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A closer look at pain and hepatitis C: Preliminary data from a veteran population

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Abstract—An association between the hepatitis C virus (HCV) and various pain diagnoses, including arthritis, fibromyalgia, and peripheral neuropathy, has been reported. In this article, we review the literature on the relationship between HCV and pain, highlighting current knowledge as well as methodological issues that exist in many studies. We also present preliminary findings from a survey conducted at two Department of Veterans Affairs facilities to assess the scope and impact of pain on functioning in veterans with HCV. Our results indicate that pain is very prevalent within this population and that HCV-positive veterans who experience persistent pain have significant depressive symptoms and engage in high-risk behaviors, such as cigarette smoking and alcohol use. Finally, we draw upon our review and preliminary results to propose areas of future rehabilitative research and to address the implications for clinicians working with patients with comorbid HCV and pain.

Key words: arthritis, depression, fibromyalgia, hepatitis C, pain, peripheral nervous system diseases, pilot projects, quality of life, rehabilitation, substance abuse.

INTRODUCTION

Chronic hepatitis C, a liver disease caused by infection with the hepatitis C virus (HCV), has been identified as a major public health problem, a leading cause of cirrhosis and hepatocellular carcinoma, and the predominant cause of death from liver disease [1–4]. In 2000, the U.S. Surgeon General declared HCV to be a "silent epidemic," affecting 2.7 million people, or 1.8 percent of the U.S. population [3, http://www.hepnet.com/hepc/news072800.html]. Of note, the prevalence of HCV among veterans who use Veterans Health Administration (VHA) facilities is more than double that of the general population, affecting approximately 5.4 to 6.6 percent of American veterans [5–6]. The optimal treatment for HCV involves a rigorous 6-month to 1-year regimen of pegylated interferon (IFN) and ribavirin. Unfortunately, this treatment is expensive, often poorly tolerated, and only successful in treating 54 to 61 percent of patients [7–9]. The financial impact of this disease is significant; HCV costs in the United States are an estimated $5 billion and are anticipated to increase to more than $10 billion in the next 10 to 20 years [10–11].

Abbreviations: anti-CCP = anticyclic citrullinated peptide, AUDIT = Alcohol Use Disorders Identification Test, CBT = cognitive-behavioral therapy, CES-D = Center for Epidemiologic Studies Depression Scale, FM = fibromyalgia, HCV = hepatitis C virus, IFN = interferon, MC = mixed cryoglobulinemia, MPQ-SF = McGill Pain Questionnaire-Short Form, NRS = Numeric Rating Scale, NSAID = nonsteroidal anti-inflammatory drug, PN = peripheral neuropathy, RA = rheumatoid arthritis, SD = standard deviation, VA = Department of Veterans Affairs, VHA = Veterans Health Administration, WHYMPI = West Haven-Yale Multidimensional Pain Inventory.

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Symptoms of HCV include fatigue, weakness, general malaise, abdominal pain, muscle and joint aches, and loss of appetite [2]. Infection with HCV is also associated with a host of disabling extrahepatic immunological manifestations, psychiatric disorders, and changes in self-perception (e.g., internalized shame, social rejection) that have pronounced implications for quality of life, independence, psychological functioning, and mortality, particularly as the liver disease progresses [12–14]. Functional health impairments in patients with HCV are comparable to or worse than impairments in patients with either type 2 diabetes or hypertension [15]. IFN treatment causes numerous psychiatric (e.g., depression, anxiety) and physical side effects (e.g., pain, fatigue) that exacerbate an already diminished quality of life in patients with HCV [9]. Opportunities for rehabilitative clinical interventions are plentiful in this population, whether or not patients are on IFN treatment.

Both researchers and clinicians have identified pain as a frequent complaint among patients with HCV, regardless of whether or not they are taking IFN treatment. However, to date, the literature on the co-occurrence of HCV and pain is limited, and a comprehensive overview of this area is lacking. We know from normative health-care-seeking populations that persistent pain is among the most commonly reported health problems in primary care, with an estimated prevalence of 22 percent [16]. Recent research suggests that pain may be an even greater problem within VHA primary care clinics; as many as half of veterans within these settings are estimated to report pain [17]. Persistent pain is a significant financial burden [18] and is associated with various psychosocial issues, including anxiety, depression, poor self-reported health status, and a notable interference in activities of daily living [16,19].

