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Stopping Marijuana Increases Alcohol Use: An Experimental Verification of Drug Substitution

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STOPPING MARIJUANA INCREASES ALCOHOL USE: AN EXPERIMENTAL
VERIFICATION OF DRUG SUBSTITUTION

A Dissertation Presented

by

Erica N. Peters

to

The Faculty of the Graduate College

of

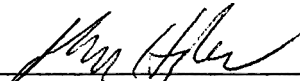
The University of Vermont

In Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy
Specializing in Psychology

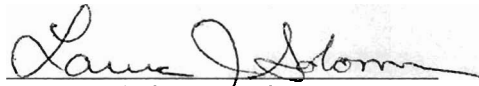
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Accepted by the Faculty of the Graduate College, The University of Vermont, in partial fulfillment of the requirements for the degree of Doctor of Philosophy, specializing in Psychology.

Dissertation Examination Committee:



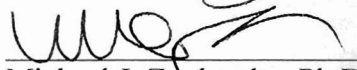
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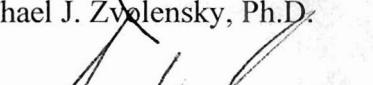
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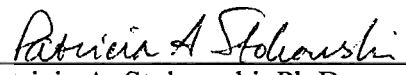
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Abstract

Many, if not most, drug abuse counselors and treatment programs recommend abstinence from all psychoactive substances, in part, because of a fear that clients who decrease or stop their use of one drug will substitute another. Research to confirm this notion of substitution, however, mostly fails to show that abstinence from one drug increases use of another. A within-subjects study investigated whether consumption of alcohol and other substances changed during marijuana abstinence. Using an ABA design, 28 individuals who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association [APA], 2000) criteria for either cannabis dependence or abuse and were not trying to stop their marijuana use completed an 8-day baseline period in which they used marijuana and other drugs as usual, then a 13-day marijuana abstinence period, and finally a 7-day return-to-baseline period. Marijuana abstinence was induced by a previously-validated contingent compensation schedule. Participants called a voicemail system daily to provide self-report of marijuana and alcohol use and visited the laboratory twice per week to provide self-report of caffeine, cigarette, and other illicit drug use, to complete self-report measures on psychological symptoms such as withdrawal and craving, and to submit urine samples to biochemically verify marijuana abstinence. Alcohol use significantly increased from a mean of 2.6 drinks/day ($SD=1.0$) during the baseline period to 3.0 drinks/day ($SD=1.0$) during the marijuana abstinence period ($p=0.03$), a 15% increase. Alcohol use then significantly decreased to 2.5 drinks/day ($SD=1.3$) during the return-to-baseline period ($p=0.03$), a 17% decrease. Although alcohol substitution occurred during marijuana abstinence, substitution of cigarettes, caffeine, and non-marijuana illicit drugs did not occur. Individuals with a diagnosis of past alcohol abuse or dependence substituted alcohol to a greater degree (52% increase) than those without this past history (3% increase). Increases in alcohol drinks/day correlated with increases in marijuana withdrawal discomfort scores and with increases in alcohol craving scores from the baseline to the marijuana abstinence period. Problems related to alcohol did not significantly increase from baseline to marijuana abstinence. This study provides empirical validation of the clinical notion of drug substitution and suggests that clinicians' concerns about drug substitution may be valid, but this study's results need to be replicated in individuals who seek treatment for marijuana problems. Whether substitution reduces the ability to abstain from marijuana also needs to be tested. If alcohol substitution does occur and interferes with the ability to quit marijuana, this would be important empirical support for the clinical practice of recommending abstinence from all substances.

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Table of Contents

List of Tables vi

List of Figures vii

Introduction..... 1

 Drug Substitution Background 1

 Drug Substitution for Particular Subgroups..... 3

 Drug Substitution in Marijuana Users 4

Method 6

 Design 6

 Participants..... 6

 Sample Size..... 8

 Procedure 9

 Screening and Consent..... 9

 Initial Assessment 9

 Baseline Period (8 days) 13

 Abstinence Period (13 days) 15

 Compensation to Induce Abstinence 15

 Return-to-Baseline Period (7 days)..... 16

 Compensation for Completing Study Procedures..... 16

 Urine Sample Collection and Analytic Methods 17

 Data Analysis 19

Results..... 24

Recruitment.....	24
Sample Characteristics.....	25
Marijuana Use.....	27
Alcohol Substitution Effect	29
Moderators of the Alcohol Substitution Effect.....	31
Correlates of the Alcohol Substitution Effect.....	33
Time Course of the Alcohol Substitution Effect	33
Mood Disturbance.....	34
Substitution of Other Substances	35
Discussion.....	36
Summary of Results.....	36
Alcohol Substitution	37
Variability of the Alcohol Substitution Effect.....	39
Possible Mediators of the Alcohol Substitution Effect.....	41
Substitution of Other Substances	43
Limitations	44
Strengths	45
Future Studies	46
Replication Tests.....	46
Drug Substitution in Different Subgroups	47
Interventions Related to the Alcohol Substitution Effect	49
Other Studies of Drug Substitution.....	49

Clinical Implications.....	50
Summary.....	50
References.....	70

List of Tables

Table 1. Power Analysis.	52
Table 2. Participant Characteristics.	53
Table 3. Outcomes Related to Marijuana Use.	55
Table 4. Outcomes Related to Alcohol Use.	57
Table 5. Outcomes Related to Mood Disturbance.	59
Table 6. Outcomes Related to Cigarette and Caffeine Use.	60

List of Figures

Figure 1. Experimental Timeline.	62
Figure 2. Participant Recruitment and Retention.....	63
Figure 3. Mean Creatinine-Normalized Tetrahydrocannabinol (THCCOOH) Levels.	64
Figure 4. Interaction between Period and Diagnosis of Past Alcohol Abuse/Dependence.	65
Figure 5. Correlates of the Alcohol Substitution Effect.	66
Figure 6. Time Course of the Alcohol Substitution Effect.	67

Introduction

Drug Substitution Background

Many, if not most, drug abuse counselors and treatment programs recommend abstinence from all psychoactive substances. One reason for this recommendation is that they believe that continued use of other psychoactive drugs can interfere with the ability to abstain from the primary drug (Hartel et al., 1995; Moore & Budney, 2001; Sobell, Sobell & Kozlowski, 1995; Stuyt, 1997; Wasserman, Weinstein, Havassy & Hall, 1998; cf., Budney, Bickel & Amass, 1998; Budney, Higgins & Wong, 1996). Another reason is that they fear that clients who decrease or stop their consumption of one drug will substitute a new drug or, more likely, increase use of a concurrently-used drug (Friend & Pagano, 2005). Such substitution could occur to replace the psychoactive effects of the abstained drug (Levison, Gerstein & Maloff, 1983), to relieve craving or withdrawal (Copersino et al., 2006a), or due to a genetic basis in the overlap between drugs (Agrawal & Lynskey, 2006). In addition, according to behavioral theories of choice (Vuchinich & Tucker, 1988), substitution occurs when access to a particular reinforcer, i.e., primary substance of abuse, is constrained, and behavior is then reallocated among other available reinforcers, i.e., secondary substances of use. Conditioning may be another explanation for drug substitution; if individuals use multiple substances simultaneously, the use of one substance can act as a cue to elicit the use of another.

Research to confirm this notion of substitution, however, mostly fails to show that abstinence from one drug increases use of another. Alcohol and cigarette use are moderately to strongly associated (Bien & Burge, 1990; Istvan & Matarazzo, 1984;

Piasecki, McCarthy, Fiore & Baker, 2008), but there is debate as to whether changing either alcohol or cigarette use changes the use of the other. No significant relations between changes in smoking and changes in alcohol drinking were found in the general population (Murray, Cribbie, Istvan & Barnes, 2002), nor among individuals seeking treatment for alcohol-related problems (Gulliver, Kalman, Rohsenow, Colby, Eaton & Monti, 2000) or smoking-related problems (Murray, Istvan & Voelker, 1996); on the other hand, smoking cessation was associated with a modest increase in alcohol consumption over a 16-year period in World War II male veteran twins (Carmelli, Swan & Robinette, 1993).

Drug substitution has also been examined in individuals with problems related to cocaine and/or opioid use, and conflicting findings have been reported. Cocaine-dependent individuals did not change their number of cigarettes smoked during early cocaine abstinence (Radzius, Gorelick & Henningfield, 1998), after an outpatient treatment program, or at a 9-month follow-up (Patkar, Mannelli, Peindl, Murray, Meier & Leone, 2006). Primary heroin users seeking treatment in the Australian Treatment Outcome Study did not show evidence of drug (i.e., cocaine, other opioids) substitution after reducing their heroin use (Darke, Williamson, Ross & Teesson, 2006). Multiple studies of methadone maintenance treatment for primary heroin users suggest that changing heroin use increases cigarette use (Conner, Stein, Longshore & Stacy, 1999), decreases alcohol and cocaine use (Maremmani et al., 2007), and has no effect on cannabis use (Epstein & Preston, 2003). However, in non-treatment studies, cocaine users reported marijuana and sedatives as substitutes for cocaine (Jofre-Benet & Petry,

2008), and heroin users reported marijuana and alcohol as substitutes for heroin (Petry & Bickel, 1998).

While research on drug substitution has focused mostly on alcohol, cigarettes, cocaine, and heroin, caffeine may also act as a substitute for other substances, notably cigarettes and alcohol. Caffeine is moderately related to tobacco (Istvan & Matarazzo, 1984) and may be associated with alcohol (Swan, Carmelli & Cardon, 1996). After alcohol detoxification, individuals reported an increase in coffee use (Aubin, Laureaux, Tilikete & Barrucand, 1999), and after coffee-drinkers quit smoking cigarettes, they consumed more coffee than nonsmokers (Swanson, Lee & Hopp, 1994).

Drug Substitution for Particular Subgroups

Despite these general patterns that mostly do not find drug substitution, it is possible that substitution does occur for subgroups of individuals. Examination of these subgroups mostly shows that those with moderate, as opposed to heavy, use of secondary substances are more likely to report drug substitution. In two studies of treatment-seekers for alcohol and substance use problems, cigarette use increased when those who were moderate smokers prior to treatment admission abstained, while cigarette use decreased for those who were classified as heavy smokers (Aubin et al., 1999; Harris, Best, Man, Welch, Gossop & Strang, 2000). Furthermore, among non-crack users of opioids at treatment intake, 22% substituted crack for opioids during the 4-5 years post-treatment, while users of both opioids and crack at treatment intake did not substitute crack after decreasing their opioid use. Of this 22%, two-thirds actually initiated crack

use, i.e., had never tried it during their drug use history (Gossop, Marsden, Stewart & Kidd, 2002). On the other hand, opioid users with high levels of cocaine use at treatment entry were most likely to substitute cocaine use for opioids during methadone maintenance treatment, in comparison to two groups of opioid users who did not use cocaine heavily at treatment entry (Bovasso & Cacciola, 2003).

Drug Substitution in Marijuana Users

Drug substitution has not been adequately examined in primary users of marijuana, although most users of marijuana also use other drugs (World Health Organization, 1997), especially alcohol (Hughes, Day, Marcantonio & Torpy, 1997; Norton & Colliver, 1988). Secondary abuse of alcohol was reported by 57% of treatment admissions for primary marijuana abuse between 1994 and 1999 (SAMHSA, 1999). In a retrospective study, at least half of current cannabis users stated that in past quit attempts, they increased their use of alcohol and tobacco (Copersino et al., 2006b). Prospective trials of outpatient treatments for adult marijuana dependence, however, reported discrepant results. One study reported a significant increase in the posttreatment frequency of alcohol use and related problems (Stephens, Roffman & Simpson, 1994), while others found either a reduction in alcohol use (Stephens, Roffman & Curtin, 2000) or no significant change in alcohol use following treatment for marijuana use (Budney, Higgins, Radonovich & Novy, 2000; The Marijuana Treatment Project Research Group, 2004). In several prospective non-treatment studies, marijuana abstinence did not change the use of alcohol, tobacco, and other drugs (Budney, Hughes, Moore & Novy, 2001;

Budney, Moore, Vandrey & Hughes, 2003; Haney, Hart, Vosburg, Nasser, Bennett, Zubaran, et al., 2004; Kouri & Pope, 2000).

The above findings on drug substitution in marijuana users should be interpreted with caution for several reasons. First, retrospective studies potentially have recall or rationalization biases. Second, the prospective studies excluded participants who were frequent alcohol users and included non-alcohol users, thereby decreasing their sensitivity to detect a change in alcohol use. Third, the treatment studies are confounded by treatment instructions to avoid drug substitution; the non-treatment studies are confounded by explicit instructions to not change alcohol use (Budney et al., 2001; Budney et al., 2003); and inpatient studies are confounded by participants not having access to alcohol (Haney et al., 2004). Fourth, alcohol use was not a major dependent variable in these studies and, thus, measurement of alcohol use was less-than-optimal; e.g., several studies measured alcohol use in a single self-report of the past 90 days. In summary, an adequate test of whether marijuana abstinence changes alcohol use has not been accomplished.

