Published in final edited form as:
Gen Hosp Psychiatry. 2010 ; 32(4): 413–418. doi:10.1016/j.genhosppsych.2010.03.010.

Predictors of Pain Intensity and Pain Functioning in Patients with the Hepatitis C Virus

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Abstract

OBJECTIVE—To examine the relationships among biological and psychological variables with pain intensity and pain functioning in patients with the hepatitis C virus (HCV).

METHODS—Participants were 49 patients with HCV who completed well-validated assessments of pain intensity and pain functioning. Participants also completed measures of psychological functioning and medical records were reviewed.

RESULTS—Thirty-three of 49 participants (67.3%) had a current diagnosis for a pain-related condition. Regression analyses were conducted to examine variables associated with pain intensity and pain functioning. The psychosocial variables, particularly depression severity, accounted for an additional 21% of the variance in average pain intensity ($p = 0.002$) and 33% of the variance in pain functioning ($p < 0.001$). These results remained significant even after controlling for demographic characteristics, opioid prescription status, and disease-related variables.

CONCLUSION—These results provide preliminary support for the role of biological and psychological factors in the development and exacerbation of pain in HCV patients. Future studies should include a more comprehensive assessment of pain-related factors and examine their associations with additional disease-related and biological variables. Developing a better

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understanding of the factors associated with pain in HCV patients will help to inform future interventions for chronic pain in this patient population.

Keywords

Chronic pain; Hepatitis C virus; Depression; Biopsychosocial model

Introduction

The hepatitis C virus (HCV) is the most common blood-borne infection and affects approximately 2% of the U.S. population [1,2]. HCV causes inflammation of the liver that can be characterized by liver enlargement, fibrosis, cirrhosis, abnormal liver function, and other symptoms. HCV is a leading cause of liver disease, cirrhosis, hepatocellular carcinoma, and liver transplantation [3].

Pain conditions in HCV patients are also common. In samples of patients treated at hepatology clinics, musculoskeletal pain was present in 50–70% of patients [4,5]. Fibromyalgia is also common in HCV patients, but prevalence rates vary across studies, ranging from 4–19% [6]. Arthritis may occur in up to 30% of patients with HCV [7]. Peripheral neuropathy is associated with chronic HCV, which is often characterized by sensory neuropathy of the lower limbs, in approximately 10% of HCV patients [7].

Several studies among veterans with HCV have found similarly high rates of pain symptomatology. In a recent study, Silberbogen and colleagues [8] examined pain severity in 33 patients presenting to liver clinics at two Veterans Administration Medical Centers (VAMCs). They found that 82.7% of participants with HCV also reported pain symptoms. Furthermore, the duration of pain symptoms was often chronic, with 65% of participants reporting pain for one year or more. In a recent study of 8,224 U.S. veterans with HCV accessing VAMCs in the Pacific Northwest (Washington, Oregon, Idaho, and Alaska), Whitehead and colleagues [9] found that 67% of patients had a comorbid chronic pain diagnosis documented in their medical record.

The etiology of pain syndromes among HCV patients is unclear. The immune system may play a role in the pathogenesis of pain and HCV, but the precise mechanisms are unknown [10]. Recent research has focused on abnormal cytokine regulation. Elevations of pro-inflammatory cytokines may be the common link between HCV and pain-related disorders [7].

The high rates of pain-related disorders among HCV patients could also be due to comorbid substance use disorders (SUDs) and/or psychiatric disorders. Chronic substance use is associated with high rates of pain [11–13], and HCV patients have high rates of SUD. Intravenous drug use is the primary cause of HCV infection [14,15] and prior studies suggest 64–90% of HCV patients have a history of SUD [16,17]. HCV patients also have high rates of psychiatric comorbidity [18,19], which are associated with increased pain [20,21].

Prior research with HCV patients indicates that behavioral factors are most predictive of the need for acute pain management [22], and BMI was a factor in pain reporting among patients with liver disease [23]. There are, however, limited studies available that have specifically examined factors associated with chronic pain among HCV patients. In this study, HCV patients were administered well-validated measures of pain intensity and pain functioning. The goal was to build upon prior research by examining psychological and disease-related factors associated with pain in HCV patients. We hypothesized that, in patients with chronic HCV, psychological variables (depression, severity of substance use) would be significantly

associated with pain-related outcomes, even after controlling for demographic and disease-related variables.

