on constant alert for signs of disease return or progression. If illness uncertainty remains elevated over time in patients undergoing watchful waiting, its impact on physical, emotional, and immune function could be harmful.
to overall health and quality of life (Koerbel & Zucker, 2007; Schneiderman, Ironson, & Siegel, 2005). Indeed, prior researchers have found that patients undergoing watchful waiting report increased perception of danger, constant worry about disease progression, and fear of death (Bailey et al., 2007; Kronenwetter, et al., 2005; Wallace, 2003). Knowing which patients have medium and high levels of illness uncertainty may encourage nurses to address uncertainty, because it is unlikely to remit without intervention.

Education level was associated with uncertainty group membership (low, medium, and high), consistent with finding from early studies using Mishel’s uncertainty model (Mishel, 1997b) showing a relationship between lower levels of education and greater uncertainty (Christman et al., 1988; Mishel, Hotsetter, King, & Graham, 1984). In this study participants with lower levels of education and more uncertainty had on average nearly two more co-morbid health conditions than participants in the other two groups. Fatigue levels were also higher in this group than in the other two groups. Level of education serves as a proxy for socioeconomic status (e.g., Paganiotakos et al., 2003), and this may explain why those with lower levels of education have poorer health (i.e., more co-morbid health conditions).

Fatigue is clearly associated with uncertainty in patients living with CHC. In this study, fatigue levels were elevated in the high uncertainty group at baseline, yet decreased over time. Fatigue levels in the low uncertainty group remained constant, and fatigue increased in the medium uncertainty group. These changes over time were relatively small, however, and the three groups maintained their relative rankings on fatigue throughout the observation period. Glacken et al. (2003) noted that the unpredictability of CHC-related fatigue is one of its most distressing features; patients must deal not only with the uncertainty of the course of their CHC infection, but also with the uncertainty of fatigue as a symptom of CHC. This experience closely parallels the experience of fatigue among HIV-infected patients, who also deal with uncertainty over the course of their illness. Patients suffering from both of these illnesses often see fatigue as an indicator that they are not doing well and their illness is worsening (e.g., Barroso, 2001). In Sheppard and Hubbert’s study (2006) participants noted how the fatigue in CHC actually changed their perceptions of themselves, framing CHC-related fatigue in a before-and-after paradigm; this illustrates the profound impact that fatigue can have on an individual. The finding in this study that participants in all three uncertainty groups maintained their rankings on both uncertainty and fatigue over the observation period indicates that neither high fatigue nor high uncertainty is likely to remit spontaneously.

Limitations of this study include the small sample size and data collection from only one site, a tertiary care center located in a southeastern state, whose patients may not be reflective of patients in other parts of the country. Further, the covariates selected constrained our modeling; the addition of other variables, such as disease stage, alcohol use, and IV drug use, may in future studies offer a richer view of these patients’ response to CHC or may change the findings and their statistical and clinical significance. Despite these limitations, the findings illuminate the relationship between illness uncertainty and fatigue over time.

Conclusions

This study is the first quantitative investigation to explore the relationship between illness uncertainty, a source of psychosocial distress in potentially life-threatening illness, and fatigue. We identified three illness uncertainty groups with levels of fatigue that differed from each other at baseline. Scores for participants who were high in uncertainty and high in fatigue were essentially unchanged over a year, which suggests that neither condition will remit on its own. These findings may inform assessment to identify CHC patients
undergoing watchful waiting who have an unmet need for intervention and to design protocols to help them manage both illness uncertainty and fatigue.

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Figure 1.
# Table 1

Mean Levels of Uncertainty and of Potential Covariates at Baseline by Illness Uncertainty Group in Patients with Chronic Hepatitis C

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Uncertainty Group</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illness Uncertainty Score (mean, SD)</td>
<td>Low IU n=13</td>
<td>Medium IU n=75</td>
</tr>
<tr>
<td></td>
<td>62.5 ± 11.8</td>
<td>81.7 ± 10.8</td>
</tr>
<tr>
<td>Education yr; (mean, SD)</td>
<td>16.5 ± 2.6</td>
<td>13.5 ± 2.3</td>
</tr>
<tr>
<td>Age yr; (mean, SD)</td>
<td>50.1 ± 13.5</td>
<td>53.1 ± 8.8</td>
</tr>
<tr>
<td># Co-morbid Conditions (mean, SD)</td>
<td>3.9 ± 3.5</td>
<td>3.4 ± 2.4</td>
</tr>
<tr>
<td>Race = White (%)</td>
<td>53.9</td>
<td>56.0</td>
</tr>
<tr>
<td>Gender = Female (%)</td>
<td>46.2</td>
<td>49.3</td>
</tr>
<tr>
<td>Piper Fatigue Scale (summary score)</td>
<td>1.75 ± 3.1</td>
<td>2.53 ± 2.8</td>
</tr>
<tr>
<td>Years since diagnosis</td>
<td>5.4 ± 3.7</td>
<td>7.5 ± 6.0</td>
</tr>
</tbody>
</table>

Note. IU = Illness Uncertainty

*p-value reflects a 2 degree of freedom test of the overall association between uncertainty group (a 3-level nominal variable) and each covariate.
## Table 2

Relationship of Illness Uncertainty (IU) Group with Baseline Fatigue and Change in Fatigue over Time in Patients with Chronic Hepatitis C

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE of Estimate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Fatigue</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Illness Uncertainty (IU) Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Intercept</td>
<td>3.97</td>
<td>1.79</td>
<td>.02</td>
</tr>
<tr>
<td>Medium IU</td>
<td>−2.50</td>
<td>0.69</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Low IU</td>
<td>−3.32</td>
<td>1.09</td>
<td>&lt;.01</td>
</tr>
<tr>
<td><strong>Change in Fatigue over Time</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall IU Group*Time Interaction</td>
<td></td>
<td></td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Time</td>
<td>−0.45</td>
<td>0.20</td>
<td>.03</td>
</tr>
<tr>
<td>Time*Medium IU</td>
<td>0.81</td>
<td>0.25</td>
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<tr>
<td>Time*Low IU</td>
<td>0.25</td>
<td>0.38</td>
<td>.50</td>
</tr>
<tr>
<td><strong>Covariates</strong></td>
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</tr>
<tr>
<td>Education</td>
<td>0.04</td>
<td>0.09</td>
<td>.67</td>
</tr>
<tr>
<td>Gender = female</td>
<td>0.75</td>
<td>0.43</td>
<td>.08</td>
</tr>
<tr>
<td>Age (years)</td>
<td>−0.04</td>
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<td>.09</td>
</tr>
<tr>
<td>Race = White</td>
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<td>0.43</td>
<td>.07</td>
</tr>
<tr>
<td>Number of Co-morbid Conditions</td>
<td>0.52</td>
<td>0.09</td>
<td>&lt;.01</td>
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</table>