Antiviral Therapy Completion and Response Rates Among Hepatitis C Patients With and Without Schizophrenia

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Background: Despite disproportionately high rates of hepatitis C (HCV) among patients with severe mental illness, to date, there is scant empirical data available regarding antiviral therapy outcomes within this population. Objective: To compare antiviral therapy completion and response rates between HCV patients with vs those without schizophrenia (SCHZ). Methods: A regional Veterans Healthcare Administration database was used to identify veterans meeting criteria for this retrospective chart review. All patients confirmed to have SCHZ and to have received antiviral therapy between 1998 and 2006 (n = 30) were compared with a control group of demographically matched (HCV genotype, age, race, gender) patients with no history of SCHZ (n = 30). Results: For HCV patients with genotype 1, antiviral completion, end of treatment response (ETR), and sustained viral response (SVR) rates did not significantly differ between groups. For those with genotypes 2 and 3 combined, antiviral therapy completion rates did not significantly differ between groups; however, the SCHZ group was significantly (P < 0.050) more likely to achieve an ETR and an SVR. For all genotypes combined, the SCHZ patients were no more likely than controls to discontinue therapy early for psychiatric symptoms, medical complications, or other adverse events, and groups did not significantly differ in terms of hospitalization rates during antiviral therapy. Conclusion: Our retrospective chart review suggests that patients with SCHZ complete and respond to antiviral therapy for HCV at rates comparable with those without SCHZ. Based on these data, SCHZ should not be considered a contraindication to antiviral therapy for HCV.

Key words: interferon/mental disorders/psychotic disorders/adverse effects

Introduction

Chronic hepatitis C (HCV) infects approximately 1.8% of adults and 5.4% of veterans in the United States,1,2 and adults with schizophrenia (SCHZ) or schizoaffective disorder are at significantly higher risk for HCV. One study prospectively tested 931 individuals with serious mental illness and found that 19.6% were confirmed to have HCV.3,4 Utilizing a Veterans Healthcare Administration (VHA) medical record database, our group found that, of those tested for HCV, 9.9% (219/2207) of veterans with SCHZ and no documented history of substance-use disorder (SUD) were confirmed to have HCV, compared with 31.1% (943/3029) of veterans with comorbid SCHZ and SUD.5

Although the prevalence of HCV among seriously mentally ill adults is disproportionately high, many providers are reluctant to treat psychiatric patients with HCV because of concerns that antiviral therapy may exacerbate psychiatric symptoms or that patients with psychiatric illness may be less compliant with antiviral therapy.6 In fact, several recent studies demonstrate that individuals with psychiatric comorbidities are significantly less likely to be deemed eligible for or to receive antiviral therapy for HCV.8–10 Our retrospective VHA database study found that patients with comorbid SCHZ and SUD were significantly less likely to receive antiviral therapy for HCV relative to controls without SCHZ or SUD.5 Another VHA database study demonstrated that SUD, major depression, mild depression, bipolar disorder, and SCHZ were each independently predictive of nontreatment for HCV.11

Despite high rates of psychiatric disorders among patients with HCV, there are limited data on HCV treatment outcomes specific to psychiatric populations. One study of 33 HCV positive veterans treated with antiviral
therapy for 6 months found that 6/19 (32%) patients with psychiatric comorbidities developed severe neuropsychiatric side effects leading to antiviral therapy discontinuation, compared with 2/14 (14%) patients without psychiatric comorbidities; both groups had similar virological response rates. Another prospective study found that, compared with nonpsychiatric controls (n = 23), patients with psychiatric comorbidities (n = 16) were no more likely to drop out of HCV treatment, to experience neuropsychiatric or other side effects, or to be nonresponders. A larger retrospective chart review similarly revealed that patients with psychiatric and/or SUDs (n = 294) were as likely as controls without psychiatric disorders (n = 353) to complete and respond to antiviral therapy for HCV. Each of these studies combined psychiatric diagnoses together, so it remains unclear whether specific diagnostic groups yield differential risk for psychiatric side effects, noncompliance, or poor response.

