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Amphetamine Self-Administration in Light and Moderate Drinkers

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Abstract

Background—Light and moderate drinkers respond differently to the effects of abused drugs, including stimulants such as amphetamine. The purpose of this study was to determine whether light and moderate drinkers differ in their sensitivity to the reinforcing and subjective effects of *d*-amphetamine. We hypothesized that moderate drinkers (i.e., participants that reported consuming at least seven alcohol-containing beverages per week) would be more sensitive to the reinforcing and positive subject-rated effects of *d*-amphetamine than light drinkers.

Methods—Data from four studies that employed similar *d*-amphetamine self-administration procedures and subject-rated drug-effect measures were included in the analysis. Light (N=17) and moderate (N=16) drinkers sampled placebo, low (8-10 mg) and high (16-20 mg) doses of oral *d*-amphetamine administered in eight (8) capsules. Following sampling sessions, participants worked for a maximum of eight capsules, each containing 12.5% of the previously sampled dose, on a modified progressive-ratio schedule of reinforcement.

Results—Both active doses of *d*-amphetamine functioned as a reinforcer in the moderate drinkers while only the high dose did so in the light drinkers. The moderate drinkers worked for significantly more capsules that contained the high dose of *d*-amphetamine than did the light drinkers. *d*-Amphetamine produced prototypical stimulant-like subjective effects (e.g. dose-dependent increases in ratings of Good Effects; Like Drug and Willing to Take Again). Moderate drinkers reported significantly greater subjective effects than the light drinkers.

Conclusion—These results are consistent with those from previous laboratory experiments and suggest that moderate alcohol consumption may increase vulnerability to the abuse-related effects of stimulants.

Keywords

d-amphetamine; alcohol; self-administration; subjective effects; drinking status

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Introduction

The non-medical use of prescription stimulants is common, especially among young adults (e.g., Hall et al., 2005; Johnston et al., 2009; Kroutil et al., 2006; McCabe et al., 2004, 2005; Poulin, 2007; Teter et al., 2006). Data from the most recent National Survey on Drug Use and Health (NSDUH), for example, found that 6.4 percent of young adults attending college reported non-medical use of prescription amphetamine (i.e., Adderall®) in the past year (NSDUH, 2009).

The results of this national survey also suggest an interesting relationship between alcohol use and prescription stimulant misuse (NSDUH, 2009). Over 95 percent of respondents that reported prescription amphetamine misuse in the past year also reported alcohol use in the past 30 days. Among those that did not report past year prescription amphetamine misuse, only 63 percent indicated past month alcohol use. Nearly 90 percent of young adults that reported prescription amphetamine misuse in the past year endorsed past month binge alcohol use as well. Among those that did not report past year prescription amphetamine misuse, only 41 percent indicated past month binge alcohol use. Heavy alcohol use in the previous 30 days was reported by more than 55 percent of young adults who also acknowledged prescription amphetamine misuse in the past year versus only 16 percent among young adults that did not report past year prescription amphetamine misuse. While these epidemiological data demonstrate a link between alcohol use and prescription stimulant misuse, the behavioral or neuropharmacological mechanisms mediating this relationship are unknown.

The results of a previous study conducted in our laboratory suggest that moderate alcohol use (e.g., consumption of seven or more alcoholic drinks per week with at least four drinking occasions per week) may increase vulnerability to the abuse-related effects of amphetamine in young adults (Stoops et al., 2003a). In this study, light (N=8) and moderate (N=8) drinkers received oral doses *d*-amphetamine (0, 5, 10, and 15 mg). Following drug administration, volunteers completed a battery of subject-rated, performance, and physiological measures periodically for 5 hours. *d*-Amphetamine produced prototypical stimulant-like subjective effects (e.g., dose-dependent increases in ratings of *Elated*). Moderate drinkers reported significantly greater drug effects than light drinkers.

