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Association between hepatitis C virus and opioid use while in buprenorphine treatment: preliminary findings

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Abstract

Background—The prevalence of hepatitis-C-virus (HCV) infections is high among opioid-dependent individuals. Prior research on the simultaneous treatment of both conditions has primarily assessed success as it pertains to HCV; although, it has been noted that favorable substance-use-therapy outcomes may improve the likelihood of HCV-treatment initiation and success. Therefore, current guidelines for the treatment of HCV among illicit drug users suggest that treatment for addiction be given the highest priority.

Objectives—To determine whether opioid-dependent participants in a clinical trial of buprenorphine-treatment tapering regimens, who tested positive for the HCV antibody, experienced significantly different levels of opioid abstinence than those not infected.

Methods—Data came from the National Drug Abuse Treatment Clinical Trial Network study 0003, in which 516 eligible opioid-dependent participants were randomized to either a 7-day or 28-day buprenorphine tapering schedule following a 4-week buprenorphine stabilization period. Generalized estimating equations were used to test the research question.

Results—Participants with the HCV antibody were significantly less likely to submit opioid-negative urine analyses during and/or immediately following active treatment [OR = 0.69; CI = 0.51–0.93], which indicates a higher rate of opioid use among this group.

Conclusion—Individualized opioid-dependence treatment strategies may be required for opioid-dependent individuals who test positive for the HCV antibody in order to ensure resources for both opioid-dependence and HCV therapies are used efficiently.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

Keywords

Opioid dependence; hepatitis C; buprenorphine

Introduction

In 2011, over 5 million US individuals aged 12 or older were using opioids (either prescription or heroin) for nonmedical purposes (1). The opioid-dependent group is relatively high-risk in terms of becoming infected with the hepatitis C virus (HCV). Intravenous drug use (IDU) is the most common risk factor for HCV (2), and is common among both heroin and prescription-opioid misusers (3–5). In fact, Gombas et al. (6) found that over 80% of the opioid-dependent patients in their sample of individuals undergoing treatment at an outpatient drug addiction clinic were positive for the hepatitis C virus antibody (HCV Ab), and almost 67% were chronically infected.

Between 70% and 85% of individuals who are infected with HCV develop a chronic infection (roughly 3.2 million US persons), which can culminate in liver damage, failure or cancer if not successfully treated (7). Patients with HCV represent a medical challenge given their relatively high likelihood of comorbidities, psychosocial instability, and non-adherence to treatment regimens (8–10). Non-adherence to HCV treatment is often attributed to a complex treatment regimen and side-effects of the medications, such as depression, anxiety, malaise, fatigue, myalgia and anemia (11). Historically, there have also been concerns of non-adherence and reinfection among illicit drug users with HCV (12,13).

Recent evidence indicates that concurrent treatment of HCV and opioid dependence can be effective for those infected with HCV, and that the risk of reinfection after HCV treatment among IDUs is sufficiently low (14–16); although, Aspinall et al. (16) found substantial uncertainty regarding the estimates for reinfection risk. Based on the general evidence, the National Institutes of Health (NIH) (17) have recommended that current drug-users with HCV receive treatment for the virus. However, the American Association for the Study of Liver Diseases (AASLD) advises that addiction therapy be given the highest priority among this population given that there may be reluctance on the part of active drug users to undertake treatment for HCV, as well as a diminished capacity for adherence to treatment (18). Moreover, the AASLD's practice guidelines for the diagnosis, management and treatment of hepatitis C state that treatment of HCV among illicit drug users be assessed on an individual basis, and that treatments for HCV and opioid dependence be integrated and overseen by a team of providers, including drug-abuse and psychiatric specialists. As alluded to above, the majority of the work on the simultaneous treatment of opioid dependence and HCV has focused on favorable outcomes regarding the latter condition; there has been little research on the association between HCV and successful treatment of opioid dependence. Moreover, much, but not all of the evidence of success with treating these conditions concurrently has been derived from patients in methadone maintenance treatment programs (14).

One of the most widespread and efficacious treatments for opioid-dependent patients is buprenorphine (Subutex®), which is often combined with naloxone (Suboxone®). Since

buprenorphine is a partial agonist, it has a ceiling effect and behaves similar to an antagonist at high doses, while also moderating withdrawal discomfort (19). Naloxone mitigates misuse of Suboxone® by triggering opioid-withdrawal symptoms if the medication is administered parenterally. Some evidence also suggests that buprenorphine is relatively low risk in terms of adverse drug-to-drug interactions for patients on antiretroviral therapy, which is important given the number of opioid-dependent patients with comorbid diagnoses of HIV and HCV (20).

