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The Impact of Lifetime Drug Use on Hepatitis C Treatment Outcomes in Insured Members of an Integrated Health Care Plan

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Abstract

Background—The relation of drug use to HCV treatment outcome in an insured household population has not been previously reported.

Methods—Lifetime frequencies of marijuana use and non-medical use of stimulants, sedatives, and opioids; hallucinogens; and inhalants were retrospectively assessed in 259 privately insured members of an integrated health care plan treated for chronic hepatitis C virus infection (HCV+) with pegylated interferon alpha and ribavirin and examined with respect to rates of sustained virological response (SVR).

Results—The majority of patients reported chronic use of multiple illegal drugs; 61.6% reported injection drug use (IDU); 79.5% abstained from drug use during the six months prior to HCV treatment. Total frequency of individual drugs, multiple drugs, and length of abstention from drugs prior to HCV treatment were not related to impaired SVR rates. Sustained viral responses were obtained in 80.2% of patients with HCV genotype 2/3 and 45.1% of patients with genotype 1/4/6. Marijuana use during HCV treatment, reported by 8.5% of patients, was associated with higher treatment adherence (95.5% compared with 78.9%, p=0.045), but lower SVR rates (40.9% compared with 62.5%, p=0.041). In addition, drug use during HCV treatment was associated with significantly higher relapse rates, 18.8% compared with 7.7% (p=.053).

Conclusion—A history of chronic illegal drug use should not be considered a deterrent to HCV treatment in members of an integrated health care plan who are motivated to seek treatment and

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closely monitored, but drug use during HCV treatment, including marijuana use, should be discouraged.

Keywords

Lifetime drug use; hepatitis C; retrospective cohort study; intravenous drug use; marijuana

1. INTRODUCTION

Prevalence estimates of chronic hepatitis C virus infection (HCV+) in the United States range from 3.2 million (Holmberg et al., 2013) to over five million persons (Chak et al., 2011) all of whom are at risk for progressive disease that can lead to cirrhosis, decompensation, hepatocellular carcinoma and death (Davis et al., 2010). Although eradication of the virus slows the progression of liver disease, improves health-related quality of life, and reduces liver-related mortality (Spiegel et al., 2005), it is estimated that only five to six percent of HCV+ cases have been successfully treated, and these estimates are based disproportionately on persons with private health insurance (Holmberg et al., 2013). Without substantial increases in the diagnosis and treatment of HCV+, it is projected that morbidity and mortality related to hepatitis C will increase markedly over the next two decades (Davis et al., 2010).

The most frequent cause of hepatitis C infection (HCV) is intravenous drug use (IDU), and it is responsible for up to 60% of recently acquired hepatitis C (Alter and Moyer, 1998). Therefore, it is not surprising that a history of IDU is often encountered when treating HCV +. Guidelines recommend that HCV treatment be individualized for patients who currently use illicit drugs, but are willing to participate in a substance abuse program (such as a methadone program), and specify that candidates should be abstinent for a minimum period of six months (Ghany et al., 2009). However, in patients who acquired their HCV from past IDU, it is often difficult to determine whether there is ongoing substance abuse. Many clinical trials exclude these patients, and they are also at risk of being excluded from treatment in clinical practice. For this reason, few studies have investigated the effect of drug use in patients treated for HCV. The largest, conducted in veterans, found that rates of HCV treatment eligibility, acceptance, treatment completion, and sustained viral response (SVR) were comparable in patients with and without a history of IDU (Seal et al., 2007). Reviews of HCV treatment among clients of methadone maintenance programs and patients with a history of IDU recruited from hospital-based clinics reported SVR rates ranging from 18 to 94% (Novick and Kreek, 2008; Hellard et al., 2009). Two studies of cannabis use during HCV treatment found that it was associated with increased treatment completion and higher SVR rates (Sylvestre et al., 2006; Costiniuk et al., 2008).

The numbers of patients who initiated HCV treatment in many of these studies were relatively small; the methodological approaches employed were quite varied; and it was concluded that more research is warranted to improve the effectiveness of HCV treatment delivery to patients with a history of IDU (Hellard et al., 2009). Unfortunately, research on health services for HCV provided in substance abuse treatment programs in the United States found barriers to treatment that included funding, health insurance benefits, patient acceptance, and staff training (Bini et al., 2011, 2012).