The purpose of the present study was to further characterize the behavioral effects of *d*-amphetamine in young adults that report light and moderate alcohol use. To accomplish this aim, we assessed the reinforcing effects of *d*-amphetamine in light (N=17) and moderate (N=16) alcohol drinkers using a modified progressive-ratio procedure. We chose to assess *d*-amphetamine self-administration in light and moderate drinkers because the reinforcing effects of stimulants may be the best predictor of their abuse potential (Foltin and Fischman, 1991). To more fully characterize the differences between light and moderate drinkers in terms of their responses to *d*-amphetamine, a battery of subjective and cardiovascular measures previously shown to be sensitive to the effects of stimulants was also used (Oliveto et al., 1992; Rush et al., 1998; Rush and Baker, 2001; Rush et al., 2001). Based on the results of our previous study, we hypothesized that moderate drinkers would be more sensitive to the reinforcing and subjective effects of *d*-amphetamine than light drinkers.

Materials and Methods

Data from four studies (Rush et al., 2001; Stoops et al., 2004; Stoops et al., 2007b; Sevak et al., under review) employing similar *d*-amphetamine self-administration procedures were included in this analysis. The reinforcing effects of *d*-amphetamine (low dose [8 or 10 mg] and high dose [16 or 20 mg]) or placebo were assessed using a modified progressive-ratio

schedule of reinforcement in each of these studies. The Institutional Review Boards at the University of Mississippi Medical Center and the University of Kentucky Medical Center approved all protocols and informed consent documents for studies conducted at their respective locations.

Participants

Thirty-three adult participants (17 males, 16 females) were included in this analysis. Participants were dichotomized into light and moderate drinkers according to self-reported, weekly alcohol consumption. To be considered a moderate drinker, participants had to report consuming at least seven alcohol-containing drinks per week. Participants who did not meet this criterion were classified as light drinkers. This criterion is similar to what has been used previously (Cho et al., 1997; de Wit and Doty, 1994; Evans et al., 1996; Rush et al., 2003a; Stoops et al., 2003a; Walker and Zacny, 2001; Zacny et al, 2008). Sixteen participants (10 males 6 females) were classified as moderate drinkers. Seventeen participants (7 males, 10 females) did not meet the criteria for moderate drinkers and were classified as light drinkers. All participants gave their sober, written informed consent. Potential participants with histories of or current physical disease or serious psychiatric disorder (i.e., Axis I, DSM IV) were excluded. Past or current presence of a serious psychiatric disorder was determined either by an interview with a psychiatrist, laboratory screening measures (e.g., Brief Symptom Inventory), medical history review and/or a computerized Structured Clinical Interview for DSM-IV (SCID) that was reviewed by a psychiatrist.

Practice Sessions

Prior to beginning the experiments proper, participants completed two “practice” sessions to familiarize them with the modified progressive-ratio procedure, subject-rated drug-effect questionnaires and daily laboratory routine described below. No experimental medication was administered during these sessions.

Experimental Sessions

Participants provided an expired air specimen that was assayed for the presence of ethanol by means of a handheld Alco-Sensor (Intoximeter, Inc., St. Louis, MO). The results of all expired air specimens had to be negative for session to continue. Urine samples collected from participants had to be negative for benzodiazepines, barbiturates, cocaine, opiates and pregnancy (female volunteers only) for session to continue. If a urine drug screen was positive for amphetamine or THC, key study personnel decided whether to allow the participant to continue in session that day.

Sampling Sessions—Sampling sessions were conducted to acquaint the participants with the effects of each drug dose. After the pre-drug questionnaires were completed and cardiovascular measures recorded, participants were administered eight identical capsules containing placebo or d-amphetamine (low dose [8-10 mg] or high dose [16-20 mg]). Each capsule contained 12.5 percent of the total dose. Participants were instructed to pay attention to and make notes about the effects of the drug, because in a future session they would be offered the opportunity to work to receive that drug again. After ingesting capsules, participants completed the subject-rated drug-effect questionnaires at hourly intervals for four hours. Cardiovascular measures were recorded immediately prior to completing the subject-rated drug-effect questionnaires.

Self-Administration Sessions—Self-administration sessions differed from sampling sessions only in that participants had to earn capsules by responding on a modified progressive-ratio procedure.