HCV and pain are chronic conditions that are extremely prevalent within the VHA, have implications for patients' quality of life and physical functioning, and are difficult and expensive to treat [10,18]. Because of the scope of these two conditions, the VHA has established separate strategies to address HCV and chronic pain. The National VHA Hepatitis C Program has been established to identify, test, and treat veterans with HCV, emphasizing clinical care and prevention through counseling, research, and education. The VHA National Pain Management Strategy is an initiative to develop a system-wide approach to pain reduction for all veterans [20]. While researchers have begun to examine the prevalence of and the clinical and biological relationships between HCV and pain, more focused work is needed to address the co-occurrence of and appropriate treatment for HCV and pain, as well as to examine whether their co-occurrence results in an additive decrease in functioning. In this article, we will first review available literature on the relationship between HCV and pain. Second, we will present preliminary findings from a survey that we conducted at two Department of Veterans Affairs (VA) hospitals to examine the scope and impact of pain in veterans with HCV. Finally, we will highlight areas for future research and discuss relevant issues for practitioners, including rehabilitative approaches to the sequelae of comorbid HCV and pain.

HEPATITIS C VIRUS AND PAIN

An association between HCV and musculoskeletal pain, including morning stiffness, joint pain, muscle pain, and all-over pain, has been described [21]. Prevalence rates for general musculoskeletal pain within HCV clinic populations are around 50 to 81 percent [21–22]. Arthralgias are also common in patients with chronic HCV infection, with prevalence rates ranging from 9 to 23 percent [23–26]. In the following sections, we will outline the available research on the co-occurrence of HCV and the pain conditions most often associated with HCV, including arthritis, fibromyalgia (FM), and neuropathy.

First, however, we must mention mixed cryoglobulinemia (MC), an extrahepatic condition that is frequently addressed in conjunction with HCV and pain. MC is caused by the presence of abnormal proteins (cryoglobulins) in the bloodstream and is characterized by purpura, weakness, and arthralgias, all of which occur primarily in the lower limbs [27–29]. Of the extrahepatic manifestations, MC has been demonstrated to have the strongest association with HCV [28]. Although not all HCV patients develop MC, HCV infection is indicated in up to 96 percent of MC cases [29]. Symptomatic MC has been observed in up to 21 percent of patients with HCV, and the percentage of HCV patients with detectable cryoglobulins may be as high as 54 percent [29]. Treatment with IFN combined with ribavirin has proven to be the most effective option for decreasing MC symptoms in patients with HCV [28–29]. While the relationship between MC, HCV, and pain is not well understood, MC is believed to be strongly associated with some types of HCV-related

pain. Thus, where appropriate, the association between MC and HCV-related pain will be discussed.

Hepatitis C Virus and Arthritis

Researchers have focused on three types of arthritis when studying the relation between HCV and arthritis. The first type is a "true" rheumatoid arthritis (RA) that fulfills the American College of Rheumatology classification criteria [30]. Patients with true RA may be more likely to contract HCV because of a depressed immune system (as a consequence of both RA and immunosuppressive treatment) or have more frequent hospitalizations and require invasive procedures that place them at risk for HCV infection [31–32]. The second type (referred to here as HCV-associated arthritis) is a polyarthritis that typically affects small joints and resembles true RA. However, it is milder than a true RA because it is usually nondeforming and has a fluctuating course. Some authors described HCV-associated arthritis as nonerosive, but others reported erosions in 20 to 30 percent of patients with HCV infection and polyarthritis [33]. Physicians often find it difficult to make a differential diagnosis between true RA and an HCV-associated arthritis that mimics RA. However, anti-cyclic citrullinated peptide (anti-CCP) antibodies are very rarely found in HCV patients with rheumatological manifestations and may be reliable serological markers for distinguishing these from patients with true RA [34]. While the exact pathogenesis of HCV-associated arthritis is unknown, it is hypothesized that pain may develop due to a compromised immune system and exposure to environmental factors, such as viral or bacterial infections [31]. The third type of HCV-associated arthritis is cryoglobulinemia-induced and typically affects the large joints of the lower limbs. Cryoglobulinemia-induced arthritis is more likely to be intermittent and benign [33,35–36].

