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An investigation of the quantity and type of female veterans' responses to Hepatitis C treatment screening and acceptance

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AN INVESTIGATION OF THE QUANTITY AND TYPE OF FEMALE VETERANS' RESPONSES TO HEPATITIS C TREATMENT SCREENING AND ACCEPTANCE

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Dissertation Abstract

AN INVESTIGATION OF THE QUANTITY AND TYPE OF FEMALE VETERANS' RESPONSES TO HEPATITIS C TREATMENT SCREENING AND ACCEPTANCE

The hepatitis C virus (HCV) is an infection that affects 5 to 25% of veterans, three times higher than the general US population. HCV is linked to cirrhosis, liver cancer, and death. Women are now the fastest growing group of veterans. Prior studies of HCV screening and acceptance among US veterans included mostly males.

The purpose of the study was to evaluate whether there were gender differences in veterans' responses to HCV treatment screening and acceptance.

This study is a secondary analysis of 4,201 veterans (4,084 male and 117 female) from 24 VA Medical Centers between December 1999 and December 2000. The study population was older (50.3 years old, $\pm$ 7.6 years) and racially diverse. Female veterans were more educated and less likely to have a history of drug use or incarceration.

Female veterans were more likely to meet inclusion criteria compared with male veterans (59.0% vs. 49.6%). There was no gender difference in the mean number of exclusion criteria met or the proportion of female and male veterans who only had modifiable criteria (47.9% vs. 44.9%).

Overall, 931 (45.3%) veterans did not accept HCV treatment. There were no differences in treatment acceptance between female and male veterans (50.0% vs. 54.9%). Reasons for treatment nonacceptance for both female and male veterans were wanting to

defer treatment (57.1% vs. 59.0%) and concern over side effects (23.8% vs. 10.6%), but these reasons were not statistically significant.

Female veterans were different socioeconomically and demographically and were more likely to meet the HCV treatment criteria. This study's data, however, suggest that the universal, gender-neutral approach to patient screening is as effective with both male and female veterans. The high rate of HCV treatment nonacceptance was not statistically significant, but concern over side effects was a greater issue for females. Although no statistically significant gender biases in HCV screening or treatment acceptance, these data suggest that providing different patient counseling, education, and referrals may be beneficial. Further study is required to evaluate the overall efficacy of the current screening tools.

Susan L Currie, Author

Dr. Patricia Busk, Chairperson,
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CHAPTER I

INTRODUCTION

Statement of the Problem

The Veterans Health Administration (VHA) is the United States' largest integrated health system (Perlin, Kolodner, & Roswell, 2004). In 2004, the VHA provided medical services to over 4.7 million veterans throughout the nation (Panangula, 2006). The number of women entering the military is increasing substantially, with women now comprising 20% of all new recruits and 15% of those who are serving in active duty (Meehan, 2006). Although the number of women veterans is currently 5% of the 27 million veterans, the number is expected to be over 10% by 2010 (Meehan, 2006; Yano et al., 2006). The VHA has made it a priority to improve women veterans' health care because of the future increase in the number of women veterans. Recent studies suggested that access to services for women veterans has improved substantially (Yano, Washington, Goldzweig, Caffrey, & Turner, 2003). Thus, the future increase in the population of veterans, coupled with the increased number of women veterans accessing veterans' health care, raises a number of potential environmental- and behavioral-care issues, including the use of standardized health-care screening (Meehan, 2006).

Health-care programs, including screening and services in the United States, traditionally have been built on the principle of evidence-based medicine (Hope, 1995). Thus, policies and decisions about screening for diseases or treatments are based upon proven, effective medical treatments and interventions that meet the ideals of beneficence and reduction of risk to patients. This form of health care would seem to improve the health of all people, including women, but there may be some issues with this model of

health-care screening and delivery (Rogers, 2004). The first issue is that current medical models are based on clinical research. If there are any past biases or gaps in the existing research and research literature regarding gender, then the evidence used to develop best practices and screening models also would be biased. The second element of bias with evidence-based models is the lack of research and evidence about the effectiveness of the screenings or interventions for women. This bias may result in the existing screening or health-care models being withheld because of a lack of evidence of whether it is effective for females, conversely, the screening or treatment may be implemented equally among males and females, which may result in inappropriate treatment (Rogers, 2004). One example of the use of gender-equal treatment that may not be appropriate is in the treatment of cardiovascular diseases. Gender differences in treatment have been well-researched, and some of the potential factors cited for this continued difference in care have been the lack of research regarding the treatment's efficacy among women (Chang, 2007).

The need to address gender and its effects on good health care of veterans also has been the subject of a number of congressional debates and hearings since 1982. At that time, the General Accounting Office (GAO) criticized the Veterans Administration (VA) for the lack of gender-specific services and again in 1992 (U.S. Government Accounting Office, 1982, 1992). Subsequently, legislation was passed earmarking funds to enhance women's healthcare, and this legislated funding has evolved into numerous comprehensive women's health centers through the VHA. In 2001, a national evaluation of women's health programs was commissioned, which showed that there were some improvements in women's health services but that gaps in service still exist for women

and that there still exists wide variations in guidelines and care services for women in the VHA (Yano et al., 2003).

Historically, with women comprising such a small percentage of veterans accessing health care, it is understandable that it was difficult to ensure gender-specific quality care within the VHA, including health-care screening. Gender-specific care has been further compounded by the fact that most health-care providers within the VHA have less interaction and experience providing care for female veterans as a result of their low prevalence in the health system (Yano et al., 2006). As such, with a traditionally male-dominated patient population, the effectiveness of universal (standardized regardless of gender, race, or other factors) health-care screening for chronic diseases for women has not been examined fully. Similarly, gender differences in treatment acceptance have not been explored for patients with the hepatitis C virus (HCV), although data suggest that there may be gender differences from other treatment modalities such as smoking cessation (Sherman, 2005).

Research also suggests that women veterans have greater physical and mental-health burdens relative to female nonveterans (Frayne et al., 2006) and equal or greater burdens than male veterans. These data suggest that female veterans thus may have a greater need for VA health-care services than their male counterparts, which would further support the need to address whether the current VA health-care services are appropriate in targeting the female veteran population.

Even though the VA has acknowledged the need to further address female veterans' health care through legislation and enhanced programming, there is very limited research or data available on women veterans and, in particular, research on women and

infectious diseases such as the HCV. In fact, a recent systematic review of 182 women veterans' studies found that most of the research on women veterans was descriptive in nature and related to psychiatric conditions such as sexual harassment or health-care utilization. This review concluded that experimental studies and studies assessing the quality of care for women were rare (Goldzweig, 2006). The lack of women veteran's research needs to be addressed, particularly for diseases that are more prevalent in veterans than nonveterans, such as the HCV.

Data suggest that HCV is three to five times more prevalent among veterans (Dominitz et al., 2005) than in the general U.S. population (Armstrong et al., 2006). HCV is a blood-borne disease, and so the higher prevalence for veterans may be a result of the higher prevalence of risk factors for HCV, including injection drug use and blood exposures while in combat (Fireman, Indest, Blackwell, Whitehead, & Hauser, 2005). Chronic HCV clearly is linked to the development of cirrhosis, hepatocellular carcinoma (HCC), and end-stage liver disease requiring liver transplantation. These medical consequences of HCV infection constitute a significant human and financial burden. According to the United Network for Organ Sharing (UNOS), estimated charges per person for liver transplantation are $314,600 and an additional $21,900 annually thereafter (UNOS, 2008). A recent projection of total HCV-related deaths in the United States in the period of 2005 to 2025 is estimated to be 196,000 (95% CI= 178,000 - 214,000) with present treatment (Deuffic-Burban, Poynard, Sulkowski, & Wong, 2007). Thus, the financial and human burden is high for the general U.S. population with respect to the hepatitis C virus. It is an even greater burden for U.S. veterans; however, with several studies estimating the prevalence in veterans to be at least three-fold higher, at 5

to 10% of veterans who access VHA services (Dominitz et al., 2005; Yee, Currie, Darling, & Wright, 2006). Unlike other hepatitis viruses, approximately 85% of persons who acquire HCV do not clear the virus without treatment. These persons are defined as having chronic HCV. The treatment of chronic HCV is aimed at reducing these health burdens by slowing disease progression, preventing complications of cirrhosis, reducing the risk of hepatocellular carcinoma, and treating extrahepatic complications of the virus (Yee et al., 2006).

Several studies have investigated HCV screening, treatment candidacy, and patient acceptance among veterans in the United States. These studies, however, included mostly male veterans. In those studies where females were included, the number of female veterans comprised less than 5% of participants. Even in a recent, large epidemiological HCV veterans study by Dominitz et al. (2005), only 51 of the 1,288 persons were women. The area of HCV disease needs further exploration, given the increasing number of women who are enrolling in the United States military service and the increasing number of women accessing health-care services within the VHA for their HCV management and care. In particular, it is important to investigate the current gender-neutral screening used to evaluate a veteran's candidacy for HCV treatment and to ascertain whether there are gender-different responses to the exclusion criteria. If there are differences in the responses to the exclusion criteria in men and women, this might indicate potential barriers to treatment candidacy for female veterans. There a need to investigate not only whether there are gender differences in responses to the criteria for treatment candidacy but also whether there are gender differences in those who are offered HCV treatment in their acceptance of treatment. The need for this HCV research

is even more paramount given the projected increase in deaths of all patients, including women, who are not screened adequately and treated for their HCV.

Purpose of the Study

The purposes of this study were to evaluate whether there were gender differences in veterans' responses to the screening for HCV antiviral treatment and gender differences in those who accept HCV antiviral treatment. HCV antiviral treatment screening and HCV treatment acceptance are two separate decision points in the treatment process for all veterans being considered for HCV treatment.

Specifically, to carry out this research, this study examined the quantity (total number) of yes responses to the 13 exclusion criteria that comprise the VA's universal screening criteria for HCV (Appendix A). To further investigate the type of responses each of the 13 exclusion criteria were examined. As well, the type of responses were assessed based on whether the criteria were modifiable (changeable by the patient individually or through medical or other supports) or nonmodifiable (permanent or unable to be changed regardless of intervention). Identifying whether there are gender differences in the responses to modifiable or nonmodifiable criteria is important to assess, because HCV treatment screening considers all of the 13 exclusion criteria in the same way. Any single positive response excludes a person from HCV treatment. If there are gender differences in the responses to the modifiable factors, it may indicate an opportunity to address or change these factors and potentially increase the number of persons eligible for HCV antiviral treatment.

Another purpose of the study was to examine whether there are gender differences in treatment acceptance of veterans who are offered HCV antiviral treatment.

Specifically, the study compared whether there are gender differences in responses to HCV treatment acceptance (the number of yes responses to acceptance of HCV treatment, Appendix B, question 4). As mentioned previously, regardless of gender, if a patient does not meet any of the 13 exclusion criteria for treatment, he or she is offered HCV antiviral treatment. HCV antiviral treatment acceptance by patients is not 100%. Unknown is whether there are gender differences in HCV antiviral treatment acceptance between men and women veterans. This lack of knowledge about gender differences may be an issue in HCV positive women because other gender-neutral treatments offered to veteran women, such as smoking cessation, have shown differences in treatment acceptance (Sherman, 2005).

Furthermore, in those veterans who do not accept HCV treatment, this study examined whether there were gender differences in the reasons why veterans chose not to accept HCV treatment, based on six of the seven potential responses to the question that asks to clarify the reason why they did not accept treatment (Appendix B, question number 5). The seventh response, which is not included in this analysis, has been excluded because it relates to patient consent in the study and not to the question of treatment acceptance.

This study will enhance the field's understanding of whether there are gender differences in the responses to treatment eligibility and treatment acceptance of female veterans with HCV. This information is important because not only of the longterm health consequences of not treating HCV but also this area has limited data and few empirical studies.

Background and Rationale for the Study

The number of female U.S. veterans is projected to double by 2010 (Yano et al., 2006). This changing gender composition of veterans results in different pressures and challenges on the Veterans Health Administration (VHA) not only in the provision of women's health services but also in ensuring that the screening of health services is appropriate for both genders. Because the VHA's health system has been built upon a biomedical model that focuses on disease and was developed on the principles of gender neutrality, the issue of whether veterans' health services are appropriate for women becomes a greater issue. Because there are gender differences in risk factors, age, and other factors between male and female veterans, one would hypothesize that there might be gender differences in responses to the HCV screening and treatment acceptance; however, no research has been conducted to examine whether gender-specific screening and treatment acceptance is needed for HCV (Bini et al., 2005). This study examined this important health-care issue.

HCV is not a rare chronic infection. In fact, it affects nearly three million Americans (1.8% of the entire U.S. population) and is the leading cause of liver transplantation and hepatocellular carcinoma (HCC) in the US (Armstrong et al., 2006). Prevalence studies of veterans accessing VHA suggest that the prevalence is much greater than in the general population, from 5 to 25% (Dominitz et al., 2005). These data suggest that it is an even bigger health issue for the veteran population given the significantly higher number of HCV-infected veterans.

HCV is primarily a blood-borne virus, which means that it is transmitted from one person's blood to another. As such, high-risk behaviors include persons who had received

a blood transfusion before 1992 (that is when the blood banks and blood supply began to screen for the hepatitis C virus) or have a history of or current injection drug use (IDU). Other potential routes of transmission include tattooing, history of multiple sex partners, and occupational exposures such as percutaneous or mucosal. In fact, IDU is now the primary and most efficient route of infection for the hepatitis C virus (HCV). Recent National Health and Nutrition Examination Survey (NHANES) data suggest that at least 48.4% of all persons with HCV antibodies have a history of IDU (Armstrong et al., 2006).