Methods

Participants

Data reported in this manuscript represent a subset from a larger study that examined cognitive deficits associated with HCV [24]. Participants were recruited into the parent study through: posted advertisements, advertisements mailed to a database of patients who had previously participated in other HCV research and consented to be contacted about future studies, verbal announcements at a bi-monthly HCV education class, and referrals from medical providers. Study procedures included a clinical interview, medical record review, psychological questionnaires, and a comprehensive battery of neuropsychological tests for which participants were compensated $30. Evaluations were reliably conducted by clinical psychology graduate who completed extensive training in study procedures and were closely supervised by a licensed psychologist. The Institutional Review Board at the Portland VAMC approved this study and all participants provided written informed consent.

All participants from the parent study were included in the present analyses if they had evidence in their medical record of a detectable HCV viral load based on polymerase chain reaction (PCR) tests and if they completed all measures of interest outlined in the following section. Exclusion criteria consisted of: non-veterans, history of severe neurological or immune dysfunction, severe traumatic brain injury with loss of consciousness ≥ 30 minutes, use of alcohol or sedating substances on the day of testing, advanced liver disease [stage 4 liver disease or grade 4 inflammation on biopsy, or classified by a hepatologist as having probable decompensated cirrhosis based on standard liver labs, or aspartate aminotransferase (AST) to platelet ratio index (APRI) ≥ 1.5 [25,26], current pregnancy, untreated severe psychiatric disorder, or history of interferon therapy or chemotherapy. Participants were also excluded for active SUD with < 90 days remission.

Measures

Demographic variables, including age, gender, race, years of education, marital status, and current occupation, were collected during the clinical interview.

HCV and liver disease variables were collected through comprehensive review of the patients' complete electronic medical records. Quantitative PCR tests were used as the indicator of viral load; viral load reflects the amount of virus present in the blood but does not necessarily correlate with liver disease severity. The APRI was used as the measure of liver disease severity, which is a noninvasive index that reliably predicts fibrosis and cirrhosis in HCV patients using routine laboratory data, with higher scores indicating more advanced liver disease [25,26]. The calculation for APRI = (AST level / upper limit of normal) / (platelet counts × [10^9 / liters]) × 100. AST is an enzyme found in high concentrations in metabolic tissues such as the liver, and injury to these tissues causes release into the blood stream. Higher serum AST levels are associated with greater tissue damage.

Pain intensity was assessed with a 0–10 Numeric Rating Scale (NRS), where 0 = "no pain" and 10 = "extremely severe pain" [27]. Pain functioning was assessed with the Bodily Pain scale of the Medical Outcomes Study – Short-Form 36 (SF-36) [28]. The SF-36 is a commonly utilized and well-validated self-report measure of quality of life. Higher scores on the SF-36 indicate better functioning. The Beck Depression Inventory – 2nd Edition (BDI-II) [29] was used to measure severity of current depressive symptoms. Higher scores indicate more severe symptoms. The Severity of Dependence Scale (SDS) [30] measured severity of prior substance

use. Although all patients reported being in remission from SUD for at least 90 days before study enrollment, participants with a SUD history identified their primary drug of abuse and completed the SDS considering that substance during their year of heaviest use.

Pain diagnoses for each participant were obtained from their electronic medical record with the assistance of the Veterans Integrated Service Network-20 Data Warehouse. The Data Warehouse extracts data from the main clinical software [31] packages of regional facilities and two national VA databases. The Data Warehouse is updated monthly, and reliability checks are performed regularly. Pain diagnoses were obtained using ICD-9 codes listed in medical encounter records for the 12 months prior the study assessment.

Body mass index (BMI) was evaluated as this has been shown to be associated with pain outcomes [32] and was obtained from medical records within six months prior to the assessment date and computed by dividing weight in kilograms by height in meters squared. Participants provided an estimate of current height and weight to their providers, which were recorded in their medical record. Although appraisal of height and weight is not precise, this method of computing BMI correlates highly ($r > 0.90$) with operationally measured BMI [33].