Furthermore, with the passage of the Drug Addiction Treatment Act (DATA) of 2000 (21), sufficiently-trained providers in office-based settings are able to prescribe buprenorphine for opioid-dependence treatment. The successful oversight of opioid-addiction and HCV therapies in a single primary-care setting would be consistent with the principles of the Patient-Centered Medical Home (22).

The objective of this study was to determine whether opioid-dependent participants in a longitudinal clinical trial of different buprenorphine treatment tapering regimens, who had tested positive for the HCV Ab, experienced significantly different levels of opioid abstinence compared to those not infected.

Methods

Study design

This was a secondary longitudinal cohort analysis from a randomized controlled trial on opioid-dependent patients undergoing buprenorphine-tapering regimens, following a buprenorphine-stabilization regimen (23). Please see Ling et al. (23) and McPherson et al. (24) for previous primary and secondary analyses using these data.

Study sample

The data for this study were obtained from the National Drug Abuse Treatment Clinical Trial Network study 0003 (23). This study was a randomized, open-label, parallel-group study design, in which eligible participants were randomized to either a 7-day or 28-day tapering schedule following a 4-week buprenorphine induction/stabilization period. Participants were followed for 28 days post stabilization, regardless of tapering assignment, and were tested for opioid use at the end of each week. Eligible participants were: (1) at least 15 years of age; (2) seeking treatment for opioid dependence at a participating treatment program in one of 10 cities across the US; (3) tested negative for methadone and benzodiazepines; (4) not in poor general health; (5) did not report an allergy to buprenorphine or naloxone; (6) not pregnant or nursing; (7) only dependent on opioids (as opposed to also being dependent on alcohol or other drugs); (8) had not participated in an investigational drug study; (9) had not undergone levo-alpha acetyl methadol (LAAM) or methadone maintenance in the 30 days prior to the trial; (10) did not have legal action pending; (11) able to remain in the area; and (12) did not have any other medical or psychiatric condition that could jeopardize their safety while participating in the trial. With regard to opioid use in the 30 days prior to the trial, participants averaged almost 23 days of

heroin use and 6.5 days of opioid analgesic use. Of those abusing heroin, roughly 57% were doing so intravenously.

Participants who were abusing opioid analgesics primarily did so orally (75%); however, roughly 6% administered the drug intravenously.

Measures

Our primary variable of interest was a binary indicator of whether the participant's urine analysis (UA) was negative for opioids at the end of each week of the trial, including stabilization, for a total of five UAs over time. Our independent variable was a binary measure of whether the individual tested positive for the HCV Ab at the beginning of the trial. The control variables in the model consisted of the participant's age, gender (1 = female; 0 = male), binary indicators of race (white/Caucasian [reference group], black/African American, Hispanic/Latino[a], or other), randomized assignment to tapering arm (1 = 28-day; 0 = 7-day), and Addiction Severity Index (ASI) Lite scores. The ASI measures the severity of an individual's problems with regard to factors that are often impacted by substance abuse (25). The ASI-Lite, which was administered at baseline, consists of seven different composite scores, all of which were included in the analysis. Each score is measured continuously on a scale from zero to one, with a higher score indicating increased severity. The components of the ASI-Lite are as follows:

- Medical – assesses severity of medical issues, including chronic conditions, hospitalizations, and medication usage.
- Employment – evaluates issues pertaining to employment, including education, income and financial support, dependents, and employment patterns.
- Alcohol – measures alcohol use and issues associated with it, such as treatment for dependence, need for additional treatment, and money spent on it.
- Drug – assesses drug use by type and route of administration, as well as issues pertaining to drug use, including treatment for dependence, need for additional treatment, and money spent on drugs.
- Legal – an evaluation of legal problems, including convictions, time incarcerated, and probation/parole status.
- Family/social – assesses family and social issues, including satisfaction with relationships, living arrangements, and conflicts.
- Psychiatric – a psychological assessment, including mental-health issues and treatment history.

