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Prospective longitudinal substance use patterns in patients preparing for hepatitis C treatment

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Abstract

Objective—This study prospectively examined the independent courses of alcohol, drugs, and smoking over 18 months in 154 patients preparing for hepatitis C (HCV) treatment in relation to functioning, negative coping, and satisfaction with quality of life, in data collected from a randomized controlled trial of multiple-family group psychoeducation for patients preparing for HCV treatment. Patients with HCV who had consistent abstinence, consistent use, or achievement of abstinence after study entry were examined for outcomes pertaining to functioning in the context of HCV, negative coping, and satisfaction with quality of life.

Methods—Of 309 patients considering treatment for HCV recruited from outpatient clinics at two major university medical centers and a Veterans Affairs medical center for a randomized controlled trial of a psychoeducation intervention, 154 completed baseline, 6-month, and 18-month assessments. The assessments included structured diagnostic interviews; questionnaires examining functioning, coping, and satisfaction with quality of life; medical record review; and urine testing for substances of abuse. For these analyses, substance use patterns were determined as consistent abstinence, consistent use, and achieving abstinence after study entry, for alcohol and drug use and smoking.

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Results—The entire sample generally improved in all of these three outcomes over the course of the study. The course of alcohol, drugs, and smoking predicted HCV-related functioning, negative coping, and satisfaction with quality of life outcomes over 18 months. Three specific patterns of substance use (consistent abstinence, consistent use, and achievement of abstinence after study entry) of these substances diverged in association with outcomes related to functioning, negative coping, and satisfaction with quality of life, not only across trajectories over time within substance types but also between types of substances.

Conclusions—This study's finding that different substances were associated with distinct clinical outcomes suggests the need to conceptually unbundle different types of substances in managing HCV. Future research is needed to examine the clinical utility of further unbundling of these substances and also to further investigate effects of various amounts of use of these substances.

Keywords

Hepatitis C; substance use; alcohol; drugs; tobacco; functioning; coping; quality of life; longitudinal; prospective

Gallia est omnis divisa in partes tres.

—Julius Caesar, 58 B.C.E.

Introduction

Recent estimates indicate that 57%-67% of people with hepatitis C virus (HCV) smoke cigarettes (Basseri et al., 2010; Chew et al., 2015; Shuter et al., 2016; Zimmermann et al., 2016), 65%-73% consume alcohol (Drumright et al., 2011; North et al., 2014; Taylor, Denniston, Klevens, McKnight-Eily, & Jiles, 2016; Tsai, Ford, Li, & Zhao, 2012), and 57%-65% use illicit drugs (Sims et al., 2016; Whitehead, Hearn, Trenz, Burrell, & Latimer, 2014). Alcohol use and smoking independently accelerate progression to HCV-related liver disease and cancer (Jeng et al., 2009; Lok et al., 2009; Soeda et al., 2012). Ethanol destroys cells that carry out primary liver functions and amplifies liver cancer risk 100-fold in patients with HCV (Osna, Ganesan, & Kharbanda, 2015; Sims, Maynard, & Melton, 2016; Younossi, Zheng, Stepanova, Venkatesan, & Mir, 2013). Cigarette smoke contains several cytotoxic chemicals metabolized in the liver that cause chronic inflammation leading to cell death and contribute to viability and replication of HCV (Costiniuk et al., 2016; Zhao, Li, & Taylor, 2013). Alcohol use and smoking are independent risk factors for suboptimal HCV treatment outcomes (Choi, 2012; Zimmermann et al., 2016; Osna, Ganesan, & Kharbanda, 2015). Clinical guidelines recommend abstaining from alcohol, and several studies have advised clinicians to recommend smoking cessation for patients with HCV (Kertesz et al., 2014; Shuter et al., 2016).

Patients with HCV have lower levels of functioning, coping, and quality of life than the general population (Boscarino et al., 2015; Cellar et al., 2016; Stewart, Mikocka-Walus, Harley, & Andrews, 2012; Strauss, Porto-Ferreira, de Almeida-Neto, & Teixeira, 2014) and higher rates of substance abuse (Cucciare, Cheung, & Rongey, 2015). Substance use problems likely compound these other factors, increase social burdens, and worsen chances

for initiating HCV treatment, successfully completing it, and achieving sustained virologic response.