Statistical Analyses

Descriptive statistics were calculated for each variable of interest. APRI scores were log-transformed due to non-normative distributions. Correlation coefficients were developed to examine the associations among variables of interest. Hierarchical multiple regression analyses were conducted to evaluate variables putatively associated with pain outcomes. One regression was conducted for pain intensity (NRS score) and a second for functioning (Bodily Pain subscale from SF-36). In these analyses, demographic variables (age and BMI) were entered in step 1, disease and treatment-related variables (viral load, APRI, prescribed an opioid medication) were entered in step 2, and psychological variables (severity of depressed mood and substance dependence severity) were entered in step 3. Opioid prescription status was a dichotomous variable and all other variables were continuous. Analyses were conducted using SPSS.

Results

Sixty-three HCV patients from the parent study met the study inclusion/exclusion criteria; however, 14 were excluded because they did not complete measures needed for this study, leaving a sample of 49 for subsequent analyses. Table 1 provides a summary of demographic characteristics of patients included. The mean age of participants was 53.7 years (SD = 5.0). A majority of participants were male (85.7%) and reported Caucasian race (91.8%). The average number of years of education was 13.6 (SD = 1.4). Over half of participants were separated or divorced (55.1%) and 32.7% reported being married/partnered. Regarding occupation, 40.8% were unemployed due to a disability, 36.7% were working, 14.3% were unemployed, and 8.2% were retired. HCV patients who were included (n=49) did not differ from those excluded (n=14) in terms of age, gender, or other demographic characteristics.

All participants recruited for this study were required to have at least 90 days remission from a substance use disorder (SUD). For those with prior SUDs, primary drugs of choice included alcohol (14/49, 28.6%), heroin (5/49, 10.2%), marijuana (4/49, 8.2%), methamphetamines (4/49, 8.2%), or cocaine (3/49, 6.1%). Nineteen participants (38.8%) did not meet criteria for a past SUD. The average score on the severity of dependence scale was 6.6 (SD=3.3). Participants with a history of a SUD averaged 8.6 years (SD=7.9) of remission.

The mean viral load was HCV RNA ($\log_{10}$ IU/ml) = 6.27 (SD=0.83). The mean APRI value was 0.5 (SD=0.2). Within the total sample, 22 of 49 subjects had HCV genotypes available in

their records (15 with genotype 1, five with genotype 2, one with genotype 3, and one with genotype 4). Seven of 49 participants had liver biopsy results available in their record; none of these subjects were assessed above stage 2 in terms of fibrosis or grade 2 in terms cirrhosis based on liver biopsy results. Of the 49 HCV participants, 33 (67.3%) had a current documented chronic pain diagnosis in their medical record. Specific disorders included neck or joint pain (49.0%), rheumatism, arthritis, or osteoarthritis (26.5%), back pain (24.5%), headache (8.2%), and neuropathy (6.1%). Fifteen of 49 participants (30.6%) were currently prescribed an opioid medication.

Also included in Table 1 are results from correlation analyses between demographic factors, disease variables, and pain scores. Results indicate that pain intensity correlated negatively with APRI and pain functioning, and correlated positively with depression severity (note that although the correlation with pain functioning is negative, the pain functioning measure is scored such that higher scores indicate better functioning and lower scores indicate poorer functioning). Pain functioning scores correlated positively with APRI and correlated negatively with BMI, depression severity, and pain intensity (all *p*-values < .05).

Table 2 displays results from the regression analyses. In the regression model predicting pain intensity, only Step 3 with the psychosocial variables included, was significant ($p = .002$) and accounted for 20.9% of the unique variance in pain intensity. The only independent predictor of pain intensity was depression severity ($\beta = .483$, $p < .001$).

In the multiple regression model predicting pain functioning, only Step 3, with the psychosocial variables included, was significant ($p < .001$). This model accounted for 33.0% of the variance in pain functioning, above and beyond the effects of demographic and disease-related variables. Independent predictors of pain functioning were BMI ($\beta = -.317$, $p = .005$) and severity of depressed mood ($\beta = -.606$, $p < .001$).