This dissertation attempted to overcome the above-listed problems by prospectively examining possible drug substitution, by recruiting regular marijuana users who use alcohol moderately, by instructing participants to use alcohol as they wish, and by assessing alcohol use on a daily basis. Although the study was designed to detect the substitution of alcohol for marijuana, whether marijuana abstinence changed the use of tobacco, caffeine, and other illicit drugs was also examined.

Method

Design

A within-subjects study investigated whether consumption of alcohol and other substances changed during marijuana abstinence. Using an ABA design, 28 individuals who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association [APA], 2000) criteria for either cannabis dependence or abuse and were not trying to stop their marijuana use completed an 8-day baseline period in which they used marijuana and other drugs as usual, then a 13-day marijuana abstinence period, and finally a 7-day return-to-baseline period. Marijuana abstinence was induced by a previously-validated contingent compensation schedule (Budney et al., 2003). Participants called a voicemail system (Hughes, Peters, Callas, Budney & Livingston, 2008) daily to provide self-report of marijuana and alcohol use. Participants visited the laboratory twice per week to provide self-report of caffeine, cigarette, and other illicit drug use, to complete self-report measures on psychological symptoms such as withdrawal and craving, and to submit urine samples to biochemically verify marijuana abstinence.

Participants

Participants in the Burlington, Vermont area were recruited via advertisements in an alternative newspaper, newspapers of local universities, and a local radio station. Advertisements specified that “regular” marijuana users who did not plan to stop their marijuana use were sought for a non-treatment study. Individuals were deemed eligible

to participate if they: a) were 18 years of age or older; b) smoked marijuana at least once per day on 25 of the past 30 days; c) used marijuana at this rate for at least 6 months; d) met DSM-IV (APA, 2000) criteria for current (i.e., within the past 12 months) cannabis dependence or abuse; e) for males, currently consumed between 3 and 16 standard drinks of alcohol per week and for females, currently consumed between 3 and 12 standard drinks of alcohol per week; f) provided a urine sample at the initial assessment that tested positive for tetrahydrocannabinol (THC), the primary psychoactive component of marijuana (Huestis, 2005); and g) were willing to abstain from marijuana for two weeks. Individuals were excluded if they: a) met DSM-IV (APA, 2000) criteria for current (i.e., within the past 12 months) alcohol or other substance abuse or dependence (not including caffeine and nicotine); b) were currently taking psychotropic medication that interacted with alcohol use or its effects; c) planned to change substance use, diet, or activity in the next four weeks; d) were actively seeking treatment for substance-related or psychiatric problems; e) reported a significant change (increase or decrease of 25%) in the amount of marijuana or other drugs used in the previous month; f) were currently incarcerated or their legal status was such that they may be incarcerated during enrollment in the study; or g) had urgent drug-related or psychiatric problems (e.g., abuse of others or suicidal ideation).

Marijuana users who met diagnostic criteria for current cannabis dependence or abuse were recruited because most treatment-seekers are dependent users (SAMHSA, 1999). Participants could report current alcohol problems but could not fulfill diagnostic criteria for current alcohol dependence or abuse. Participants who consumed between 3

and 16 (for males) or between 3 and 12 (for females) standard drinks of alcohol each week were included to avoid ceiling and floor effects that would prevent seeing an increase or decrease in alcohol use during marijuana abstinence. Furthermore, these are the maximums for moderate drinking, according to empirically-based guidelines (Sanchez-Craig, Wilkinson & Davila, 1995). Individuals who planned to change their alcohol or substance use were excluded in order to avoid changes in alcohol use that were specifically done to aid in marijuana abstinence. Recruiting individuals who were not trying to change their marijuana use allowed an ethical return-to-baseline condition; however, this strategy minimized external validity to those who are actively trying to quit marijuana.

Sample Size

In a power analysis to determine a sample size adequate to detect a significant change in alcohol consumption during marijuana abstinence, a significant change was defined as being an increase or decrease of 30%-50% of baseline alcohol use. Although an increase in alcohol use (i.e., drug substitution) was the main outcome of interest, a decrease in use was also of interest; thus, two-tailed tests were used. Data from Budney et al. (2003) and from a preliminary study of tobacco smokers (Peters, Hughes, Callas & Solomon, 2007) reported within-subject correlations of alcohol consumption of 0.6 and 0.8, respectively. Scenarios with within-subject correlations of 0.6 and 0.8 were run, with changes in alcohol use of 30% and 50%, and with power of 0.80. In all scenarios, alpha was set at 0.05 (two-tailed). A sample size of 28 was chosen because this was

sufficient for most of the scenarios (i.e., those marked by bold font and asterisks in Table 1).

Procedure

Screening and Consent

Individuals were screened for eligibility via telephone. Those eligible were read a brief description of the study, and those interested visited the laboratory to provide written informed consent. To decrease experimenter demand, participants were not informed that the focus of the study was on drug substitution; instead, the stated purpose was to determine how difficult individuals find it to abstain from marijuana for two weeks. Immediately after providing informed consent to participate, individuals provided a breath alcohol level (BAL; Intoximeters, Inc., St. Louis, MO) sample to measure recent alcohol intake and verify that they were capable of providing consent. No participant submitted a positive BAL sample.

Initial Assessment

The author, a doctoral student in clinical psychology previously trained in the Structured Clinical Interview Diagnostic (SCID; First, Spitzer, Gibbon, & Williams, 1995) for the DSM-IV (APA, 2000), administered the following modules: alcohol use disorders, substance use disorders, mood disorders, anxiety disorders, and psychotic disorders. Five individuals met criteria for a current Axis I disorder; the interviewer

informed them of their diagnosis and ineligibility for the study, and referred them to treatment. Those participants who appeared to be eligible after the interview then completed self-report measures on demographics, current and past drug use history, and nicotine dependence (i.e., Fagerstrom Test of Nicotine Dependence [FTND]; Heatherton, Kozlowski, Frecker & Fagerstrom, 1991). They also completed the following self-report measures on psychological symptoms related to substance use:

1) Marijuana withdrawal: *The Marijuana Withdrawal Checklist* (MWC; Budney et al., 2003) is a 31-item checklist of symptoms of marijuana withdrawal, as well as general symptoms (e.g., stuffy nose) to estimate over-endorsement due to experimenter demand or expectancy effects. Individuals rate the severity of symptoms on a 4-point scale (0=not at all, 1=mild, 2=moderate, 3=severe). Prior studies have shown this measure to be sensitive to the effects of marijuana abstinence (Budney et al., 1999; Budney et al., 2001; Budney et al., 2003). A Withdrawal Discomfort Score (WDS) is computed by summing severity ratings of twelve items that previous studies documented as possible withdrawal symptoms: aggression, anger, decreased appetite, depressed mood, irritability, nervousness/anxiety, restlessness, shakiness, sleep difficulty, stomach pains, strange dreams, and sweating (Budney et al., 2003). The range of possible Withdrawal Discomfort Scores is 0-36.

2) Marijuana craving: *The Marijuana Craving Questionnaire* (MCQ; Heishman, Singleton & Liguori, 2001) is a 45-item questionnaire that is a valid and reliable

instrument for assessing marijuana craving in individuals not seeking drug abuse treatment. The original MCQ required items to be rated on a 7-point Likert scale from “strongly disagree” to “strongly agree,” but the version used in this study had each item rated as “true” or “false,” with a point value of 1 corresponding to “true” and 0 corresponding to “false.” Subscales include compulsivity, emotionality, expectancy, and purposefulness. The range of possible scores for the version used in this study is 0-45.

3) Marijuana problems: *The Cannabis Problems Questionnaire* (CPQ; Copeland, Gilmour, Gates & Swift, 2005) is a list of 27 possible problems related to marijuana use that are scored as dichotomous yes/no responses. The CPQ is a valid, reliable, and sensitive measure of cannabis-related problems and provides subscale scores for social, psychological, and physical problems. The range of possible scores is 0-27.

4) Alcohol craving: *The Penn Alcohol Craving Scale* (PACS; Flannery, Volpicelli & Pettinati, 1999) is a five-item measure that includes questions about the frequency, intensity, and duration of craving and asks for an overall rating of craving for alcohol. Individuals rate their responses on a scale of 0 to 6, and the range of possible scores is 0-30.

5) Alcohol problems: *The Short Index of Problems* (SIP; Feinn, Tennen & Kranzler, 2003) is a short form of the Drinker Inventory of Consequences (Miller, Tonigan & Longabaugh, 1995). The SIP consists of 15 questions about problems related to alcohol

use with response choices of “yes” and “no,” and it has good internal consistency, good concurrent validity, and adequate stability. The range of possible scores is 0-15.

6) Cigarette craving: *The Brief Questionnaire of Smoking Urges* (QSU; Sanderson Cox, Tiffany & Christen, 2001; Tiffany & Drobes, 1991) consists of ten items with two subscales: one that reflects a strong desire and intention to smoke, and one that reflects anticipation of relief from negative affect with an urgent desire to smoke. Individuals rate items on a 4-point Likert scale from “strongly disagree” to “strongly agree.” The range of possible responses is 10-40.

7) Mood disturbance: *The brief version of the Profile of Mood States* (POMS; McNair, Lorr & Droppelman, 2003) is a 30-item list of mood states. Individuals rate the frequency of experiencing each mood state on a scale of 0 (“not at all”) to 4 (“extremely”). This measure provides six subscale scores: tension, depression, anger, vigor, fatigue, and confusion. A total mood disturbance score is calculated by summing the subscale scores of tension, depression, anger, fatigue, and confusion and then subtracting the vigor subscale score. The range of possible total scores is -20 to +100.

Participants provided a urine sample that was tested for THC onsite via Enzyme Multiplied Immunoassay Technique (EMIT; Microgenics MGC 240 EMIT Benchtop Analyzer, Thermo Scientific, Fremont, CA). Results greater than 50 ng/mL signified that individuals had used marijuana within the past 1-2 days (Huestis, Mitchell & Cone,

1995). Only participants who provided a positive urine sample were included in the study. This sample was also tested for pregnancy in females; no female participant provided a positive sample. Eligible participants were scheduled for their first laboratory visit of the baseline period.

Baseline Period (8 days)

Figure 1 presents the experimental timeline of the study. To minimize the effect of specific days on substance use and psychological symptom measures, all participants began the study on a Thursday. Female participants began on the Thursday following the onset of menses. Participants were instructed to use their usual amounts of marijuana, alcohol and other substances during the baseline period.

Participants were instructed to call a voicemail system when they awoke each morning to report the number of sessions in which they used marijuana and standard drinks of beer, wine, and liquor they consumed the previous day. Participants were informed that a single marijuana smoking session represented one sitting in which they used marijuana (i.e., smoking one marijuana cigarette in two separate sittings equaled two sessions). They were further informed that a standard drink of alcohol is 12 ounces of beer, 5 ounces of wine, and 1.5 ounces of liquor (U.S. Department of Health and Human Services, 2007). To maximize confidentiality, participants were given unique study identification numbers and directed to identify themselves only with this number in their daily calls. They began their calls the morning after the first laboratory visit. The

study coordinator received the voicemail messages at noon each day and reminded any participant who did not provide a voicemail to call the system immediately.

Participants visited the laboratory again on Monday and Thursday. Timeline Follow-Back (TLFB; Sobell & Sobell, 1992) procedures gathered data on participants' use of caffeine, cigarettes, and non-marijuana illicit drugs on each day since the previous laboratory visit. Separate questions were asked about caffeine use (i.e., consumption of coffee, tea, or caffeinated soda) (Hughes & Oliveto, 1997), and responses were coded into standard drinks, where a standard drink equaled 6 ounces of brewed coffee, 24 ounces of tea, and 48 ounces of soda (Barone & Grice, 1994). Participants reported number of tobacco cigarettes smoked, as well as pharmacological class (e.g., stimulants, sedatives) and number of sessions using any non-marijuana illicit drugs. Perseus Survey Solutions (Perseus Development Corporation, Braintree, MA), an Internet-based survey system, collected participants' responses to the seven self-report measures described in the "Initial Assessment" section. Participants were instructed to provide responses based on their experiences since the prior laboratory visit. BAL samples (Intoximeters, Inc., St. Louis, MO) to measure recent alcohol intake and breath carbon monoxide (CO; Bedfont Scientific Ltd., Rochester, UK) samples to measure recent cigarette smoking (i.e., within the past 24 hours; Benowitz, Jacob, Ahijevych, Jarvis, Hall, LeHouezec, et al., 2002) were collected. Body weight was obtained without shoes and heavy clothing.

On the last visit of this period, participants provided a urine sample to establish their baseline level of marijuana use and were then instructed to abstain completely from marijuana beginning the next morning. Participants were only directed to use alcohol,

cigarettes, caffeine, and non-marijuana drugs “as they wish” so their use of other substances could naturally increase, decrease, or stay the same. They were informed of the contingent payment system to reinforce abstinence.

Abstinence Period (13 days)

The abstinence period began on a Friday and lasted 13 days in order to encompass two weekends, assuming that participants would be more likely to consume alcohol on weekend-days than weekdays. Participants continued making daily calls each morning. At Monday and Thursday laboratory visits, participants underwent the same assessments described in the “Baseline Period” section. Additionally, they provided urine samples at all visits to verify abstinence from marijuana.