While several case studies report on individuals with SCHZ who have successfully adhered and responded to antiviral therapy for HCV, larger empirical studies investigating HCV treatment outcomes specific to patients with SCHZ have not yet been published. The primary objective of this study was to compare rates of antiviral completion, reasons for early treatment termination, and viral response between HCV patients with vs those without SCHZ.

Methods

We conducted a retrospective medical record review of all patients with SCHZ who received antiviral therapy for HCV between 1998 and 2006 at VHA facilities in the Veterans Integrated Service Network 20 (VISN 20) (Oregon, Washington, Idaho, and Alaska). Using the VISN 20 CHIPS data warehouse, which extracts data from electronic patient medical records at each facility, we first identified a pool of potential study candidates using broad search terms—patients who had a detectable HCV viral load by polymerase chain reaction, were prescribed antiviral therapy between 1998 and 2006 and had a diagnosis of SCHZ on at least one clinic encounter or their problem list (n = 76). Complete medical record reviews were then conducted for patients who met full eligibility criteria for inclusion: (1) laboratory record and progress notes confirmed that the patient was treated for HCV with antiviral therapy and (2) there was no evidence within the medical record that the patient ever met criteria for SCHZ. In total, 10 cases were reviewed and then excluded because 6 had not yet initiated or completed antiviral therapy and 4 had insufficient progress notes to allow review. We made every effort to match cases by age (±5 years), HCV genotype, race, and gender. However, in order to accommodate genotype matching, one SCHZ patient was matched to one control who was 7 years younger. Also, one African American patient with SCHZ was matched to one Caucasian control, and one Caucasian with SCHZ was matched to one African American control. Additionally, 4 patients had unknown genotypes. In 2 of these cases (both SCHZ patients), genotyping was completed, but the results were indeterminate. In the 2 other cases (one control and one SCHZ), genotyping records were unavailable in the chart. Therefore, the one SCHZ with unavailable genotyping records (recommended for 24 weeks of antiviral therapy) was matched to a control with genotype 3 (recommended for 24 weeks of antiviral therapy). One SCHZ with indeterminate results (recommended for 48 weeks of antiviral therapy) was matched to the one control with unavailable genotyping records (recommended for 24 weeks of therapy). The other SCHZ with indeterminate results (recommended for 48 weeks of therapy) was matched to a control with genotype 2 (recommended for 24 weeks of therapy).

Complete medical record reviews were conducted using structured data collection forms to collect data on demographics, mental health history and treatment, psychotropic/antiviral/growth factor prescriptions, liver biopsy and laboratory results, reasons for incomplete antiviral treatment, end of treatment response (ETR), sustained viral response (SVR), and emergency room visits/inpatient hospitalizations during antiviral therapy.

In order to ensure the reliability and validity of our data collection forms and procedures, 7/60 (11.7%, 4 SCHZ, 3 controls) records were reviewed by 2 separate reviewers, blind to each other’s responses. Interrater
agreement on items ranged from 71.4% to 100%; the average rate of agreement was 93.3%.

Definitions

Antiviral therapy included either monotherapy or combination therapy with pegylated or nonpegylated interferon and, in the case of combination therapy, ribavirin. When available, liver biopsy results included both grade of inflammation and stage of liver disease. Reasons for early discontinuation of antiviral therapy were included as described by the treating clinicians and were not mutually exclusive. Treatment completion was defined as a patient completing either 80% or 100% (analyzed separately) of the recommended length of antiviral treatment as indicated by treating providers; typically, recommended treatment length was 24 weeks for genotypes 2 and 3 and 48 weeks for genotype 1 and indeterminate genotypes. ETR was defined as an undetectable HCV viral load upon treatment termination. SVR was defined as an undetectable HCV viral load at least 6 months after treatment termination. Psychiatric disorders and SUDs were based on definitions in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Alcohol-use disorders included abuse as well as dependence. SUDs included abuse of or dependence on any substance other than alcohol or nicotine. Lifetime history of a disorder was based on evidence of the disorder at any point in the medical record. Active diagnoses were based on diagnoses addressed in patient progress notes within 6 months of antiviral therapy initiation. Alcohol and drug use was based on progress notes and urine drug analysis results. A patient was considered to be receiving alcohol or substance-abuse therapy if they were followed by any addiction specialist for individual or group therapy or case management (not just medication management) to specifically address SUD. A patient was considered to be receiving mental health services if they were seen by any mental health specialist (eg, psychiatrist, psychiatric nurse practitioner, psychologist, mental health therapist, psychiatric social worker). A patient was considered to be receiving psychotropic medications regardless of who prescribed them (eg, primary care provider).