We know of no studies on the lifetime history of drug use and its relation to HCV treatment in privately insured populations. National survey data indicate that 61% of subjects positive for HCV antibody (anti-HCV+) are insured, and 35% of these are privately insured (Stepanova et al., 2011). Accordingly, privately insured subjects accounted for more than half of the anti-HCV+ cases having the greatest potential to access HCV treatment. In this

study we address the lack of data on this important subgroup by reporting lifetime drug use in a cohort of privately insured HCV+ patients and its effect on treatment with pegylated interferon alpha and ribavirin. We previously reported the effect of lifetime alcohol use on HCV treatment outcome in this cohort (Russell et al., 2012). The current report contributes to the literature on HCV treatment in three ways. One, HCV treatment outcomes have been understudied in insured patients. Two, it contributes to the limited information available on the relation of drug use to outcomes of treatment with pegylated interferon alpha and ribavirin (P/R). Three, and most significantly, it is based on an in-depth assessment of lifetime drug use, including marijuana, stimulants, sedatives, opioids, hallucinogens, and inhalants, as related to the length of abstinence prior to initiation of antiviral therapy and drug use during four critical periods: 1) prior to HCV diagnosis; 2) from HCV diagnosis to initiation of antiviral therapy; 3) during HCV treatment; and 4) the six-month period after the end of treatment. Specific goals were: 1) to determine the impact of non-medical prescription drug and marijuana use on HCV treatment completion and outcomes; 2) to investigate the relation of pretreatment length of abstinence to treatment outcomes; and 3) to determine whether former drug users began using drugs again while receiving P/R treatment.

2. MATERIALS and METHODS

Patients were members of an integrated health care system in Northern California with HCV naïve to previous treatment with interferon based antiviral therapy, who initiated treatment with P/R between January, 2002 and June, 2008. Hepatitis C treatment was headed by a HCV registered nurse (RN) and a hepatologist with back up from all sub-specialties including psychiatry, chemical dependency, and internal medicine. All patients presenting for treatment were assessed for drug dependency by the referring gastroenterologist, and policy was to require a six-month period of abstinence from alcohol and drugs prior to HCV treatment. Patients thought to be abusing substances were referred to a chemical dependency specialist for evaluation and treatment if necessary prior to antiviral treatment. The RN monitored patients closely during treatment for treatment adherence and side effects, but no routine toxicology tests were done.

2.1 Procedures

Patients were identified by searching the electronic pharmacy records between January, 2002 and June, 2008 for initial ribavirin prescriptions. Their primary care physicians were sent a description of the study and asked if any of the identified patients should be excluded because they were too ill, did not speak English, were cognitively impaired, or otherwise thought to be ineligible. Eligible patients were sent a letter inviting them to participate in the study. It explained the purpose of the study; its requirements (i.e., a 90-minute interview covering sensitive material, including questions on alcohol and drug use, and extraction of data from patients' electronic and paper medical records); its voluntary nature; and the complete confidentiality of all information provided. Participants were offered a subject fee of $75 to compensate them for their time and travel expenses. A telephone number was provided to schedule an interview appointment, or to request removal from the list of eligible participants. Patients were given time to respond and then telephoned by our project manager who offered to answer any questions patients had about the study and to schedule an interview appointment. Prior to the interview patients were sent a Lifetime Event Calendar and asked to use it to record ages at which significant events occurred in their lives and bring it to the interview. The interview was conducted in a completely different site from where they received their HCV treatment. The interviewer obtained a signed informed consent and reviewed the Lifetime Event Calendar prior to administering the interview. Plans for safeguarding human subjects were approved by Institutional Review Boards at the

Kaiser Permanente Sacramento Health Care Center and the Pacific Institute for Research and Evaluation.