Compensation to Induce Abstinence

In order to obtain a high rate of compliance with the 13-day abstinence requirement, participants were contingently compensated with an escalating schedule of reinforcement. This compensation schedule has been used effectively in prior studies of marijuana abstinence (e.g., Budney et al., 2003). Participants earned vouchers if urine specimens indicated no recent marijuana use (see “Urine Sample Collection and Analytic Methods” below for the definition of “no recent marijuana use”). The value of the initial voucher given for abstinence from marijuana was \$15, and each subsequent voucher for abstinence increased in value by \$5 (i.e., to \$20, then \$25, then \$30). The seven

participants who either self-reported marijuana use during the abstinence period or provided samples that did not verify abstinence were discontinued and received the amount they earned to that point.

Return-to-Baseline Period (7 days)

Participants were informed that after the last visit of the abstinence period, they could return to marijuana use. However, in order to not coerce participants to engage in an illegal behavior, participants were told that they could remain in the study whether or not they returned to use. Participants continued with daily calls and Monday and Thursday laboratory visits. Participants provided a urine sample at the first visit of this period to confirm reinstatement of marijuana use. At the last visit, the study coordinator debriefed participants about the primary aims of the study and interviewed them about reasons why their use of other drugs did or did not change.

Compensation for Completing Study Procedures

The value of the voucher for completing the initial assessment was \$15, and the value for each laboratory visit was \$5. The value of the voucher for completing each daily call was \$1. Participants who completed all scheduled laboratory visits and daily calls and who abstained from marijuana for every day of the abstinence period were compensated a bonus of \$50. Thus, the total maximal compensation was \$253 in

vouchers. Vouchers were redeemed for retail goods designated by participants; no cash was provided.

Urine Sample Collection and Analytic Methods

Participants provided six urine samples throughout the study: at the last visit of the baseline period, at each visit of the marijuana abstinence period, and at the first visit of the return-to-baseline period. A temperature gauge on the collection container verified the validity of the sample (i.e., the temperature within 3-minutes post-collection must have been between 90 and 100 degrees Fahrenheit) (Dominion Diagnostics, Providence, RI). Each sample was split into two samples: one was mailed overnight to Dominion Diagnostics (Providence, RI) for immediate analysis, and one was saved for later analysis or in case of errors. Results from each visit were available on Dominion Diagnostics' (Providence, RI) password-protected website before the subsequent visit.

Marijuana use and abstinence were quantitatively measured by enzyme immunoassay (EIA), with positive results confirmed by Gas Chromatography/Mass Spectrometry (GC/MS) (Dominion Diagnostics, Providence, RI). GC/MS levels of 11-nor-9-carboxy- Δ^9 -tetrahydrocannabinol (THCCOOH), the primary marijuana metabolite, were normalized to urine creatinine concentration to obtain a metabolite/creatinine ratio (Budney et al., 2003; Huestis & Cone, 1998). According to Huestis (2005), normalization of the THCCOOH concentration to the urine creatinine concentration aids in the differentiation of new vs. prior cannabis use, reduces the variability of drug measurement due to urine dilution, and facilitates interpretation of consecutive urine drug test results.

Marijuana use during the baseline period was validated if the EIA result for cannabinoids was greater than 25 ng/mL (Dominion Diagnostics, Providence, RI). Abstinence was validated by examining the metabolite/creatinine ratio because this ratio can reliably document short periods of marijuana abstinence (Huestis & Cone, 1998). An empirically-derived algorithm developed by Huestis & Cone (1998) has been used in previous studies to validate marijuana abstinence (e.g., Budney et al., 2003), in which abstinence is confirmed if the metabolite/creatinine ratio on any day does not increase by more than 50% from the ratio obtained on the previous day. Because of financial constraints, we could only collect samples twice-weekly and thus, this algorithm was not applicable. We reasoned that with abstinence of three to four days, there should be a decrease in the metabolite/creatinine ratio from one visit to the next and used this as the abstinence criterion (Dominion Diagnostics, Providence, RI). An increase in the metabolite/creatinine ratio from the last visit of the abstinence period to the first sample of the return-to-baseline visit confirmed return to marijuana use.

Urine samples were also tested for cotinine, the primary nicotine metabolite (Benowitz et al., 2002), via EIA to determine cigarette use. The cut-off for a positive cotinine result was 500 ng/mL (Dominion Diagnostics, Providence, RI). Biochemical validation of alcohol use was considered, but biomarkers such as carbohydrate-deficient transferrin (CDT) indicate alcohol abuse and long-term alcohol consumption rather than short-term consumption (Bortolotti, De Paoli & Tagliaro, 2006). Due to financial constraints, quantitative analysis of illicit drugs and caffeine was not possible.

Data Analysis

Among the 28 individuals who completed the study, missing data were minimal: 24 of 784 days (3%) of daily call data were missing, and 6 of 252 (2%) laboratory visit data (i.e., TLFB and biochemical data) were missing. All missing visit data occurred during the return-to-baseline period when three participants unexpectedly left the Burlington area. There were no missing data from the questionnaires completed at laboratory visits because Perseus Survey Solutions (Perseus Development Corporation, Braintree, MA) did not allow missing responses.

Because most data were contained in written records, a technician in the University of Vermont Department of Medical Biostatistics double-entered written records into Microsoft Excel. Self-report data collected at laboratory visits were downloaded from Perseus Survey Solutions (Perseus Development Corporation, Braintree, MA) to Microsoft Excel. Data were screened for missing and illogical values and outliers. Missing data were imputed using the mean of adjacent values when possible, and last point carried forward when not possible (i.e., when a missing value occurred on the last day or visit of the study). Most analyses were performed with SPSS 16.0 (Chicago, IL), but analyses regarding residual data were examined with SAS (version 9, SAS Institute, Cary, NC).

Sundays through Thursdays were defined as weekdays and Fridays and Saturdays as weekend-days because substance use often occurs in the evenings of these days. Because participants tended to consume more alcohol on weekend-days ($M=4.4$ [$SD=1.5$]) than weekdays ($M=2.2$ [$SD=1.0$], $t(27)=8.30$, $p<0.01$), mean alcohol

drinks/day of each period were adjusted to ensure the same ratio of weekdays to weekend-days occurred in each of the three periods. For example, during the baseline period, the ratio of weekdays to weekend-days was 3:1, but during the marijuana abstinence period, the ratio was 9:4. With a ratio of 9:4, the mean alcohol drinks/day during the abstinence period may have been inflated in comparison to the baseline period because of more weekend-days during abstinence than during baseline. To create a weekday to weekend-day ratio during abstinence that was similar to the ratio during baseline, the desired ratio of weekdays to weekend-days during the abstinence period was 12:4. Thus, each weekday value of alcohol drinks during the abstinence period needed to be weighted, or multiplied, by 1.33 (i.e., 12/9). With this weighting procedure, there were three additional weekdays accounted for during abstinence, so the new total alcohol drinks during the abstinence period were divided by 16 days to arrive at mean alcohol drinks/day. A similar weighting procedure was undertaken for the return-to-baseline period, where the original ratio of weekdays to weekend-days was 5:2.

The major specific aim was to examine whether there were changes in use of alcohol during marijuana abstinence. A repeated-measures analysis of variance (ANOVA) tested differences in weighted mean number of alcohol drinks per day among the three periods, with period as the within-subjects factor. The following two *a priori* comparisons were examined in paired-samples *t*-tests: a) mean alcohol drinks/day in the baseline period vs. that in the abstinence period, and b) mean alcohol drinks/day in the abstinence period vs. that in the return-to-baseline period. Similar repeated-measures ANOVAs and follow-up comparisons were conducted for other alcohol use outcomes,

such as weekday and weekend-day mean alcohol drinks/day and mean drinks/day only on days when individuals consumed at least one drink of alcohol. Because sphericity assumptions were often violated in the repeated-measures analyses, main effects for period are reported using Huynh-Feldt tests, and percent of variance accounted for provides a relative magnitude of the differences among the three periods. Wilcoxon tests examined differences in percentage of binge-drinking episodes (for males, consumption of 5+ drinks on one day and for females, consumption of 4+ drinks on one day [Wechsler & Austin, 1998]) and percentage of days on which individuals drank at least one alcohol drink. In order to examine the 13 days of the marijuana abstinence period with a similar number of days in the Wilcoxon tests, the baseline and return-to-baseline periods were combined and then contrasted with the marijuana abstinence period. Mean percentages in the baseline and return-to-baseline periods did not significantly differ for either outcome (mean percent of binge-drinking episodes: 23% [$SD=15\%$] in baseline and 23% [$SD=17\%$] in return-to-baseline, $z=-0.24$, $p=0.81$; mean percent of days on which individuals drank at least one alcohol drink: 69% [$SD=19\%$] in baseline and 68% [$SD=26\%$] in return-to-baseline, $z=-0.42$, $p=0.68$).

A secondary aim was to examine whether there were changes in use of substances other than alcohol during marijuana abstinence. To examine whether cigarette or caffeine use changed, similar ANOVAs and follow-up comparisons tested for similar effects. Because illicit drug use was so infrequent, these trends were only examined graphically.

Another secondary aim was to examine changes in psychological symptoms during marijuana abstinence. Because these data were collected at laboratory visits and because differing number of visits occurred during each period, mean values were computed for each period in the following manner: the baseline period encompassed data from the first three laboratory visits, the marijuana abstinence period encompassed the next four laboratory visits, and the return-to-baseline period encompassed the final two laboratory visits. Repeated-measures ANOVAs and follow-up comparisons were conducted to examine changes in psychological symptoms across the three study periods. Overall questionnaire scores and subscale scores, if applicable, for marijuana WDS, marijuana craving, marijuana problems, alcohol craving, alcohol problems, cigarette craving, and mood disturbance were examined.

Hypothesized moderators that might influence the effect of marijuana abstinence on alcohol use included demographic variables (e.g., sex, age, race, education status, and employment status) and substance use history variables collected at the initial assessment. For example, possible moderators related to substance use history included:

1. current cannabis diagnosis (i.e., dependence vs. abuse);
2. diagnosis of past alcohol abuse or dependence vs. no diagnosis;
3. diagnosis of past non-marijuana substance dependence vs. no diagnosis;
4. marijuana problems during the baseline period;
5. marijuana craving during the baseline period;
6. alcohol drinks/day during the baseline period;
7. alcohol problems during the baseline period; and

8. alcohol craving during the baseline period.

Another possible moderator was overall mood disturbance score during the baseline period. All possible moderators of the alcohol substitution effect were investigated by inspecting the interaction between these variables and the main effect for period in the repeated-measures ANOVAs. In order to graphically inspect possible interactions, continuous moderating variables (#4-8 listed above) were recoded into categorical variables by performing median splits. The interaction between these categorical moderating variables and the period effect was then statistically examined using Wilks' Lambda tests for between-group comparisons.

Hypothesized mediators of the effect of marijuana abstinence on alcohol use included marijuana withdrawal discomfort and other psychological symptoms collected at laboratory visits (see #1-7 of "Initial Assessment" section). Formal mediational tests were not conducted because of concern about small sample size. Thus, for those psychological symptoms that significantly changed from baseline to marijuana abstinence, we examined correlations between such changes and changes in alcohol drinks/day from baseline to marijuana abstinence. Because the small sample size may have precluded statistically significant results, trends were also examined graphically.

To examine the time course of any substitution effect during marijuana abstinence, i.e., whether alcohol use significantly increased for the first few days of abstinence but then returned to normal, we computed residual alcohol use scores. Residual scores reflected the difference between alcohol drinks/day that would be expected based on the baseline and return-to-baseline periods vs. actual observed alcohol

drinks/day during the marijuana abstinence period. Because the mean alcohol drinks/day during the baseline ($M=2.6$ [$SD=1.0$]) and return-to-baseline ($M=2.5$ [$SD=1.3$]) periods were not significantly different ($t(27)=0.29, p=0.78$), we used data from both periods to compute expected number of alcohol drinks/day. To control for weekday vs. weekend-day alcohol use variability, we calculated residuals separately for a weekday and a weekend-day. We then calculated residual alcohol scores by subtracting the expected number of drinks for weekdays and weekend-days during the two baseline periods from the observed number of drinks on weekdays and weekend-days during the marijuana abstinence period.

Results

Recruitment

Figure 2 presents a flowchart of recruitment and retention of participants. Of 420 individuals who responded to advertisements, 312 (74%) were able to be reached by telephone for screening for inclusion into the study, and 245 (78% of those screened) were ineligible. The most common reasons for ineligibility included: a) currently consumed more than 16 alcohol drinks/week for males or 12 drinks/week for females (38%); b) currently consumed less than 3 alcohol drinks/week (33%); and c) currently used marijuana on fewer than 25 of the past 30 days (27%).

Of the 67 individuals who were eligible, 18 (27%) were not interested in participating. Of the 49 who were interested, 11 (22%) were not eligible after the initial in-person assessment; the most common reason for ineligibility was meeting diagnostic

criteria for current alcohol or substance use disorder ($n=4$, 36% of those not eligible). Of the 38 individuals who were eligible after the initial assessment, two were no longer interested and did not begin the study. 36 participants enrolled in the study, and 29 participants completed the study. Of the seven participants who did not complete the study, six self-reported marijuana use during the marijuana abstinence period, and one participant cited personal reasons for withdrawing during the baseline period. Of the 29 participants who completed the study, two lived together and thus may not have provided independent data; the urinalysis testing of one of these individuals showed lower than expected creatinine-normalized THCCOOH levels during the baseline period, so she was omitted from data analysis. Thus, 28 participants were included in the analysis.