Modified Progressive-Ratio Procedure

The modified progressive-ratio procedure has been used previously and is a sensitive measure of drug reinforcement in humans (Comer et al., 1997, 1998, 1999; Rush et al., 2001; Stoops et al., 2005a, 2005b, 2007a). The procedure has been modified so that participants receive a fraction of the previously sampled dose for each ratio completed. Participants were given a total of eight opportunities at the beginning of each self-administration session to work on a computer to earn 12.5% ($1/8^{\text{th}}$) of the previously sampled dose. Prior to each opportunity, participants were asked if they wanted to work for a capsule. If they responded YES, they were required to click the mouse a predetermined number of times to earn the capsule. In three experiments, participants were required to click the mouse 25 times to earn the first capsule, (Stoops et al., 2007b) or 50 times (Rush et al., 2001; Stoops et al., 2004). To earn each additional capsule, the number of required responses doubled (e.g., 25, 50, 100, 200, 400, 800, 1600, 3200 [Stoops et al., 2007b]). In the fourth experiment, participants were required to click the mouse 400 times to earn the first capsule (Sevak et al., under review). To earn each additional capsule, the number of required responses increased arithmetically by 200 clicks (i.e., 600, 800, 1000, 1200, 1600, 1800, 2000). If at any point the volunteer responded NO when asked if they wanted to work for a capsule the task was terminated. Due to different increases on the modified progressive-ratio procedure, data were analyzed as number of capsules earned rather than breakpoint (i.e., the last ratio completed).

Volunteers ingested all earned capsules after completing the modified progressive-ratio procedure. After ingesting the capsules, participants completed subject-rated drug-effect questionnaires and cardiovascular measures at hourly intervals. If a volunteer did not respond for any capsules, he/she still completed the subject-rated drug-effect questionnaires and cardiovascular measures as scheduled to ensure that he/she did not avoid self-administering capsules in an attempt to shorten the session.

Subject-Rated Drug-Effect Questionnaires and Cardiovascular Measures

The subject-rated drug effect questionnaires were administered on an Apple Macintosh computer (Apple, Cupertino, CA, USA).

Drug-Effect Questionnaire—The Drug-Effect Questionnaire is an investigator-developed questionnaire that includes 20 items and is sensitive to the effects of stimulants (Rush et al., 2003b; Stoops et al., 2003b). For this analysis, the 17 items identical across all studies were included. In this questionnaire, items are presented one at a time on a video screen. In three experiments, participants answered the questionnaire by using a computer mouse to point and select among one of five response options: “not at all”, “a little bit”, “moderately”, “quite a bit”, and “very much” or “extremely” (scored numerically from 0-4, respectively) (Rush et al., 2001; Stoops et al., 2004; Stoops et al., 2007b). In the fourth experiment, participants responded by using a computer mouse to place a mark on a 101-unit computerized line anchored with Not At All on the left side and Extremely on the right side (scored numerically on a gradient from 0 to 100, respectively) (Sevak et al., under review). Data from the Drug-Effect Questionnaire from the fourth experiment (Sevak et al., under review) were transformed by dividing the values by twenty-five, allowing the values to approximate the scoring scale of the other three experiments (Rush et al., 2001; Stoops et al., 2004; Stoops et al., 2007b).

Addiction Research Center Inventory (ARCI)—The short form of the ARCI consists of 49 true-false questions, presented one at a time, and is designed to yield information on five major subscales: Amphetamine (A, empirically derived amphetamine-sensitive scale), Benzedrine-Group (BG, empirically derived amphetamine-sensitive scale), Morphine-Benzedrine Group (MBG, a measure of euphoria), Lysergic Acid Diethylamide (LSD, a measure of dysphoria), and Pentobarbital, Chlorpromazine, Alcohol Group (PCAG, a measure of sedation) (Haertzen et al., 1963; Jasinski, 1977; Martin et al., 1971).

Cardiovascular Measures—Cardiovascular measures were recorded during all sessions using automated vital signs monitoring equipment. Heart rate and blood pressure were recorded before drug administration and at regular intervals for four hours after drug administration.

Drug Administration

Doses were prepared using commercially available d-amphetamine. In one study, each capsule contained 0 mg (placebo), 1.25 mg (10 mg, low dose), or 2.5 mg (20 mg, high dose) d-amphetamine (Rush et al., 2001). In three studies, each capsule contained 0 mg (placebo), 1 mg (8 mg, low dose), or 2 mg (16 mg, high dose) d-amphetamine (Stoops et al., 2004; Stoops et al., 2007b; Sevak et al., under review). Cornstarch or lactose was used as filler. All drug doses were administered in a double-blind fashion. Capsules were ingested with approximately 150 mL of water. Drug administration procedures were designed to ensure that volunteers swallowed the capsules and did not open them in their mouths and taste the contents (Abreu et al., 1996).