Although research has extensively described negative medical outcomes associated with specific substance use in people with HCV, little is known about the associated functioning, coping, and quality of life outcomes in association with use of substances in general, and even less with specific substances. This would be useful information for hepatology clinical care teams and especially for behavioral health care providers. The purpose of this study was to prospectively examine functioning, negative coping, and satisfaction with quality of life longitudinally in relation to the independent courses of alcohol, drugs, and smoking over 18 months in a sample of 309 patients participating in a randomized controlled trial of multifamily psychoeducation to help ready them to receive HCV treatment (North et al., 2017). This study specifically compares outcomes of patients with HCV who were consistently abstinent, consistently using, and achieved abstinence after study entry.

Methods

Sample

A sample of 309 patients undergoing HCV treatment readiness was recruited from outpatient clinics at two university medical centers (Washington University School of Medicine in St. Louis, Missouri and The University of Texas Southwestern Medical Center in Dallas, Texas) and the Veterans Affairs North Texas Health Care System medical center in Dallas, Texas as part of a randomized controlled trial of a psychoeducation intervention.

Procedures

Sample recruitment and baseline interviews were initiated beginning in December 2008 and continued over a 2-year period; final 18-month follow-up data collection was completed in April 2012. As reported in a previous article describing results of the randomized controlled trial of multifamily group psychoeducation (North et al., 2017), the rate of participation in the intervention was very low and no differences in clinical outcomes were demonstrated between the intervention and control groups; therefore, effects of the intervention on outcomes examined in this analysis are unlikely. The Institutional Review Boards of the participating institutions approved the study. All participants provided informed consent after a complete discussion of the study with them.

Assessments were conducted at baseline and follow-up assessments using the same instruments to measure improvement at 6 months and whether improvement was sustained at 18 months. Follow-up assessments were conducted with 225 participants at 6 months (representing 80% of 282 eligible for re-assessment, e.g., alive, in geographic area, not incarcerated or too ill) and with 180 at 18 months (representing 67% of 268 eligible for reassessment). Study data were available at baseline and both follow-ups for 154 (50%) of the 309 baseline study participants; one additional participant had missing data for recency of alcohol use.

Assessment measures

For further detail, measures for this study were fully described in a previous publication (North et al., 2014). Information on substance use and other psychiatric disorders was collected at each assessment point using the National Institute of Mental Health Diagnostic Interview Schedule for DSM-IV Text Revision (American Psychiatric Association, 2000), the World Health Organization Composite International Diagnostic Interview - Substance Abuse Module (World Health Organization, 2004), various modules of the Special Projects of National Significance Module 20 (www.TheMeasurementGroup.com) modified to assess HCV-specific risk behaviors, medical records, and urine testing for substances of abuse. Composite substance use variables for alcohol, drugs (amphetamines, cocaine, other stimulants, cannabis, opiates, sedatives, phencyclidine, hallucinogens, volatile inhalants), and smoking were created from all data obtained from interviews, self-report measures, medical records, and urine testing. Any use of these substances was determined for the year before the baseline assessment and for any time during the 18-month study follow-up.

To simplify and unify measures of functioning, coping, and satisfaction with quality of life addressed by the various modules, a set of questions was developed for this study to succinctly address six life domains (employment, home management, social leisure, personal leisure, personal relationships, and sex) and negative coping using a 10-point Likert scale (0="Not at all" to 10= "Totally"). A series of six questions using the 10-point Likert scale measured HCV-related effects on functioning (worded "Because of my hepatitis C, in the last month, [DOMAIN] was affected,") reflecting subjective patient perceptions rather than objective measures of HCV-related effects for the six domains. These item scores were averaged to generate a variable reflecting level of HCV-related functioning mastery (higher numbers reflecting greater functioning). Negative coping was measured with two questions using the 10-point Likert scale to assess recent coping with HCV illness (higher numbers reflecting more negative coping) through denial (refusing to believe in or address having HCV) or through substance use. The scores of these two items were averaged. Satisfaction with quality of life in the last month was measured with a series of six questions using the 10-point Likert scale for the six domains. These item scores were averaged to generate a variable reflecting satisfaction with HCV-related quality of life (higher numbers reflecting greater satisfaction).