The natural history of HCV is highly variable, with approximately 15 to 20% of all persons who are infected with the HCV able to clear the virus without treatment. The other 85% who do not clear the virus are considered to have chronic hepatitis C, and these are the persons who are at risk of developing complications related to the infection. Of the persons who develop chronic hepatitis C, approximately 15% of them eventually will develop cirrhosis (Strader, Wright, Thomas, & Seeff, 2004), and up to 5% of all persons with chronic hepatitis C may die as a result of it. HCV is now the primary cause of advanced liver disease and hepatocellular carcinoma (HCC) in the United States, as well as the leading indication for liver transplantation (Spaulding et al., 2006; Strader et al., 2004).

Dominitz et al. (2005) conducted a prevalence study from 20 randomly selected VA medical centers, which comprised 3,184,687 veterans seen at these facilities during the period of 1998 to 2000. Using a randomized number generator, 200 veterans were selected from each of the 20 facilities for a total sample of 4,000. All patients were approached, consented, and asked to complete a self-administered risk questionnaire and

had their blood drawn to ascertain their HCV status. Dominitz et al. employed two separate techniques to account for nonparticipation: the first involved multiple imputations to develop a multiple regression model to predict probability of participation and the second methodology used nonparticipation weighting. Of the available 4,000 potential participants, 1,288 blood results and data were collected for the purposes of this study. In this study, 52 of the 1,288 (4.03%, 95% CI = 2.6 to 5.5%) tested positive for HCV. Regardless of the correction method used for nonparticipation, the prevalence estimate increased to 5.4% (95% CI = 3.3 to 7.5%). This study's data also suggested that prevalence was higher among males (5.6 vs. 1.2); however, the difference in prevalence between males and females was not statistically significant, perhaps as a result of the small sample size of women (n = 51). The data also showed that prevalence was statistically significantly higher among Vietnam era veterans when compared with all other service periods (11.0% vs. 2.2%).

Another important component of this study was its examination of HCV in relation to other clinical diagnoses. The examination of other clinical factors is particularly important given the universal factors used for screening for HCV antiviral treatment and part of the current study's investigation. Persons with HCV were statistically significantly more likely to have a history of, or current, alcohol abuse (15.1 vs. 3.7), mental illness (11.4 vs. 3.2), or substance use disorder, excluding alcohol (22.6 vs. 3.9). These three factors, alcohol abuse, mental illness, and other substance use disorders excluding alcohol, are all modifiable factors. Although this study was one of the largest HCV prevalence studies of veterans undertaken and validated prior studies suggesting that the HCV prevalence of veterans is higher than the general U.S.

population, there are a number of limitations to this study. One limitation is the large number of veterans who chose not to participate (over 68% of the potential sample) and thus did not provide a blood specimen for the study. Another issue is that this study was a predominantly male population, which also might suggest that risks and behaviors and even overall HCV prevalence figures may not be generalizable to female veterans.

Since 2000, the treatment for HCV has evolved such that two drugs, pegylated interferon and ribavirin, taken in combination, are now the standard of care, leading to viral clearance in approximately 40% of those with genotype 1 infection, the predominant genotype in the US. There are controversies concerning those who are appropriate candidates for therapy and whether therapy improves survival. Part of the controversy stems from the indolent nature of HCV infection such that many with HCV will die *with* HCV rather than *from* complications of disease associated with persistent HCV infection. Nevertheless, a recent National Institutes of Health (NIH) Consensus Development conference clearly recommended screening for HCV infection in high-risk individuals and treatment of those with "significant" HCV-associated liver disease (NIH, 2002), generally defined as those patients with at least an inflammation of their liver resulting from the hepatitis C virus.

In contrast, recent guidelines by the U.S. Preventive Services Task Force (USPSTF) advised against testing for HCV infection in those with risk factors (USPSTF, 2004). Although the Task Force recognized that complications of chronic HCV infection are rising and represent an important public-health burden in coming decades and that antiviral therapy can eradicate infection, the Task Force found insufficient evidence to recommend for, or against, routine screening for HCV infection in asymptomatic adults

at risk. Part of the reluctance to identify those with HCV infection comes from the lack of data regarding the benefits of antiviral therapy in preventing long–term complications of HCV disease. This lack of data is further compounded by the fact that the majority of those with HCV infection are entering the fifth decade of life. As such, they may be at greater risk of developing life-threatening nonhepatic comorbidities than of dying from complications of HCV disease. Even though there is debate in the general public about health screening, the VHA, with a higher prevalence of HCV, has adopted a universal screening for HCV treatment (Yee et al., 2006).

Universal screening of veterans for HCV treatment has not been static. Because these guidelines are based on a biomedical model that includes both clinical study data and best practices, there have been changes or modifications to the universal screening prior to the existing screening guidelines. For example, patients with ongoing injection drug use were previously excluded or "screened out" of HCV treatment until 2002 (Bini et al., 2005; Dalgard et al., 2002; NIH, 2002). Injection drug users were excluded because there was a concern about the potential for HCV reinfection as well as the concern for treatment adherence (Currie et al., 2008). In 2002, however, the NIH Consensus Statement changed the screening criteria, allowing for all patients with chronic HCV infection to be considered for HCV antiviral therapy (NIH, 2002; Yee et al., 2006). Even though the HCV treatment criteria have broadened, there is still limited access to HCV treatment for IDU patients. This limited access to treatment can be attributed to a number of modifiable factors, including concern for ongoing drug use and its impact on treatment adherence and the potential for lower responses to HCV therapy, but also, for those who

are treated successfully, the concern for potential reinfection (Dalgard et al., 2002, Spaulding et al., 2006).

Sociodemographic and epidemiological studies have shown that persons with chronic hepatitis have a high prevalence of current or past medical, psychiatric, and substance-use disorders (Lehman & Cheung, 2002). These factors are important for a number of reasons. First, HCV and related liver-disease progression can affect negatively mental health, quality of life, and other medical symptoms (Yee et al., 2006). Second, the higher prevalence of nonmodifiable factors such as medical and modifiable factors such as psychiatric, and substance-use comorbidities can exclude persons from HCV antiviral treatment if not controlled. Third, these symptoms actually can worsen as a result of the HCV treatment, which can lead to reduced compliance and reduce positive treatment outcomes to HCV treatment.

Chronic hepatitis C is a disease that, if untreated, can lead to scarring of the liver (cirrhosis), hepatocellular carcinoma (liver cancer), or even death. The primary means of managing veterans with HCV disease is through HCV antiviral therapy. The success of antiviral therapy is dependent on the patient's ability to take the medication as directed and to be knowledgeable about managing the treatment's side effects that otherwise could lead to noncompliance, dose reduction, and treatment discontinuation (Yee et al., 2006).

In an effort to maximize HCV treatment success, the VHA has developed standardized screening criteria to assist medical providers with the management and education of veterans with chronic hepatitis C (see Appendix A). This standardized screening includes 13 criteria. These 13 are considered exclusion criteria because a patient will be excluded from treatment if he or she has a positive (yes) response to any

one of the criteria. It is this standardized screening that not only forms the basis of HCV treatment eligibility but also the type of patient education and counseling patients receive. The standardized criteria, like many VHA health-screening tools, were developed within a traditionally homogeneous male patient population (Goldzweig, 2006). Until recently, with a small female veteran population, the use of this VHA screening tool did not appear to be problematic; however, with the increasing number of women veterans accessing VHA services for all health services, including HCV, there is little known whether existing health-screening tools are appropriate for both male and female veterans.

The second key decision point after the universal screening for HCV treatment eligibility is when veterans who are eligible for HCV treatment are offered treatment. The offering of HCV treatment is not gender-specific; however, it might be influenced by concerns of side effects, ability to comply and other medical and nonmedical issues (Yee et al., 2006). It is not known whether there are gender differences in HCV treatment acceptance or if there are gender differences in the reasons for nonacceptance of HCV treatment. The examination of gender differences in acceptance of treatment, again, is important, because if there are gender differences in acceptance of antiviral treatment, then the way that providers educate and counsel patients during their discussions about HCV treatment may need to be changed.

Theoretical Rationale

The theoretical rationale that has contributed to the current standardized patient screening and subsequent treatment acceptance for chronic hepatitis C is the biomedical model. The biomedical model is built upon the principle of identifying the soma or symptom of a disease or medical problem independent of the social, psychological, or

human context of the issue (Alonso, 2004). Advocates of the biomedical model suggest that it insures that the physician obtains information from the patient that is neutral to gender, race, and social circumstances and is relevant only to the disease and diagnosis. On the surface, this gender-neutral approach appears appropriate; however, there may be several flaws with this approach for many diseases, including HCV. First, this model cannot take into account actual physiological, social, behavioral, or other gender-related differences. This means that contextualizing screening responses or integrating other factors in health-care screening is excluded. Second, the biomedical model is developed based on clinical evidence, which, historically, has been conducted in a homogeneous, predominantly male population. If health-care screening and decisions are being made based upon clinical trials and evidence from a male-oriented, homogeneous population, it is unclear if these data would be generalizable to females or other diverse population groups (such as persons from different races, ethnic backgrounds, and ages). It is these two factors that may bring in to question the appropriateness of the biomedical model.

The biomedical model formed the basis of universal-health screening forms to assess for disease well into the 1970s (Engel, 1979). The principles of this model are the foundation of Western Medicine, which eschews two dominant ideas: dualism and reductionism (Rasmussen, 1975). Dualism can be defined as a means for the physician to separate the mind from the body and the behavior of the disease from the person's behavior or other social or psychological components. The second parameter of this model is reductionism. In science or medicine, this principle takes a complex organism such as a human being and builds upon the idea that it can best be understood by focusing on discrete parts of the whole rather than as a complete entity. For example, hepatitis C is

a virus that affects the liver, and so, to address this disease, one would focus attention specifically on this area of the body, and all screening questions and clinical tests would be related directly to this part of the organism. This type of reductionism looks at cause and effect and may incorporate the ideas of clinical research and evidence-based medicine to confirm its validity (Engel, 1977).

The reductionist model is the basis of screening for disease detection, including hepatitis C. In using the biomedical model's reductionism in screening, all of the responses to the universal screening for hepatitis C are viewed as a discrete yes-or-no binary response to screening questions in order to ascertain the information and assess a person's eligibility or appropriateness for treatment. Using this model, the hepatitis screening form uses a number of clinical laboratory tests, including liver function tests, liver biopsy data, and blood-cell counts to determine the probability of the patient with hepatitis C being a good candidate for HCV treatment (Yee et al., 2006).

In the late 1970s, Engel (1979), a physician, challenged this traditional biomedical model and advocated for a biopsycho-social model of medicine that would integrate psychological and social factors with the existing biomedical model. The biopsycho-social model argued that this integration would provide a better context and a more holistic means of assessing patients and patient health (Engel, 1979). This model attempts to integrate a more holistic approach to medicine and medical screening and to replace the idea of dualism and reductionism with a more systems-wide approach to medicine, including screening and assessment (Engel, 1979). As such, the screening for diseases and treatment eligibility has expanded to incorporate mental health, behavioral, and other nonbiomedical questions (see screening form, Appendix A). The possible advantages to

this approach are that the physician, health-care provider or health-educator, can use this approach to identify not only the biomedical criteria but also risks and behaviors that might affect outcomes.

The current hepatitis C treatment screening exclusion-criteria form screens for both biomedical and nonbiomedical criteria. For the purposes of this study, biomedical criteria are considered nonmodifiable criteria or criteria that cannot be easily changed or modified. The nonbiomedical criteria are the criteria that may be changed through treatment or changes in behaviors (see Definitions of Terms). The hepatitis C- screening exclusion-criteria form includes 13 criteria in which 4 of the criteria are nonbiomedical, ongoing or recent substance use, preexisting psychiatric conditions (including depression), inability to remain compliant, and pregnancy (see screening form, Appendix A, and Table 1 in Chapter III for more details). The issue is, however, that the method of HCV screening still treats all of the factors as biomedical and in a reductionist way (as a yes-or-no response to any of the exclusion criteria). Also, rather than taking a holistic approach to these criteria, a patient must meet none of the exclusion criteria to be eligible for treatment, regardless of the number (quantity) or type (modifiable or unchangeable) of the patient's responses, which suggests that this type of screening adheres to the traditional biomedical model.

The biomedical model also provides the theoretical foundation for the approach to patients (regardless of their gender) who are eligible to treatment and who are offered treatment. The biomedical model is based on evidence-based medicine, most of which have been developed using a male population (Rogers, 2004). If the evidence that forms the basis of medical screening and decisions is built upon data or evidence from clinical

trials that were primarily male and homogenous, it is not certain if the evidence is, in fact, generalizable to females or other populations. This theoretical approach is important in understanding how the health education and counseling that is provided to patients with hepatitis C who are eligible for HCV antiviral treatment addresses the patient equally, regardless of gender. This model also does not allow for variations in the process to address any additional factors specific to women or even historic differences in acceptance.

In summary, the biomedical model's dualism and reductionist approach underlies the management approaches to most chronic medical conditions, including the current standardized screening for hepatitis C. This model also is the foundation for the method of offering treatment to those patients who are eligible for hepatitis C treatment because it is objective and is not varied in approach as a result of gender or other social, environmental, or other nonbiomedical factors. The HCV screening and subsequent counseling and patient education within this approach have been based on male-dominated clinical trials and clinical-research experience. This theoretical rationale, however, does not recognize that there may be biological and other differences between males and females. The current study examines whether there are such gender differences to provide better understanding whether the biomedical-based theoretical rationale for HCV treatment candidacy and education is appropriate for male and female veterans.

Research Questions

The following research questions will be investigated:

1. To what extent are there gender differences in the quantity and type (whether they are modifiable or not) of responses to standardized patient screening in veterans with chronic HCV?

2. If there are gender differences in the type of responses to standardized patient screening, is this difference associated with risk factors, such as alcohol use, socioeconomic differences, such as level of education, and demographic factors, such as race or ethnicity, of veterans with chronic HCV?

3. To what extent are there gender differences in treatment acceptance in veterans who are offered HCV antiviral treatment?