Analysis

We tested for differences between participants who tested positive for the HCV Ab and those who did not, using Chi-square tests for the binary variables and *t*-tests for the continuous variables. The effect that a positive HCV Ab test result had on the likelihood that a participant's UA was negative for opioids throughout the trial was analyzed using generalized estimating equations (GEE). GEE is a technique used to estimate longitudinal

data, which controls for within-subject correlation and allows for non-normally distributed dependent variables such as binary, count, multinomial, and other types of distributed variables (26,27). Analyses utilized bi-directional tests to protect against a Type-I error. Odds ratios with 95% confidence intervals are presented for our longitudinal binary outcome.

Sensitivity analysis

After confirming that there were no statistically significant differences between those with missing information in the dependent variable and those without, we tested the sensitivity of our estimates to missing data using multiple imputation (MI) (28,29). In instances where data are believed to be missing at random (MAR), as is the case here, MI has been shown to be superior to other missing data techniques (30–32). Fifty datasets were created and analyzed via the MI procedure in order to produce efficient standard errors. The parameter estimates and standard errors were combined using Rubin's rules (33).

Results

The descriptive statistics, as well as the results of the bivariate analyses, are presented in Table 1. The mean age of the participants in the total sample was 36 and roughly 33% were female. The majority were white/Caucasian (71%); an additional 11% were black/African American, 7% were Hispanic/Latino(a), and 11% identified with a category other than those just mentioned. In terms of our primary variables of interest, approximately 36% of the participants in the overall sample tested positive for the HCV Ab (51% of which were in the 28-day tapering arm), and of the five UAs given throughout the trial, the average number that were negative for opioids among this group was 1.8.

Regarding gender mix, participants with the HCV Ab did not differ significantly from those without; this was also true of tapering arm assignment. Participants with the HCV Ab were significantly older. In terms of race, a significantly larger proportion of patients with the HCV Ab were Hispanic/Latino(a), while the opposite was true for whites/Caucasians. Furthermore, the mean ASI-Lite medical, employment, and legal component scores were significantly higher for the HCV Ab group.

The results from the GEE analysis can be viewed in Table 2. Having tested positive for the HCV Ab decreased the odds of having a UA that was negative for opioids by 31% (95% CI: 0.51–0.93). Other factors that affected the likelihood of participants testing negative for opioids were age (OR = 1.03; 95% CI: 1.01–1.04), and the ASI-Lite medical (OR = 1.75; 95% CI: 1.07–2.87), employment (OR = 0.56; 95% CI: 0.37–0.86) and alcohol (OR = 9.09; 95% CI: 2.02–40.80) components.

Discussion

Opioid-dependent participants who tested positive for the HCV Ab were older and more racially diverse than those who were negative for the HCV Ab. The HCV Ab group also appeared to have more severe medical and employment issues, which was not surprising given that individuals with HCV have been shown to be at higher risk for comorbidities and

psychosocial instability, and often have problems adhering to their medication regimen (8–10).

In terms of the estimated effect of HCV on opioid abstinence throughout the trial, those who tested positive for the HCV Ab were significantly less likely to test negative for opioids, indicating a higher rate of opioid use among this group, a finding that held after controlling for the ASI components. This finding indicates that individuals entering treatment for opioid-dependence who test positive for the HCV Ab may warrant special consideration with regard to their treatment strategy. Our findings also support the notion that information obtained from the ASI can be useful in a clinical setting (34). For example, our results indicate that patients with more severe employment issues were also significantly less likely to submit UAs that were negative for opioids, while patients with complex medical and alcohol issues were more likely to test negative. These findings warrant further investigation.

Strengths and limitations

The longitudinal nature of the data represents a strength of this study. Furthermore, we focused on the association between HCV and opioid use while receiving opioid-agonist therapy for opioid dependence. Prior work on the simultaneous treatment of HCV and substance abuse has centered on successful treatment of the former. Furthermore, our work focused on treatment of opioid dependence via buprenorphine, a drug that has begun to garner a great deal of attention in this context.

The primary limitation of this study is that our measure of HCV merely indicates the presence of the antibody, that is, it does not indicate activity of the virus. Additionally, patients in our sample were on a buprenorphine regimen and were then transitioned onto a tapering regimen. Moreover, the exclusion criterion that participants could only be dependent on opioids limits the generalizability of our findings. For example, this is likely reflected in the ASI-Lite drug-severity score, which, as can be seen in Table 1, had a mean of only 0.33 (SD = 0.07).