A previous article comparing groups with different alcohol use patterns found significant differences among these groups in terms of gender, psychiatric diagnosis, and other substance use, justifying the division of substance use patterns into distinct groups for the current study. For this study, individuals reporting substance abstinence in the pre-enrollment year and continued abstinence throughout the study were considered "consistently abstinent." Individuals using substances during the pre-enrollment year and throughout the study were considered "consistently using." Individuals using substances during the pre-enrollment year but abstinent throughout the study were labelled "achieving abstinence after study entry."

Statistical analysis

Analysis of data was conducted using SAS 9.4 (SAS Institute, Cary, NC). Descriptive findings include frequencies, proportions, means, standard deviations, and medians. Chi-square analysis was used to compare two dichotomous variables, substituting Fisher's exact test for instances of expected cell counts < 5. Dichotomous and continuous variables were compared using Student's *t*-tests, substituting Satterthwaite analyses for instances of unequal variance. Paired *t*-tests were used to compare repeated measurements of numeric variables within individuals. Effect sizes were calculated for *t*-test comparisons, using Morris and DeShon's equation eight correction for dependence between paired *t*-test means (Morris & DeShon, 2002).

Specific analyses conducted to produce the findings presented in Figures 3–5 involved comparisons of three outcome variables based on scale scores (see above) for HCV-related effects on functioning, negative coping, and satisfaction with quality of life. These analyses investigated whether specific use patterns by substance use type were associated with scores on these scales.

Results

Table 1 lists the demographic characteristics of 154 participants with assessments at baseline, 6 months, and 18 months. The sample was slightly over half male, more than two-thirds Black, with just over half educated through high school, and with a median age of 53 years. Nearly half were disabled. Those who did not complete both follow-up assessments were significantly more likely to be male (75% vs. 46% of those who completed both follow-up assessments; $\chi^2 = 25.47$, $df = 1$, $p < .001$) and less likely to be nonwhite (62% vs. 74%; $\chi^2 = 4.76$, $df = 1$, $p = .029$) or living with a romantic partner (20% vs. 32%; $\chi^2 = 5.64$, $df = 1$, $p = .018$), but no attrition differences were found in proportions with high school education, employment, psychopathology, HCV functioning mastery, negative coping behaviors, or satisfaction with quality of life.

Figure 1 shows sample proportions with each substance use pattern by substance type. The sample included nine individuals (6% of the sample) who had no lifetime use of alcohol, 39 (25%) with no lifetime drug use, 31 (21%) with no lifetime smoking, and two (1%) with no lifetime history of alcohol or drug use or smoking. More than one-third of the sample used alcohol after study entry and one-fourth (25%) of the sample achieved abstinence from alcohol during the study. Nearly half (44%) of the sample achieved abstinence from drugs after study entry. Few (11%) achieved smoking abstinence.

Figure 2 presents Venn diagrams illustrating the overlap among alcohol, drugs, and smoking for patterns of consistent use, consistent abstinence, and achieving abstinence after study entry. In all three Venn diagrams, overlap among substances is distributed across all possible combinations—with representation in categories of all three substances, pairs of substances, and single substances. Thus, considerable overlap is seen among types of substance use within individuals, the lack of consistent pairings of substances suggests that examination of each substance separately is needed as well as combined substance use pattern variables.

Further, among participants with consistent substance use during the study, those with consistent alcohol use were more likely than others to be male (72% vs. 50%; $\chi^2 = 4.65$, $df = 1$, $p = .031$), and those with consistent smoking were more likely than others to be female (81% vs. 59%; $\chi^2 = 5.71$, $df = 1$, $p = .017$). Similarly, among participants with consistent substance use during the study, those with consistent drug use were more likely than others to be black (52% vs. 30%; $\chi^2 = 3.89$, $df = 1$, $p = .049$) and those with consistent smoking were less likely than others to have a high school education (61% vs 84%; $\chi^2 = 5.98$, $df = 1$, $p = .015$). These findings justified the division of substance use patterns into separate groups for alcohol, drugs, and smoking.