2.2 Sample

Of 2,315 patients with HCV+, 608 (26.3%) initiated treatment with P/R from January, 2002 to June, 2008; 421 were eligible for the present study. Reasons for exclusion included the following: not treatment naïve (n=62), no longer members of the health care plan (n=61), died (n=35), post-transplant (n=20), four were co-infected with HBV or HIV, three were not recommended for study by their primary care physicians, one was not English-speaking, and one was too ill. Data for three additional patients were lost due to a computer failure; 95 (22.6%) refused, and we were unable to contact 67 (15.9%). Interviews were completed with 259 (61.5%) of the eligible patients.

2.3 Measures of drug use

Use of the following drugs was assessed retrospectively using the Lifetime Drug History (LDH), a computer-assessed personal interview adapted from the Cognitive Lifetime Drinking History (CLDH), which was developed to improve recall in studies relating alcohol consumption to chronic disease (Russell et al., 1997): marijuana; stimulants (amphetamines, methamphetamines, cocaine/crack or diet pills); opiates (heroin, codeine, Demerol, morphine, Percodan, methadone, Darvon, opium, or Dilaudid); sedatives (tranquilizers, sleeping pills, barbiturates, Seconal, Valium, Xanax or Quaaludes) and Inhalants or solvents (glue, gasoline).

A lifetime history of use was obtained for every drug patients reported using five or more times. Intervals of life during which drug use was either relatively homogeneous, or respondents did not use drugs were defined by asking patients their *age at first drug use*; when their drug use changed; whether they used more, less, or stopped using; and if they stopped using, whether they ever started using the drug again. Frequency of drug use (i.e., every day, nearly every day, three to four times a week, twice a week, once a week, two to three times a month, once a month, seven to 11 times in a year, three to six times in a year, once or twice in a year), was assessed for each of the defined intervals. Frequency of use was summed across intervals to yield *total days of drug use in lifetime*. Patients were encouraged to use the Lifetime Event Calendar during the interview to help them recall their activities during different periods of their life and whether drug use was associated with these activities. In addition to asking about lifetime drug use, *patients were asked about the frequency of drug use after HCV+ was diagnosed (coded yes/no), during HCV treatment (coded yes/no), or after HCV treatment while waiting six months for their follow-up SVR test (coded yes/no)*.

Information on chemical dependence (CD) diagnosis was extracted from an electronic database for Outpatient Services Clinical Records dating back to 2000. Primary care physicians and specialists complete an outpatient services clinical record on which they check off patients' current and ongoing medical problems, including alcohol and drug abuse, every time they see a patient. Date and type of visit to the health care plan's Chemical Dependency Recovery Program have been recorded electronically since 2000. Patients having a record of at least one group visit were considered to have a recent history of CD treatment.

2.4 HCV treatment measures

Information on HCV treatment was extracted from the electronic medical records and medical records kept by the Gastroenterology (GI) department. Treatment records were kept by a single nurse who recorded all HCV-related laboratory and pathology findings; she

completed a flow sheet summarizing adverse reactions and changes in interferon and ribavirin dose for each patient at each visit to the GI Department. Visits were scheduled at week one, week two, and at least every four weeks thereafter. Study measures extracted from these records included genotype (2/3 vs. 1/4/6), pretreatment viral load (<600,000 IU/ml vs. >600,000 IU/ml), and Metavir stage 3 or 4 (advanced fibrosis) vs. stage 0–2 (not advanced). Stage was determined by histology, but in the absence of a liver biopsy, patients were also considered to have advanced fibrosis if they had platelet count <110,000, AST>ALT, and splenomegaly. Records contained data on all premature treatment discontinuations, including date and reason (i.e., adverse reactions to treatment or noncompliance). Treatment that was appropriately stopped because of early non-response was coded as failure to obtain an SVR, not treatment discontinuation. Dose reductions were evaluated as to whether or not patients received 80% of recommended pegylated interferon alpha, 80% of ribavirin, 80% of the time (80-80-80) (McHutchison et al., 2002). Also extracted were data on end of treatment response (ETR) and SVR.

2.5 Analyses

Relations of known host and viral risk factors and lifetime drug use to SVR were examined using Chi-square statistics for cross-tabulations. Cross-tabulation analyses were also conducted to detect potentially confounding relationships between host and viral risk factors and lifetime drug use. Multiple logistic regression analyses were used to determine the independent contributions of host, viral, and drug use factors to SVR failure.