Discussion

This preliminary study examined predictors of pain intensity and pain functioning in HCV patients. The findings support the biopsychosocial model and, in particular, indicate that depression severity is associated with pain outcomes in this clinical population. In a regression model examining variables associated with pain intensity, after controlling for demographic characteristics, opioid prescription status, and HCV disease-related variables, psychosocial factors accounted for a significant portion of the variance (20.9%) in pain intensity. Depression severity was the only variable significantly associated with pain intensity. Further, psychosocial factors accounted for significant variance (33.0%) in pain functioning. Severity of depressed mood and BMI were the only significant predictors of pain functioning. In both regression analyses, severity of depressed mood was the most significant independent predictor of pain intensity and pain functioning, and correlations between these variables and depression severity were moderate to large. Our results further indicate that increasing body mass index is associated with poorer pain functioning, an observation that is supported in the literature [23;32], though this has not previously been studied in HCV patients.

Our findings are consistent with prior studies showing that pain conditions are common in HCV patients [8,9], as 67.3% of HCV patients had a chronic pain diagnosis documented in their medical record. This rate is markedly higher than the 35% rate reported in general primary care samples [34], as well as the nearly 50% rate that may be evident in primary care samples of veterans [35]. Our study additionally extends the literature by directly examining variables putatively associated with pain in HCV patients (*e.g.*, specific demographic, disease-related and psychological variables), an area with limited empirical data. Consistent with research establishing a significant relationship between chronic pain and depression [36,37], we found

that depressive symptoms were the most significant predictor of pain intensity and functioning in HCV patients. This finding is in line with numerous prior studies documenting high comorbidity between chronic pain and depression [38]. However, it is not clear whether chronic pain conditions precede depression or vice versa. There are data suggesting that chronic pain is more likely to lead to depression [39], but in the present study with HCV patients, there may be an underlying feature that contributes to both increasing pain and worsening mood.

Prior research also suggests that psychosocial factors and depression predict fatigue in HCV patients [40]. In a stepwise multiple regression analysis with 94 HCV patients, the strongest predictors of fatigue were poor social functioning, poor physical functioning, depression, and female gender, accounting for 68% of the variance in fatigue [40]. In the parent study [24], HCV patients had significant cognitive deficits, even after controlling for pain, depression, and SUD history; however, both pain and severity of depressed mood significantly correlated with cognitive performance. Taken together, these findings suggest that HCV is associated with a constellation of symptoms, including pain, fatigue, depressed mood, and cognitive impairment, that these symptoms are inter-related, and that there may be common underlying mechanisms contributing to their development.

In addition to demographic and psychological variables, the roles of viral load and liver disease severity on pain outcomes were investigated. We found a negative correlation between liver disease severity and pain intensity and pain functioning. As severity of liver disease increased, patients reported lower pain intensity and better pain functioning. This finding is consistent with a recent study that analyzed the association between the severity of histological liver inflammation and the presence of joint pain in HCV patients. The authors did not identify disease or medication-related variables that predicted joint pain in HCV patients [41].

There exist several limitations to this study. First, our sample size was small, limiting our power to detect significant results. Additionally, the present study is a secondary data analysis, and the original study design was not focused on assessment of pain intensity or pain functioning [24]. Our study used the APRI as a measure of disease severity, which has been validated in HCV patients [25,26] but has limited sensitivity and specificity for values of 0.5 [42] and is a less reliable estimate of liver disease severity than liver biopsies or measures of portal vein hypertension, which were beyond the resources of this study to obtain. In addition, laboratory findings were collected from patient medical records and we cannot rule out the possibility that participants may have used substances prior to their laboratory tests, which may have impacted the reliability of the APRI scores. However, all participants in this reported remission from an alcohol or SUD for at least 90 days, decreasing the likelihood that participants would have been using alcohol or illicit substance prior to clinical care visits. This study was conducted exclusively with veterans, and results may not generalize to other clinical populations. Scores of pain intensity in this sample were modest compared with other chronic conditions considered painful. However, these ratings were provided by the entire study population, not all of whom had a chronic pain diagnosis (67.3% had a chronic painful condition). Finally, given the cross-sectional nature of this study, the finding of a relationship between biological and psychological factors with self-reported pain cannot be considered causal. A prospective, longitudinal design is required to understand the relationships between these variables.