Prevalence rates of HCV-associated arthritis vary in the literature due to small samples, participant selection biases, inconsistencies in arthritis definitions, and varying geographical differences in HCV rates. In general, most studies report a 4 to 12 percent prevalence rate of HCV-associated arthritis [24–25,37]. The association between true RA and HCV, however, remains equivocal. While some studies have found a 5 to 8 percent prevalence of HCV infection in patients with true RA [33,38], other studies report no increased prevalence of HCV, which argues against a role for HCV in the etiology of true RA [26,31–32,39].

The relationship between IFN and arthritis pain is unclear, particularly since most published reports are case studies or have very small samples. IFN has been shown to improve arthritic symptoms in HCV-associated arthritis and cryoglobulinemia-induced arthritis [37,40] but has also been shown to induce autoimmune symptoms, including new cases of polyarthritis and myalgias [36,41–43]. The latter may be particularly true for patients with true RA and a concomitant HCV infection. Additionally, as discussed previously, IFN is known to have many psychiatric and physical side effects that can cause distress and exacerbate preexisting or co-occurring pain symptoms [44].

Firm conclusions regarding the optimal treatment for arthritic pain in patients with HCV are unavailable due to small sample studies. However, treatment focusing on relieving the pain associated with joint inflammation without worsening liver damage caused by HCV has been recommended [45]. Medical treatment may involve the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in patients who do not have a cirrhotic process, cyclooxygenase inhibitors, corticosteroids, disease-modifying antirheumatic drugs, and antiviral therapies [45–46]. Medications such as methotrexate or immunosuppressants have not been recommended, at least as an initial effort, given their toxic effect on the liver [47]. Large-scale controlled treatment trials are needed to establish the gold standard for treating HCV-positive arthritic patients.

Hepatitis C Virus and Peripheral Neuropathy

Peripheral neuropathy (PN), a diagnosis resulting from damaged or diseased peripheral nerves, is associated with chronic HCV infection. PN that occurs with HCV is characterized by axonal damage, usually related to MC and vasculitis, and often presents as a sensory neuropathy of the lower limbs. Sensory or motor PN has been found in up to 9 percent of patients chronically infected with HCV [23–24]. In HCV patients who have MC, prevalence rates of PN are estimated to range from 30 to 78 percent [48–49].

Research suggests that the presence of MC in patients with HCV may influence the type and severity of neuropathy. For example, a recent study found that patients with MC were more likely to experience moderate-to-severe polyneuropathy, while those without MC were more likely to experience mild-to-moderate mononeuropathy or multiple neuropathy [49]. These data suggest that MC may have a detrimental additive effect on the development of PN in the presence of HCV.

The prevalence of PN in patients with HCV (without an MC diagnosis) suggests a role for HCV itself in the

pathogenesis of nerve damage [23,27,50]. Additionally, other factors beyond the presence or absence of MC may mediate the relationship between PN and HCV. For example, some studies suggest symptomatic neuropathy may be more prevalent in certain HCV genotypes [51]. Other evidence suggests that factors such as age and duration of HCV infection may mediate the relationship between MC and PN [48]. Further research should examine the relationships among HCV, factors such as age or duration of HCV infection, and presence of PN, since currently available studies often have methodological flaws such as small and biased sample sizes and limited inclusion of both clinical and biological findings.

Currently, no guidelines are available for the treatment of HCV-associated PN. Some findings indicate that PN improves during treatment with IFN [50,52–53]; in other studies, however, IFN has caused worsening of PN in patients with HCV and MC [54]. PN has even been suggested as a possible side effect of IFN treatment [55]. A recent review of treatment options for extrahepatic manifestations of chronic HCV suggests corticosteroids and/or IFN monotherapy as the best initial treatment option for patients with slight to moderate PN. In nonresponsive patients, combining antiviral therapy or intravenous immunoglobulins has been recommended, while plasmapheresis should be reserved for severe or refractory cases [46]. Clearly, more research is needed to inform treatment options for patients experiencing chronic HCV and PN.

Hepatitis C Virus and Fibromyalgia

FM is a common clinical syndrome characterized by widespread musculoskeletal pain and stiffness that are accompanied by tenderness at specific anatomical sites known as tender points [56]. Symptoms associated with this condition include fatigue, sleep disturbances, paresthesias, cognitive difficulties, and irritable bowel syndrome. Little is known about the pathogenesis of FM, though infections such as HCV have been implicated.