Change in outcomes over time

Overall, functioning increased from baseline to the conclusion of the study, with a small but significant mean (*SD*) increase of 0.8 (3.7) functioning points ($t = 2.64$, $df = 146$, $p = .009$; Cohen's $d = .24$). Negative coping decreased from baseline to the conclusion of the study, by a mean (*SD*) of 1.0 (3.5) negative functioning points ($t = -3.46$, $df = 143$, $p < .001$; Cohen's $d = .28$). No significant change in satisfaction with quality of life was observed from baseline to study conclusion.

Figure 3 shows the relationship between alcohol use pattern and functioning, negative coping, and satisfaction with quality of life. Consistent abstinence from alcohol was associated with a significant increase in functioning and a significant decrease in negative coping from baseline to the last study measure. Achievement of abstinence from alcohol after study entry was associated with significantly increased satisfaction with quality of life over time.

Figure 4 shows relationships between drug use pattern and functioning, negative coping, and satisfaction with quality of life. Consistent abstinence from drugs was associated with a significant increase in functioning and a significant decrease in negative coping from baseline to study completion. Achieving abstinence from drugs after study entry was also associated with a significant reduction in negative coping over time.

Figure 5 shows the relationships between smoking patterns and functioning, negative coping, and satisfaction with quality of life. Consistent abstinence from smoking was associated with a significant improvement in functioning and a significant decrease in negative coping from baseline to study completion.

Differences in outcomes across usage patterns at specific time points

For alcohol, the consistent use pattern was associated with significantly greater functioning at baseline compared to the consistent abstinence pattern, and the consistent abstinence pattern was associated with significantly greater satisfaction with quality of life compared to the pattern of achieving abstinence after study entry. The consistent use pattern was associated with significantly higher functioning at 18 months, compared to the pattern of achieving abstinence after study entry.

For drugs, the pattern of achieving abstinence after study entry was associated with significantly more negative coping at baseline, compared to the consistent use pattern. The

consistent abstinence pattern was associated with significantly less negative coping at 6 months compared with the consistent use pattern and also compared to the pattern of achieving abstinence after study entry. The consistent use pattern was associated with significantly higher functioning at 18 months compared to the pattern of achieving abstinence after study entry. The consistent abstinence pattern maintained its 6-month association with less negative functioning compared to the consistent use pattern at 18 months.

For smoking, the consistent abstinence pattern was associated with significantly less negative coping 18 months compared to the consistent use pattern. The consistent abstinence pattern was associated with significantly greater satisfaction with quality of life at 18 months compared to the consistent use pattern.

The combined substance variables had few significant associations with functioning, negative coping, or satisfaction with quality of life. At baseline, the consistent use pattern was associated with significantly higher functioning compared to the consistent abstinence pattern (mean = 6.7, *SD* = 3.2 vs. mean = 5.2, *SD* = 3.3; $t = 1.99$, $df = 112$, $p = .049$; Cohen's $d = .45$). The consistent abstinence pattern was associated with significant improvements from baseline to 18 months in functioning (mean = 5.2, *SD* = 3.3 to mean = 6.9, *SD* = 3.6; $t = 2.18$, $df = 24$, $p = .029$; Cohen's $d = .94$) and negative coping (mean = 2.8, *SD* = 2.6 to mean = .8, *SD* = 1.8; $t = 3.22$, $df = 24$, $p = .004$; Cohen's $d = .27$). The pattern of abstinence after baseline was associated with significant improvement in satisfaction with quality of life from baseline to 18 months (mean = 6.3, *SD* = 2.2 to mean = 6.5, *SD* = 2.7; $t = 2.39$, $df = 33$, $p = .023$; Cohen's $d = .09$).