Sample Characteristics

Table 2 presents demographic and substance use characteristics for the 28 individuals who completed the study and were included in data analysis. Because the findings from this study may have relevance to individuals seeking treatment for marijuana dependence, the current sample was compared to treatment-seeking, daily users in the largest marijuana treatment study – The Marijuana Treatment Project (MTP; The Marijuana Treatment Project Research Group, 2004). Our participants were younger (23 vs. 36 years); more likely to be male (75% vs. 68%), Caucasian (93% vs. 69%), and unmarried (100% vs. 60%); and less likely to be employed full-time (36% vs. 69%). However, many were full-time students (21%).

Participants currently used marijuana almost every day and almost three times each day, rates similar to those in the MTP (The Marijuana Treatment Project Research Group, 2004). Nineteen participants (68%) met DSM-IV (APA, 2000) criteria for current cannabis dependence, and nine (32%) met criteria for current cannabis abuse.

Participants currently drank about ten alcohol drinks/week and reported binge-drinking (Wechsler & Austin, 1998) on three days of the past month. Even though participants had to currently use at least three alcohol drinks/week, five participants (18%) met DSM-IV (APA, 2000) criteria for past alcohol abuse, and two (7%) met criteria for past alcohol dependence.

Most participants ($n=18$, 64%) drank coffee regularly. These participants drank coffee about six days/week ($M=5.9$, $SD=2.0$) and consumed about two cups of coffee/day ($M=2.1$, $SD=0.9$). Eight participants (29%) drank tea regularly. They drank tea less than 4 days/week ($M=3.6$, $SD=2.1$) and consumed less than 2 drinks/day ($M=1.7$, $SD=0.9$). Ten participants (36%) drank soda regularly. They drank soda on less than 3 days/week ($M=2.6$, $SD=1.8$) and consumed about 1 soda drink/day ($M=1.3$, $SD=0.5$). This caffeine consumption appears similar to that for individuals of the state of Vermont (Hughes & Oliveto, 1997).

A minority of participants ($n=7$, 25%) currently smoked cigarettes; six of these consumed 1-5 cigarettes per day, while one smoked 20 cigarettes/day. This consumption is less than that for Vermont smokers (mean of 14.7 cigarettes/day; Vermont Department of Health, 2008a). Their mean FTND score was 1.1 ($SD=1.9$), compared to 3.6 for

Vermont smokers (Vermont Department of Health, 2008b). No information was gathered regarding whether participants used cigarettes on a less-than-daily basis.

Participants reported infrequent current use of illicit drugs other than marijuana, similar to those of the MTP (The Marijuana Treatment Project Research Group, 2004). Two participants used stimulants (e.g., cocaine) once in the past month, and two participants used hallucinogens (e.g., lysergic acid diethylamide) once in the past month. Three participants (11%) met DSM-IV criteria for past substance dependence (one cocaine, one opioid, one both cocaine and opioid).

Marijuana Use

The 28 designated participants used marijuana on a mean of 7.8 ($SD=0.5$) of the 8 days (98%) of the baseline period and 5.8 ($SD=1.8$) of the 7 days (83%) of the return-to-baseline period. Self-reported marijuana use (i.e., sessions/day) significantly changed across the three periods of the study ($F(2,54)=84.80, p<0.01$) (Table 3). Marijuana use significantly decreased from a mean of 2.9 sessions/day ($SD=1.3$) during the baseline period to 0 sessions/day ($SD=0.0$) during the marijuana abstinence period ($t(27)=12.01, p<0.01$), and use then significantly increased to 2.2 sessions/day ($SD=1.3$) during the return-to-baseline period ($t(27)=-8.94, p<0.01$). Marijuana use significantly differed between the two baseline periods ($t(27)=3.21, p<0.01$), with use greater in the baseline period than in the return-to-baseline period. Creatinine-normalized THCCOOH levels significantly changed across the three periods ($p<0.01$; Figure 3). Mean THCCOOH levels significantly decreased from the baseline period (350.1 [$SD=432.5$]) to the

marijuana abstinence period (36.7 [$SD=37.6$]; $t(25)=3.96$, $p<0.01$), and mean levels significantly increased from the marijuana abstinence period to the return-to-baseline period (127.5 [$SD=123.5$]; $t(27)=-4.39$, $p<0.01$).

Marijuana withdrawal discomfort scores significantly changed across the three periods of the study ($p<0.01$), accounting for 36.1% of the variance. Mean WDS significantly increased from the baseline period (2.9 [$SD=2.9$]) to the marijuana abstinence period (5.1 [$SD=4.0$]; $t(27)=-3.98$, $p<0.01$), and scores significantly decreased from the marijuana abstinence period to the return-to-baseline period (2.5 [$SD=2.7$]; $t(27)=4.44$, $p<0.01$). Participants' weight (in pounds) significantly changed across the three periods of the study ($F(2,54)=10.37$, $p<0.01$). Weight significantly decreased from the baseline period ($M=163.4$, $SD=32.9$) to the marijuana abstinence period ($M=161.3$, $SD=32.2$, $t(27)=5.13$, $p<0.01$), and it then significantly increased from the abstinence period to the return-to-baseline period ($M=162.5$, $SD=32.2$, $t(27)=-2.39$, $p=0.02$).

Overall marijuana craving scores did not significantly change across the three periods of the study ($p=0.73$), nor did scores change on any marijuana craving subscales (compulsivity: $p=0.94$; emotionality: $p=0.27$; expectancy: $p=0.20$; and purposefulness: $p=0.29$). Overall marijuana problem scores significantly changed across the three periods of the study ($p<0.01$), accounting for 38.1% of the variance. Mean marijuana problem scores significantly decreased from 3.1 ($SD=2.5$) during the baseline period to 0.9 ($SD=1.0$) during the marijuana abstinence period ($t(27)=6.24$, $p<0.01$), and then increased to 1.9 ($SD=2.6$) during the return-to-baseline period ($t(27)=-2.73$, $p=0.01$). Furthermore, mean marijuana problem scores were significantly greater during the baseline period than

during the return-to-baseline period ($t(27)=2.83, p<0.01$). All scores of marijuana problem subscales significantly changed across the three periods (physical problems: $p<0.01$; psychological problems: $p<0.01$; and social problems: $p<0.01$), with all subscale scores significantly decreasing from the baseline period to the marijuana abstinence period and all except psychological problems increasing from abstinence to the return-to-baseline period.

Alcohol Substitution Effect

Table 4 shows outcomes related to the alcohol substitution effect. Self-reported alcohol use showed a trend towards changing across the three periods of the study ($p=0.06$), accounting for 10.1% of the variance. Alcohol use significantly increased from a mean of 2.6 drinks/day ($SD=1.0$) during the baseline period to 3.0 drinks/day ($SD=1.0$) during the marijuana abstinence period ($t(27)=-2.29, p=0.03$), a 15% increase. Alcohol use then significantly decreased to 2.5 drinks/day ($SD=1.3$) during the return-to-baseline period ($t(27)=2.33, p=0.03$), a 17% decrease.

Changes in alcohol drinks/day from the baseline to the marijuana abstinence period across participants ranged from a decrease of 42% to an increase of 143%, suggesting significant between-person variability in the alcohol substitution effect. Eleven of the 28 participants (39%) decreased their alcohol use by 2%-42%, while 9 (32%) increased their alcohol use by 3%-50%, and 8 (29%) increased their alcohol use by 51%-143%.

The percentage of days of consuming at least one alcohol drink in each period was significantly greater in the marijuana abstinence period ($M=77\%$, $SD=16\%$) compared to the two baseline periods ($M=69\%$, $SD=19\%$; $p<0.01$). The percent of binge-drinking episodes was marginally greater in the marijuana abstinence period ($M=27\%$, $SD=14\%$) than the two baseline periods ($M=23\%$, $SD=14\%$, $p=0.05$). When only days that participants consumed at least one drink of alcohol were examined, alcohol use did not significantly change across the three periods ($p=0.30$). When weekday and weekend-day alcohol use were examined separately, both showed similar trends towards increasing alcohol use during marijuana abstinence but neither trend was statistically significantly (weekday: $p=0.32$, 13% increase; weekend-day: $p=0.17$, 17% increase).

Alcohol craving scores significantly changed across the three periods of the study ($p<0.01$), accounting for 19.6% of the variance. Mean alcohol craving scores significantly increased from the baseline period ($M=6.1$ [$SD=3.4$]) to the marijuana abstinence period ($M=7.2$ [$SD=4.1$]; $t(27)=-2.70$, $p=0.01$), and mean scores then significantly decreased from abstinence to the return-to-baseline period ($M=5.5$ [$SD=3.4$]; $t(27)=3.41$, $p<0.01$).

Alcohol problem scores did not significantly change across the three periods of the study ($p=0.28$). However, in an individual analysis of participants' change in alcohol problem scores, one participant reported a substantial increase in alcohol problems from the baseline period to the marijuana abstinence period. This individual reported a mean of 0.3 alcohol problems in the baseline period but then reported 6 alcohol-related problems after one week of abstaining from marijuana. Throughout visits during the

second abstinence week and the return-to-baseline period, he reported a mean of 2.0 alcohol-related problems.

All but one of the 252 BAL samples collected at laboratory visits were negative for alcohol. The one positive BAL sample (BAL=0.01) occurred at the last visit of the baseline period, and the participant who submitted this breath sample reported that he had consumed one beer shortly before his visit. He was required to remain at the laboratory until his BAL was negative for alcohol.

Moderators of the Alcohol Substitution Effect

Period and diagnosis of past alcohol abuse/dependence significantly interacted to predict alcohol substitution ($F(2,25)=9.81, p<0.01$), accounting for 44% of the variance (Figure 4). The seven participants with a diagnosis of past alcohol abuse or dependence (but currently non-abstinent from alcohol) significantly increased their mean alcohol drinks/day from 2.5 ($SD=1.3$) during the baseline period to 3.7 ($SD=1.2$) during the marijuana abstinence period, a 52% increase ($t(6)=-5.18, p<0.01$). They did not significantly decrease their mean alcohol drinks/day from the marijuana abstinence period to the return-to-baseline period ($M=3.5, SD=1.1, t(6)=0.61, p=0.57$). The 21 participants without this diagnosis reported a minimal increase in mean alcohol drinks/day from 2.6 ($SD=1.0$) during the baseline period to 2.7 ($SD=0.8$) during the marijuana abstinence period, a 3% increase ($t(20)=-0.46, p=0.65$) but a significant decrease (19%) from the marijuana abstinence period to the return-to-baseline period ($M=2.2, SD=1.2, t(20)=2.36, p=0.03$).

Period and alcohol use during the baseline period significantly interacted to predict alcohol substitution ($F(2,25)=5.80, p<0.01$), accounting for 32% of the variance. Those participants who consumed fewer than the median number of drinks/day during the baseline period were more likely to increase their alcohol use in the marijuana abstinence period ($M=1.7 [SD=0.4]$ in the baseline period to $M=2.6 [SD=0.9]$ in the marijuana abstinence period, $t(11)=-3.99, p<0.01$, a 53% increase) than those who drank more than the median number of drinks/day ($M=3.3 [SD=0.7]$ in the baseline period to $M=3.2 [SD=1.0]$ in the abstinence period, $t(15)=0.23, p=0.82$, a 3% decrease).

Period and diagnosis of current cannabis dependence vs. abuse did not significantly interact to predict alcohol substitution ($F(2,25)=2.00, p=0.16$), nor did period and diagnosis of past drug dependence vs. no diagnosis ($F(2,25)=0.07, p=0.92$). There were no significant interactions between period and any demographic characteristics (sex: $F(2,25)=1.30, p=0.29$; age: $F(2,25)=1.99, p=0.16$); race: $F(2,25)=0.22, p=0.80$); education: $F(2,25)=0.59, p=0.56$); employment: $F(2,25)=0.61, p=0.55$). Period did not significantly interact with any psychological characteristics during the baseline period to predict alcohol substitution, including marijuana withdrawal discomfort ($F(2,25)=0.37, p=0.70$), marijuana craving ($F(2,25)=0.48, p=0.62$), marijuana problems ($F(2,25)=0.21, p=0.81$), alcohol craving ($F(2,25)=0.46, p=0.64$), alcohol problems ($F(2,25)=1.54, p=0.23$), and mood disturbance ($F(2,25)=0.62, p=0.55$).

Correlates of the Alcohol Substitution Effect

The change in mean alcohol drinks/day from the baseline period to the marijuana abstinence period significantly correlated with the change in mean marijuana withdrawal discomfort scores between these two periods (Pearson $r=0.47$, $p=0.01$). The change in mean alcohol drinks/day also significantly correlated with the change in mean alcohol craving scores (Pearson $r=0.41$, $p=0.03$) and with the change in mean alcohol problem scores (Pearson $r=0.50$, $p<0.01$) (Figure 5). The change in mean alcohol drinks/day did not significantly correlate with the change in mean marijuana problem scores (Pearson $r=-0.03$, $p=0.89$).