Statistical Analysis

Groups were compared in terms of characteristics before, during, and after antiviral therapy. Antiviral completion and response rate comparisons were also subgrouped by genotype. For continuous variables, Mann-Whitney U tests were used to account for nonnormal distributions. Dichotomous variables were evaluated with chi-square statistics if all expected cell counts exceeded 5; otherwise, Fisher exact tests were used. A post hoc binary logistic regression with both groups combined was also conducted, with selected treatment factors entered as categorical independent variables on a single step, and SVR entered as the dependent variable.

Results

Baseline characteristics for the total sample and for each group are included in table 1. The total sample (n = 60) was predominantly male, Caucasian, and middle aged. Due to case matching, groups did not differ in terms of demographic variables or HCV genotype. Within the total sample, 46.7% had genotype 1 and 46.7% had either genotype 2 or 3. The majority of patients had a lifetime history of alcohol-use disorder (65.0%), but only 7.7% of these patients were using within 6 months of antiviral therapy. Half of the total sample had a lifetime history of other SUD (50.0%), and 26.7% of these patients were using within 6 months of antiviral therapy. Groups did not significantly differ in terms of rates of alcohol-use disorders or other SUDs. High rates of active psychiatric disorder (other than SCHZ) were present across both groups. As expected, compared with controls, the SCHZ group was significantly more likely to have been prescribed psychotropic medications at baseline and to have been hospitalized for psychiatric reasons within 5 years of antiviral therapy. Only one patient in the SCHZ group had no evidence of psychotropic medication prescriptions at baseline. This patient reportedly declined psychotropic medications and providers felt this to be acceptable because his course included predominantly negative symptoms and relatively few positive symptoms of SCHZ.

As expected in patients receiving antiviral therapy, most patients within the total sample evidenced abnormally high alanine aminotransferase (75.0%) and aspartate aminotransferase (70.2%) baseline concentrations. Of those with available liver biopsy results within the total sample, 51.6% evidenced advanced stages of liver disease (stage 3 or 4) and 39.3% evidenced advanced inflammation (grade 3 or 4). Groups did not significantly differ in terms of liver functioning laboratory tests or biopsy results. As expected in patients receiving antiviral therapy, most patients within the total sample evidenced abnormally high alanine aminotransferase (75.0%) and aspartate aminotransferase (70.2%) baseline concentrations. Of those with available liver biopsy results within the total sample, 51.6% evidenced advanced stages of liver disease (stage 3 or 4) and 39.3% evidenced advanced inflammation (grade 3 or 4). Groups did not significantly differ in terms of liver functioning laboratory tests or biopsy results.
groups; however, the SCHZ group was significantly more likely than controls to achieve an ETR and an SVR.

Table 3 compares antiviral therapy course characteristics across groups. Within the total sample, most patients received combination therapy with ribavirin (96.7%) and only 2 patients received monotherapy (one in each group). Most patients were prescribed peginterferon alfa-2a (58.3%) or peginterferon alfa-2b (10.0%), but...
31.7% were prescribed nonpegylated interferon (interferon alfacon-1, interferon alfa-2a, or interferon alfa-2b). Although groups did not differ in terms of rates of monotherapy vs combination therapy, controls were significantly more likely than SCHZ patients to have received pegylated vs regular interferon.