Data Analysis

Group data from demographic indices, modified progressive-ratio tasks, subject-rated drug-effect questionnaires, and cardiovascular measures were analyzed statistically as raw scores (Stat View 5.0.1, SAS Institute Inc., Cary, NC). For the demographic data and modified progressive-ratio task, effects were considered significant for $p \leq 0.05$. A modified Bonferroni adjustment was used with the remaining data to correct for multiple statistical comparisons and decrease experiment-wise error. This was done with the following modification: $\alpha_{\text{actual}} = [(\alpha/\text{number of comparisons}) \times 2]$ (Saladin et al., 1995). This procedure produced the following adjusted alpha levels: Drug-Effect Questionnaire ($p = 0.006$), ARCI ($p = 0.02$) and cardiovascular measure ($p = 0.03$). Demographic data from study participants were compared using unpaired t-tests.

Number of capsules administered in the modified progressive-ratio task (i.e., self-administration sessions) was analyzed by a mixed-model analysis of variance (ANOVA) with the between-subjects factor of Drinking Status (i.e., light and moderate drinkers) and the within-subjects factor of Dose (i.e., placebo, low or high dose d-amphetamine). If ANOVA indicated a main effect of Dose, *post hoc* comparisons were conducted to compare each active dose to placebo. If an active dose differed from placebo, light and moderate drinkers were compared within that dose.

Data from the sampling sessions were analyzed to determine the acute effects of d-amphetamine on the subject-rated drug-effect questionnaires and cardiovascular measures. Three sets of analyses were conducted. First, area-under-the-time-action curve (AUC) was calculated for each subject-rated drug-effect and cardiovascular measure using the trapezoidal method and analyzed in the same fashion as the modified progressive-ratio data. Next, each subject-rated drug-effect and cardiovascular measure was analyzed as peak effect (i.e., the maximum value from 0 to 4 hr after drug administration) in the same fashion as the modified progressive-ratio data and AUC analysis. The final analysis used a mixed-model

ANOVA with Drinking Status (i.e., light and moderate drinkers) as the between-subjects factor and Dose (i.e., placebo, low or high dose d-amphetamine) and Time (i.e., pre-drug, 1, 2, 3, and 4 hours after drug administration) as the within-subjects factors. If ANOVA indicated an interaction of Dose and Time, *post hoc* comparisons were conducted to compare placebo to the active doses at corresponding times. If an active dose differed from placebo, light and moderate drinkers were compared within that dose and time. Subject-rated drug-effect and cardiovascular measures were not analyzed from self-administration sessions because participants determined the amount of drug they would ingest. Analysis of AUC and peak effect data produced nearly identical results. For the sake of brevity, only peak effect results are presented.

Results

Demographics

Tables 1 present the demographics for participants as a function of Drinking Status. Light and moderate drinkers differed significantly from each other on the self-reported number of alcoholic drinks consumed each week, number of participants reporting amphetamine use, total years of amphetamine use, and the number of days of benzodiazepine use in the last month participants (i.e., moderate drinkers > light drinkers).

Modified Progressive-Ratio

ANOVA revealed a significant main effect of Dose ($F_{2,62} = 9.6$, $p < 0.001$) for the number of capsules earned on the modified progressive-ratio procedure. High dose d-amphetamine increased drug-taking significantly above placebo levels in both light and moderate drinkers while low dose d-amphetamine did so only in moderate drinkers. Moderate Drinkers self-administered significantly more capsules containing the high dose of d-amphetamine than did light drinkers (Figure 1).