3. RESULTS

Analyses for response bias: comparison of eligible patients who were and were not interviewed revealed that interviewed patients tended to have somewhat higher SVR rates (60.6% vs. 55.4%, p = .304) and were somewhat more likely to have a chemical dependency diagnosis mentioned in their medical record (30.9% vs. 26.6%%, p = .357); or a record of recent treatment for chemical dependency (7.7% vs. 4.5%%, p = .207), but none of these differences were statistically significant.

Patient demographics, medical risk factors, and drug use are reported according to SVR in Table 1. SVR was obtained for 80.2% of patients with genotype 2 or 3 and 45.1% of those with genotype 1, 4, or 6 (p <.001). As expected, SVRs were highest among patients who completed treatment; somewhat lower, but not significantly so, among patients whose doses were reduced to less than 80-80-80; and significantly lower among patients who discontinued treatment prematurely. Discontinuation was most often related to adverse effects (10.6%); only 2.4% of the cohort discontinued because of non- compliance. Lower SVR rates were also associated with ethnicity other than White, not Hispanic, pretreatment viral load > 600,000, and advanced fibrosis. Drug use was prevalent among the cohort. Only 11.6% reported using no drugs; 57.9% used 3 or more drugs; and 61.2% of our patients reported an IDU history. However, SVR rates were not lower among patients reporting drug use.

The relation of lifetime frequency of drug use to SVR is examined in Table 2. It revealed a tendency for frequency of drug use to be higher among patients who obtained an SVR, reaching statistical significance for stimulant use and inhalants. This finding was investigated further using multiple logistic regression analysis to estimate the relation of drug years to SVR taking potentially confounding factors into consideration (Table 3). An odds ratio of less than one was observed for drug years, indicating a somewhat lower likelihood of failing to achieve an SVR associated with higher lifetime frequency of total lifetime drug use.

We also determined length of abstinence prior to HCV treatment, use during HCV treatment, and use during the six months following treatment for each drug (Table 4). The greatest number of patients reported having abstained for 10 years or more prior to treatment, often having quit using drugs prior to HCV diagnosis. Sustained viral response rates were not significantly influenced by length of abstinence prior to treatment from any of the individual drugs listed in Table 4. Abstinence from any drug use during the six months prior to HCV treatment was reported by 79.5% of the cohort; SVR rate was 62.1% among patients abstinent for six months or more compared to 54.7% (p = .324) among those who used one or more drugs during the six months prior to HCV treatment.

Although no patients prospectively reported drug use during treatment, 27 (10.4%) retrospectively reported using drugs during HCV treatment, most often marijuana (N=22, 8.5%). Indeed, several patients who had quit using marijuana reported that they started using it again to cope with side-effects caused by HCV therapy. Marijuana use was associated with a higher likelihood of reported adherence to both pegylated interferon and ribavirin; 80-80-80 rates were 95.5% in patients using marijuana during HCV treatment compared with 78.9% in those who did not (p for one-sided exact test = 0.045). However, it was associated with significantly lower SVR rates, 40.9% in patients who used marijuana during HCV treatment compared with 62.5% in patients who did not (p for one-sided exact tests of significance = 0.041). This effect on treatment outcome remained significant even after adjusting for other demographic and viral risk factors (Table 5).

None of the patients reported relapsing to IDU during HCV treatment. Although 22 patients reported using drugs either during treatment or during the 6 months after treatment, only 12 patients used drugs during both time periods. The relation of drug use during and after HCV treatment was examined with respect to relapse in 188 patients who obtained an ETR; 32 (17%) relapsed. Drug use was associated with significantly higher relapse rates: 18.8% compared to 7.7% in patients who did and did not use drugs during HCV treatment (p=0.053), and 15.6% compared to 7.7% in patients who did and did not use drugs in the six-month period after treatment (p=0.154).