In summary, the results of this preliminary study indicate that certain factors, particularly severity of depressed mood, are robust predictors of both pain intensity and pain functioning in HCV patients. The biopsychosocial model, which posits that the expression of pain is impacted by biological, psychological, and social factors, is the most common and empirically-supported theory of pain [37]; however, this model has not been tested in HCV patients. Given the high rates of pain disorders in HCV populations, additional studies are warranted. Future

studies should account for the limitations of the present study and include a broader range of potential pain correlates and social factors, as well as investigation of immune factors to assess the extent to which these contribute to the expression of pain in HCV patients.

Acknowledgments

This study was supported in part by a VA Career Development Award and Northwest Health Foundation grant awarded to Dr. Huckans. Dr. Morasco was supported by award K23DA023467 from the National Institute on Drug Abuse. The content of this manuscript is the responsibility of the authors and does not necessarily represent the official views of the Department of Veterans Affairs or the National Institute on Drug Abuse.

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Table 1

Demographic Characteristics and Correlations between Psychosocial Variables and Pain Intensity and Pain Functioning (n=49).

Variable	Mean	Standard Deviation	Correlation with Pain Intensity	Correlation with Pain Functioning
Age	53.7	5.0	−.113	.006
Body Mass Index	38.7	33.1	−.203	−.486*
HCV Viral Load	6.3	0.8	−.170	.151
APRI	0.5	0.2	−.372*	.314*
Depression Severity	13.6	12.2	.543**	−.623**
Substance Dependence Severity	6.6	3.3	.079	−.022
Pain Intensity	3.7	2.5	1.0	−.63**
Pain Functioning	48.9	29.7	−.63**	1.0

Note. HCV = Hepatitis C Virus. Depression severity was assessed with the Beck Depression Inventory – Second Edition. Substance Dependence Severity was assessed with the Severity of Dependence Scale. Pain intensity was measured with a numeric rating scale from 0 – 10, where 0 = “no pain” and 10 = “extremely severe pain.” Pain functioning was assessed with the Bodily Pain subscale of the SF-36; higher scores indicate better functioning.

* $p < 0.05$, two-tailed.

** $p < 0.01$, two-tailed.

Table 2

Regression Analyses Examining Predictors of Pain Intensity and Pain Functioning (n=49).

	R^2	R^2 Change	F Change	β	P-Value
Pain Intensity					
Step 1. Demographic Variables	.035	.035	0.83		.443
Age				−.130	
Body Mass Index				−.135	
Step 2. Disease and Treatment-Related Variables	.181	.147	2.57		.067
Viral Load				−.200	
APRI				−.143	
Prescribed Opioid Medication				.091	
Step 3. Psychosocial Variables	.390	.209	7.02		.002
Depression Severity				.483**	
Substance Dependence Severity				−.033	
Pain Functioning					
Step 1. Demographic Variables	.072	.072	1.77		.181
Age				−.052	
Body Mass Index				−.317*	
Step 2. Disease and Treatment-Related Variables	.199	.127	2.27		.093
Viral Load				.078	
APRI				.111	
Prescribed Opioid Medication				−.108	
Step 3. Psychosocial Variables	.528	.330	14.33		< .001
Depression Severity				−.606**	
Substance Dependence Severity				.058	

Note. Pain intensity was measured with a numeric rating scale from 0 – 10, where 0 = “no pain” and 10 = “extremely severe pain.” Pain functioning was assessed with the Bodily Pain subscale of the SF-36; higher scores indicate better functioning. Depression severity was assessed with the Beck Depression Inventory – Second Edition. Substance Dependence Severity was assessed with the Severity of Dependence Scale.

* = $p < 0.01$.

** $p < 0.001$.