Time Course of the Alcohol Substitution Effect

The expected number of alcohol drinks/day based on participants' alcohol use during weekday and weekend-days in the baseline and return-to-baseline periods were compared to that observed in the abstinence period. As Figure 6 shows, greater than expected increases in alcohol use occurred on 8 of the 13 days of the abstinence period (62%). The most substantial increase in alcohol use occurred on the second day of the marijuana abstinence period (mean of 1.45 alcohol drinks more than expected), and consistent increases were observed on days 5 – 9 of the abstinence period (Tuesday through Saturday). Decreases were observed on days 3 (Sunday), 10 (Sunday), and 11 (Monday). After the second day of abstinence, the alcohol substitution effect did not appear to substantially increase or decrease over time.

Mood Disturbance

Mood disturbance scores significantly changed across the three periods of the study ($p < 0.01$), accounting for 20.5% of the variance (Table 5). Overall mean POMS scores did not significantly change from the baseline period to the marijuana abstinence period ($t(27) = 0.06, p = 0.96$), but they did significantly decrease from the abstinence period to the return-to-baseline period ($t(27) = 3.64, p < 0.01$), indicating decreased mood disturbance over time. Similar non-significant differences between baseline and marijuana abstinence but significant differences between abstinence and return-to-baseline occurred for tension subscale scores ($t(27) = 3.31, p < 0.01$), depression subscale scores ($t(27) = 3.23, p < 0.01$), and anger subscale scores ($t(27) = 3.07, p < 0.01$). Fatigue subscale scores significantly changed across the three periods of the study ($p < 0.01$), accounting for 24.6% of the variance. The mean fatigue subscale score significantly decreased from the baseline period to the marijuana abstinence period ($t(27) = 2.23, p = 0.04$), and the mean fatigue subscale score marginally decreased again from the abstinence period to the return-to-baseline period ($t(27) = 2.06, p = 0.05$). Confusion subscale scores significantly changed across the three periods of the study ($p < 0.01$), accounting for 16.6% of the variance. The mean confusion subscale score significantly decreased from the baseline period to the marijuana abstinence period ($t(27) = 2.53, p = 0.02$), but the mean confusion score of the abstinence period did not significantly differ from that of the return-to-baseline period ($t(27) = 1.14, p = 0.26$). Mean vigor subscale scores did not significantly change across the three periods of the study ($p = 0.26$).

Substitution of Other Substances

Although seven participants were current smokers at the initial assessment, 13 participants smoked at least one cigarette during the baseline period. Of these 13 participants, one participant initiated and sustained a quit attempt during the marijuana abstinence period. Of the remaining 12, self-reported cigarettes/day did not significantly change across the three study periods ($p=0.28$) (Table 6). Mean carbon monoxide levels did not significantly change across the three study periods ($p=0.49$). Surprisingly, 10 of the 12 smokers submitted urine samples that were negative for cotinine throughout the study; it is likely that most samples were negative for cotinine because its cut-off was high (i.e., 500 ng/mL; Dominion Diagnostics, Providence, RI) and because participants did not smoke cigarettes on a daily basis. Craving for cigarettes showed a trend toward changing across the three study periods ($p=0.13$); although craving did not significantly change from the baseline period to the marijuana abstinence period, it significantly decreased from the marijuana abstinence period to the return-to-baseline period (marijuana abstinence period: $M=12.0$, $SD=2.6$; return-to-baseline period: $M=10.8$, $SD=1.6$; $t(11)=2.7$, $p=0.02$). Craving subscales related to relief from negative affect and desire to smoke did not significantly change across the three periods (relief from negative affect: $p=0.14$; desire to smoke: $p=0.16$). Of the 15 participants who did not smoke any cigarettes during the baseline period, 9 did not smoke any during the marijuana abstinence period. However, three non-smoking participants during baseline smoked 1-2 cigarettes, two smoked 6-7 cigarettes, and one smoked 16 cigarettes during abstinence.

All 28 participants consumed at least one caffeinated drink (i.e., coffee, tea, or soda) during the baseline period; thus, all were retained in analyses related to caffeine. Mean total number of caffeinated drinks/day did not significantly change across the three periods of the study ($p=0.46$).

Eleven participants used illicit drugs other than marijuana during the study: three used them only during baseline or return-to-baseline; four participants used them on one day of the baseline period and one day of the marijuana abstinence period; one used them on one occasion during abstinence only; and three participants used them on one day during baseline and multiple days during abstinence. Of these latter three participants, two used illicit drugs twice during marijuana abstinence, and one used them four times during abstinence.

Discussion

Summary of Results

Results indicate that alcohol substitution occurred during marijuana abstinence. Although substitution of cigarettes, caffeine, and non-marijuana illicit drugs did not occur, this may be due to methodological limitations (see below). Results also indicate that individuals with a diagnosis of past alcohol abuse or dependence substituted alcohol to a greater degree than those without this past history. Finally, they indicate that increases in alcohol drinks/day significantly and positively correlated with increases in marijuana withdrawal discomfort scores and with increases in alcohol craving scores

from the baseline to the marijuana abstinence period. Problems related to alcohol did not significantly increase from baseline to marijuana abstinence.

Alcohol Substitution

In this study, daily marijuana users who met diagnostic criteria for cannabis dependence or abuse reported a 15% increase in their alcohol consumption from a one-week period of using marijuana as usual to a two-week period of abstaining from marijuana. The alcohol substitution effect appeared to be due to an increased percentage of days consuming at least one drink of alcohol from baseline to marijuana abstinence. Non-significant trends for increases in binge-drinking episodes and increased alcohol drinks/day on weekends were observed, but power to detect these differences may have been low. Alcohol problem scores did not significantly increase from baseline to marijuana abstinence, but they did significantly correlate with increases in alcohol use and there was some evidence for an increase in alcohol problems in a minority of regular marijuana users. Although the two-week marijuana abstinence period may not have been lengthy enough to result in a clinically-significant increase in alcohol problems, there was not a trend for alcohol problems to worsen as the abstinence period continued. Nonetheless, given the increase in alcohol use and the positive correlation between increased alcohol use and increased alcohol problems, these results suggest that clinicians should regularly assess for alcohol use and alcohol-related problems when treating marijuana users who continue to use alcohol during marijuana cessation. Even without a

significant increase in alcohol consumption during marijuana cessation, alcohol problems can still worsen (Stephens et al., 2000).

When individuals stop use of one substance, they might substitute another pharmacologically-similar substance or one that antagonizes withdrawal symptoms of the originally-used substance. Although marijuana and alcohol belong to different drug classification classes (i.e., hallucinogens vs. sedatives) and have different chemical structures, they both increase dopamine release in the nucleus accumbens (Boileau et al., 2003; Tanda & Goldberg, 2003), part of the neurobiological pathway of the mesocorticolimbic system that is implicated in drug reinforcement (Gardner and Lowinson, 1991; Koob, 1992). This common enhancement of brain reward mechanisms may explain the shared behavioral effects of marijuana and alcohol. For example, individuals report feelings of sedation, relaxation, euphoria, and relief from anxiety, as well as disinhibition, after using marijuana and alcohol (Julien, 2001; Rang, Dale, Ritter & Moore, 2003). Thus, individuals who use marijuana daily and alcohol moderately may use alcohol on more days when abstaining from marijuana in order to achieve the subjective feelings listed above that are related to intoxication. It is also possible that conditioning plays a role in the substitution of alcohol for marijuana. Because most marijuana users tend to use marijuana and alcohol simultaneously (i.e., at the same time; Midanik, Tam & Weisner, 2007), use of one substance could act as a cue to elicit the use of another. These findings are consistent with the expectation of current marijuana users themselves: 31% of Australian survey respondents who currently use marijuana indicate

they would consume more alcohol if cannabis became harder or more expensive to obtain (Jones & Weatherburn, 2001).

Variability of the Alcohol Substitution Effect

There was substantial between-person variability in the degree of alcohol substitution. In particular, regular marijuana users with a diagnosis of past alcohol abuse or dependence substituted alcohol to a greater degree than those without this diagnosis (52% vs. 3% increase). This finding echoes findings of prior studies that substitution can be especially prominent for particular subgroups of substance users (Aubin et al., 1999; Bovasso & Cacciola, 2003; Gossop et al., 2003; Harris et al., 2000) and is especially important for the substantial percent of heavy marijuana users with a lifetime diagnosis of alcohol abuse or dependence (Kouri, Pope, Yurgelun-Todd & Gruber, 1995).

Participants in the current study had been in remission from alcohol abuse or dependence for at least one year, yet their risk for reverting to heavy alcohol use appears to still be high. Importantly, this subgroup did not decrease their alcohol use during the return-to-baseline period, but they resumed their marijuana use to near-baseline levels after marijuana abstinence ended. The lack of decrease in alcohol use in combination with a return to marijuana use suggests that these individuals may be at high risk for polydrug abuse. On the other hand, participants were only examined for one week after resuming marijuana use, so this subgroup might require more time to decrease their alcohol use. The finding that regular marijuana users with a diagnosis of past alcohol abuse or dependence drive the alcohol substitution effect has significant implications for

marijuana treatment. First, clinicians who treat individuals for marijuana-related problems should carefully monitor alcohol use in those with a past history of alcohol problems. Second, this subgroup of daily marijuana users should be apprised of the possibility of increasing their alcohol use upon marijuana cessation. Third, this subgroup might need additional interventions related to their alcohol use. Fourth, although equivocal findings have been reported regarding whether a lifetime history of alcohol dependence impairs smoking cessation (Breslau, Peterson, Schultz, Andrews & Chilcoat, 1996; Covey, Hughes, Glassman, Blazer & George, 1994; DeSoto, O'Donnell & DeSoto, 1989; Hughes, 1993; Hughes, Callas, & High Dose Study Group, 2003; Sobell, Sobell & Toneatto, 1992), it remains to be seen whether this lifetime history impairs marijuana cessation.

Another subgroup that especially substituted alcohol was comprised of those individuals who consumed alcohol at levels below the median number of drinks/day during the baseline period (53% increase in those who drank less the median number of drinks/day during baseline vs. 3% decrease in those who drank more than the median number). It is possible that those with higher levels of alcohol use during the baseline period were aware that their use was high and thus consciously limited their alcohol use during the marijuana abstinence period. Conversely, those with lower levels of alcohol use during the baseline period may not have been concerned about their drinking and thus did not consciously limit their alcohol use. This finding suggests that marijuana users who are also moderate alcohol drinkers should be advised before initiating marijuana abstinence that although their alcohol use might not be problematic, they are still at high

risk for increasing their alcohol use and should closely monitor their drinking during abstinence.

Possible Mediators of the Alcohol Substitution Effect

Although the sample size prohibited formal mediational tests, the strong correlations between alcohol consumption and marijuana withdrawal discomfort scores and alcohol craving scores indicate that these are important factors related to the alcohol substitution effect. Increases in alcohol drinks/day correlated with increases in marijuana withdrawal discomfort scores and increases in alcohol craving scores but not with increases in marijuana craving scores. The significant increase in marijuana withdrawal discomfort scores from baseline to marijuana abstinence supports the validity of the marijuana withdrawal syndrome upon marijuana cessation (Budney, Hughes, Moore & Vandrey, 2004), and the correlation between these scores and increases in alcohol consumption adds evidence to its clinical significance. Consistent with this, in other studies using retrospective reports, marijuana users stated that they have used alcohol and other substances to relieve the discomfort associated with marijuana withdrawal (Copersino et al., 2006b), suggesting that the marijuana withdrawal syndrome is severe enough to warrant action to minimize symptoms and their associated distress. Perhaps regular marijuana users consume alcohol to blunt their mood and thus manage the withdrawal symptom of irritability (Budney et al., 2003). They may also use more alcohol to aid in falling asleep, as sleep problems are another commonly-reported marijuana withdrawal symptom (Budney et al., 2003). The correlation between alcohol

increases and marijuana withdrawal discomfort increases also suggests that alcohol substitution should abate as withdrawal abates over time. Most marijuana withdrawal symptoms discontinue after 14 days (Budney et al., 2003), so if withdrawal were driving the alcohol substitution effect, the effect should discontinue after 14 days.

The alcohol substitution effect's correlation with alcohol craving indicates that the increase in alcohol consumption may not be sufficient to relieve all of the increase in alcohol craving during marijuana abstinence. It also suggests that unavailability of one substance can increase craving or urge for another substance; for example, nicotine deprivation increases the urge to drink alcohol (Palfai, Monti, Ostafin & Hutchison, 2000). Surprisingly, marijuana craving scores did not significantly increase from baseline to marijuana abstinence, possibly because participants suppressed their craving for marijuana. In a previous laboratory-based study, when participants were instructed to suppress their urge for alcohol, they increased the intensity of their cigarette smoking (i.e., took more puffs from cigarettes) (Palfai, Colby, Monti & Rohsenow, 1997). Thus, suppression of craving or urge for one substance that is being controlled can increase the use of an associated substance that is not being controlled. Furthermore, drug availability may be a necessary condition for craving (Juliano & Brandon, 1998), and participants in the current study were aware that they were not permitted to use marijuana during the abstinence period. Also, perhaps the lack of a significant increase in marijuana craving was due to the transformation of the 7-point Likert craving scale into a dichotomous true/false scale, thus decreasing the measure's sensitivity to detect differences.