4. For those who do not accept HCV treatment, to what extent do the reasons for nonacceptance differ by gender?

Significance of the Study

This study may have an educational impact not only on the way that veterans with hepatitis C are screened for HCV antiviral treatment but also on the way that physicians, nurses, and other health-care providers offer and educate patients who are eligible for HCV antiviral treatment. The results of this study may provide a better understanding of whether there are differences between male and female veterans to the standardized screening for HCV treatment. These data are important to ascertain in order to assess whether the current screening is appropriate and relevant to both men and women. The outcomes from the current screening are the foundation of patient education, patient counseling, and the offering of treatment for any patients infected with hepatitis C, regardless of gender. If this study identifies differences in gender, then the postscreening education and counseling process may be affected. A second significant element of this

study is the examination of whether there are gender differences in acceptance of treatment. This examination of gender differences in acceptance of treatment, again, is important, because if there are gender differences in acceptance of antiviral treatment, then the way that providers educate and counsel patients during their discussions about HCV treatment may need to be changed.

Furthermore, by having a better understanding of gender differences in veterans with hepatitis C who are being screened and cared for, the VA healthcare system may be able to use these data to modify or further examine patient screening and education for other chronic diseases such as HIV. Another potential finding of this study is the absence of gender differences in responses to the current standardized HCV treatment screening and subsequent HCV treatment acceptance. This finding also will be important because it will provide additional support to continuing the existing standardized screening, patient education, and counseling that currently is available within the VHA system.

Overall, this study is significant because it will expand the field of knowledge regarding HCV management and care of female veterans, a group that has been understudied and underrepresented due to the historically small numbers of female veteran patients. The need to examine the current HCV treatment screening and treatment acceptance for both male and female veterans is an increasingly important research area for a number of reasons. First, it can impact the increasing number of the 225,000 veterans (both male and female) who already have been identified as having hepatitis C infection in the VA. Second, because the number of female veterans accessing VHA services is expected to almost double from 5.5% in 2000 to 10% by 2010, and the number of veterans (both male and female), additional research examining the current HCV

treatment screening and patient acceptance of both male and female veterans may affect the current quality and standard of care of veterans with hepatitis C. Finally, there are more global veterans' health implications of this study because of the opportunity to evaluate the biomedical model's appropriateness in addressing gender issues. The current study may provide additional insight into the need to address and expand the current model within the VHA.

Definition of Terms

The following are the operational definition of key terms used in this study. There may be other definitions for the terms listed below; however, for the purposes of this study, the stated definitions apply.

Biomedical criteria: These are medical criteria that are not changeable or modifiable by behavior change or treatment intervention. These are also known as unchangeable factors in HCV patients. Nine of the 13 exclusion criteria for HCV screening are considered biomedical (Bini et al., 2005).

Exclusion criteria: These are the 13 items (Appendix A) that are used as part of the standardized screening to evaluate veterans eligibility for HCV antiviral treatment. If a patient has a positive response to any one of the 13 items, he or she is considered not eligible for HCV treatment (Bini et al., 2005)

Fibrosis: Is an indication of liver disease. There are generally four stages of liver disease with stage zero indicating no disease and stage four indicating cirrhosis or scarring of the liver. Fibrosis is usually identified through a liver biopsy (Poynard et al., 2003).

Hepatitis: Means inflammation or irritation of the liver (NIH, 1997; Armstrong et al., 2006).

HCV RNA test: The presence of HCV Ribonucleic acid (RNA) means that there is still HCV virus present in the blood. A patient has a laboratory test before being screened for HCV treatment to see whether there is virus in their system. If a patient has no detectable virus, then it means that he or she has cleared the virus and do not require HCV treatment. The HCV RNA test also is done while someone is being treated for their HCV and immediately following treatment to assess whether the treatment is being effective or not. If they have an HCV RNA test that is undetectable 6 months after completing HCV treatment, they are said to have a sustained virological response (SVR) and are cured of their HCV (NIH, 2002; Yee, Currie, Darling, & Wright, 2006).

Hepatitis C virus: There are a number of viruses that can affect the liver, such as hepatitis A, hepatitis B, and hepatitis C. The Hepatitis C virus (HCV) is a blood-borne virus, which means that it is spread through hepatitis C infected blood-to-blood contact. Primary modes of transmission of the HCV virus are through sharing needles and other equipment to inject drugs, sharing unsterile tattooing equipment, and, persons who received blood transfusions with blood that was infected with hepatitis C (prior to screening for this in the blood banks). Approximately 15% of those who are infected with the virus are able to clear it without treatment. The other 85% are considered to have chronic HCV. Persons with chronic HCV are the individuals who would be screened to try and clear or "cure" the virus. There is no vaccine for HCV. As a virus that affects the liver, HCV can lead to cirrhosis (scarring of the liver) and even death (NIH, 2002; Armstrong et al., 2006).

HCV Treatment: All patients with chronic HCV infection are potential candidates for antiviral therapy. Currently, standard antiviral treatment for chronic HCV involves once

weekly pegylated interferon (peginterferon alfa) injections and daily oral ribavirin. The duration of HCV treatment varies, but it is usually 6 months or 12 months depending on the strain of the HCV virus (genotype) and a number of other factors. The effectiveness of the treatment ranges from 30 to 45% in patients with genotype 1 to 90% in those with genotypes 2 or 3 (NIH, 2002; Yee, Currie, Darling, & Wright, 2006).

Modifiable factors in HCV patients: These factors are screening factors used to assess patient eligibility for HCV treatment that potentially are modifiable or changeable by the patient individually or through medical or other supports. Examples of these types of factors are four criteria on the VA universal screening form: ongoing or recent substance use, preexisting psychiatric conditions, inability to remain compliant with treatment, and patient or partner is pregnant or actively nursing (Bini et al., 2005)

Nonbiomedical criteria: These are modifiable or changeable criteria that potentially are changeable or modifiable by the patient individually or through medical or other supports. These are known also as modifiable criteria. Four criteria on the VA universal screening form are considered nonbiomedical: ongoing or recent substance use, preexisting psychiatric conditions, inability to remain compliant with treatment, and a patient or partner who is pregnant or actively nursing (Bini et al., 2005).

Nonmodifiable factors in HCV patients: Nonmodifiable factors in HCV patients are the screening factors used to assess patient eligibility for HCV treatment that would be impossible to change or are absolute exclusions for HCV treatment. Examples of these types of factors would include 9 of the 13 criteria on the HCV treatment exclusion form (see Appendix A) , prior treatment, hypersensitivity to the medications, hemoglobinopathies, evidence of advanced liver disease, having hepatitis B, preexisting

medical conditions, evidence of ischemia, concurrent use of other investigational therapies, and a history of organ transplantation (Bini et al., 2005).

Quantity of HCV screening responses: A person is excluded from HCV treatment if he or she responds yes to just one of the 13 exclusion criteria. As such, a person who had 4 yes responses (met four exclusion criteria) is treated no differently than a person who has only one exclusion criteria. The quantity of HCV screening responses will be defined as the number of persons who responded to yes for one, two, three, and up to 13 potential exclusion criteria screening responses, rather than just a single determination of yes or no treatment candidacy based on a single yes response (Bini et al., 2005).

Sustained virological response: A sustained virological response (SVR) is defined as someone who has been treated for their chronic HCV and has no presence of virus based on laboratory tests 6 months after completion of the HCV treatment. This patient is considered "cured" of HCV (NIH, 1997; Yee, Currie, Darling, & Wright, 2006).

Treatment Acceptance for HCV Treatment: Treatment acceptance for HCV treatment is the number of persons who responded yes to the offer of HCV treatment, which is question #4 on the Treatment Candidacy and Decision form (see Appendix B). When a person did not accept HCV treatment (a no response), he or she was asked the reasons why he or she did not accept treatment, and the potential responses are recorded accordingly. These two questions were used in a standardized patient teleform in all study patients who did not meet any of the exclusion criteria for HCV treatment (see Appendix B) (Bini et al., 2005).

Type of HCV screening responses: The current HCV treatment screening exclusion criteria do not differentiate between the 13 yes-and-no responses. This study evaluated

the responses as individual responses and qualified the types of responses into either modifiable or nonmodifiable responses. For example, ongoing or recent substance use is a modifiable factor that is different than advanced liver disease, which is an unchangeable factor (Bini et al., 2005).

Universal screening for HCV treatment: Universal screening for HCV treatment in the VA involves the use of a standardized set of 13 questions that veteran patients are used to determine eligibility for HCV antiviral treatment. These questions were used in a standardized patient teleform in all patients in the original source of this study (see Appendix A) (Bini et al., 2005).

Summary

An overview of the background and need for the study, which included the higher prevalence of HCV infection in veterans, as well as the increasing growth in the number of female veterans accessing VHA was provided. HCV infection was then discussed in the context of the long-term health consequences of patients who are not treated for this chronic disease. This overview of HCV infection was followed by a discussion of the use of the gender-neutral biomedical model as the rationale for medical screening, including the VHA's universal screening for HCV treatment.

In this chapter, an overview of recent research and epidemiological data were provided. These data highlighted two important points: first, that there may be gender differences in screening and in treatment acceptance for other chronic diseases and, second, that there was a lack of females (and, in many cases, no female) veterans included in the clinical research that provided the foundation for the current HCV treatment screening. These two points support the need to examine whether there are

gender differences in both screening for HCV treatment, as well as whether there are gender differences in acceptance of HCV treatment. Additionally, a definition of terms was provided in this chapter to clarify special term used for the purposes of this dissertation.

Chapter II contains a review of the relevant empirical research literature pertaining to the independent variable gender and its association with VA health-care and treatment services. Chapter III provides a framework of this study's methodology, including an overview of the original study that is the basis of the current study. Chapter IV contains the results of this study with respect to the four research questions. Chapter V provides a discussion of these data in the context of the limited published data in this area, its implications for practice, and for future research.

CHAPTER II

REVIEW OF LITERATURE

The purposes of this study were to evaluate whether there are gender differences in veterans' responses to screening for HCV antiviral treatment and gender differences in the acceptance of HCV antiviral treatment. In reviewing the literature, however, the number of empirical studies of women veterans is limited, which may be due to the historically low numbers of women veterans or the historical perspective of providing gender-neutral services within the military and subsequently to its military veterans. As recently as 2004, the bulk of the research on gender and veterans issues has focused on sexual harassment and specific women's health issues rather than on chronic diseases (Goldzweig, 2006).

In this chapter, there is a review of the existing literature available on gender differences in veterans accessing the Veterans Health Administration (VHA) services, gender differences in other kinds of treatment services, and gender differences in treatment acceptance. Additionally, there is a review of empirical research regarding hepatitis-C-virus (HCV)-treatment adverse events as well as studies that address liver-disease progression between genders.

Gender Differences in Veterans Accessing VHA Services

There are differences in patient characteristics between male and female veterans accessing VHA services, as well as gender differences of their utilization of these services. Historical data suggest that women veterans, on average, are younger, more educated, and less likely to have served in an active combat zone (Skinner, 2002). These are all factors that one might consider positive from a health perspective. Contrarily,

other data suggest that women are more likely to have a history of sexual trauma and self-reported mental-health issues (Frayne et al., 2006). Results of research also suggest that women veterans have less social-support than their male counterparts (Frayne et al., 2007). These are all factors that might affect the response to a universal screening.

A large study by Frayne et al. (2006) examined the health status of women veterans compared with male veterans using the Large Health Survey of Veteran Enrollees database. This data set included 28,048 women and 651,811 men who accessed VHA in the years 1996 to 1999. This study used the Veterans Short Form-36 (SF-36) instrument and data about veteran's social support. Frayne et al. used Student's t tests to compare the eight dimensions of the SF-36 across three age groups: less than 45, 45 to 64, and greater than or equal to 65. The investigators considered a small effect of 20% of one SD for the 8 scales of the SF-36 to be clinically significant. In each age stratum (18 to 44, 45 to 64, and ≥65 years), Physical Component Summary (PCS) and Mental Component Summary (MCS) scores were compared using gender as the independent variable. They also performed multiple regression analyses on Physical Component and Mental Component Summary scores using gender as the independent variable and controlling for age, race, and education. The investigators also conducted a Student's t-test analysis by gender and age for patients with and without social support.

The results from the Frayne et al. (2006) study showed that women had less social support (defined as married or having someone to take them to the doctor if they were unwell) than men across all age groups. For example, in veterans over 75 years of age, over 15.1% of women had no one to take them to the doctor compared with 9.6% of the men. When mean SF-36 summary scores for physical- and mental-health status of

women versus men were compared against the three age groups, women had statistically significantly higher values than men on all components, with the exception of the 18 to 44 age group, where women had lower values on the MCS (42.8 vs. 43.4).

This study also compared SF-36 scores from this veterans' cohort with women seeking care in the private sector from the Medical Outcomes study (mean age was 52 for the veteran women vs. 46 for the nonveteran women). Women veterans consistently had lower values, on average, on all domains, in particular, Bodily Pain (49.1 vs. 65.1), Role Emotional (60.6 vs. 76.2), and Social Function (59.8 vs. 80.0). The reported poorer overall health of female veterans compared with females in the general population suggests that female veterans may not be different than male veterans, but they may be different than their nonveteran female counterparts, which further supports the need for an investigation into this group of women with reported poorer overall health than women in the general U.S. population. The strength of this study is that it is a large study of male and female veterans, but there may be some response bias between those who responded to this survey and those who did not. For example, the persons who responded might be more or less healthy than those who did not. Another potential bias is the use of the SF-36 in a veterans' population. There is the potential for construct validity issues of such an instrument, similar to what the current study is examining with the HCV screening form. Another limitation of the study is the definition of social support, which was defined by having someone able to take them to the doctor if they were unwell. This definition is very narrow and may exclude persons, for example, with social supports who have transportation or mobility issues.