4. DISCUSSION

Our main finding is that a history of chronic, illegal drug use was prevalent among our cohort of privately insured patients, but that it was not associated with lower SVR rates in patients who did not use drugs during HCV treatment. However, SVR rates were significantly lower among patients who reported smoking marijuana during HCV treatment, even though marijuana smoking was associated with higher treatment completion rates. This is in contrast to what has been reported by others (i.e., that marijuana use during treatment was associated with both increased adherence to therapy and higher SVR rates (Sylvestre et al., 2006; Costiniuk et al., 2008). This difference may be related to the fact treatment completion rates in our cohort of patients who did not use marijuana during treatment were higher than those in previous studies--78.9% compared to 49% in clinic patients who did not take oral cannabinoid-containing medication (Costiniuk et al., 2008) and 59% in methadone maintenance patients who did not smoke marijuana (Sylvestre et al., 2006). Thus, it may be that smoking marijuana or using oral cannabinoid-containing medication during HCV treatment has a negative effect on SVR that is evident only in patient populations having high HCV treatment completion rates, and that these negative effects are offset in patient populations having lower treatment completion rates by positive effects on treatment adherence. Herzode and colleagues have reported that marijuana smoking is associated with accelerated fibrosis in patients with hepatitis C (Mallet et al., 2008).

Findings that more frequent use of stimulants, inhalants, and total drug use were associated with somewhat higher SVR rates are counter-intuitive, and we do not believe that they are clinically meaningful. Patients were told their data would be kept confidential, even from their care providers, but it is possible that patients who did not obtain an SVR might have minimized their drug use if they thought it might jeopardize their future treatment. However, successfully treated patients had little reason to exaggerate their drug use, and the high numbers of drugs used and high frequencies of use reported both by patients who did and did not recover supports our conclusion that SVR rates were not impaired by a history of chronic, illegal drug use in this population.

This is the first time that the relationship of lifetime drug use to HCV+ diagnosis and treatment in privately insured patients has been reported. We took a retrospective approach to assessing lifetime drug use in treated HCV patients because we thought that patients would be more forthcoming about drug use immediately prior to and during HCV treatment if they were no longer preoccupied with maintaining treatment eligibility. Indeed, this was the case, although no drug use in the six months prior to and during treatment had been noted by clinic staff prospectively, retrospectively about 20% of the patients said they had used use one or more drugs during the six months prior to treatment, and about 10% used during treatment, mostly marijuana. Heavy use of multiple drugs in late adolescence and early adulthood was reported by many patients, but the majority of patients who used drugs stopped taking them more than ten years prior to treatment, often before HCV was diagnosed.

A potential limitation of these findings concerns the validity of retrospective measures for lifetime patterns of drug use. Prospective ascertainment of drug use poses fewer problems concerning memory than retrospective ascertainment, but this advantage is offset by the problems involved in long-term studies of rare chronic diseases. In the short-term, intense pressure on patients to reduce their drug use prior to treatment seemed likely to foster denial. We chose to study patients who had already been treated to reduce denial. As indicated earlier, the LDH was patterned after CLDH, which was designed to stimulate memory of past drinking, and test-retest studies of the latter indicated good reliability (Russell et al., 1997). In addition, several studies have found that heavy drinkers report higher alcohol intakes retrospectively than prospectively (Czarnecki et al., 1990; Ernhart et al., 1988; Simpura and Poikolainen, 1983), which suggests that people may be more comfortable reporting past rather than current drug use.

Our cohort represents a privately insured population. Although, consistent with the fact that the majority of HCV transmission takes place via contaminated drug paraphernalia (Alter and Moyer, 1998), the majority of our patients had a history of chronic, illegal drug use in late adolescence and early adulthood, they differ from patients recruited from drug treatment programs in that few, if any, were withdrawing from recent heavy drug use or coping with methadone maintenance. Drug use in our cohort tended to decrease with age, often leading to abstinence even before HCV was diagnosed. This may reflect a maturing out of drug use, a phenomenon studied in greatest depth with respect to alcohol abuse (Verges et al., 2012). One explanation for the decrease in drug use during early adulthood is that continued use is incompatible with assuming responsibilities associated with adult roles, such as getting a job, getting married, and having children. This explanation is consistent with the high rates of employment and marriage seen in this privately insured cohort. It may also be that the prevalence and/or severity of lifetime drug dependence in these patients was relatively low, given that severely dependent patients who were unable to stop using drugs were screened out of HCV treatment. Fewer than 30% of HCV+ members of the health care plan had been treated at the time of this study, and additional research is urgently needed to ascertain the

extent to which ongoing substance abuse may be a barrier to HCV treatment in these patients.