Substitution of Other Substances

Although regular marijuana users substituted alcohol during marijuana cessation, they did not appear to substitute other substances. Overall, in the current study, there was no consistent evidence of significant cigarette substitution, but a minority of participants (20% of nonsmokers during the baseline period) did initiate new cigarette use during marijuana abstinence. This percentage is similar to that found for initiation of cigarette use during alcohol abstinence in Project MATCH (Friend & Pagano, 2004). Individuals might substitute or initiate cigarettes to experience sensory aspects that are associated with smoking marijuana, such as the sensation of smoke in the lungs. Additionally, because many individuals smoke both cigarettes and marijuana (Moore & Budney, 2001; SAMHDA, 2005; Stephens, Roffman & Simpson, 1993), they might be subject to the same conditioning cues as those related to using alcohol and marijuana simultaneously. Nicotine, the psychoactive ingredient in cigarettes, is a stimulant, and although its effects are not similar to the effects of marijuana, its stimulatory effects might counteract withdrawal symptoms, such as irritability (Budney et al., 2003). Because the participants in this study are not regular or dependent smokers, cigarette substitution might appear in heavier, more dependent cigarette smokers.

Individuals in this study did not substitute non-marijuana illicit drugs during marijuana cessation. Three participants increased their use of other illicit drugs, and one participant initiated non-marijuana illicit drug use (i.e., inhalant use) during marijuana abstinence. However, none of these increases was clinically-significant. Only one of these four individuals met criteria for a diagnosis of past substance abuse or dependence:

the individual who initiated inhalant use during the marijuana abstinence period met criteria for past opioid dependence. It is possible that different outcomes could be observed with a larger sample of those with a diagnosis of past substance abuse or dependence.

Finally, individuals did not substitute caffeine for marijuana. This trend is not unexpected, as caffeine and marijuana do not share many psychoactive properties, and individuals probably do not use marijuana and caffeine simultaneously. Thus, the drug substitution effect in this study is limited to alcohol.

Limitations

Findings from the present study may be tempered by possible limitations on the external validity of the study, i.e., the exclusion of individuals who used marijuana less than five times per week, did not meet diagnostic criteria for current cannabis abuse or dependence, were light or heavy alcohol users, met diagnostic criteria for current alcohol or non-marijuana substance abuse or dependence, or were trying to stop their marijuana use. Although participants reported at study entry that they usually consumed a mean of about 10 alcoholic drinks/week, they consumed a mean of 18 drinks/week during the baseline period. Because their weekly alcohol use is higher than moderate drinking guidelines (Sanchez-Craig et al., 1995), this study's findings may apply more to heavier drinkers than moderate drinkers. While individuals with marijuana use patterns similar to those who seek treatment for marijuana-related problems were targeted for inclusion in this study, the sample differs from treatment-seekers (The Marijuana Treatment Project

Research Group, 2004) by being younger and more likely to be male and Caucasian. These differences may limit the generalizability of this study's findings.

There were also limitations related to internal validity. Alcohol use was not biochemically verified, but participants had no incentive to falsify their self-reports of alcohol use. Furthermore, they provided their self-report of alcohol use via voicemail; this type of confidential and impersonal system might increase the accuracy of self-report (Moskowitz, 2004). Importantly, the criteria for biochemical verification of marijuana abstinence could be said to be too lenient.

Perhaps the most significant limitation is that the findings of this study do not completely negate the concern about using alcohol or other substances during marijuana abstinence. While alcohol substitution and some cigarette initiation were observed in this study, it is not known if these increases in other substances undermine the ability to abstain from marijuana. It is possible that even without an increase in other substances, continued use of secondary substances could impair the ability to initiate or maintain abstinence from the primary drug of abuse.

Strengths

A significant strength of this study is its methodology. First, the use of a within-subjects design with baseline, experimental, and return-to-baseline periods confers high experimental validity. Second, in contrast to previous studies of marijuana cessation, alcohol use was examined prospectively and on a daily basis, allowing for a detailed picture of the time course of alcohol substitution. Third, the collection of multiple self-

report measures repeatedly during the study allowed for examination of specific patterns of alcohol use and of possible moderators and mediators of the alcohol substitution effect. Fourth, by recruiting individuals who were not trying to quit marijuana, contamination of outcomes due to voluntary restrictions on alcohol use to aid in marijuana abstinence that may cause false negative results were avoided. Other strengths include the compliance of the majority of recruited participants with the 2-week period of marijuana abstinence and the biochemical verification of abstinence. Among those who completed the study, there was very little missing data.

Future Studies

Replication Tests

Because this is one of the first studies directly examining drug substitution, rigorous replication tests are needed. First, a 2-week marijuana abstinence period may not have been sufficiently long for individuals to develop alcohol problems, so with an extended marijuana abstinence period, whether alcohol problems develop over time can be understood. Second, building from the current ABA design, a study with an ABAC design is possible. The “C” period could entail abstinence from both marijuana and alcohol to determine if marijuana and alcohol withdrawal symptoms and craving are additive. Additionally, many treatment programs recommend this type of abstinence (i.e., from all substances), so it is important to understand if this recommendation is problematic. Third, with a larger sample size, formal mediational tests would be possible.

Finally, marijuana users actively trying to stop their marijuana use could be studied to determine whether drug substitution interferes with the ability to quit marijuana. People who use more than one substance regularly are at higher risk for poor treatment retention and abstinence rates, as well as relapse to substance use (Hartel et al., 1995; Moore & Budney, 2001; Sobell, Sobell & Kozlowski, 1995; Stuyt, 1997; Wasserman et al., 1998), and drug substitution might worsen these problems (Friend & Pagano, 2005).

Drug Substitution in Different Subgroups

Given that drug substitution may be limited to certain subgroups of substance users, studies similar to the current one but with different subgroups can be undertaken to further examine what these subgroups are. Similar studies can be conducted with individuals who use marijuana daily but do not consume any alcohol or with individuals who consume more alcohol than moderate alcohol drinking guidelines suggest (Sanchez-Craig et al., 1995). By studying these different subgroups, it can be seen whether marijuana abstinence leads alcohol abstainers to initiate alcohol use or if it causes even more alcohol consumption in heavy drinkers. The same methodology with marijuana treatment-seekers who are also moderate alcohol drinkers can be employed; findings that are similar to those with non-treatment-seekers in the current study would provide external validity for the drug substitution effect. Expectations of treatment-seekers about whether they think their alcohol use will increase and whether they believe they need to be concerned about this possible increase could be *a priori* assessed.

Although negative conclusions regarding substitution of cigarettes, caffeine, and non-marijuana illicit drugs during marijuana abstinence were obtained in this study, it is unclear whether different conclusions would be obtained with different populations. A study of cigarette substitution with regular marijuana users who are also regular (i.e., at least 10 cigarettes/day) and dependent smokers could be conducted. Such a study has been accomplished, but individuals in this study were instructed to not change their use of cigarettes during marijuana abstinence (Vandrey, Budney, Hughes & Liguori, 2008). A study of non-marijuana illicit drug substitution with regular marijuana users with a past history of illicit substance dependence could also be conducted.

Finally, negative conclusions regarding an increase in mood disturbance scores from the baseline to the marijuana abstinence period were obtained, but these participants did not report any significant mood problems (i.e., current mood or anxiety disorders) at study entry. Thus, a study of drug substitution in individuals with current mood problems could be conducted to see if mood disturbance scores increase from baseline to marijuana abstinence and whether these increased mood problems result in even greater alcohol substitution or vice versa, i.e., whether alcohol substitution worsens or improves mood. This type of study would increase the external validity of the substitution effect, given that most marijuana users have co-occurring mood problems (Agosti, Nunes & Levin, 2002).

Interventions Related to the Alcohol Substitution Effect

Because alcohol use increases during marijuana abstinence, the efficacy of interventions to prevent an increase in alcohol use during marijuana treatment could be examined. Kahler and colleagues (Kahler, Metrik, LaChance, Ramsey, Abrams, Monti, & Brown, 2008) compared the efficacy of an alcohol-related intervention in conjunction with smoking cessation treatment to standard smoking cessation treatment alone in heavy drinkers. Those who received interventions related to both cigarette and alcohol use reported fewer drinks per week and greater smoking abstinence than did those in standard smoking cessation treatment, but the effects related to smoking were mostly evident soon after the quit date and were essentially absent by 16 weeks. On the other hand, in some studies concurrent alcohol and smoking treatment worsened alcohol-related outcomes in comparison to a delayed smoking intervention after alcohol treatment (Joseph, Willenbring, Nugent & Nelson, 2004). Thus, integrating additional alcohol-related interventions to marijuana cessation treatment appears feasible, but timing of the interventions might need to be examined first.

Other Studies of Drug Substitution

The above-suggested studies have addressed what occurs during marijuana cessation. Studies examining other drug substitutions can also be undertaken using the same methods. Several studies have already investigated whether alcohol use increases during smoking cessation (Carmelli, Swan & Robinette, 1993; Murray, Cribbie, Istvan & Barnes, 2002; Murray, Istvan & Voelker, 1996) and whether smoking increases after

alcohol abstinence (Gulliver et al., 2000), but whether marijuana use increases during smoking cessation or during alcohol cessation can be examined. Substitution of other substances should be examined prospectively and with precise measurement (i.e., daily assessments), and initiation of other substances should also be assessed.

Clinical Implications

If these results are replicated and if increased alcohol use during marijuana abstinence were shown to cause problems or interfere with marijuana abstinence, then clinicians treating marijuana users should continue to recommend complete abstinence from all substances. In order to assist individuals in abstaining from all substances, clinicians ought to deliver interventions that either separately address marijuana and alcohol use or interventions that address addictive behaviors in general. They might also assess for initiation of new substances, given some evidence for cigarette initiation in the current study. However, if individuals abstain only from marijuana, clinicians should be aware that continued alcohol use, even without a significant increase, might undermine marijuana abstinence.

Summary

This study provides empirical validation of the clinical notion of drug substitution, although the substitution effect was restricted to alcohol use during marijuana abstinence, to the subgroup of daily marijuana users with a past history of

alcohol abuse or dependence, and to the subgroup of daily marijuana users with low alcohol use during the baseline period. These findings suggest that clinicians' concerns about drug substitution may be valid, but they need to be replicated in individuals who seek treatment for marijuana problems. If replicated, then whether alcohol substitution interferes with the ability to quit marijuana or if increased alcohol use causes problems in its own right needs to be determined. If so, this would be important empirical support for the clinical practice of recommending abstinence from all substances. If not, then not insisting on abstinence from other drugs could remove an important barrier to entering treatment among marijuana users.

Table 1. Power Analysis.

Within-subject Correlation	Change in Alcohol Use	Power	Sample Size Needed
0.6	30%	80%	53
0.6	50%	80%	21*
0.8	30%	80%	28*
0.8	50%	80%	12*

Note. Within-subject correlations of alcohol consumption were derived from data from Budney et al. (2003) and from a preliminary study of tobacco smokers (Peters, Hughes, Callas & Solomon, 2007).

Table 2. Participant Characteristics.

Demographic Characteristics	
Age (<i>M</i> [<i>SD</i>])	23.0 (3.4)
Sex (% male)	75
Race (% non-Hispanic Caucasian)	93
Marital status (% unmarried)	100
Employment (% full-time)	36
Education (% completed high school)	100
Substance Use Characteristics - History	
Age first tried marijuana (<i>M</i> [<i>SD</i>])	14.9 (1.5)
Age first used marijuana regularly (<i>M</i> [<i>SD</i>])	17.1 (2.6)
Age first tried alcohol (<i>M</i> [<i>SD</i>])	14.2 (1.6)
Age first used alcohol regularly (<i>M</i> [<i>SD</i>])	17.8 (1.7)
Met DSM-IV criteria for past alcohol abuse or dependence (%)	25
Met DSM-IV criteria for past non-cannabis substance dependence (%)	7
Substance Use Characteristics - Current	
Days/week currently use marijuana (<i>M</i> [<i>SD</i>])	6.3 (0.8)
Sessions/day currently use marijuana (<i>M</i> [<i>SD</i>])	2.7 (2.2)
Standard alcohol drinks/week (<i>M</i> [<i>SD</i>])	9.7 (4.7)
Binge-drinking days/month (<i>M</i> [<i>SD</i>])	3.3 (3.0)
Caffeinated drinks/day (<i>M</i> [<i>SD</i>])	2.3 (1.6)
Current cigarette smokers (%)	25

FTND score for current cigarette smokers ($M [SD]$)

1.1 (1.9)

Note. Characteristics are for 28 participants who completed the study and are included in data analysis. DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (APA, 2000); FTND = Fagerstrom Test of Nicotine Dependence.

Table 3. Outcomes Related to Marijuana Use.