Overall, studies estimate the prevalence of FM in patients with HCV at 10.0 to 18.9 percent [22,57–59]. These prevalence rates are higher than rates of FM in patients with cirrhosis (not due to HCV) and healthy controls [57–58]. While these studies point to an association between FM and chronic HCV, at least one recent study challenges this association. This study prospectively compared the prevalence of HCV infection in patients with FM with the prevalence of HCV in a general community population [60]. Narvaez and colleagues found that the prevalence of HCV infection in patients with FM was not significantly higher than the prevalence of HCV in the general population, which suggests that the relationship between HCV and FM may be explained by chance rather than pathogenesis [60].

To date, two pathogenetic mechanisms for explaining how HCV infection might trigger FM have been proposed. The first suggests that the viral infection and subsequent inflammation due to HCV can initiate a chain of biochemical events that lead to FM development [61]. Given evidence to date, however, whether FM, as an extrahepatic manifestation, is mediated by immune mechanisms or hepatic damage is unclear. For example, some studies have demonstrated a higher prevalence rate of FM in patients with advanced HCV liver disease [21,57]. Other studies have shown no relationship between FM symptoms and severity of liver disease, route of infection, or treatment status [21]. Additionally, codiagnosis of FM and HCV has been shown to occur even without associated alterations in liver enzymes [22].

A second hypothesis suggests that the stress and anxiety of chronic infectious disease management can trigger FM. While stress has been implicated as an important component of FM pathology, it is unclear whether the stress of having HCV could alone result in FM. In fact, one study found that more than half of the participants diagnosed with FM did not know that they had HCV [22]. This finding suggests that the stress hypothesis, by itself, is unlikely.

Treatment recommendations for FM and HCV are limited. Very little is known about the relationship between IFN and FM or whether successful treatment of HCV improves FM symptoms. At least one study suggests that IFN therapy may trigger FM symptoms in some patients [62]. Guidelines for treatment of FM in non-HCV populations suggest the use of antidepressant medications along with nonpharmacological treatments such as exercise, cognitive-behavioral therapy (CBT), and patient education [63]. More research is needed to develop treatment recommendations that address the needs of patients with HCV and FM.

Hepatitis C Virus and Pain within Department of Veterans Affairs Liver Clinics: Preliminary Findings

In the following sections, we report preliminary results of a self-report survey study that we conducted in two VA hospitals to examine the relationship between HCV and pain symptoms.

METHODS

Participants

Participants were 38 veterans recruited from the Liver Clinics of the Edward Hines Jr VA Hospital (Hines, Illinois) and the VA Boston Healthcare System (Boston, Massachusetts). Eighty-four percent were male and seventy-nine percent were between 41 and 60 years of age. Self-reported racial/ethnic group representations were 68.4 percent Caucasian, 26.3 percent African American, and 5.3 percent Hispanic. Approximately 39.5 percent of the sample was married or in a committed relationship; 31.7 percent were divorced, separated, or widowed; and 26.3 percent had never been married. Five cases were dropped due to missing data on items relevant to the present analyses, leaving a sample size of 33. When a case had data missing on no more than one item relevant to current analyses, the missing observation was substituted with the average score for that participant on that measure.

Measures

Demographic Information

Participants provided information on various demographics, including sex, decade of birth, race/ethnicity, relationship status, and history of HCV symptoms and treatment.

Pain Intensity

Patients rated their pain intensity using the Numeric Rating Scale (NRS) [64], an 11-point numeric rating scale (0 = no pain, 10 = worst pain imaginable). Participants were asked to rate their pain intensity at its least, average, and worst intensities.

Pain-Related Disability

Pain-related disability was measured with items from the Interference subscale of the West Haven-Yale Multidimensional Pain Inventory (WHYMPI) [65]. This subscale measures perceived interference of pain in vocational, social/recreational, and family/marital functioning and includes nine items measured on a 7-point Likert scale (0 = no change, 6 = extreme change). This subscale has been shown to have adequate reliability and validity and to be responsive to therapeutic change. Cronbach α was 0.95 in this study.

Sensory Pain

The McGill Pain Questionnaire-Short Form (MPQ-SF) [66] was developed for use in time-limited research settings. As adapted for this survey, it consists of 15 representative words from the Sensory and Affective categories of the standard MPQ. The 15 descriptors used in the MPQ-SF were selected based on their frequency of endorsement by patients with various acute, intermittent, and chronic pains. Participants were asked to circle all words that described the quality of their most troubling pain condition. The MPQ-SF correlates highly with the major Pain Rating Indexes of the MPQ [66–67], and concurrent validity of the MPQ-SF with the MPQ is high [67]. Cronbach α for this study was 0.83.