Table 3 also compares reasons for early discontinuation of antiviral therapy across groups. Of those who did not complete 100% of the recommended length of antiviral treatment, 20.8% discontinued early for neuropsychiatric side effects, 37.5% for medical side effects, 25.0% for noncompliance issues, and 29.2% for inadequate viral response early into treatment. Only 3 patients discontinued due to serious adverse events. Specifically, one control discontinued for interferon-induced sarcoidosis and one SCHZ patient discontinued for gastrointestinal bleeding. A second SCHZ patient discontinued antiviral therapy due to HCV-related complications, unrelated to antiviral therapy, which led to his death 8 days later. Only one patient (a control) was lost to follow-up during treatment. No patients with a history of alcohol abuse were known to be drinking during antiviral therapy. Although 16.7% of patients with a history of other SUD were using illicit substances during antiviral therapy (4 were using marijuana, one was using nonprescribed morphine), no patient discontinued antiviral therapy early due to substance use. The SCHZ patients were no more likely than controls to have discontinued treatment early for neuropsychiatric symptoms, medical side effects, or other adverse events; however, the SCHZ patients were significantly more likely to discontinue due to noncompliance issues.

Relatively few patients in either group required emergency room visits or inpatient hospitalizations during antiviral therapy, with no significant differences between groups.

Table 3 additionally compares selected treatment factors present during antiviral therapy across groups. Within the total sample, despite high rates of lifetime alcohol-use disorder and SUD, only one patient was followed by an addiction specialist during antiviral therapy. During antiviral therapy, 76.7% of patients received mental health services from a mental health specialist and 61.7% had psychotropic medication dose adjustments. As expected, during antiviral therapy, compared with the control group, the SCHZ group was significantly more likely to have received mental health services from a mental health specialist and to have been prescribed psychotropic medications by any provider; however, groups did not significantly differ in terms of other selected treatment factors.

In order to determine whether patients were more or less likely to achieve an SVR if our selected treatment factors were present during antiviral therapy, a priori chi-square and Fisher exact tests were used to compare patients with and without an SVR regardless of diagnostic group. There was one trend ($P = 0.059$), suggesting that patients who achieved an SVR were more likely
to have received mental health services from a mental health specialist during antiviral therapy than patients who did not achieve an SVR (88.5% vs 67.6%, $P = 0.059$). Comparisons did not approach significance ($P < 0.100$) for other selected treatment factors. A post hoc binary logistic regression similarly revealed that patients who received mental health services during antiviral therapy had a higher likelihood of achieving an SVR (odds ratio = 12.2, confidence interval = 1.2–125.2, $P = 0.035$); no other treatment factors were significantly predictive of SVR.

### Discussion

Our retrospective chart review suggests that patients with SCHZ complete and respond to antiviral therapy for...
HCV at rates comparable to patients without SCHZ. Additionally, our results indicate that patients with SCHZ are no more likely to terminate treatment early due to psychiatric side effects, substance-abuse relapse, or other adverse events. Among those who terminated treatment early, patients with SCHZ were more likely than controls to have noncompliance listed as a reason for early discontinuation, but, based on intention to treat, patients with SCHZ were at least as likely as controls to achieve an ETR and an SVR. In summary, we found no evidence to suggest that a diagnosis of SCHZ uniformly contraindicates antiviral therapy for HCV. Nevertheless, our modest sample size limited our power to detect differences across groups, and replication of results using larger samples is required to confirm conclusions and further clarify outcomes within this population.

Although additional studies are clearly needed, our data and the disproportionately high rates of HCV among patients with SCHZ suggest that excluding this population from antiviral therapy is likely not justified. Indeed, both the National Institutes of Health and the VHA have issued HCV treatment guidelines in which they recommend “establishment of screening tests for all groups at high risk of HCV infection” and the extension of appropriate treatment to special populations infected with HCV, such as those with psychiatric disorders. Our data would, therefore, support treatment of patients with SCHZ who otherwise meet medical criteria for antiviral therapy.