Missing information in our dependent variable is also a limitation. Due to a lack of evidence that the information was missing-not-at-random, we employed the MI procedure, which relies on the missing-at-random assumption. The lack of difference between the results obtained via the intention-to-treat analysis, which employs the missing-completely-at-random assumption, and the MI results, indicates that the missing information does not invalidate our findings. Finally, the fact that the clinical trial from which this data was obtained was not designed to answer our research question limits our ability to make causal inferences about the role that HCV plays in opioid abstinence. However, our data clearly represent an association worth pursuing.

Conclusion

Due in large part to intravenous drug use being the leading risk factor for HCV transmission, many individuals with an opioid-dependence disorder are also infected with HCV (2). Given the hardships faced by individuals with these comorbid conditions, not to mention the

substantial economic costs associated with opioid dependence and HCV, it is imperative that effective treatment is received. Although there is evidence that patients with HCV and an opioid dependence can be effectively treated for both simultaneously, it has been suggested that successful treatment for substance use disorders may both increase the likelihood of HCV-positive patients undergoing treatment for HCV, and increase the probability of successful HCV-treatment outcomes. Therefore, it has been recommended that addiction therapy be given special consideration in the treatment of those with substance use disorders and HCV (18). However, much of the literature on treating patients with HCV and an opioid dependence has focused solely on successful HCV treatment. Our findings indicate that opioid-dependent individuals who were being treated with buprenorphine and tested positive for the HCV Ab were significantly less likely to submit opioid-negative UAs, indicating a higher rate of opioid use; thus, individualized opioid-dependence treatment strategies may be required for this group in order to ensure resources for both opioid-dependence and HCV therapies are used efficiently.

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Table 1

Descriptive statistics.

Variable	Total sample		HCV-Ab positive		HCV-Ab negative	
	n	**%**	***n***	**%**	***n***	**%**
Positive for HCV Ab	515	36	184	100	331	0
Urine analysis negative for opioids after:						
Stabilization	513	63	182	59	330	65
7 days	202	57	75	53	127	60
14 days	431	57	153	54	277	59
21 days	364	51	129	52	235	51
28 days	146	41	49	43	96	41
Female	516	33	184	31	331	34
Race						
White/Caucasian*	515	71	184	66	330	74
Black/African American	515	11	184	12	330	10
Hispanic/Latino(a)**	515	7	184	13	330	4
Other	515	11	184	10	330	12
28-day tapering arm	516	51	184	51	331	50
	N	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
Number of urine analyses negative for opioids	516	1.81 (1.44)	184	1.73 (1.47)	331	1.85 (1.43)
Age**	516	35.91 (10.45)	184	41.97 (9.23)	331	32.52 (9.54)
ASI-Lite components						
Medical*	516	0.16 (0.28)	184	0.19 (0.32)	331	0.13 (0.25)
Employment**	516	0.48 (0.32)	184	0.62 (0.32)	331	0.40 (0.29)
Alcohol	506	0.05 (0.10)	183	0.04 (0.10)	322	0.05 (0.09)
Drug	506	0.33 (0.07)	184	0.33 (0.06)	321	0.33 (0.07)
Legal*	512	0.08 (0.15)	180	0.10 (0.16)	331	0.07 (0.14)
Psychiatric	512	0.19 (0.20)	182	0.17 (0.21)	331	0.19 (0.20)
Family/social	516	0.14 (0.20)	184	0.14 (0.20)	331	0.14 (0.20)

* indicates significant difference between HCV-Ab positive and negative groups at $p \leq 0.05$;

** indicates significant difference between HCV-Ab positive and negative groups at $p \leq 0.01$.

Table 2

GEE regression results for predictors of opioid abstinence.

Variable	Odds ratio	95% CI
Positive for HCV Ab*	0.69	0.51–0.93
Age**	1.03	1.01–1.04
Female	0.84	0.64–1.10
Race		
Black/African American	1.20	0.78–1.82
Hispanic/Latino(a)	0.86	0.53–1.38
Other	1.38	0.92–2.08
ASI-Lite components		
Medical*	1.75	1.07–2.87
Employment**	0.56	0.37–0.86
Alcohol**	9.09	2.02–40.80
Drug	0.23	0.03–1.55
Legal	1.31	0.53–3.25
Psychiatric	1.25	0.63–2.46
Family/social	1.72	0.89–3.32
28-day tapering arm	1.04	0.82–1.33

* indicates $p \leq 0.05$;

** indicates $p \leq 0.01$.