Discussion

This study demonstrated that the course of alcohol, drugs, and smoking predicted improved functioning, reduced negative coping, and greater satisfaction with quality of life over 18 months in patients undergoing HCV treatment readiness. However, three specific patterns of substance use (consistent abstinence, consistent use, and achievement of abstinence after study entry) of these three substances diverged in association with functioning, negative coping, and satisfaction with quality-of-life outcomes, not only across trajectories over time within substance types but also between types of substances. The individual substance variables yielded more complex and varied associations with outcomes than with the combined substance variables, indicating the importance of separate consideration of the patterns of use of each substance. Despite generally modest effect sizes, the findings have potential implications for clinical decision-making pertaining to HCV treatment.

For all three substance types, consistent abstinence patterns were associated with significant improvements over the 18 months in both functioning and negative coping, but not with quality-of-life satisfaction. The pattern of achieving abstinence after study entry was associated with significantly improved quality-of-life satisfaction over time for alcohol and reduced negative coping for drugs. For all three substance types, the consistent use pattern showed no associations with significant changes over time on any of the three outcomes. Outcomes associated with the pattern of achieving abstinence after study entry did not show

as many improvements over time as those observed with the consistent abstinence pattern. However, outcomes associated with the pattern of achieving abstinence after study entry had more improvements over time compared to outcomes observed with the consistent use pattern. Quality-of-life satisfaction did not improve over time in association with the consistent abstinence pattern, possibly reflecting greater illness associated with this pattern, or alternatively perhaps because quality-of-life satisfaction associated with this pattern began at a higher level than for the other patterns. No pattern of use for any substance was associated with declining quality-of-life satisfaction over time, although one pattern with one substance—achievement of abstinence from alcohol after study entry—was associated with a significant quality-of-life satisfaction improvement. This finding potentially reflects the unique role of alcohol in accelerating HCV progression, providing the link between alcohol cessation and greater quality-of-life satisfaction.

In addition to these differences in outcomes over time in the distinct patterns of use, differences in outcomes were also found between substance use patterns at specific points in time. Patterns of consistent use and achieving abstinence from substances after study entry did not differ on any measure at baseline except for negative coping in relation to drug use, with consistent use being associated with more negative coping. Similarities on negative coping at baseline in these two groups may reflect the fact that both groups were using substances. The consistent abstinence pattern for drugs and/or smoking was distinguished by less 6-month negative coping compared to one or both of the other patterns of use. Relative to the consistent use pattern, the patterns of abstinence from alcohol and/or drugs were associated with significantly worse 18-month functioning, but the pattern of achieving abstinence from smoking was not different from the others in 28-month functioning. These differences in functioning between the consistent use pattern and the pattern of achieving abstinence after study entry for alcohol and drugs were significant only at 18 months; however, the differences in functioning were already emerging at baseline and 6 months, albeit not yet significant. A possible contributor to this finding may be that changes in perception of functioning related to the state of use or abstinence resulted in the drifting apart of the consistent use pattern from the pattern of achieving abstinence after study entry observed for alcohol and drugs. Use of alcohol and drugs may affect cognition in ways that smoking does not in generating accurate self-appraisal.

Negative coping had noteworthy associations with substance use patterns both over time and between patterns at specific time points. The negative coping items specifically reflect only denial and substance use. The finding that both patterns of consistent use and achieving abstinence after study entry involved substance use in the year before baseline means that the difference in associations of change in negative coping with these two patterns of use over time must be in negative coping through denial, which predicted subsequent achievement of abstinence. Similarly, the significant separation of the consistent abstinence pattern at 6 months for drug use and smoking must represent continuing denial variably associated with the other two patterns. Based on the significant improvements in negative coping associated with abstinence patterns over time and the differences for these patterns that emerged at 6 months, it appears that changes in negative coping represent interplay between cessation of drug use or smoking and reduction of denial over time.