Of note, our study design does not directly explore whether special treatment precautions are necessary to optimize outcomes and safety for patients with SCHZ. Although empirically validated treatment guidelines do not exist for this population, several groups provide HCV treatment recommendations based on their clinical expertise with psychiatrically complex patients. In general, these groups recommend that psychiatric patients be offered antiviral therapy for HCV if they are medically eligible, if they are able to attend medical appointments regularly, and if they are willing to engage in psychiatric and substance-abuse therapy during antiviral therapy. Education about disease course, treatment efficacy, and side effects is strongly encouraged prior to treatment initiation; the Northwest Hepatitis C Resource Center at the Portland VA Medical Center, eg, offers a one-time HCV education group to individuals initially diagnosed with HCV. Mental health and substance-abuse screenings are conducted during this education group and prior to treatment initiation. Individuals who screen positive are referred to psychiatric and substance-abuse treatment programs prior to antiviral therapy initiation and for monitoring of symptoms at regular intervals throughout antiviral therapy. In general, psychiatric medication adjustments and increased supports may be required throughout antiviral therapy should symptom exacerbations or relapses arise. To this end, an increasing number of programs have successfully utilized a multidisciplinary approach to HCV care.

One question that arises is why patients with SCHZ had higher SVR rates relative to controls (with differences reaching significance for all genotypes combined and for genotypes 2 and 3 combined). This finding is particularly surprising given that SCHZ patients were more likely than controls to have received regular interferon, which has been shown to have lower response rates than pegylated interferon. Our study design did not allow us to directly test possible explanations, but we did find that patients with SCHZ were more likely than controls to have received mental health services and psychotropic medications during antiviral therapy. Moreover, we found a trend suggesting that, for both groups combined, patients who achieved an SVR were more likely to have received mental health services from a mental health specialist during antiviral therapy than those who did not achieve an SVR. Future studies should examine whether mental health services or other treatment factors help promote completion and response rates in various populations.

Our study’s primary limitations include its relatively small sample size and its reliance on categorical data, which in combination may have limited our power to detect group differences. For example, although patients with SCHZ did have higher rates of emergency room visits and inpatient hospitalizations during interferon therapy than patients without SCHZ, these differences did not reach statistical significance, raising the possibility of type II error. Results should, therefore, be interpreted cautiously, and prospective studies are needed to better explore the effect of interferon therapy on medical and psychiatric outcomes in patients with SCHZ.

Our study design has several additional limitations. First, the retrospective chart review design precluded use of standardized side effect and symptom rating scales, so it is unclear to what extent providers may have inconsistently documented adverse events. Second, it is unclear to what extent patients who were selected for antiviral therapy may have differed from patients with SCHZ who did not receive antiviral therapy. Providers may have had a tendency, eg, to select certain SCHZ patients for antiviral therapy because they were psychiatrically stable, more likely to attend medical appointments, or had stronger psychosocial supports or resources. Lastly, because so few patients with SCHZ have received antiviral therapy for HCV, our design did not include all patients who received any type of monotherapy or combination therapy with ribavirin, including pegylated and regular interferons. Although response rates appear comparable to those found in clinical trials, they are not specific to one type of interferon therapy, and our small sample size precludes meaningful subanalyses by interferon type. However, because the percentage of those on combination therapy, with the majority being on peginterferon
alfa-2a plus ribavirin, did not significantly differ across groups, we believe our conclusion that group outcomes were similar remains valid.

Despite limitations, our design has certain important strengths. To our knowledge, our study represents the only published empirical data on HCV treatment outcomes for patients with SCHZ. Unlike previous research, our study specifically focuses on patients with SCHZ, rather than combining patients with diverse psychiatric diagnoses together. In order to ensure validity, we confirmed all diagnoses by thorough medical record review and established high interrater agreement for individual data points and the overall study. Moreover, in addition to case matching by salient demographic features, we demonstrated that our SCHZ and control groups were also equivalent in terms of liver disease severity and substance-abuse history. Thus, we have eliminated important factors that could have otherwise differentially impacted group outcomes. Based on these findings, HCV patients with SCHZ should be considered potential candidates for antiviral therapy.

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