Success in treating IDUs recruited from methadone maintenance programs has been achieved by providing intensive, integrated care (Novick and Kreek, 2008). Integrated care and aggressive follow up by telephone and in clinic may have contributed to the high treatment completion rates and SVR achieved in this cohort, but adherence may also have been in part due to the patients' stable life circumstances and support of the family. We do not believe that our cohort is unique. An increasing percentage of the U.S. population is enrolled in integrated health care plans. Kaiser Permanente provides medical care to 44% of the population in Sacramento. Except for extremes of income, membership of the health care plan is representative of the total area's population, and demographics of the Sacramento area are similar to those for the U.S. as a whole (Weisner et al., 2002).

Meanwhile, the fact that pretreatment abstinence was not associated with treatment outcome in the cohort as a whole suggests that requiring six months of abstinence prior to treatment in all patients is less critical to outcome than ensuring patients are committed to treatment, are abstaining during treatment, and receive close monitoring and ancillary care. The active use of marijuana during treatment and in the six months after treatment was associated with lower SVR and higher relapse rates that could not be explained by non-adherence, or premature treatment discontinuation.

In conclusion, these findings suggest that a past history of heavy drug use and recent drug use represent low treatment risk in patients of an integrated health care plan who are motivated to seek HCV treatment, aggressively supported, and closely monitored. However, the significantly lower SVR rates observed among patients who used marijuana during HCV treatment suggest that such use should be discouraged, at least among patient populations where high rates of treatment adherence can be achieved without it.

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References

Alter MJ, Moyer LA. The importance of preventing hepatitis C virus infection among injection drug users in the United States. J Acquir Immune Defic Syndr Hum Retrovirol. 1998; 18(Suppl 1):S6–10. [PubMed: 9663617]

Bini EJ, Kritz S, Brown LS Jr, Robinson J, Alderson D, Rotrosen J. Barriers to providing health services for HIV/AIDS, hepatitis C virus infection and sexually transmitted infections in substance abuse treatment programs in the United States. J Addict Dis. 2011; 30:98–109. [PubMed: 21491291]

Bini EJ, Kritz S, Brown LS Jr, Robinson J, Calsyn D, Alderson D, Tracy K, McAuliffe P, Smith C, Rotrosenet J. Hepatitis B virus and hepatitis C virus services offered by substance abuse treatment programs in the United States. J Subst Abuse Treat. 2012; 42:438–445. [PubMed: 22035702]

Chak E, Talal AH, Sherman KE, Schiff ER, Saab S. Hepatitis C virus infection in USA: an estimate of true prevalence. Liver Int. 2011; 31:1090–1101. [PubMed: 21745274]

Costiniuk CT, Mills E, Cooper CL. Evaluation of oral cannabinoid-containing medications for the management of interferon and ribavirin-induced anorexia, nausea and weight loss in patients treated for chronic hepatitis C virus. Can J Gastroenterol. 2008; 22:376–380. [PubMed: 18414712]

Czarnecki DM, Russell M, Cooper ML, Salter D. Five-year reliability of self-reported alcohol consumption. J Stud Alcohol. 1990; 51:68–76. [PubMed: 2299853]

Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology. 2010; 138:513–521. [PubMed: 19861128]

Ernhart CB, Morrow-Tlucak M, Sokol RJ, Martier S. Underreporting of alcohol use in pregnancy. Alcohol Clin Exp Res. 1988; 12:506–511. [PubMed: 3056071]

Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009; 49:1335–1374. [PubMed: 19330875]

Hellard M, Sacks-Davis R, Gold J. Hepatitis C treatment for injection drug users: a review of the available evidence. Clin Infect Dis. 2009; 49:561–573. [PubMed: 19589081]

Holmberg SD, Spradling PR, Moorman AC, Denniston MM. Hepatitis C in the United States. N Engl J Med. 2013; 368:1859–1861. [PubMed: 23675657]

Mallat A, Hezode C, Lotersztajn S. Environmental factors as disease accelerators during chronic hepatitis C. J Hepatol. 2008; 48:657–65. [PubMed: 18279998]