Another cross-sectional study by Frayne et al. (2007) investigated whether there were any gender differences in outpatient and inpatient use and costs of care of veterans accessing VHA services. It was a large study of all veterans who had utilized VHA services in 2002 with confirmed gender data, and it had a total study population of 4,122,381 (178,849 women). The independent variable for this study was gender and the dependent variables were VHA services utilization and VHA service costs. Other variables that were controlled were age and psychiatric conditions. Chi-square analyses were performed to compare sociodemographic and other medical conditions. Means were compared by gender on inpatient and outpatient utilization. Overall, female veterans were younger with a mean age of 50.1 (SD=17.0) compared with men (63.6, SD=13.9). The unadjusted differences comparing outpatient utilization and inpatient days suggested that female veterans compared with male veterans had statistically significant more outpatient utilization (11.8%) and less inpatient days (25.9%). A log-linear analysis was performed on these results, controlling for age and medical conditions. The results of this study suggest that there were statistically significant differences in women's usage of outpatient-care days (1.3%) and less inpatient-care days (10.9%) after adjusting for age and medical conditions (including mental health). The limitations of this study are that Frayne et al. (2007) did not account for female or male veterans' utilization of non-VHA services. The strengths of this study are its large size and comprehensive single VHA database that records all medical data for all veterans accessing VHA. These data suggest that there are gender differences in accessing VHA health-care services, which supports the need to assess where there are gender differences in treatment acceptance for HCV treatment, which is an outpatient service.

There has been empirical research that suggests that there are differences in treatment and treatment services for male and female veterans (Hoff & Rosenheck, 1998; Stecker, Han, Curran, & Booth, 2007). These study data support this study's examination of gender differences for persons with chronic hepatitis C. The study by Sherman et al. (2005) examined gender differences in smoking-cessation services. The VHA has implemented universal-screening guidelines to ascertain treatment eligibility and treatment initiation for smoking-cessation services (Sherman et al., 2005). These universal guidelines are similar to the universal treatment screening for HCV in the fact that they are used for all veterans being screened for that chronic disease regardless of their gender. The Sherman study involved a random sample of 26,966 eligible patients, of whom 10,567 consented to participate in the study (comprising a 44% refusal rate). Of those veterans who agreed and participated in baseline surveys, 1,941 were defined by the screening criteria as smokers and were part of the 12-month followup. Followup data were collected on 1,150 (59.2%) of the baseline smokers (129 women and 1,812 men) from 18 VA medical facilities to assess smoking-cessation services received by this group. The researchers conducted chi-square tests to compare discrete variables and analyses of variance (ANOVA) for continuous variables for the 1,150 veterans who had provided baseline and followup data. Logistic regression was used to evaluate factors associated with receipt of smoking-cessation treatment services. Baseline demographics showed that women were statistically significantly younger than men (50 vs. 58) and were statistically significantly more likely to have a college education (80 vs. 54%). At baseline, the rates of education and counseling for smoking cessation were the same for women and men, but the rates of prescription treatment, using the universal screening,

was much lower among women than among men (16 vs. 25%, Odds Ratio (OR)=.5, 95% CI=.3-.9). Twelve-month followup of these persons at baseline showed similar results. Multivariate analysis showed that gender (OR=.5, 95% CI=.3-.9), better self-perceived health (OR=1.5, 95% CI=1.1-2.0), and chronic obstructive pulmonary disease (COPD) (OR=1.6, 95% CI=1.2-2.0) were independently associated with prescription nicotine treatment.

There are a number of limitations of this study including the large number of persons who did not participate in the study. This large number of nonparticipants may suggest a skewed sample of either healthier individuals or persons who were not interested in obtaining universal screening for smoking cessation. Also, the attrition rate of the sample in one year was just over 40%. The high attrition rate in the study also may skew the results to the study participants who are healthier or more able to adhere to study and smoking treatment protocols of the study. Finally, the number of women, similar to many VA studies, was low relative to the number of men. Even though there are these limitations, the results of this study suggest that there are gender differences to universal screening for smoking-cessation treatment services in veteran patients.

The studies in this section suggest that there are gender differences in patient characteristics, such as age, mental- and physical-health scores on SF-36, and in environmental factors, such as social supports. As well, the studies that were cited in this section suggest that there are not only differences between genders for age and medical conditions but also differences in health-care utilization between male and female veterans in inpatient, outpatient, and specialized outpatient services. The gender differences identified in these studies may suggest that there are also gender differences

in patient responses to the universal (gender-neutral) screening form for hepatitis treatment, thus supporting the current study's purpose. The studies in this section were also limited to other disease modalities and different treatment focus, further supporting the need to examine whether the findings of these studies are generalizable to female veterans with chronic hepatitis C.

Female Veterans' Acceptance of Treatment

There are many factors associated with whether a person accepts treatment or initiates medical treatment. One such factor is self-perceived health. Many studies have shown that if a person perceives himself or herself to be unhealthy, then he or she will require more supports and are less functional than a person who perceives himself or herself as healthy (Idler, 1997). Even with the research contributions examining self-perceived health, little research has been conducted to assess whether perceived health affects health-care utilization and treatment and, in particular, in women. Bosworth, Butterfield, Stechuchak, and Bastian (2000) conducted a study of women veterans to assess whether self-rated health status was associated with health-service use (treatment) in a primary-care clinical setting. In this study, 139 female veterans, with consecutive appointments at a single VA medical center completed the Primary Care Evaluation of Mental Disorders questionnaire (PRIME-MD). This is a one-page self-administered questionnaire consisting of 28 yes-or-no questions about symptoms or signs present during the past month. This questionnaire serves as an initial screen for mental disorders and has good agreement with independent mental-health providers ($\kappa = .65$, overall accuracy, 85%, sensitive and specificity .75 and .90, respectively; Spitzer, 1999). Health-care utilization and treatment data were collected from the VHA's comprehensive patient

record system. The investigators used Cochran-Armitage Trend Tests to examine trends between demographics and self-reported symptoms and Kruskal-Wallis tests to examine the relationship between self-reported health and actual health-care utilization and treatments.

The Bosworth (2000) study data showed that fair or poor self-reported health when compared with excellent health was related statistically significantly to an increased percentage of physical- and mental-health symptoms in all medical symptom categories including depressed mood (68.5 vs. 35.7), headaches (71.7 vs. 42.9), and joint pain (94.4 vs. 55.6). Logistic regression analysis examined self-rated health with the number of outpatient hospital visits over a year and, using a stepwise method, adjusted for age, race, and marital status. Women who reported their health as being fair or poor when compared with those reporting excellent or very good health were statistically significantly 5.2 times more likely to have more than 12 outpatient visits in the previous year (5.2, 95% CI = 2.2 – 12.3). Race also was statistically significantly associated with healthcare utilization and treatment. European American women were statistically significantly 2.4 times more likely to access health-care services than non-European American women (2.4, 95% CI = 1.1 – 5.2). These study data suggest that self-reported health status is reflective of additional health-care utilization and treatment. Although this study was informative, it was at a single VA center and may not be generalizable to the general VA female veteran population. These data may provide additional information into patient acceptance of HCV treatment because, if this model were applied to the HCV patient acceptance, the persons who self-report excellent health and who in essence

would be the better candidates for HCV treatment may be less likely to engage or utilize health-care compared with persons in poorer health.

Another study by Stecker et al. (2007) investigated treatment utilization and acceptance of female veterans for intensive outpatient substance-use treatment services. The study population was identified as all veterans who had received at least one inpatient or outpatient substance-use service in 1999 from the VHA's national medical record database. The investigators obtained a matched no-treatment group of veterans who received a substance-use diagnosis but who had not accepted substance-use treatment. They had 8,329 total veterans who had received treatment (247 women) and in the matched no treatment group, 7,328 (198 women). Age, gender, race, and medical and psychiatric cormorbidity data were collected. Chi-square tests of independence for categorical variables and two independent-sample t tests were conducted on continuous variables. Using treatment as the dependent variable, logistic regression was performed on the subset of all women in both treated and untreated groups, using age, marital status, race, and diagnostic variables as the explanatory variables.

Overall, in the Stecker et al. (2007) study, women were statistically significantly younger (41.3 vs. 47.1 years) and statistically significantly less likely to be homeless (5.4% vs. 9.3%). In the treatment group, only 2.8% were women, even though 31% of female veterans reported hazardous or problem drinking. In this study, female veterans do not access substance-use treatment services equally as men. Bivariate analyses suggested that women veterans were statistically significantly more likely to have anxiety, bipolar, depression personality disorders, and Post Traumatic Stress Disorder (PTSD) than men. In the subset of women veterans, the results of the logistic regression examining factors

associated with substance-use treatment indicated that having major depression (OR=3.18) and having bipolar disorder (OR=2.44) were the only diagnostic variables associated with treatment participation. One of the limitations of this study is the fact that female veterans may access substance-use services outside the VHA, and so this study may underreport women's acceptance of substance-use treatment services.

These studies are important to the current study because they suggest that female veterans may have different health-care utilization and patient acceptance compared with male veterans. These differences in outpatient service utilization and in treatment acceptance provides additional support for the current study's investigation into whether there are gender differences in patient acceptance for HCV treatment.

Studies of Hepatitis C Screening and Treatment Referrals

There have been a number of studies examining patient differences and treatment referrals in patients with hepatitis C (Bini, 2005; Dominitz, 2005). Many of these studies were in large cohorts of patients in both veteran and nonveteran populations. These studies are important in fostering understanding that the hepatitis C-infected population is not homogenous and that there may be differences in this population; however, these studies either specifically excluded women due to the small number of women available for their study or did not focus on gender in their investigation. Nonetheless, these studies are important for a better understanding of potential differences in risks and screening for hepatitis C that might challenge the use of universal screening for HCV treatment. These screening and treatment differences are exemplified by the original data source of the current study.

A large U.S. multicenter prospective study of veterans with hepatitis C was conducted by Bini et al. (2005), in which all patients were screened for HCV treatment candidacy. Demographic, risk factors, such as alcohol use and injection drug use, and clinical data were collected at baseline, and a screening for treatment candidacy was conducted and recorded. Persons who met treatment criteria were offered treatment, and, if accepted, were treated. In persons who did not meet criteria for treatment, reasons for ineligibility to HCV treatment were recorded. A convenience sample of 4,084 veterans from 24 VA medical centers was enrolled in the study.

Overall, the study was predominantly male (97.2%); 59.5% reported injection drug use and 75.4% reported consuming more than 3 drinks of alcohol per day on a regular basis. In this study, only 32.2% were candidates for HCV treatment. The reasons for ineligibility of persons for treatment were ongoing or recent substance use (20.2%) and active psychiatric disease, including depression and other comorbid diseases (17.9%). Multivariate analysis of factors associated with not being a treatment candidate showed that persons with preexisting psychiatric disease, including depression, were statistically significantly 9.45 (95% CI=6.70-13.32) times less likely to be treatment candidates than those without mental-health issues. In the group of persons eligible for treatment, there was a high rate of refusal, with 23.8% not accepting treatment. The primary reasons for declining therapy included deferring for future treatments (50.3%), concerns regarding potential side effects, such as depression (21.6%), and concerns regarding their ability to comply with therapy (2.2%).

There are a number of limitations and strengths of this study. For instance, this study population may underreport risk factors and behaviors such as depression and

mental health in veterans with HCV because the study represents patients who already were referred for screening for HCV treatment, and, therefore, persons who had severe mental-health and substance-use issues may not have been referred because they would not have been deemed good HCV-treatment candidates. Another limitation is that it did not address gender-specific questions pertaining to HCV patient screening and acceptance. The strengths of this study were its large sample size and multicenter population. This study was well designed and identified the high prevalence of mental health and behaviors that might affect negatively a person's ability to initiate therapy and identified self-reported concerns about adherence and concern for management of side effects. This well-defined group of veterans with hepatitis C from a broad range of sites across the nation provides the foundation of the current study. It is important to further examine these data to assess whether there are gender differences in HCV treatment screening and treatment acceptance.

A second, large non-VA retrospective study by Trooskin et al. (2007) examined HCV risks, testing, and referrals in the general patient population in four medical facilities in the Philadelphia area. This study of 4,407 patient records (1,818 males and 2,469 females) from both academic and community-based clinics' primary study aim was to investigate the role of race and ethnicity on patient screening and treatment referrals. To examine this aim, the investigators used chi-square tests and logistic regression analysis to assess statistical differences between race and ethnicity, at which time they also examined gender differences. This study found that males were statistically significantly more likely to have a positive risk-factor history when compared with females (54 vs. 30%). The positive-risk factors that men were more likely to have

included a history of injection drug use, a history of heavy (3 or more drinks per day) alcohol use, and a history of other blood and other bodily fluid exposures. These data suggest that there are gender differences for risk factors for HCV. Another not statistically significant finding of the study was that, of the 93 patients who had chronic HCV, 71% of European American patients were referred to treatment compared with 40% of Hispanic Americans and 32% of African Americans. These data suggest that there may be screening differences associated with race and ethnicity and that universal screening may not be appropriate for the entire HCV population.

This study had a number of limitations. First, the sample was only from clinics in the Philadelphia area, which might mean there are geographic differences that would limit generalizability to the general HCV population. Another limitation is that the study obtained data only from patient medical records, which might introduce specific physician or clinical bias in their reporting of risk factors and referrals. It also did not account for the fact that some patients might access their health care at other facilities and thus these data would underreport treatment and referrals to other studies. This study did have a large population of both men and women and did review chart records consistently at each of the four medical centers. Although this study did not focus specifically on treatment acceptance and referrals among women, it does suggest differences in risk factors and behaviors between men and women and also suggest that other factors (in this case race and ethnicity) are associated with differences in treatment acceptance and referrals.

Results from these HCV studies suggest that there may be patient differences for the current HCV screening criterion, such as modifiable factors like substance use and

mental health. These studies suggest that there also might be factors associated with differences in HCV treatment acceptance among different groups of veterans. These studies, however, did not address the issue of whether there were gender differences associated with HCV treatment screening and HCV treatment acceptance, which further supports the need for the current study.