Alcohol Use

Alcohol use was assessed with the Hazardous Alcohol Use domain of the Alcohol Use Disorders Identification Test (AUDIT) [68]. This subscale measures hazardous alcohol use and alcohol consumption and is composed of three items that measure frequency and quantity of alcohol use and binge drinking on a 5-point scale. It has been shown to be a practical and valid screening test for alcohol consumption [69]. Cronbach α for this study was 0.89.

Depression

Depression was assessed with the Iowa form of the Center for Epidemiologic Studies Depression Scale (CES-D) [70]. This 11-item measure assesses depressive symptomatology within the past month on a 3-point numeric scale (1 = rarely or never, 3 = much or most of the time) in response to items such as “I felt that people disliked me” and “I felt that everything I did was an effort.” Reliability of the Iowa form has been found to be high (Cronbach $\alpha = 0.81$) [70]; for this study, Cronbach α was 0.82.

Procedures

Veterans who presented for appointments in the Liver Clinics at the VA Boston Healthcare System (December 2005 through April 2006) and the Edward Hines Jr Hines VA Hospital (March 2005 through April 2006) were asked by administrative and clinical staff whether they were interested in completing the Liver Disease and Pain questionnaire. Questionnaires were also available in the waiting area for veterans to complete while waiting for their appointments. Each questionnaire

was accompanied by a cover letter that explained the purpose of the survey and the anonymity of results. So that participants did not complete the survey multiple times, the cover letter indicated in bold font that participants should not fill out the questionnaire more than once. Study procedures were approved by the appropriate institutional review boards, and data were collected in compliance with the standards of these boards.

RESULTS

Results are presented as mean ± standard deviation (SD) unless otherwise noted. Of the 33 participants, 29 (76.3%) were diagnosed with HCV. The four participants who were not diagnosed with HCV were excluded from further analyses. The resulting sample reported many symptoms of HCV, including fatigue, depression, and trouble sleeping (**Table 1**). Thirty-two percent of participants were taking combination IFN/ribavirin treatment for HCV at the time they completed the survey. Participants reported that they had been diagnosed with HCV an average of 4 years ago. Data were not available to indicate when the disease was contracted.

Pain symptoms were highly prevalent in this population of veterans. A majority (82.7%) of participants diagnosed with HCV also reported pain symptoms. Approximately 23.1 percent of participants reported having been previously diagnosed with arthritis, although no participants reported a prior diagnosis of FM. The duration of pain symptoms varied; approximately 30 percent of the sample reported a duration of 5 years or more, 35 percent reported a duration of 1 to 5 years, and 35 percent reported a duration of 1 year or less. Participants were asked to report on a 5-point scale (0 = not at all, 5 = completely) whether their pain symptoms had worsened since being diagnosed with HCV; participants' responses indicated that they felt their pain had "somewhat" worsened since their diagnosis (mean = 2.7 ± 1.3). Using the same scale, participants were asked to indicate whether they thought their pain was related to their HCV; participants reported that they believed their pain was "somewhat" related to their HCV (mean = 2.7 ± 1.4).

Participants were most likely to report pain in their shoulder, arm, or hand; hip, leg, or foot; or lower back. Frequency of pain sites in this population can be found in **Table 2**. On the NRS, participants reported a mean lowest pain intensity of 4.2 ± 3.1, a mean average pain intensity of 5.4 ± 2.4, and a mean worst pain intensity of 7.9 ± 2.0, indicating that, even on days when participants experienced the least amount of pain, they still experienced mild-to-moderate pain levels. Participants' mean score on the Interference scale of the WHYMPI was 3.4 ± 1.8, which indicates moderate interference. However, this is below the mean level of interference found in a normative chronic pain population (mean = 4.3 ± 1.2) [64,70]. On the MPQ-SF, participants were most likely to describe their pain as "aching" (70.8%), "sharp" (41.7%), "throbbing" (37.5%), and "tiring/exhausting" (37.5%). Participants endorsed an average of 3 pain descriptors on the MPQ-SF Sensory subscale and an average of 0.72 pain descriptors on the Affective subscale.

Although we were unable to conduct formal significance testing on these preliminary results because of our small sample size, we noted that participants with both HCV and pain (n = 24) were more likely to endorse HCV-associated symptoms, including muscle and joint aches, fatigue, depression, loss of appetite, trouble sleeping, pain in abdomen, and general malaise, as compared with participants with an HCV diagnosis but no pain

Table 1.
Hepatitis C virus symptoms endorsed by 29 survey respondents.