McHutchison JG, Manns M, Patel K, Poynard T, Lindsay KL, Trepo C, Dienstag J, Lee WM, Mak C, Garaud JJ, Albrecht JK. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. Gastroenterology. 2002; 123:1061–1069. [PubMed: 12360468]

Novick DM, Kreek MJ. Critical issues in the treatment of hepatitis C virus infection in methadone maintenance patients. Addiction. 2008; 103:905–918. [PubMed: 18422827]

Russell M, Marshall JR, Trevisan M, Freudenheim JL, Chan AW, Markovic N, Vana JE, Priore RL. Test-retest reliability of the cognitive lifetime drinking history. Am J Epidemiol. 1997; 146:975–981. [PubMed: 9400340]

Russell M, Pauly MP, Moore CD, Chia C, Dorrell J, Cunanan RJ, Witt G, Martin S. The impact of lifetime alcohol use on hepatitis C treatment outcomes in privately insured members of an integrated health care plan. Hepatology. 2012; 56:1223–30. [PubMed: 22488513]

Seal KH, Currie SL, Shen H, Anand BS, Bini EJ, Brau N, Jeffers L, Wright TL. Hepatitis C treatment candidacy and outcomes among 4318 US veterans with chronic hepatitis C virus infection: does a history of injection drug use matter? J Clin Gastroenterol. 2007; 41:199–205. [PubMed: 17245220]

Simpura J, Poikolainen K. Accuracy of retrospective measurement of individual alcohol consumption in men; a reinterview after 18 years. J Stud Alcohol. 1983; 44:911–917. [PubMed: 6645551]

Spiegel BM, Younossi ZM, Hays RD, Revicki D, Robbins S, Kanwal F. Impact of hepatitis C on health related quality of life: a systematic review and quantitative assessment. Hepatology. 2005; 41:790–800. [PubMed: 15791608]

Stepanova M, Kanwal F, El-Serag HB, Younossi ZM. Insurance status and treatment candidacy of hepatitis C patients: analysis of population-based data from the United States. Hepatology. 2011; 53:737–745. [PubMed: 21319199]

Sylvestre DL, Clements BJ, Malibu Y. Cannabis use improves retention and virological outcomes in patients treated for hepatitis C. Eur J Gastroenterol Hepatol. 2006; 18:1057–1063. [PubMed: 16957511]

Verges A, Jackson KM, Bucholz KK, Grant JD, Trull TJ, Wood PK, Sher KJ. Deconstructing the age-prevalence curve of alcohol dependence: why “maturing out” is only a small piece of the puzzle. J Abnorm Psychol. 2012; 121:511–523. [PubMed: 22060948]

Weisner C, Mertens J, Parthasarathy S, Moore C, Lu Y. Integrating primary medical care with addiction treatment: a randomized controlled trial. JAMA. 2001; 286:1715–1723. [PubMed: 11594896]

Table 1

Patient Demographics, Medical, and Drug-Related Risk Factors, According to HCV Treatment Outcome, SVR

Risk Factor	N (%)	SVR %	ρ*
Age			
< 50 years	116 (45.1)	60.3%	.916
≥ 50 years	141 (54.9)	61.0%	
Sex			
Male	154 (59.5)	59.7%	.726
Female	105 (40.5)	61.9%	
Race/Ethnicity			
White, non-Hispanic	207 (79.9)	64.3%	.017
Other	52 (20.1)	46.2%	
Pretreatment Viral Load			
≤ 600,00 I.U.	115 (44.4)	68.7%	.017
> 600,000 I.U.	144 (55.6)	54.2%	
Fibrosis			
Grade 0–2	132 (65.3)	63.6%	.024
Grade 3–4	70 (34.7)	47.1%	
HCV Genotype			
Genotype 2/3	116 (45.0)	80.2%	<.001
Genotype 1/4/6	142 (55.0)	45.1%	
Treatment Completion			
Completed 80-80-80 dose[a]	204 (79.9)	66.7%	<.001[ac]
Dose reduced to less than 80-80-80[b]	17 (6.7)	58.8%	.531[ab]
Discontinued[c]	34 (13.4)	20.6%	.006[bc]
For adverse effects	27 (10.6)	18.5%	
For non-compliance	6 (2.4)	33.3%	
For unrelated illness	1 (0.4)	0%	
PRETREATMENT SUBSTANCE USE			
Marijuana			
No	42 (16.2)	52.1%	.233
Yes	217 (83.8)	62.2%	
Sedatives			
No	152 (58.7)	60.5%	.971
Yes	107 (41.3)	60.7%	
Stimulants			
No	73 (28.2)	52.1%	.077
Yes	186 (71.8)	65.0%	
Opioids			