Gender Differences in the Natural History of Liver Disease and Treatment Outcomes

Universal screening for HCV treatment is based on the principle that there are no differences in the effects of HCV on liver disease based on gender. Research data, however, suggest that there are differences in the progression of liver disease between men and women. A study by Poynard et al. (2002) examined fibrosis progression in a large cohort of 4,852 patients from patient records in France, Germany, China, and the US. In the natural history of liver disease associated with HCV, fibrosis is an inflammation of the liver, which, overtime, can lead to cirrhosis or scarring of the liver and possibly death. The study investigators used hazard function, log-rank test, and proportional regression analysis as described previously. These data suggest liver disease progression (fibrosis) in HCV-infected women is different than for HCV-infected men. Women have a steeper acceleration in liver disease at age 60 and that fibrosis started earlier and progressed faster for advanced liver disease in women. Further analysis showed that alcohol use accelerated liver disease in women statistically significantly faster than men (20 vs. 35 years). Using exposure modeling, age at HCV infection was a statistically significant independent factor for disease progression (relative risk = 11.1 after 40 years) and, in those who consumed alcohol, HCV-related disease progression was associated statistically significantly and independently with age at onset of alcohol

use (relative risk = 8.1 after 40 years of age), and gender, with slower progression in males (relative risk = .6).

There are several limitations of this study. Fibrosis progression scores are based on a liver biopsy test, both of which are dependent on the skills and expertise of the individual pathologist. The dependence of the skills of the pathologist means that there may be significant differences in scoring (or interrater reliability) between fibrosis scores across sites and countries. The large data set and the high-volume centers involved in the study might eradicate some of these potential reliability issues. This study's data also are reliant on medical record for behaviors such as date of infection (and, therefore, date of a risky blood-to-blood exposure) and alcohol use, and it may underreport these risky behaviors based on patient disclosure to his or her physician. These data, however, suggest variability in disease progression as a result of age, gender, and other risk behaviors, such as alcohol use. The Poynard study data suggest the need to further examine the specific type (or quality) of responses, by gender, to the current HCV treatment screening, which is one of the purposes of this study.

HCV Treatment and its Potential Serious Side Effects

The standard treatment for HCV is now a combination of pegylated interferon and ribavirin. The pegylated interferon is a one-time per week injection, and the ribavirin involves a daily dose of pills. This combination of therapy has improved patient outcomes substantially since 2003 and, unlike many other infectious diseases such as HIV, a large percentage (40 to 90%) of patients who are treated are able to clear the virus and essentially be cured (Manns, Wedemeyer, & Cornberg, 2006). Thus, with such a high potential benefit or success rate for treating HCV and the high potential costs or

consequences with not treating HCV, including liver transplant or even death, one might question the necessity of universal or any type of screening for HCV treatment in lieu of treating all patients with HCV. Unfortunately, the success of HCV treatment, however, does have its costs. Persons undergoing HCV treatment often have side effects that are a direct result of the treatment. These include flu-like symptoms, nausea, temporary impotence, hair loss, and even mental-health effects including depression or even suicidal ideation (Yee, Currie, Darling, & Wright, 2006). As such, the benefits of not treating some patients for their HCV may outweigh the potential costs, supporting the current universal screening to assess these potential costs or benefits. There are little data, however, on the effects of improvements to modifiable, preexisting negative screening factors, such as depression, on HCV treatment outcomes, especially in women. These data might affect the universal screening by stratifying and qualifying modifiable exclusion criterion from changeable criteria, which is a component of the existing study. The remainder of this section contains some of the limited studies in this area.

Approximately 80% of patients with hepatitis C at VA Medical Centers have psychiatric diagnoses (El-Serag et al., 2002). As such, depression has been considered an exclusion criterion for receiving HCV therapy due to the concern that the treatment itself has been shown to cause or exacerbate depressive symptoms. Risk factors for developing depression while on HCV therapy include the presence of mood and anxiety symptoms prior to antiviral therapy, a history of major depression, being female, higher interferon (HCV treatment) dosage, and longer therapy duration (Raison, Demetrashvili, & Capuron, 2005). Dollarhide et al. (2007) examined the role that a psychiatric condition had on HCV treatment outcomes. This retrospective study of 130 HCV positive veterans

reviewed their medical records for baseline psychiatric and substance-use diagnoses for all patients started on treatment between the period of 2000 and 2004 at a single VA medical center. Chi-square analyses were conducted to examine the association between nominal variables and treatment completion. A logistic regression model was developed within patients who completed HCV therapy using a backward Wald method with only statistically significant variables entered into the model.

The study group was 96.2% male, with a high prevalence of substance use (85.8%) and 52.8% having a comorbid psychiatric disorder and substance-use dependence. Forty percent of all veterans in the study had a history of depression, and 60% were prescribed antidepressants during the course of treatment. After excluding persons who were discontinued due to nonresponse, 13% of patients discontinued therapy as a result of psychiatric adverse effects. The logistic regression analysis, however, showed that only weight ($\geq$ 100 kg) was associated with statistically significantly greater odds of completed treatment (OR = 2.90, 95% CI=1.07 – 7.91) and history of psychiatric or substance-use issues, ethnicity or race, and other comorbid conditions such as cardiac, diabetes, and hypertension were not statistically significant and excluded from the model.

This study has several limitations, including its smaller sample size and its homogeneous, predominantly male population from a single VA medical facility. These issues might limit the study's generalizability to the entire VA population; however, the study's utilization of medical, substance use, and psychiatric medical records does suggest that at least two of the modifiable factors in the current universal HCV treatment screening, substance use and mental health, may not play as great a role in HCV treatment adherence and outcomes as initially proposed. The results of this study also

suggest that, once again, little data are available to validate whether these results are relevant for female veterans.

A number of other research studies (Bini et al., 2005; Fireman et al., 2005; Knott et al., 2006) have investigated some of the modifiable or unchangeable factors that are included in the current VA screening criteria, but the lack of number of women included in these studies make it difficult to examine whether these factors have an impact on women similar to men. For example, the study by Rowan et al. (2005) investigated the role that physical and psychosocial factors played in HCV veteran patients' quality of life.

The Rowan (2005) study utilized validated study instruments including the Short Form 36 and Beck Depression Inventory (BDI) as well as other sociodemographic and clinical measures, such as cirrhosis, comorbid conditions, and HCV virological data. The results of this study showed that depression (according to the BDI) showed the strongest statistically significant relationship to health-related quality of life in patients not on HCV treatment and being considered for treatment (Pearson Product-Moment Correlation Coefficient of -.71). These data suggest also that chronic HCV affects depression and mental health in patients prior to therapy, which does support the current use of mental health, including depression on the current study's HCV screening form. The limitation of the Rowan study, however, is that it was a small study of only 62 patients, it only included 3 women, and, therefore, it may not be generalizable to the entire VA patient population.

Summary

An overview of the increasing number of women veterans in the VA health-care system as well as the high prevalence of HCV infection among veterans was provided in Chapter I. Further outlined in this chapter is the general issue of whether veterans' health services, which are based on a male-dominated biomedical model, are effective and appropriate. Specifically, in this chapter, the need to evaluate gender-neutral screening for health services for female veterans HCV is outlined. This historical lack of women veterans and lack of clinical evidence suggests that little is known in this area, even though there is an increasing prominence of HCV-related health issues and women accessing VA health services.

Chapter II contained a review of the relevant literature pertaining to the independent variable gender and its association with VA health-care and treatment services. This chapter provided a review of the limited empirical studies of other health services for veterans suggesting that there are gender differences in screening factors for other chronic diseases in veterans. This chapter also provided data from other studies suggesting gender differences in health-care utilization and in acceptance for other treatments such as smoking cessation. A review of the literature also examined studies specific to HCV screening and referrals, including some of the 13 screening factors that comprise the standardized HCV screening criteria. Overall, this review of literature suggests that there are contradictory data on the role of gender in overall health and health-services access, including universal screening, among veterans. This literature review also suggests that there are gender differences in treatment acceptance for other diseases; however, there are few empirical VA studies in HCV that would allow the

existing research data to be generalizable or applicable to female veterans with HCV. Furthermore, the review of the literature provides information that there exist data in other chronic diseases suggesting gender differences in medical conditions, including liver-disease progression, risk behaviors, treatment screening, and treatment utilization. Even though literature exists for other diseases, there are no empirical studies that specifically examined gender differences in veterans being screened for HCV treatment, further supporting the need for the current investigation.

Chapter III provides a framework of this study's methodology, including an overview of the original study that is the basis of the current study. Chapter IV provides the results of this study with respect to the four research questions. Chapter V provides a discussion of these data in the context of the limited published data in this area, its implications for practice, and for future research.

CHAPTER III

METHODOLOGY

The purposes of this study were to evaluate whether there are gender differences in veterans' responses to the screening for hepatitis C virus (HCV) antiviral treatment and in those who accept HCV antiviral treatment. HCV antiviral treatment screening and HCV treatment acceptance are two separate decision points for all veterans being considered for HCV treatment. Specifically, this study examined the responses to the 13 exclusion criteria that comprise the Veterans Administration's (VA) universal screening criteria for HCV (Appendix A) not only in the types of responses but also total number of yes responses to the exclusion criteria between female and male veterans. In the group of veterans who are eligible for and offered treatment, this study investigated whether there were gender differences in acceptance of HCV antiviral treatment. This chapter contains a section on the methodology for the study. The chapter includes an overview of the study's research design, study population, data collection, and subsequent data analyses.

Research Design

This study was a secondary analysis of data from a study by Bini et al. (2005) of 4,269 veteran patients recruited from the Gastroenterology, Hepatology, and Infectious Diseases clinics at 24 geographically diverse Veterans Administration (VA) Medical Centers throughout the US between December 1999 and December 2000. The present study examined the data from the Bini study by comparing the responses between the 4,151 male and 118 female respondents to the 13 HCV treatment exclusion criteria as well as the proportion of HCV-infected female veterans who were HCV treatment candidates according to these 13 screening exclusion criteria (see Appendix A).

In order to be considered a treatment candidate for HCV, patients could not have a single yes response to any one of the 13 screening exclusion criteria (see Appendix A). If a patient responds yes to any one of the 13 screening exclusion criteria, he or she was excluded from HCV treatment. The number of persons who did not have a yes response to any of the 13 exclusion criteria comprised the number of persons who meet HCV treatment eligibility, and it is these results that provided the comparison of the number of male and female veterans eligible for HCV treatment. The 13 exclusion criteria comprised the 13 dependent variables for this research question (see Table 1).

This study compared the quantity of responses to all 13 variables between male and female veterans screened for HCV treatment (see Table 1). The quantity of responses is defined as the number of persons who responded to yes for one, two, three, and up to 13 potential screening exclusion criteria responses, rather than just a single determination of yes or no treatment candidacy based on a single yes response. The quality of responses to each variable also was compared by gender, for each of the 13 responses. This was done by categorizing screening factors as modifiable (changeable) factors or unchangeable factors. The responses to unchangeable factors (which are defined as medical laboratory test results, existing medical diseases, or contraindicated other treatments that would be difficult or impossible to change for the patient) and modifiable factors (which are defined as behaviors, conditions, or factors that potentially can be changed by the patient, such as mental health, substance use, and adherence for HCV) were examined (see Table 1). The study also was designed to investigate other factors (such as alcohol use), socioeconomic differences (such as education level), and demographic factors (such as race or ethnicity), if there were gender differences in the

quality of responses; however, these analyses were not necessary and were not conducted.

Table 1
Exclusion Criteria or Dependent Study Variables by Research Question

Research Question (number of variables)	Exclusion Criteria or Variable name
#1 HCV treatment screening (13)	Unchangeable Factors
	Prior HCV treatment
	Hypersensitivity to HCV
	Hemoglobinopathies
	Advanced liver disease
	HBsAb positive
	Preexisting medical condition
	Evidence of ischemia (cardiac)
	Concurrent use of other HCV drugs
	History of organ transplant
	Modifiable Factors
	Ongoing substance use
	Preexisting psychiatric conditions
	Inability to remain compliant
	Patient or partner is pregnant
#2 Other factors associated with gender (6)	Current or recent alcohol use
	Current or recent injection drug use
	Income level $\geq$ \$10,000
	Completed high school or more
	Age $\geq$ 50 years of age
	African-American
#3 HCV treatment acceptance (1)	Treatment acceptance
#4 Reasons for HCV Treatment Nonacceptance (6)	Potential side effects
	Ability to comply
	Contraception issues
	Concerns over substance abuse
	Treatment at a later date
	Other

This study compared the proportion of female and male veterans who were considered treatment candidates according to the universal screening exclusion criteria and who, when offered, accepted the HCV treatment. This comparison was done by comparing the number of yes responses to treatment acceptance by gender. For the purposes of this research question, treatment acceptance was the dependent variable.

Additionally, in the subset of all male and female veterans with hepatitis C who were offered treatment and did not accept treatment, a phi coefficient was used for each of the six potential reasons why the patient did not choose treatment. The six potential responses to HCV treatment nonacceptance comprise the dependent variables for research question number 4. Table 1 provides an overview of the dependent variables for each of the study's four research questions.

Population

Patients were eligible for the Bini et al. (2005) study if they were a U.S. veteran receiving care at one of the 24 participating study sites, were older than 18 years of age, had a positive HCV antibody test (Ortho HCV ELISA version 3.0; Ortho-Clinical Diagnostics, Inc., Raritan, NJ), and were under consideration for HCV treatment with interferon alfa-2b and ribavirin. Patients were excluded from the Bini et al. study if they had no presence of HCV virus by polymerase-chain-reaction testing or if they were coinfected with HIV. There were 4,201 veterans included in the study, of which 4,084 (97.2%) were male and 117 (2.8%) were female. The study population was 50.3 years old ($\pm$ 7.6 years) and racially diverse with 56.9% European American, 29.9% African American, 9.2 % Hispanic American (Black or non-Black), and 3.7% Other. Table 2 provides an overview of the demographics of the study population, stratified by gender. The female veterans in the study were statistically significantly younger. Table 3 provides the results of the independent t tests of age, grouped by gender.