Symptom	% Endorsed	*n*
Fatigue	58.6	17
Depression	55.2	16
Trouble Sleeping	55.2	16
Muscle/Joint Aches	51.7	15
General Malaise	44.8	13
Loss of Appetite	37.9	11
Abdominal Pain	31.0	9

Table 2.
Frequency of pain sites endorsed by 24 survey respondents with hepatitis C virus and pain.

Pain Site	% Endorsed	*n*
Shoulder, Arm, or Hand	70.8	17
Hip, Leg, or Foot	58.3	14
Low Back	54.2	13
Head	33.3	8
Abdomen or Pelvis	25.0	6
Neck	16.7	4
Upper Back	12.5	3
Chest	8.3	2
Genitalia or Rectum	8.3	2
Face	4.2	1

symptoms. Of note, even with the small sample size, persons with both HCV and pain were significantly more likely to experience muscle and joint aches than those with only HCV diagnoses ($\chi^2(1) = 6.5$, $p < 0.02$).

In addition to pain symptoms, we were interested in the impact of HCV and pain on smoking status and alcohol use. Of participants with both HCV and pain, 62 percent reported that they currently smoked and 45.8 percent reported that they had consumed alcohol in the past year. The mean score for patients with HCV and pain on the AUDIT subscale indicated risky or hazardous drinking (mean = 4.5 ± 4.3). Interestingly, although we did not conduct formal analyses, 45.8 percent of those with HCV and pain had consumed alcohol within the past year as compared with 25 percent of those with HCV but no pain symptoms.

Participants also responded to questions about depressive symptoms. To compare scores on the CES-D (Iowa form) with the original CES-D, we used recommended conversion procedures [69]. Results indicated a mean converted score of 19.6 ± 8.9, which indicates significant depressive symptoms (the clinical cutoff score is 16). A prior diagnosis of depression was reported by 58 percent of participants, while a previous diagnosis of anxiety was reported by 30.8 percent. Additionally, 28 percent of participants with HCV and pain reported that they did not have anyone to help them with daily tasks and 25 percent did not feel they had anyone they could rely on for emotional support.

DISCUSSION

Preliminary results from this study demonstrate that a large majority of our sample (82.7%) reported pain symptoms, which indicates that pain is a significant problem in patients diagnosed with HCV. Even on their "good" pain days, patients with HCV and pain symptoms reported pain intensity levels that met VHA criteria for comprehensive pain assessment and intervention [71]. Patients with HCV reported that their pain symptoms interfered with their daily activities and relationships. Our data also suggest that, across the board, patients with both HCV and pain symptoms were more likely to endorse HCV-associated symptoms than patients who did not experience any pain. Together, these preliminary data strongly suggest that pain is highly prevalent and significantly affects patients' functioning and experience of HCV.

We also sought to determine the prevalence of cigarette smoking, alcohol use, and depressive symptoms in those with comorbid HCV and pain. To our knowledge, this is the first study to examine the relationship between these variables and an HCV-pain comorbidity. Smoking was more prevalent in this sample than a normative comparison sample of veterans (45.8% vs 33.9%, respectively) [72]. This finding is particularly important because recent studies suggest that cigarette smoking aggravates liver functioning, increases the risk of liver fibrosis, and decreases the efficacy of IFN treatment [73–75]. Alcohol use was also very prevalent in our sample and at an intensity that is described as "risky or hazardous" and in need of further assessment. This high rate of alcohol use is concerning, given research documenting that alcohol use is associated with more severe liver injury, increased risk of cirrhosis and hepatocellular carcinoma, and decreased efficacy of IFN treatment [76–77]. Although no formal significance testing was conducted, we found that participants with HCV and pain were more likely to have consumed alcohol within the past year than HCV positive patients with no pain symptoms. Finally, participants in this sample reported problematic depressive symptoms. These findings are also significant, given the detrimental impact of mood on one's ability to cope effectively with the intricacies of managing chronic medical conditions, such as HCV and pain.