Strengths of this study include its large ($N=309$) sample of patients with HCV from clinical settings and the 18-month longitudinal follow-up design. The sample was drawn from three different major treatment centers for HCV in geographically distinct locations. An additional strength is that substance use in specific periods of relevance to the study was determined through multiple sources of data, including several self-report instruments with multiple questions about substance use in various time periods, medical record reviews completed on each participant over the course of the study, and urine drug testing for presence of multiple substances of abuse at baseline with repeated testing during the follow-up. The major strength of this study is its design to separate the investigation of use of alcohol and other drugs and smoking, allowing the disaggregation of substance-related outcomes by type of substance use, in contrast to clinical practices that do not routinely distinguish the use of one substance from another.

A study limitation is that only half of the sample had complete follow-up data at both 6 and 18 months. No attrition differences were found in baseline proportions with high school education, employment, alcohol or drug use disorders, HCV functioning mastery, negative coping behaviors, or satisfaction with quality of life. However, males, non-minorities, and non-cohabitating participants had more study attrition than others, representing potential sources of attrition bias related to these variables. The substance use variables provided only the presence or absence of use in specific time frames, and the data did not include the specific quantity of the amounts of substances used. This strategy was chosen because of the interest of this study in examining the presence of any substance use, which is most relevant, especially for alcohol because of its unique role of even small amounts in accelerating the course of HCV (North et al., 2014). The outcomes presented in this analysis were limited only to functioning mastery, negative coping, and quality-of-life satisfaction, all self-reported findings rather than objectively-measured medical outcomes. The 18-month follow-up period represents not only a strength because it provided sufficient time to demonstrate significant differences between patterns and changes over time, but also a limitation because this study end point may not coincide with the end point of the clinical course of HCV outcomes.

Given the rising prevalence and diagnosis of HCV, these findings have vital clinical implications. Although long-term general health is a worthy goal of HCV treatment, of more immediate clinical importance is the cessation of alcohol use. For any population, the value of abstinence from unhealthy substances is an accepted virtue, but specifically for HCV, abstinence from alcohol is of far greater importance than is cessation of drug use or smoking for health benefits. Global focus on general health can distract needed attention from the immediate need for alcohol cessation in particular. This point is reinforced by the distinct differences across patterns of use for the three types of substances as demonstrated in this study and the comparatively few findings in association with the combined substance variables.

The practice of bundling all substances together in HCV clinical care considerations has at least in part evolved from the concept that any illicit substance use may represent an indicator of potential poor adherence to treatment. This study's finding that different substances were associated with distinct clinical outcomes further suggests the need to

conceptually unbundle the different types of substances in managing HCV. Unbundling smoking from other drugs and drugs from one another may also be warranted, based on substance-related differences in addictiveness. In this study, the largest movement into abstinence was found for drugs, followed by alcohol; smoking, however, uncommonly proceeded to abstinence. To some degree, this may also reflect a clinical focus in treatment of HCV primarily on alcohol and drug use behaviors. Future research is needed to further investigate effects of various amounts of use of these substances and to examine the clinical utility of unbundling of these substances.

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Figure 1.
Proportions with substance use patterns by substance type

Figure 2.
Overlap of substance types among substance use patterns

Figure 3.
 Functioning mastery, negative coping behaviors, and satisfaction of quality of life by alcohol use pattern

Figure 4.
 Functioning mastery, negative coping behaviors, and satisfaction of quality of life by drug use pattern

Figure 5.
 Functioning mastery, negative coping behaviors, and satisfaction of quality of life by smoking pattern

Table 1

Baseline characteristics of HCV study participants completing all study assessments

TOTAL (N=154)	Mean (SD)
Mean (SD) age	52.6 (7.5)
	N (%)
Sex	
Male	81 (53.9)
Female	73 (46.1)
Race	
White	40 (26.0)
Black	110 (71.4)
Other	4 (2.6)
High school education	85 (55.2)
Marital status	
Married	35 (22.7)
Divorced	36 (23.4)
Separated	22 (14.3)
Widowed	11 (7.1)
Never married	50 (32.5)
Living with intimate partner	50 (32.5)
Current employment status (N=151)	
Employed	29 (19.2)
Unemployed	39 (25.8)
Disabled	68 (45.0)