Table 2
Frequencies of Demographic and Socioeconomic Variables of 4,201 Veterans by Gender

Demographic	Females			Males		
Characteristics	Total	f	%	Total	f	%
Age ≥ 50	104	47	46	3,783	1,909	50
African American	117	33	28	4,068	1,220	30
Income <10,000/year	116	38	33	4,046	1,578	30
≤ High-school education	117	22	19	4,064	2,032	50
History of incarceration	84	36	43	3,474	2,570	74
History of drug use	99	43	43	3,677	2,500	68
Alcohol use in past 12 months	116	36	31	4,035	1,949	48

Table 3
Means, Standard Deviations, and Independent t-Test Result for Age
in 3,887 Veterans by Gender

Demographic variable	Gender	f	Mean	SD	t df
Age	Female	104	45.63	7.20	-6.40*
	Male	3,783	50.46	7.61	3,885

*Statistically significant when overall error rate controlled at .05 level

Table 4
Chi-square Results Comparing Demographic and Socioeconomic Variables of Female Veterans Compared with Male Veterans (N = 4,201)

		Female		Male			
Variable	Response	f	%	f	%	Total	χ^2
African American	Yes	33	28	1,220	30	1,253	0.17
	No	84	82	2,848	70	2,932	
Income <10,000/year	Yes	38	33	1,578	39	1,616	1.67
	No	77	67	2,468	61	2,545	
≤ High-school education	Yes	22	19	1,951	48	1,973	38.92*
	No	95	81	2,113	52	2,208	
History of incarceration	Yes	36	43	2,571	68	2,607	40.64*
	No	48	57	903	32	951	
History of drug use	Yes	43	43	2,500	74	2,543	26.43*
	No	56	57	1,177	26	1,233	
Alcohol use, past 12 months	Yes	36	31	1,493	37	1,529	1.73
	No	80	69	2,542	63	2.622	

*Statistically significant when overall error rate is controlled at .05 level

Table 4 provides the results of the chi-square tests of the other socioeconomic and demographic variables, grouped by gender. In addition to being younger, female veterans

were statistically significantly more educated and less likely to have a history of drug use or a history of incarceration compared with the male veterans in the study.

Protection of Human Subjects

For the Bini et al. (2005) study, all persons provided written informed consent to participate. All study data were entered on case-report forms and faxed to a central location (Therapeias Health Management, Claremont, CA) for review and processing. The original study data were cleaned and coded for Excel, Statistical Analysis System (SAS), and Statistical Package for the Social Sciences (SPSS), and these data were stripped of any patient identifiers prior to data analyses. It was in this form that these data were obtained for this study. The Bini et al. study was approved by the local Institutional Review Board (IRB) at each of the 24 medical centers. This study did not require IRB consent from the University of San Francisco because the IRB determined that it was a post-hoc analysis of an existing data set and no additional review was needed.

Study Instruments

This study's two instruments, the HCV treatment screening form containing 13 exclusion criteria and questions #4 and #5 of the HCV treatment candidacy and decision form, were developed and created for a large VA multicenter HCV treatment study in 1999 known as the VA-HCV-001 study group (Bini et al., 2005).

The HCV treatment exclusion criteria form was developed based on the VHA's Standardized HCV Treatment Criteria (Veterans Affairs, 2003). The form is comprised of 13 items. These 13 items were developed utilizing the biomedical model and require a yes-or-no response to each item. A person is defined as being excluded from HCV treatment if he or she responds yes to just one of the 13 responses. The 13 items include

four modifiable factors, ongoing or recent substance use, pregnancy, medical compliance, and preexisting psychiatric conditions (including uncontrolled depression). These factors are part of the HCV screening because they not only can have a negative impact on treatment outcomes or success but also have the potential to cause or exacerbate other adverse effects or medical conditions in patients. For example, substance use, similar to medical compliance, has been linked with treatment adherence and, therefore, treatment success. The HCV treatment is teratogenic, which means that it potentially can cause birth defects. Pre-existing medical conditions are screened for because the HCV treatment can exacerbate existing mental-health conditions. HCV treatment has been associated with depression and suicidal ideations. The screening also identifies nine unchangeable factors, such as a history of organ transplantation or having cardiac issues that also might put the patient at risk (see Appendix A for further details).

The HCV treatment candidacy and decision form was codeveloped by the 24 original VA multicenter study investigators. This form was developed to summarize data on whether a veteran who was screened for HCV treatment was considered a candidate for treatment; using this form, data also were collected on whether the patient agreed to receive treatment or not, as well as seven reasons for not accepting treatment (Appendix B, question # 5). The response choices for each of the questions on this form were developed by the 24 study investigators. These responses were based on the investigators' opinions of what the most frequent responses to each question would be using their clinical experience and available data. The instrument allows for only a single response to this question, which means that only a single yes-or-no response could be recorded to indicate the primary reason that the patient did not accept HCV treatment.

For the purposes of this study, 6 of 7 reasons for not accepting treatment were examined and analyzed. The seventh reason, which states that patients did not want to be in a study, was excluded from the analysis because this was an indicator of study acceptance and was not relevant to the analysis of treatment acceptance. Both study instruments were designed to be completed by the healthcare provider and were developed in a teleform format. This format helped facilitate data collection by allowing each site to scan the forms to a centralized data server.

The HCV treatment screening exclusion-criteria form and the HCV treatment candidacy and decision forms were administered by the study investigator, who was the treating clinician or the study nurse at each site. There are no validity and reliability data available for these forms. Prior to the forms' use in the Bini et al. (2005) study, the forms were piloted at a single site. The single-site pilot including the use of the forms as screening tools with 10 veterans with chronic hepatitis C who were being considered for HCV treatment to assess responses and length of time for completion of each form. Additionally, prior to study enrollment, all study staff met as a group and were trained, as a group, on the use of the forms and data collection for the study. This training included the review of each question and clarification of types of responses, as well as all study protocols and procedures, including patient education and counseling that might result from this screening.

Data Collection

At the time of the original study enrollment, all patients received comprehensive HCV counseling and education, including the risks of HCV transmission, potential positive lifestyle changes, the natural history and prognosis of chronic HCV infection,

and HCV treatment options. Patients were interviewed by trained research coordinators who obtained detailed demographic, clinical, and risk-factor information. Data collected on each patient included age, gender, race or ethnicity, era of military service, level of education, annual household income, use of alcohol, and risk factors for HCV infection, including injection drug use, blood transfusions prior to 1990, combat-related injuries, blood contact during combat, needlestick injuries, acupuncture, tattoo, body piercing, incarceration for more than 48 hours, intranasal cocaine use, and sexual history.

All patients were evaluated for HCV therapy by a trained clinical research coordinator or the study clinician using the standardized 13 exclusion criteria form (see Appendix A), which was based on the current Veterans Health Administration's (VHA) HCV Treatment Recommendations. This standardized screening form was used at all 24 participating medical centers. In addition to determining treatment candidacy according to the 13 standardized exclusion criteria, the study collected data on those veteran patients who were considered eligible for antiviral therapy by the treating clinician. The treating clinician at each medical center was a Gastroenterologist, Hepatologist, or Infectious Diseases specialist who was experienced in the management of patients with chronic HCV infection.

All of the patients who did not meet any of the 13 exclusion criteria for HCV treatment were considered eligible for, and offered, HCV treatment by the trained clinical research coordinator or study clinician. The patient responses to whether he or she accepted treatment was recorded on the treatment candidacy and decision form (see Appendix B), as well as the reasons why they refused therapy (see Appendix B).

Research Questions

The following research questions were investigated:

1. To what extent are there gender differences in the quantity and type (whether they are modifiable or not) of responses to standardized patient screening in veterans with chronic HCV?

2. If there are gender differences in the type of responses to standardized patient screening, is this difference associated with risk factors, such as alcohol use, socioeconomic differences, such as level of education, and demographic factors, such as race or ethnicity, of veterans with chronic HCV?

3. To what extent are there gender differences in treatment acceptance in veterans who are offered HCV antiviral treatment?

4. For those who do not accept HCV treatment, to what extent do the reasons for nonacceptance differ by gender?

Data Analysis

To address the quality of responses in research question one, a phi coefficient was used for each of the 13 screening criteria. All responses were considered statistically significant when the overall error rate is controlled at a .05 level using the Bonferroni correction. To further address the quality of responses in research question number one, a subgroup analysis was performed in those veterans who had at least one yes response to any of the 13 screening criteria. This subgroup of veterans who met at least one exclusion criteria were categorized into a group with only changeable exclusion criteria and a group with at least one unchangeable criteria. A chi-square analysis was performed where gender was one variable and the other variable was whether they had only changeable

exclusion screening criteria or not. To further examine the quality of the screening exclusion criteria responses by gender, another chi-square analysis was performed comparing the proportion of female veterans who did not meet any screening exclusion criteria with male veterans. Finally, to address the quantity of responses in research question one, the number of yes responses to the 13 criteria was compared for men and women using an independent-samples t test with a significance level of .05.

To address research question two regarding differences in risk factors (such as alcohol use), socioeconomic differences (such as education level), and demographic factors (such as race or ethnicity), a log-linear analysis was designed to be performed on the risk factors, gender, and exclusion criteria only if there were gender differences in the quality and quantity of responses to standardized HCV treatment screening.

To address research question three regarding differences in patient acceptance, a chi-square analyses was performed where gender is one variable and the other variable was the response to the question whether the patient agreed to receive treatment (see Table 1 or Appendix B, #4).

To address research question four, a phi coefficient was used for each of the six potential reasons why the patient did not choose treatment and the other variable was gender. The overall error rate was controlled at the .05 level using the Bonferroni correction for the coefficients.

Summary

In this chapter, an overview of the population, the data-collection instruments and data analyses for the study were provided. This information highlights the fact that it was a large study population, with a large amount of data collected to examine potential

differences in HCV treatment screening and HCV treatment acceptance. Chapter IV contains the results of this study with respect to the four research questions. Chapter V has the discussion of these data in the context of the limited published data in this area, its implications for practice, and for future research.

CHAPTER IV

RESULTS

The purposes of this study were to examine gender differences in veterans' responses to screening for HCV antiviral treatment and gender differences in the acceptance of HCV antiviral treatment. Chapter IV provides the results of this study by each research question.

Research Question 1

To what extent are there gender differences in the quantity and type (whether they are modifiable or not) of responses to standardized patient screening in veterans with chronic HCV?

The 13 universal screening criteria were analyzed using a phi coefficient to investigate whether there were differences in the type of responses for female and male veterans. The results of the phi coefficient for all 13 universal criteria were all close to zero (see Table 5 for more details). Overall, only 4 of the 13 universal screening criteria had more than 5% yes responses for either male or female veterans, preexisting medical conditions, evidence of advanced liver disease, substance use, and psychiatric issues. For these criteria, female and male veterans had psychiatric conditions (18.8% and 18.0%), preexisting medical conditions (16.2% and 19.3%), and evidence of advanced liver disease (3.4% and 6.0%), but these differences were not statistically significant. The proportion of female veterans who were excluded from HCV treatment due to substance use was 12.8% compared with 20.3% for male veterans; this difference was not statistically significant when the overall error rate was controlled at a .05 level using the Bonferroni correction. Table 5 shows further details of this analysis.

Table 5
Phi Coefficient Results Comparing the Yes and No Responses to the 13 Standardized Patient Screening Exclusion Criteria in Veterans

Screening Criteria	Total	Response	Gender: Female f	Female %	Male f	Male %	Phi
Prior HCV treatment	4,133	No	115	98.3	4,018	98.6	-.004
		Yes	2	1.7	59	1.4	
Hypersensitivity	4,193	No	117	100.0	4,076	100.0	.003
		Yes	0	0.0	1	0.0	
Anemia	4,120	No	116	99.1	4,004	98.5	.008
		Yes	1	0.9	59	1.5	
Liver disease	3,927	No	113	96.6	3,814	94.0	.018
		Yes	4	3.4	244	6.0	
Hepatitis B Positive	3,974	No	117	100.0	3,857	98.3	.022
		Yes	0	0.0	66	1.7	
Preexisting conditions	3,364	No	98	83.8	3,266	80.7	.013
		Yes	19	16.2	781	19.3	
Unapproved treatment	4,159	No	116	99.1	4,043	99.4	-.005
		Yes	1	0.9	25	0.6	
Ischemia	3,996	No	115	98.3	3,881	95.9	.020
		Yes	2	1.7	167	4.1	
Organ transplant	4,146	No	115	98.3	4,031	99.0	-.011
		Yes	2	1.7	41	1.0	
Substance Use	3,338	No	102	87.2	3,236	79.7	.031
		Yes	15	12.8	824	20.3	
Psychiatric conditions	3,420	No	95	81.2	3,325	82.0	-.003
		Yes	22	18.8	730	18.0	
Inability to comply	4,017	No	114	97.4	3,903	95.9	.013
		Yes	3	2.6	167	4.1	
Pregnancy	4,180	No	117	100.0	4,063	99.9	.006
		Yes	0	0.0	5	0.1	

An examination of the quantity of yes responses to any of the 13 screening criteria showed that 2,106 (50.1%) of both male and female veterans had at least one yes response to one of the 13 HCV treatment screening exclusion criteria, and, therefore, were ineligible for HCV treatment. The number of yes responses to the 13 screening exclusion criteria was compared for female and male veterans using an independent-sample t test with a significance level of .05. Overall, there was no statistically significant

difference in the mean number of exclusion criteria between female and male veterans. Table 6 shows the results of this analysis.