Our results should be interpreted with caution given the small sample size and preliminary nature of our analyses. Additionally, these results cannot be generalized to a nonveteran population. This project is ongoing, however, and we will continue to collect data that will allow us to address some of these shortcomings in future analyses. Thus far, results indicate that pain is common in patients with HCV and that the impact of pain and HCV on functioning is significant. However, this area is rich for future study. In the next section, we propose further areas to be addressed both in research and practice in order to clarify our understanding of this comorbidity, provide beneficial and quality rehabilitative treatment, and attend to the psychosocial functioning of patients with both HCV and pain.

Future Research

The literature on HCV and pain is riddled with case studies, small and unrepresentative samples, and methodological problems (e.g., poorly defined pain diagnoses, reliance on cross-sectional design). Consequently, the

biological relationships between HCV and different pain conditions remain unclear [78]. We recommend that basic science research focus on large-scale, methodologically sound, prospective studies that can more clearly identify the relationship between various pain conditions and HCV. These studies should focus on both the biological mechanisms and the clinical presentations of HCV and pain assessed by appropriate laboratory and diagnostic evaluation. In addition, little is known about those factors that may mediate the relationship between HCV and pain. Other conditions that frequently co-occur with HCV may contribute to the development of pain syndromes. For example, patients with HCV frequently have a history of substance abuse. Substance abuse may influence the relationship between HCV and pain because it has been directly implicated in the development of some pain conditions and increases the risk of trauma (e.g., falls, motor vehicle accidents) that could affect pain. The potential impact of substance abuse and other conditions on this population of patients should be carefully examined. Additionally, well-executed studies are needed to determine which medical treatments optimally reduce pain symptoms and/or treat HCV without interfering with liver health or exacerbating pain [45–46]. Such studies will help providers choose treatment courses that maximize efficacy while minimizing detrimental effects on functioning. Because the majority of the research on HCV and pain has been conducted in European, Asian, and Middle Eastern countries, we recommend that these studies also be conducted with a North American population, since geographical differences exist in HCV prevalence rates and genotype compositions that could result in different clinical manifestations of pain. Replicating these studies with veterans is also essential because this population has increased prevalence rates of both HCV and pain [5–6,17].

Empirical research documenting the psychosocial factors relevant to patients living with both HCV and pain is sparse. Similarly, little is known about the efficacy of behavioral interventions to help HCV-positive patients cope with pain. As stated earlier, both HCV and pain can significantly compromise physical functioning, quality of life, social support, and psychiatric status; combined, they are likely to further exacerbate impairments in functioning. Our preliminary results indicate problematic smoking and alcohol use, as well as significant depressive symptoms. Future studies should further explore the effect of this comorbidity on various psychosocial variables—including quality of life and physical functioning—and explore the nonpharmacological pain treatments that have shown such promise in other chronic pain populations.

Clinical Implications

Results from studies on the relation between HCV and pain need to be widely disseminated to providers who work in pain and hepatology clinics. Provider education is essential for accurate and early diagnosis and optimal treatment of patients with this comorbidity. As a first step, we recommend that providers in pain clinics routinely review risk factors for contracting HCV with their patients and refer those with identified risk factors for testing [79–80]. Similarly, providers in hepatology clinics should regularly assess for pain symptoms and conduct or refer patients for a comprehensive pain assessment when a patient endorses unacceptable levels of pain. A careful history and physical examination, followed by laboratory tests and imaging studies (when necessary), can be important tools in evaluating any patient with pain. We recommend that providers in both pain and hepatology clinical settings receive training on querying patients about these conditions in a manner that does not stigmatize the patients, particularly when speaking about risk factors for HCV (e.g., including intravenous or intranasal drug use).

Management of pain symptoms and treatment of HCV are inherently more complicated in patients diagnosed with both conditions. Therefore, providers must take a multidisciplinary, collaborative approach when developing treatment plans for a patient with HCV and pain. Case reports have demonstrated that IFN treatment can induce pain symptoms, particularly in patients with preexisting pain [41,55,62]. Additionally, some of the medications ordinarily used for pain (e.g., NSAIDs) are contraindicated in patients with cirrhosis, since they can exacerbate impairments in liver functioning [46]. Patients should be informed about such risks and complications prior to making treatment decisions. If treatment with narcotic medication is warranted, providers should follow appropriate guidelines and take precautions to ensure that they reach adequate pain management while also considering the patient's safety and substance abuse history. (For a more comprehensive discussion, please see the VA guidelines on opioid therapy for chronic pain at <http://www.oqp.med.va.gov/>.) All of these factors point to the importance of close collaboration between providers

treating pain symptoms and providers treating HCV to ensure that patients receive the highest quality care.