Risk Factor	N (%)	SVR %	ρ*
No	157 (60.6)	58.0%	.278
Yes	102 (39.4)	64.7%	
Hallucinogens			
No	126 (48.6)	54.8%	.060
Yes	133 (51.4)	66.2%	
Inhalants			
No	216 (83.4)	57.9%	.043
Yes	43 (16.6)	74.4%	

* Based on a 2-sided significance test.

Table 2

Mean Days of Lifetime Drug Use (Standard Errors), According to SVR.

Drug	Mean Days of Drug Use (SE)		ρ
	No SVR (n = 102)	SVR (n = 156)	
Marijuana	2232 (308)	2701 (267)	.258
Stimulants	734 (128)	1679 (192)	< .001
Hallucinogens	80.0 (22)	152 (42)	.122
Inhalants	6.6 (3.2)	23.6 (7.5)	.038
Opioids	296 (85)	489 (97)	.134
Sedatives	241 (60)	436 (116)	.138

Table 3

The Relation of Lifetime Years of Drug Use to HCV Treatment Failure, Adjusted for Host and Viral Risk Factors. Multiple Logistic Regression, Adjusted Odds Ratios, 95% Confidence Intervals (CI), and Significance Levels (N = 173).

Risk Factors	Odds Ratios (95% CI)	ρ Values
Hispanic and/or non-White	2.18 (.936 – 5.07)	.071
Pretreatment Viral Load	2.22 (1.11 – 4.40)	.025
HCV Genotype 1/4/6	4.48 (2.18 – 9.20)	<.001
Advanced Fibrosis	1.57 (.777 – 3.19)	.208
Treatment Discontinuation	10.76 (3.26 – 35.5)	<.001
Lifetime drug use (years)	.972 (.948– .996)	.023

Table 4

Percent using Drugs, According to Duration of Pretreatment Abstinence, During HCV Treatment, and After HCV Treatment. (N=259)

Drug	Duration of Pretreatment Abstinence					Use During HCV Treatment	Use After HCV Treatment
	Lifetime	>10 Yrs.	2–10 Yrs.	6–24 Mos.	<6 Mos.		
Marijuana	16.0%	55.9%	7.8%	3.5%	16.7%	8.5%	8.5%
Stimulants	27.4%	49.8%	16.6%	3.1%	3.1%	0.4%	1.5%
Hallucinogens	48.1%	49.6%	1.6%	0.4%	0.4%	0.8%	0.8%
Inhalants	83.4%	15.0%	1.2%	0%	0.4%	0.8%	0.8%
Opioids	59.3%	26.4%	10.1%	1.6%	2.7%	1.2%	1.9%
Sedatives	57.6%	35.0%	3.9%	1.6%	1.9%	0.4%	1.2%

Table 5

The Relation of Marijuana Use during HCV Treatment to Treatment Failure, Adjusted for Host and Viral Risk Factors. Multiple Logistic Regression, Adjusted Odds Ratios, 95% Confidence Intervals (CI). (N = 173)

Risk Factors	Odds Ratios (95% CI)	ρ Values
Hispanic and/or non-White	2.30 (.998 – 5.29)	.051
Pretreatment Viral Load	2.19 (1.11 – 4.33)	.024
HCV Genotype 1/4/6	4.32 (2.15 – 8.70)	<.001
Advanced Fibrosis	1.86 (.933 – 3.71)	.078
Treatment Discontinuation	7.85 (2.66 – 23.2)	<.001
Marijuana Use During Treatment	3.45 (1.04– 11.5)	.043