Table 6
Means, Standard Deviations, and t-Test Result Comparing Female Veterans with Male Veterans on the number of the 13 HCV Treatment Screening Exclusion Criteria (n= 2,106)

Gender	Mean	Standard Deviation	t df = 2,105
Females	1.48	0.71	.53
Males	1.57	0.74	

Veterans are excluded from HCV treatment if they have a yes response to any one of the 13 exclusion criteria. To further examine the quantity of the screening exclusion criteria responses by gender, a chi-square test was performed comparing the proportion of female veterans who did not meet any screening exclusion criteria with male veterans. Female veterans were significantly less likely to have one or more exclusion criteria when compared with male veterans (41.0% vs. 50.4%). This means that more female veterans were HCV treatment candidates (having no exclusion criteria) when compared with male veterans (see Table 7 for more details).

Table 7
Results of Chi-square Test Comparing the Proportion of Female Veterans Who Met Screening Exclusion Criteria With Male Veterans (N = 4,201)

	Female		Male			
Variable	f	%	f	%	Total	χ^2
No Exclusion Criteria	69	59.0	2,026	49.6	2,095	3.99*
One or more Exclusion Criteria	48	41.0	2,058	50.4	2,106	

*Statistically significant at the .05 level.

To further assess the type of the responses of exclusion criteria, a subgroup analysis of those 2,106 veterans who had at least one yes response to any of the 13 exclusion criteria was further analyzed based on those who had modifiable criteria. There

were no significant differences between the proportion of female and male veterans who had at least one modifiable (potentially changeable) criteria (47.9% vs. 44.9%). Table 8 shows the results of this analysis.

Table 8
Results of Chi-square Test Comparing the Proportion of Veterans Who Had at Least One Exclusion Criteria That Was Only Modifiable Exclusion Criteria With Those Who Only Had Unchangeable Criteria by Gender (n = 2,106)

	Female		Male			
Exclusion Criteria	f	%	f	%	Total	χ^2
Only Modifiable Criteria	23	47.9	923	44.9	946	.66
Nonmodifiable Criteria	25	52.1	1,135	55.1	1,160	

Research Question 2

If there are gender differences in the type of responses to standardized patient screening, to what extent are these differences associated with risk factors, such as alcohol use, socioeconomic differences, such as level of education, and demographic factors, such as race or ethnicity, of veterans with chronic HCV?

This data analysis was not performed because there were no statistically significant differences in the type of responses to standardized patient screening criteria

Research Question 3

To what extent are there gender differences in treatment acceptance in veterans who are offered HCV antiviral treatment?

In this study, 2,095 veterans did not have any exclusion criteria; 2,026 men and 69 women were eligible for HCV treatment. There were 39 veterans excluded from the treatment acceptance phase of the study because of their nonconsent to participate. This meant that 2,056 (98.1%) of all veterans without any exclusion criteria were included in this analysis.

Overall, 931 (45.3%) veterans did not accept HCV treatment. There were no statistically significantly differences in the number of female veterans who accepted HCV treatment compared with male veterans (50.0% vs. 54.9%). Table 9 shows the details of this analysis.

Table 9
Chi-square Results Comparing the Proportion of Female Veterans Who Were Offered HCV Treatment But Did Not Accept Compared With Male Veterans (n = 2,056)

	Female		Male			
Variable	f	%	f	%	Total	χ^2
Did not accept HCV Treatment	33	50.0	898	45.1	931	.61
Accepted HCV Treatment	33	50.0	1,092	54.9	1,125	

Research Question 4

For those who do not accept HCV treatment, to what extent do the reasons for nonacceptance differ by gender?

There were 931 persons who did not accept treatment. Of these, 62.2% provided a reason why they did not choose to accept treatment. The primary reason for not accepting treatment for both female and male veterans was wanting to defer treatment (57.1% vs. 59.0%); there was no statistically significant difference in this response. The second most common reason for not accepting HCV treatment was the concern over HCV treatment side effects, (23.8% of all female veterans compared with 10.6% male veterans), but the difference in the concern over HCV treatment side effects was not statistically significant. The results of this analysis are provided in detail in Table 10.

Table 10
Phi Coefficient Results Comparing the Reasons for HCV Treatment Nonacceptance by Gender (n = 579)

		Gender				
Reason for HCV Tx		Female		Male		
Nonacceptance	Response	f	%	f	%	Phi
Side effects	No	16	76.2	499	89.4	-.02
	Yes	5	23.8	59	10.6	
Inability to comply	No	20	95.2	522	93.5	.01
	Yes	1	4.8	36	6.5	
Pregnancy	No	21	100.0	557	99.8	.85
	Yes	0	0.0	1	0.2	
Substance Use	No	21	100.0	553	99.1	.02
	Yes	0	0.0	5	0.9	
Treatment Later	No	9	42.9	229	41.0	.01
	Yes	12	57.1	329	59.0	
Other	No	18	83.8	492	88.2	-.01
	Yes	3	16.2	66	11.8	

Summary

In this chapter, the results of the data analyses for the study's four research questions were provided. These data highlight the fact that female veterans were statistically significantly more likely to be considered candidates for HCV treatment than male veterans. These analyses also suggest that none of the individual responses to the 13 screening criteria for HCV treatment differed statistically between female and male veterans. There also were no statistically significant differences in the quality of responses when comparing female veterans with only modifiable exclusion criteria with male veterans with only modifiable criteria. This chapter also provided results that suggested that there were no gender differences in the acceptance of HCV treatment. In terms of the reasons for nonacceptance, there were no statistically significant differences in the six reasons for nonacceptance either. Chapter V provides a discussion of these data

in the context of the limited published data in this area, its implications for practice, and for future research.

CHAPTER V

DISCUSSION, CONCLUSIONS, AND IMPLICATIONS

The purposes of this study were to evaluate whether there were gender differences in veterans' responses to the screening for Hepatitis C Virus (HCV) antiviral treatment and gender differences in those who accept HCV antiviral treatment. HCV antiviral treatment screening and HCV treatment acceptance are two separate decision points in the treatment process for all veterans being considered for HCV treatment. This study then would provide additional data to evaluate the efficacy of the Veterans Administration (VA) current utilization of its universal, gender neutral screening for HCV treatment. This chapter provides a discussion of this study's results, as well as any conclusions and implications these may have for current practice and future research.

In chapter IV, the study data highlighted the fact that female veterans were statistically significantly more likely to be considered candidates for HCV treatment than male veterans. Other than the gender difference in the quantity of female veterans who were considered HCV treatment candidates, there were no statistically significant gender differences in the quality of responses when comparing female veterans with only modifiable exclusion criteria with male veterans with only modifiable criteria or in acceptance of HCV treatment.

Limitations

There are several limitations of this study. First, this study's findings address a veteran population and may not be generalizable to a nonveteran population. Second, although the process of patient screening and eligibility utilized a standardized screening form, the process of patient treatment acceptance within the study did not follow a similar

standardized protocol, which might introduce providers' bias in their approach to educating and offering HCV treatment. In other words, the way that a provider counsels and offers treatment to a patient may have differed between sites. This provider bias could potential skew the patient treatment acceptance responses, but the large sample size and multiple sites could reduce any individual site-specific responses to this issue.

Third, known factors not collected in the original study may have affected the patient's decision to accept HCV treatment, which include a patient who is moving or in transition from one city or region to another, or it might include the patient's HCV genotype (genotype 1 is more difficult to treat than genotypes 2, 3, or 4). Fourth, patients who participated in this study may have non-VA medical insurance (through their employment or a spouse) and had the opportunity to receive medical care and support for HCV outside of the VHA, which might have affected their HCV treatment acceptance decision within the VA. This is not a major limitation, however, because veterans do have access to comprehensive medical coverage within the VA.

A fifth limitation to this study is the large attrition rate of responses for veterans who did not accept HCV treatment. The lower number of responses recorded for veterans who did not accept treatment was probably the result of an oversight of the original study's protocols, which did not require study staff to obtain a response to treatment accceptance. Of the 931 veterans who did not accept treatment, only 62% provided a reason why they did not accept treatment, which might skew or bias the aggregate results; however, the number of male and female nonrespondents was not different, and so it should not be problematic for the examination of differences by gender. A sixth potential limitation is the construct validity and the discriminant ability of the VA's 13 Screening

Exclusion Criteria. In reviewing the responses or lack of responses to many of the 13 criteria, there may be limitations to the screening ability of the current form, and it also limits the statistical power of this study to examine differences between female and male veterans with HCV. In nonveterans studies, there is a potential for participants to underreport their risky or undesirable behaviors; however, in a veteran population, where there is a singular medical record system that includes all of a patient's mental health, substance use, prescription, and related behaviors and where there are no negative repercussions or loss of services due to reporting of undesirable behaviors underreporting would be minimized.

Finally, although this is a very large, multicentered data set and a larger number of women veterans with HCV than previously examined, there are still a disproportionate number of men to women in the data set, which might affect the statistical power of some of the statistical analyses such as the examination of the subset of veterans who did not accept treatment.

Discussion

The prevalence of HCV in the U.S. veteran population is almost three times what it is in the general US population (Dominitz et al., 2005). It is also the leading cause of liver transplantation and liver cancer in the US (Armstrong et al., 2006). At the same time that this high prevalence of HCV and high morbidity and mortality is occurring, the gender composition of veterans is changing, with the number of female veterans accessing VA healthcare services expected to double by 2010 (Meehan, 2006). The high prevalence of HCV, its health toll, and the changing gender composition of VA population raise the issue of whether the existing screening is, indeed, appropriate for

both male and female veterans. An examination of HCV screening and treatment acceptance is especially important to assess because the universal HCV screening form was based on a biomedical model that assesses the symptom regardless of gender, race, ethnicity, and social circumstance. The biomedical model also is built upon evidence-based medicine that has been historically male-oriented (Alonso, 2004).

This study investigated the issue of whether there were gender differences in screening and treatment acceptance in veterans with HCV, and, by this examination, any potential gender biases in the current universal screening. These data suggest that the universal, gender-neutral approach to patient screening appears to be effective for both male and female veterans and, therefore, unbiased based on gender. These study data also highlight the need for further study of the construct and discriminant validity of the screening tool itself. Although there were no statistically significant gender biases in HCV screening, these data suggest that providing different patient counseling, education, and referrals based upon the current set of universal responses may be beneficial. This issue will be further delineated.

In this large multicentered national study of 4,201 male and female veterans with chronic hepatitis C, there was a low prevalence of female veterans (117), which is similar to other studies in the VA (Dominitz et al. 2005; Yano et al., 2006). An analysis of this study's population showed that there were demographic and socioeconomic differences between female and male veterans. In this study, females were statistically significantly younger, more likely to have completed high school, and less like likely to have been incarcerated or to have a history of injection drug use. The younger age of female veterans, as well as female veterans' higher level of education and lower risk factors

relative to male veterans is similar to the population differences identified by a number of other large VA studies by Frayne et al. (2007) and Stecker, Han, Curran, and Booth (2007). These socioeconomic and demographic gender differences are similar to a non-VA study of patients with chronic hepatitis C by Trooskin et al. (2007).

The first research question was designed to examine gender differences in the quantity and type of response to universal screening criteria for chronic hepatitis C, and results of this analysis highlighted the fact that only 49.9% of both male and female veterans with chronic hepatitis C did not have any of the 13 exclusion criteria and, therefore, were eligible for HCV treatment. A further examination of male and female veterans' responses to the exclusion criteria did show a statistically significant difference in the number of female veterans who were eligible for HCV treatment when compared with male veterans. These data suggest that 41.0% of female veterans compared with 50.4% of male veterans were excluded from HCV treatment.

This study's examination of whether there were gender differences in the type of response to each of the 13 exclusion criteria suggested that there were no statistically significant differences between male and female veterans on any of the 13 exclusion criteria. Although not statistically significant, however, 20.3% of all male veterans compared with 12.8% of female veterans reported substance use. This higher substance use among male veterans also was similar to findings by Stecker et al. (2007). Both female and male veterans had a high number of positive responses to substance use (12.8% vs. 20.3%), psychiatric conditions (18.8% vs. 18.0%), and preexisting medical conditions (16.2% vs. 19.3%). The high percentages of veterans with these health conditions are confirmed by other veterans' studies such as the Lehman and Cheung

(2002) study, which reported 44.2% prevalence of depression and 26.7% prevalence of substance use in veterans with hepatitis C, and the Fireman et al. (2005) study that reported 35% prevalence of depression and 21% alcohol issues, respectively.

To further examine the type of response to the 13 exclusion criteria, the subgroup of 2,106 veterans who responded positively to at least one of the 13 exclusion criteria was stratified by those who had only modifiable or changeable conditions versus those who had at least one nonmodifiable criterion. This subgroup qualification is a potentially important distinction to make because if a veteran had at least one of nine nonmodifiable criteria, he or she would never be a candidate for HCV treatment regardless of any health improvements or behavioral modifications. In essence, they will never be eligible for HCV treatment given the current screening exclusion criteria. Those veterans who had only modifiable criteria, however, are patients who may be able make changes and, therefore, change their HCV screening status. This categorization is of great potential importance, because if there were, indeed, gender differences between the groups with unchangeable criteria and those with only modifiable or changeable criteria, it might suggest the need for different management and followup strategies between genders. These study data show that there were no differences between female and male veterans (47.9% vs. 44.9%) with only modifiable criteria. These data suggest that almost half of all veterans, both female and male, with potentially modifiable conditions were excluded from HCV treatment.

Although there were no differences between male and female veterans, almost half (44.9%) of all veterans reported having only modifiable or changeable exclusion factor. These data suggest that a stratified approach to patient education, referrals, and

management should be in place to increase the opportunities for changeable exclusion criteria to be eliminated and thus to increase the number of female and male veterans eligible for HCV treatment. For example, a veteran who is excluded from HCV treatment as a result of his or her substance use could be referred and followed up with substance use counseling and later would be a candidate for HCV treatment.

Another indirect result of the examination of the type of response to the 13 screening exclusion criteria was the low prevalence of yes responses to the majority of these 13 criteria. For example, only three of the 13 responses had more than 5% positive responses for both male and female veterans. This finding suggests the need to further investigate the validity and reliability of the HCV treatment screening criteria for both male and female veterans. The HCV treatment screening form appeared to be fast and easy to complete, so feasibility may not be the issue, but perhaps the discriminant ability of the form should be further examined with so few responses to many of the 13 criteria.