In many facilities, mental health clinicians are routinely involved in the care of patients with HCV or chronic pain, providing assessments and treatment to help patients manage these chronic conditions and their sequelae. Psychological treatment is a cost-effective approach that increases adherence to medical interventions, enhances quality of life, and manages distress in patients with a variety of chronic conditions, including HCV and pain [81–82]. Our data suggest that mental health clinicians play an important role in the care of patients with HCV-pain comorbidity.

First, mental health providers can supplement the education provided to patients by their medical providers and help engage them in the appropriate care of their chronic medical conditions. Patient education programs are informative and help demystify medical issues, thereby increasing patients' self-confidence in their ability to adjust to the diseases and make informed treatment decisions. Patient education positively affects disability and psychological functioning and may result in improved treatment effects, increased self-management behaviors, improved quality of life, and reduced healthcare use [83–84]. Clinicians can provide patients with basic information on pain, HCV, liver functioning, the relationship between HCV and pain, and treatment options. Interestingly, only 50 percent of our participants with comorbid HCV and pain knew their HCV genotype, as compared with 80 percent of those with HCV and no pain symptoms. Because one's genotype has significant implications for treatment response and treatment regimen, we find it striking that half the sample of patients with HCV and pain were unaware of their genotype. Mental health providers can work with patients to identify gaps in their understanding, such as knowledge of genotype, and address particular patient concerns.

Second, it is well established that complex biopsychosocial interactions and diverse personal factors are associated with impaired function, emotional distress (e.g., depression, anxiety), and increased pain. Our results demonstrate that this population engages in unhealthy, high-risk behaviors (e.g., cigarette smoking, alcohol consumption) and experiences problematic depressive symptoms. Patients with HCV and pain would benefit from education as well as psychological treatment to help them abstain from unhealthy behaviors and to address mental health concerns. CBT can effectively teach skills such as behavioral goal setting, pleasant activity scheduling, problem solving, and relaxation and can address maladaptive pain- or HCV-related thought patterns (e.g., "I'm useless and ashamed of who I am."). Clinicians can also play an important role in helping their patients adjust to managing two chronic medical conditions and the associated changes in identity, relationships, work functioning, and quality of life. While the research on psychological interventions for HCV-related difficulties is in its infancy, one study demonstrated that CBT effectively decreased the dropout rate of patients undergoing IFN treatment for HCV [85]. In non-HCV populations, research suggests that these strategies are effective for decreasing pain and disease impact and for increasing self-efficacy and physical functioning in FM [63] and arthritis [86–87].

In addition to helping patients abstain from unhealthy behaviors, mental health providers can offer education on the importance of healthy behaviors that improve functioning. For example, exercise is a powerful tool that helps patients cope with pain symptoms and is an important treatment component for patients with HCV who are not experiencing decompensated cirrhosis [88]. Those diagnosed with HCV and pain may lead very sedentary lifestyles, since the pain symptoms, fatigue, and/or depression associated with HCV and pain may limit patients' motivation to incorporate activity into their daily lives. Light exercise, however, can reduce symptoms of HCV, side effects of IFN treatment, and pain symptoms while improving mood [88]. Furthermore, exercise has been demonstrated to improve arthritis, PN, and FM pain, as well as increase physical functioning [89–92].

CONCLUSIONS

In summary, our preliminary data indicate that pain is very prevalent in veterans diagnosed with HCV and that those with this comorbidity report significant factors that can impair quality of life and physical functioning, including depressive symptoms, alcohol use, and tobacco use. These initial data extend the available literature on HCV and arthritis, PN, and FM and have important clinical implications. In particular, we recommend provider education and close collaboration between medical practitioners who treat HCV and those who treat pain so that these two conditions are accurately identified and appropriately treated. This recommendation is highly consistent with the VHA's pain and HCV directives. Our findings also speak to the importance of involving mental

health clinicians in the treatment and rehabilitation of patients with HCV and pain symptoms. Mental health clinicians can supplement the education provided to this population by their medical providers and can be available to address unhealthy behaviors and emotional distress (e.g., depression). Future research is needed in this domain, including large-scale, methodologically sound studies that can evaluate the relationships between HCV and specific pain diagnoses, determine appropriate medical treatments for those with comorbid HCV and pain symptoms, and assess the impact of these diagnoses on a variety of psychosocial and quality of life variables.

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