Outcome	Period			Significance Testing
	Baseline	Marijuana Abstinence	Return-to-Baseline	
Self-reported use (sessions/day)	2.9 (1.3) _a	0.0 (0.0) _b	2.2 (1.3) _c	$F(2,54)=84.80$, $p<0.01$
Creatinine-normalized THCCOOH (ng/mL)	350.1 (432.5) _a	36.7 (37.6) _b	127.5 (123.5) _c	$F(1.1,28.1)=11.98$, $p<0.01$
WDS	2.9 (2.9) _a	5.1 (4.0) _b	2.5 (2.7) _a	$F(1.6,44.0)=15.26$, $p<0.01$
Weight (pounds)	163.4 (32.9) _a	161.3 (32.2) _b	162.5 (32.2) _a	$F(2,54)=10.37$, $p<0.01$
Craving				
Overall	6.9 (2.5)	6.7 (2.7)	6.7 (2.8)	$F(2.0,52.7)=0.32$, $p=0.73$
Compulsivity	0.9 (0.8)	1.0 (1.0)	0.9 (1.0)	$F(2,54)=0.07$, $p=0.94$
Emotionality	3.0 (1.3)	3.2 (1.3)	3.2 (1.4)	$F(1.6,44.1)=1.33$, $p=0.27$
Expectancy	1.3 (0.8)	1.2 (0.8)	1.1 (0.9)	$F(1.9,52.1)=1.67$, $p=0.20$

Purposefulness	1.7 (0.8)	1.4 (0.8)	1.5 (1.0)	$F(2,54)=1.27,$ $p=0.29$
Problems				
Overall	3.0 (2.5) _a	0.9 (1.0) _b	1.9 (2.6) _c	$F(2,54)=16.63,$ $p<0.01$
Physical	1.3 (1.4) _a	0.4 (0.6) _b	0.9 (1.5) _a	$F(1.9,50.7)=8.84,$ $p<0.01$
Psychological	0.9 (0.9) _a	0.4 (0.6) _b	0.5 (0.8) _b	$F(1.9,50.7)=9.44,$ $p<0.01$
Social	0.8 (0.8) _a	0.1 (0.4) _b	0.5 (0.8) _a	$F(2.0,53.7)=10.9,$ $p<0.01$

Note. Data presented as means and standard deviations. *F*-values are presented from Huynh-Feldt tests of repeated-measures ANOVAs, $p<0.05$, with study period as the within-subjects factor. Different subscripted letters denote significant between-period differences from paired samples *t*-tests, $p<0.05$. THCCOOH = 11-nor-9-carboxy- Δ^9 -tetrahydrocannabinol; WDS = Withdrawal Discomfort Score.

Table 4. Outcomes Related to Alcohol Use.

Outcome	Period			Significance Testing
	Baseline	Marijuana Abstinence	Return-to-Baseline	
Drinks/day	2.6 (1.0) _a	3.0 (1.0) _b	2.5 (1.3) _a	$F(1.9,51.2)=3.02$, $p=0.06$
Drinks/day: days drunk ≥ 1 drink	3.7 (1.2)	4.1 (1.2)	3.7 (1.4)	$F(1.9,52)=1.25$, $p=0.30$
Drinks/day: weekend-days	4.2 (1.9)	4.9 (2.0)	3.8 (2.5)	$F(1.8,49.7)=2.38$, $p=0.11$
Drinks/day: weekdays	2.0 (1.1)	2.3 (1.1)	2.1 (1.2)	$F(1.9,51.7)=0.59$, $p=0.40$
Percentage of days drunk ≥ 1 drink	69% (19%) _a	77% (16%) _b	68% (26%) _a	$Z=-2.69$, $p<0.01$
Percentage of binge-drinking days	23% (15%)	27% (14%)	23% (17%)	$Z=-1.96$, $p=0.05$
Craving	6.1 (3.4) _a	7.2 (4.1) _b	5.5 (3.4) _a	$F(2.0,53.4)=6.56$, $p<0.01$
Problems	0.6 (0.9)	0.8 (1.1)	0.6 (0.9)	$F(2.0,54.0)=1.31$, $p=0.28$

Note. Data presented as means and standard deviations. *F*-values are presented from Huynh-Feldt tests of repeated-measures analyses of variance (ANOVAs), with study period as the within-subjects factor. *Z*-values are presented from Wilcoxon signed ranks tests. Different subscripted letters denote significant between-period differences from paired samples *t*-tests, $p < 0.05$, except with Wilcoxon signed rank tests, where the baseline and return-to-baseline periods were combined and contrasted with the marijuana abstinence period.

Table 5. Outcomes Related to Mood Disturbance.

Outcome	Period			Significance Testing
	Marijuana		Return-to-	
	Baseline	Abstinence	Baseline	
Overall mood disturbance	4.9 (7.8) _a	4.8 (9.9) _a	1.3 (7.6) _b	$F(2.0,53.6)=6.96$, $p<0.01$
Tension	1.7 (1.5) _a	2.1 (2.2) _a	1.1 (1.5) _b	$F(1.7,44.5)=7.13$, $p<0.01$
Depression	1.7 (1.9) _a	1.8 (2.3) _a	1.0 (1.8) _b	$F(2.0,52.9)=4.91$, $p<0.01$
Anger	1.4 (1.6) _a	1.9 (2.6) _a	0.6 (1.3) _b	$F(1.7,46.3)=7.01$, $p<0.01$
Fatigue	3.7 (2.4) _a	2.9 (2.7) _b	2.1 (2.2) _c	$F(2.0,54.0)=8.79$, $p<0.01$
Confusion	2.7 (1.5) _a	2.3 (1.6) _b	2.1 (1.5) _b	$F(1.9,50.1)=5.36$, $p<0.01$
Vigor	6.3 (3.2)	6.2 (3.5)	5.6 (3.4)	$F(2.0,53.5)=1.37$, $p=0.26$

Note. Data presented as means and standard deviations. *F*-values are presented from Huynh-Feldt tests of repeated-measures ANOVAs, $p<0.05$, with study period as the within-subjects factor. Different subscripted letters denote significant between-period differences from paired samples *t*-tests, $p<0.05$.

Table 6. Outcomes Related to Cigarette and Caffeine Use.

Outcome	Period			Significance Testing
	Baseline	Marijuana Abstinence	Return-to-Baseline	
Cigarettes/day	1.6 (2.4)	2.1 (3.1)	2.2 (2.9)	$F(2,22)=1.34$, $p=0.28$
Carbon monoxide (ppm)	4.4 (4.6)	3.4 (3.4)	3.7 (3.7)	$F(1.4,14.8)=0.62$, $p=0.49$
Cigarette craving				
Overall	12.8 (4.6)	12.0 (2.6)	10.8 (1.6)	$F(1.2,13.6)=2.53$, $p=0.13$
Relief	4.7 (1.5)	4.3 (0.5)	4.1 (0.3)	$F(1.2,16.7)=2.39$, $p=0.14$
Desire	6.8 (2.8)	6.5 (1.8)	5.7 (1.6)	$F(1.5,16.7)=2.11$, $p=0.16$
Caffeinated drinks/day	1.4 (1.0)	1.3 (0.7)	1.3 (0.7)	$F(1.6,42.4)=0.73$, $p=0.46$

Note. Data presented as means and standard deviations. *F*-values are presented from Huynh-Feldt tests of repeated-measures ANOVAs, $p<0.05$, with study period as the within-subjects factor. 12 participants who smoked at least one cigarette during the baseline period and did not abstain from cigarettes during marijuana abstinence were

retained in cigarette-related analyses. 28 participants who consumed at least one caffeinated drink during the baseline period were retained in caffeine-related analyses.

Figure 1. Experimental Timeline.

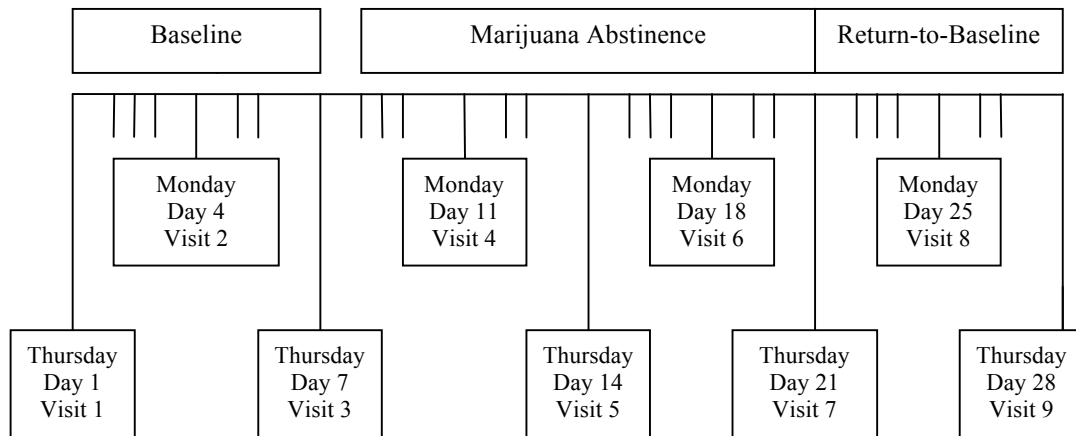


Figure 2. Participant Recruitment and Retention.

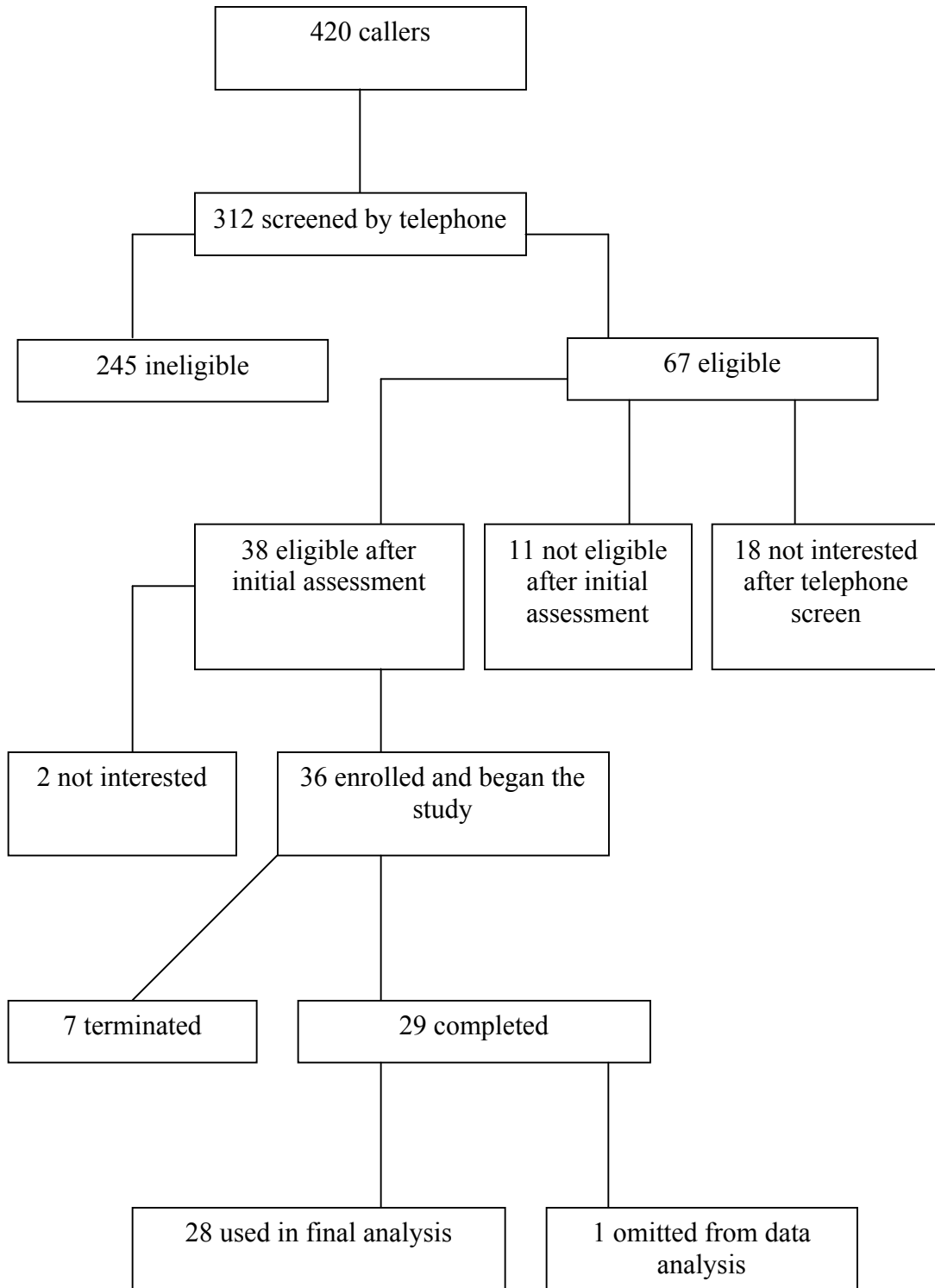


Figure 3. Mean Creatinine-Normalized Tetrahydrocannabinol (THCCOOH) Levels.