The final research questions (questions 3 and 4) addressed whether there were gender differences in treatment acceptance in veterans who were offered HCV antiviral treatment. In this subanalysis, 45.3% (931) of those who were eligible for HCV treatment did not accept treatment. This result is surprisingly low when one considers these respondents already had participated in a number of procedures to get to the point of an HCV treatment decision, including agreeing to be screened and the full screening criteria, which includes both biomedical (laboratory) and nonbiomedical processes. Given the context of this process, this low percentage of HCV treatment acceptance in this study population even may be higher than a nonstudy population. Regardless, these results highlight the need to further examine patient education and counseling of both male and

female veterans who are eligible for treatment but do not accept HCV treatment. Although HCV antiviral treatment is not 100% effective, it is effective in 30 to 90% of all persons (Yee, Currie, Darling, & Wright, 2006); on this basis, treatment acceptance should be higher for such a high potential cure rate. There were no statistically significant gender differences in HCV treatment acceptance between female and male veterans. This result did not support the findings of the Sherman, Fu, Joseph, Lanto, and Yano (2007) study that concluded that male veterans more likely to access outpatient treatment services for smoking cessation or the Stecker et al. (2007) study where male veterans were more likely to access substance use treatment services compared with women. This study's data did not support the Frayne et al. (2006) study, finding that female veterans were more likely to access outpatient services compared with male veterans.

In this study's examination of whether there were gender differences in the quality of responses to nonacceptance of HCV treatment, the most common responses for nonacceptance in both female and male veterans were concern of side effects and deferring treatment until a later date. The concern over side effects highlights the need for additional patient education and discussion with the veteran patient to insure that they are aware of the potential prevalence of side effects and that they are better able to make an informed decision about HCV treatment. This is important given the ability to manage most of the side effects that patients might encounter and the efficacy of the HCV treatment (Yee et al., 2006). Similarly, it is important to counsel and discuss why a veteran is deferring treatment until a later date. This may relate to a patient's overall health or to his or her decision to wait for new and evolving therapies. Regardless, deferring treatment should be discussed further with the patient to insure that the veteran

patient is making an informed decision. Although there were no statistically significant gender differences in responses to not accepting HCV treatment, there did appear to be a higher percentage of female veterans not accepting treatment compared with male veterans (23.8% vs. 10.6%).

Implications for Practice

There were socioeconomic and demographic differences in female and male veterans with HCV. These data may suggest the need to provide different patient education and counseling services (e.g., brochures or patient videos for different reading levels) to male and female veterans with HCV given that females have a higher level of education than male veterans. These data also revealed that female veterans are less likely to have had a history of drug use compared with male veterans. In planning for appropriate referrals and other linkages to care, it may be beneficial to have more referrals and residential treatment options available for male veterans compared with female veterans.

Another implication of these data for practice is that female veterans were more likely to meet the criteria for HCV treatment than male veterans. The higher treatment eligibility of female veterans should be disseminated during the training and orientation of VA providers throughout health departments and outpatient clinics that are providing care for female veterans with HCV. This training would direct providers to refer and counsel female veterans with HCV to be screened for HCV treatment.

Although only half of all veterans were excluded from treatment, this study's results suggest that almost half of both female and male veterans had potentially modifiable factors and, therefore, should be the target of health education, counseling,

and appropriate referrals (such as substance use counseling and treatment) to improve both female and male veterans' abilities to be eligible for HCV treatment in the future. The data suggest that there is a high prevalence of substance use and psychiatric conditions (12.8 to 20.3%) excluding both female and male veterans from HCV treatment. A multidisciplinary team that included mental-health workers and substance-use counselors who were integrated into the current liver clinic setting where HCV screening occurs would allow for immediate and direct referrals and linkages to these necessary psychiatric and substance use resources. Another potential opportunity is to integrate substance-use and mental-health education into the existing HCV screening brochures that are available to veterans.

Another very important implication for practice is the large number of both female and male veterans who were eligible for treatment and did not accept treatment. In particular, the majority of veterans who did not accept treatment wished to defer treatment or were concerned about the HCV treatment's side effects. Given the opportunity to cure chronic HCV with a short-term (6 months to a year) treatment, it is important that HCV providers are further educated on the topic of HCV side effects, as well as the appropriate management of any potential side effects and potential strategies to improving patient-centered approaches to addressing concerns about side effects for veterans with HCV.

This HCV side-effect education could be implemented through the VA's existing biweekly national teleconference calls with providers, as well as the VA's Hepatitis C Resource Center program by adding side-effect education, patient counseling, and patient communication to its existing training programs. This training could include the addition

of this side-effect and patient-sensitivity training on this topic to the currently available live programs, as well as online for remote HCV providers, and print materials for those who prefer this educational format. HCV provider education on this topic would enhance his or her ability to better educate, counsel, and discuss the concerns about side effects for veterans with HCV and potentially increase the number of veterans who have an opportunity to be cured of their chronic HCV disease.

Finally, although not statistically significant, female veterans did appear to have more concerns with HCV treatment side effects, so there may be a need to provide additional clinical visit time allotted for female veterans to allow for further education and counseling to address the concerns about side effects. Another potential opportunity would be to provide gender-specific group-education classes about HCV. This class could better address side-effect concerns in a safe, nonthreatening group environment. Group education classes have been effective in the VA for substance use and mental-health group counseling for female veterans and could be modeled for female veterans with HCV.

Implications for Future Research

The results of this study suggest a number of areas for future research. One would be an examination of the construct validity and discriminant ability of the VA's current HCV Screening Form. For example, further studies are required to assess whether there is collinearity within the screening criteria and whether this form based upon the biomedical reductionist model actually is screening out the appropriate persons for HCV treatment. A study could be conducted on the existing study data to assess those veterans with successful treatment outcomes with those who were not successful to evaluate the

factors associated with treatment failure. These factors might help identify appropriate screening factors for this patient population. Another correlational study of the 13 exclusion criteria responses should be conducted to investigate if some of these data are addressed by another criterion. For example, if 90% of the persons who responded yes to substance use also responded yes to having a psychiatric condition, it might suggest that only one of these exclusion criteria are necessary for patient screening. As well, a qualitative study of the 13 criterion should be undertaken to address and examine the prevalence of responses to some of the screening questions. In a large study population of over 4,000 patients, 6 of the 13 criteria had fewer than 2% positive responses. A panel or focus group of HCV treatment experts could be convened to examine the 13 criteria and their benefits of inclusion and risks of exclusion on the screening form. This panel or focus group discussion could further examine the positive predictive values and negative predictive values of each of the current 13 screening criteria. For example, the benefit of finding one patient with hypersensitivity to the HCV medication might outweigh the time and burden of screening 4,000 patients for this criterion.

Future research study would be to examine whether the socioeconomic and demographic differences of female and male veterans with HCV is related to their entry into the VA's health system or creates any barriers to accessing healthcare. For example, if male veterans have higher risk factors and are more likely to be incarcerated, are they more or less likely to be able to access VA healthcare than their female counterparts? The results of this study might have major implications for outreach services for patients with HCV.

Other future research studies could include the implementation and evaluation of a number of different patient education or counseling strategies at the screening stage and then at the treatment acceptance stage to learn which were the more effective at increasing the number of veterans who might be eligible for HCV treatment and in increasing the number of veterans who were willing to accept HCV treatment.

Conclusions

The purposes of this study were to evaluate whether there were gender differences in veterans' responses to the screening for HCV antiviral treatment and gender differences in those who accept HCV antiviral treatment. HCV antiviral treatment screening and HCV treatment acceptance are two separate decision points in the treatment process for all veterans being considered for HCV treatment. These study data suggest that there are gender differences in the population of female and male veterans in which females were younger, more educated, and had fewer risk factors.

These study data suggest that there may be gender differences in the quality of responses to HCV treatment screening. Female veterans are more likely to be eligible for HCV treatment than male veterans, because they are more likely to have no exclusion criteria compared with male veterans.

This analysis highlighted the fact that half of all veterans, regardless of gender, were not eligible for HCV treatment. It also appears that half of these veterans, both male and female, had potentially modifiable or changeable exclusion criteria that would indicate that there may be a need for different categorization or use of the existing HCV Screening Exclusion Criteria form: not on the basis of gender but on the basis of whether

an HCV patient has potentially modifiable criteria or unchangeable criteria for further referrals, counseling, and education.

This study did not find any gender differences in the quantity of responses for HCV treatment acceptance but that the rate of treatment acceptance, across genders was extremely low, with only half of those who met the criteria for HCV treatment accepting it. This is a potential source for additional patient education, counseling, and subsequent intervention to increase the number of veterans (both female and male) who accept treatment and potentially are cured of their HCV. Finally, although there does appear to be gender differences in the reasons for nonacceptance, with female veterans more concerned about side effects than male veterans, these data suggest that further intervention and counseling of all patients who do not accept HCV treatment out of concern for side effects is warranted.

The high proportion of all veterans with HCV, as well as this study's identification of the low proportion of veterans who are eligible for HCV treatment, suggests the need to further evaluate the efficacy of the VA's current HCV screening criteria. There are two distinct areas to be considered. One is the need to categorize responses to the current screening criteria into only modifiable or changeable criteria. This categorization would help facilitate patient education, intervention, and treatment for those patients who might be eligible for HCV treatment in the future if they address these modifiable exclusion criteria. The second component is the need to evaluate the actual screening criteria itself. In this large study of veterans with HCV, it is unclear whether the current form has the construct validity and discriminant ability to insure that all veterans, regardless of gender, are being screened appropriately to insure that the greatest

number of veterans who would benefit from HCV treatment are eligible for HCV treatment, with the least amount of risk.

Finally, the universal, gender-neutral approach to patient screening appears to be as effective with both male and female veterans. The need to provide different patient counseling and education, however, based upon this set of universal responses, may be beneficial. For example, the proportion of veterans who do not accept HCV treatment because of fear of side effects may receive different counseling than those who wish to defer treatment. This targeted strategy may improve the number of veterans (male or female) who are eligible for and accept treatment and ultimately increase the numbers of veterans who clear the HCV virus and improve their overall health, by reducing or eliminating the complications of HCV such as cirrhosis, hepatocellular carcinoma, end-stage liver disease, and even death.

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Appendix A
HCV Universal Screening Form

8415

A Multi-Center HCV Treatment Response Trial in U.S. Veterans

Patient Number | Patient Initials | Site Number

FORM S5 PAGE 2

Exclusion Criteria

Patients will be excluded from entry into the Treatment Phase of the study if any of the following criteria apply:

YES	NO	
○	○	Prior treatment with alpha interferon and/or ribavirin.
○	○	Hypersensitivity to alpha interferon or ribavirin.
○	○	Hemoglobinopathies (such as Thalassemia) or any other cause of hemolytic anemia.
○	○	Evidence of advanced liver disease (presence of ascites, bleeding varices, or spontaneous encephalopathy).
○	○	Positive HBs Ag.
○	○	Preexisting medical conditions which could interfere with the patient's participation in the protocol.
○	○	Evidence of ischemia on stress testing, or significant cardiac disease, such as ECG evidence of ischemia, a significant arrhythmia, cardiac failure, recent coronary surgery, angina, or a myocardial infarction within the past 12 months.
○	○	Ongoing or recent substance abuse, such as excessive alcohol, illicit IV drugs, and/or inhaled drugs.
○	○	Concurrent use of unapproved/investigational therapies for HCV during the study period.
○	○	History of organ transplantation.
○	○	Preexisting psychiatric conditions, especially unconrolled depression, or a history of severe psychiatric disorder, such as major psychosis, suicidal ideation, and/or suicidal attempt.
○	○	Inability to remain compliant with the treatment and follow-up procedures outlined in the protocol.
○	○	Patient or their partner is pregnant or actively nursing.

Signature of Submitter

Date of Submission

Please print in capital letters and avoid contact with the edge of the box, as shown below:

1 2 3 4 5 6 7 8 9 0 A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

Appendix B
HCV Treatment Candidacy and Decision Form

55694

Patient Number

Patient Initials

Site Number

A Multi-Center HCV Treatment Response Trial in U.S. Veterans (VA-HCV-001)

FORM S7 10.1999

Form has been sent ☐ Read this form manually ☐

Treatment Candidacy and Decision

1. Did the patient meet the outlined treatment eligibility criteria?

○ Yes ○ No

2. Based on the investigator's judgment, is the patient an interferon/ribavirin treatment candidate?

○ Yes ○ No

3. If you answered "no" to question 2, please classify the reason why.

○ Extrahepatic medical condition
○ Decompensated liver disease
○ Psychological/psychiatric condition
○ Other: _____
○ Ongoing substance abuse
○ Non-compliance with medical regimen
○ Non-compliance with contraception during therapy

4. Did the patient agree to receive treatment?

○ Yes ○ No

5. If you answered "no" to question 4, please classify the reason why.

○ Concerns over potential side-effects
○ Concerns over ability to comply with therapy
○ Concerns over contraception issues
○ Concerns over substance abuse
○ Treatment at a later date
○ Patient did not want to be in a study
○ Other: _____

6. Was the patient enrolled into the Treatment Phase of clinical trial VA-HCV-001?

○ Yes ○ No: Physician's decision ○ No: Enrolled into other investigational study or clinical trial
○ No: Patient's decision ○ No: Received other approved therapy ○ No: Other: _____

7. Patient completed the Screening Phase of clinical trial VA-HCV-001 on

☐☐ / ☐☐☐ / ☐☐☐☐
(DD/MMM/YYYY)

Signature of Submitter

☐☐ / ☐☐☐ / ☐☐☐☐
Date of Submission

Please print in capital letters and avoid contact with the edge of the box, as shown below:

1 2 3 4 5 6 7 8 9 0 A B C D E F G H I J K L M N O P Q R S T U V W X Y Z