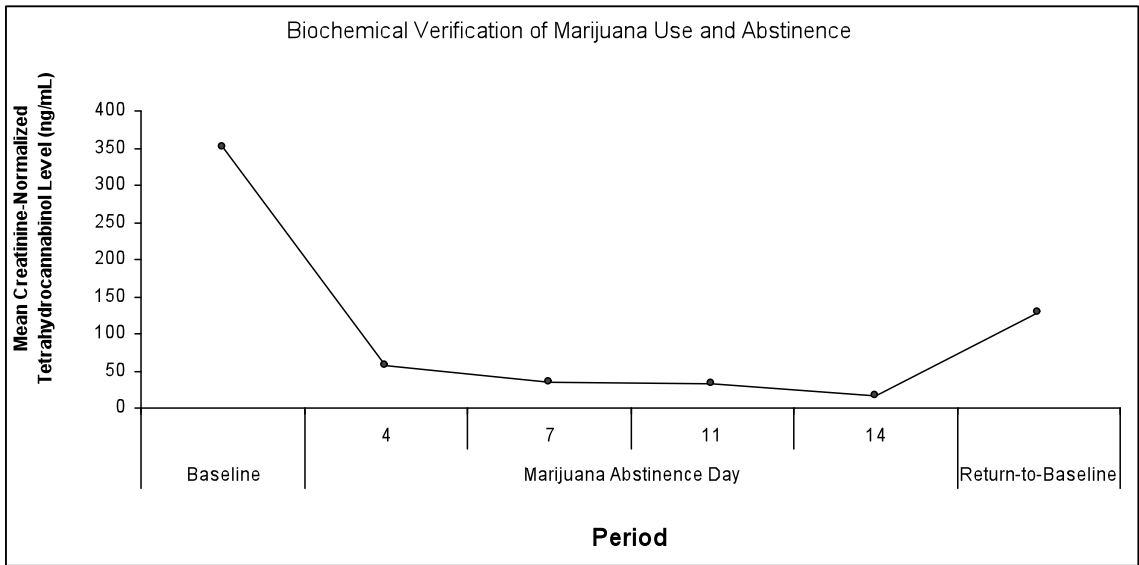


Figure 4. Interaction between Period and Diagnosis of Past Alcohol Abuse/Dependence.

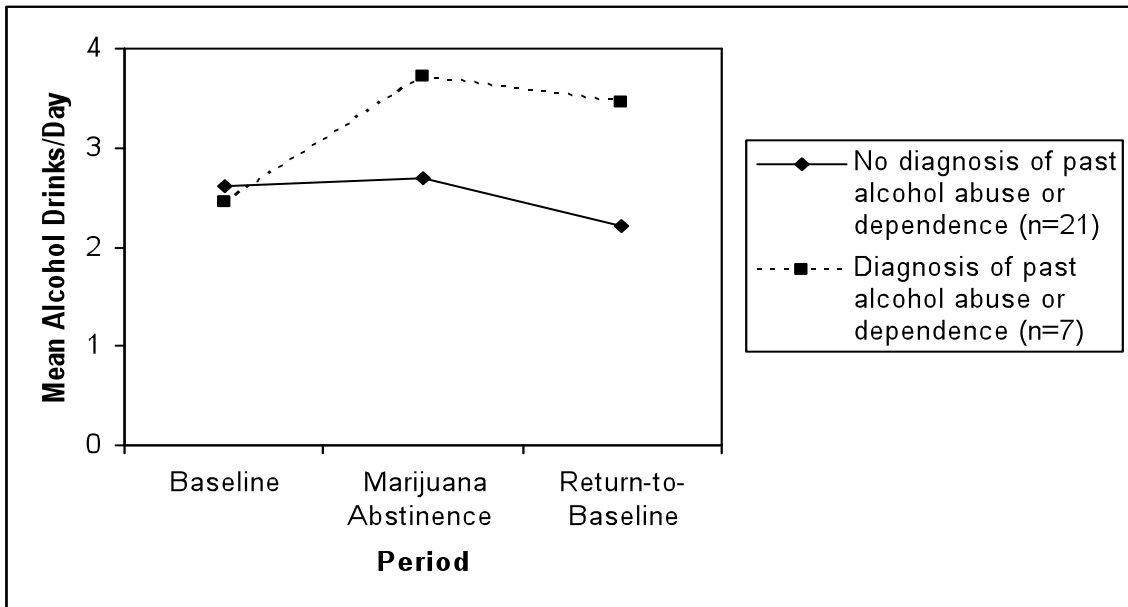


Figure 5. Correlates of the Alcohol Substitution Effect.

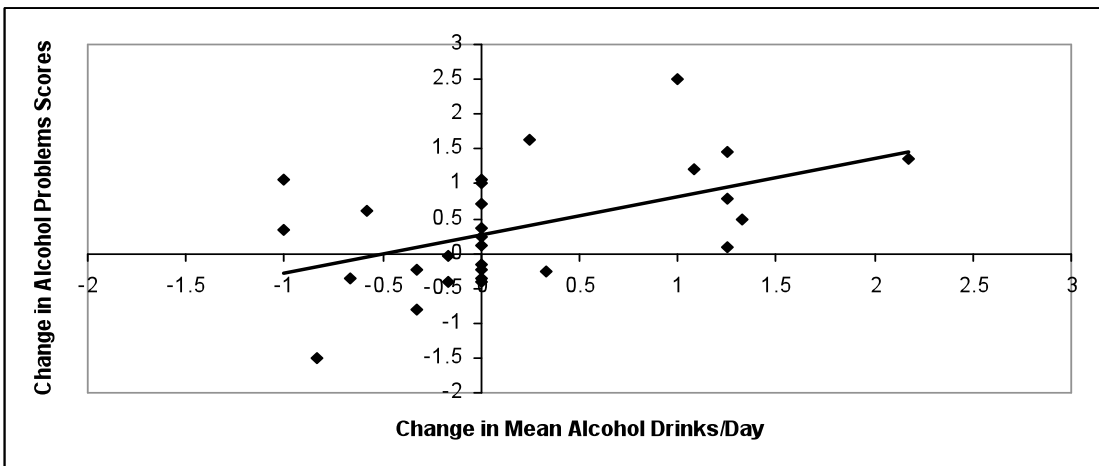
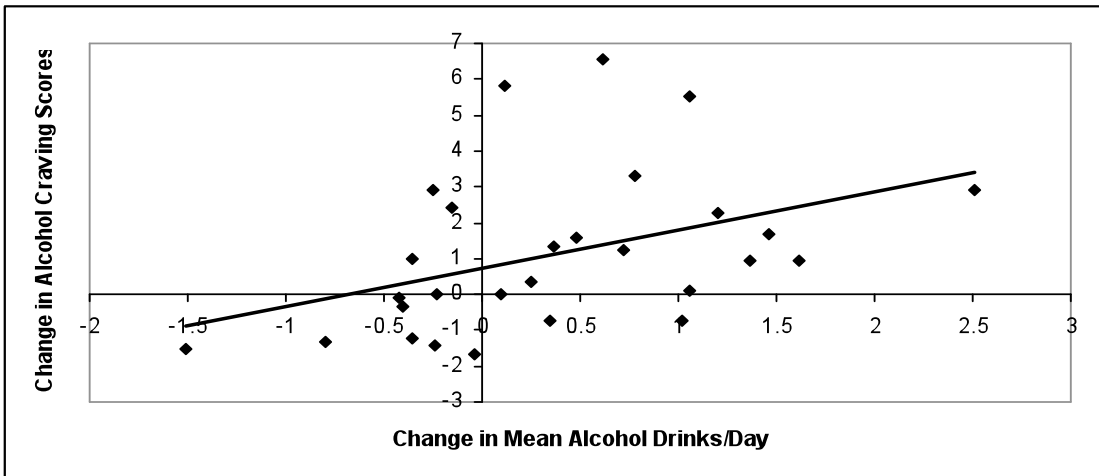
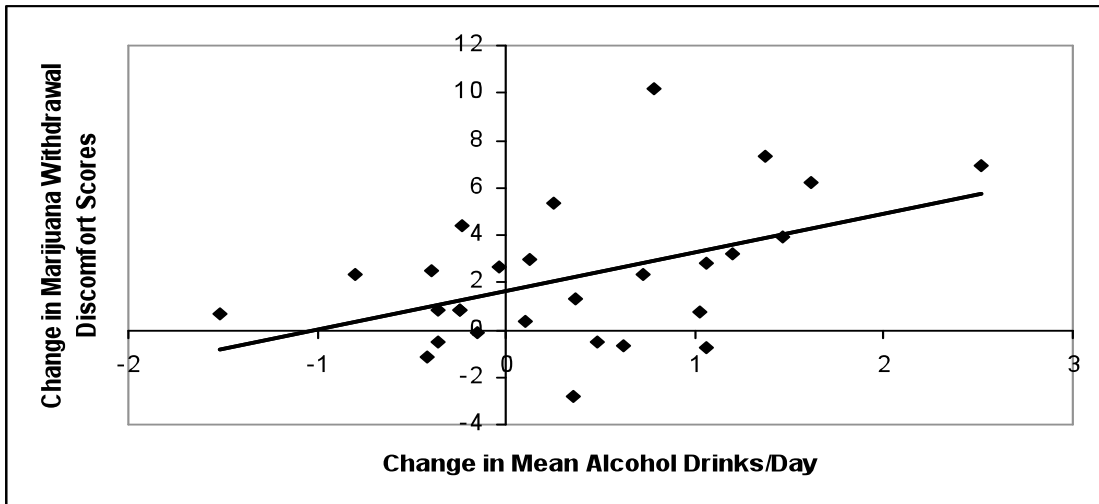


Figure 6. Time Course of the Alcohol Substitution Effect.

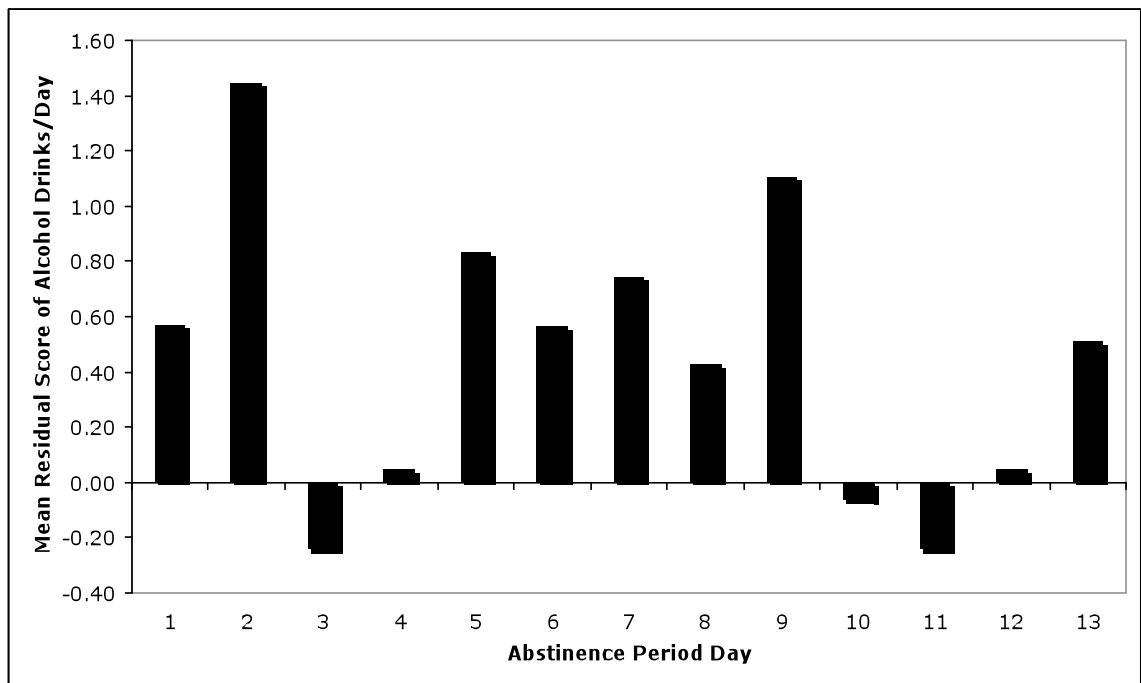


Figure Captions.

Figure 1. Experimental timeline. Tick marks represent each study day. The marijuana abstinence period and return-to-baseline period overlap on day 21: participants reported data related to marijuana abstinence when they visited their seventh laboratory visit on day 21; after leaving the laboratory they were allowed to use marijuana, so substance use data for day 21 represent the return-to-baseline period.

Figure 2. Participant recruitment and retention.

Figure 3. Mean creatinine-normalized tetrahydrocannabinol (THCCOOH) levels. The baseline level was collected one day before initiating marijuana abstinence, and the return-to-baseline level was collected 4 days after resuming marijuana use.

Figure 4. Interaction between period and diagnosis of past alcohol abuse/dependence. Mean alcohol drinks/day are presented, and bars represent standard error of the mean.

Figure 5. Correlates of the alcohol substitution effect. Change scores represent the change between the baseline period and the marijuana abstinence period, with positive scores indicating an increase from baseline to abstinence. Lines represent linear trends.

Figure 6. Time course of the alcohol substitution effect. Mean residual scores were calculated as the difference between observed alcohol drinks/day on each abstinence day and expected alcohol drinks/day based on participants' baseline and return-to-baseline alcohol use, calculated separately for weekdays and weekend-days.

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