Subject-Rated Drug-Effect Questionnaires

ANOVA revealed a significant main effect of Dose on eleven items from the Drug-Effect Questionnaire: Alert, Active, Energetic; Any Effect; Good Effects; Irregular, Racing Heartbeat; Like Drug; Performance Improved; Restless; Rush; Talkative/Friendly; Willing to Pay For; and Willing to Take Again ($F_{2,62}$ values = 6.6, $p = 0.002$). Figure 2 shows the effects of d-amphetamine as a function of drinking status for five of these items: Alert, Active, Energetic; Good Effects; Rush; Willing to Pay For; and Willing to Take Again. This figure shows that the high dose of d-amphetamine increased ratings significantly above placebo level in moderate drinkers on all five measures. The high dose of d-amphetamine increased ratings of Active, Alert, Energetic; Any Effect; Willing to Pay For; and Willing to Take Again significantly above placebo levels in light drinkers. Moderate drinkers reported significantly higher scores at the high dose of d-amphetamine than did light drinkers on all five measures. The low dose of d-amphetamine increased ratings Active, Alert, Energetic; Willing to Pay For; and Willing to Take Again significantly above placebo level in light drinkers and increased ratings of Active, Alert, Energetic and Good Effects significantly above placebo level in moderate drinkers. However, there were no significant differences between light and moderate drinkers at the low dose of d-amphetamine (Figure 2).

ANOVA revealed a significant main effect of Dose on three scales from the ARCI: A, BG, and MBG ($F_{2,62}$ values = 4.2, $p = 0.02$). The high dose of d-amphetamine increased scores significantly above placebo levels in light and moderate drinkers on the A and MBG scale and in light drinkers only on the BG scale. The low dose of d-amphetamine increased scores significantly above placebo levels on all three scales in light drinkers. For both doses of d-

amphetamine, there were no significant differences between light and moderate drinkers (data not shown).

Cardiovascular Measures

ANOVA revealed a significant main effect of Dose on systolic ($F_{2,62}$ values = 18.3, $p < 0.001$) and diastolic ($F_{2,62}$ values = 8.0, $p < 0.001$) blood pressure. Both active doses of d-amphetamine significantly increased systolic blood pressure above placebo level in light and moderate drinkers. The high dose of d-amphetamine increased diastolic blood pressure significantly above placebo levels in light and moderate drinkers while low dose d-amphetamine did so only in moderate drinkers. The pressure-increasing effects of d-amphetamine did not differ significantly as a function of drinking status (Figure 3).

Time Course

ANOVA revealed a significant interaction of Dose and Time on ten items from the Drug-Effect Questionnaire: Active, Alert, Energetic; Any Effect; Good Effect; High; Like Drug; Performance Improved; Rush; Talkative/Friendly; Willing to Pay For; and Willing to Take Again ($F_{8,248}$ values = 2.7, $p = 0.006$). Figure 4 shows the time-action curve for d-amphetamine as a function of Drinking Status and Dose for three of these items: Any Effect; Active, Alert, Energetic; and Like Drug. This figure shows that the effects of d-amphetamine were an orderly function of Dose and Time in both light and moderate drinkers. The effects of d-amphetamine were discernible from placebo one hour after drug administration in both groups, peaked at two hours, and remained elevated throughout most of the experimental session. Consistent with peak effect analyses, moderate drinkers reported significantly greater ratings than light drinkers on subjective effect items, especially following administration of the high dose of d-amphetamine.

ANOVA revealed a significant interaction of Dose and Time on three scales from the ARCI: A, MBG, and PCAG ($F_{8,248}$ values = 2.3, $p < 0.02$). ANOVA also revealed a significant interaction of Dose and Time on systolic blood pressure, diastolic blood pressure, and heart rate ($F_{8,248}$ values = 3.3, $p < 0.01$). The time-action curves for d-amphetamine were similar to those observed with the Drug-Effect Questionnaire ratings described, and generally did not differ as a function of drinking status (data not shown).

Discussion

The present study examined the influence of drinking status on the reinforcing, subjective, and cardiovascular effects of two d-amphetamine doses (low dose [8 or 10 mg] and high dose [16 or 20 mg] d-amphetamine) and placebo. The results indicate that moderate drinkers (i.e., individuals consuming ≥ 7 alcoholic drinks/week) were more sensitive to the reinforcing and subject-rated drug-effects (i.e., ratings of Like Drug, Good Effects, Willing to Take Again, High, Willing to Pay For, and Any Effect) of d-amphetamine than light drinkers. Light and moderate drinkers did not differ in their sensitivity to the cardiovascular effects of d-amphetamine.

The present study used a modified progressive-ratio procedure to measure the reinforcing effects of d-amphetamine. d-Amphetamine increased responding as a function of dose in both groups. Low and high dose d-amphetamine increased drug taking significantly above placebo in moderate drinkers, while only the high dose did so in light drinkers. Moderate drinkers self-administered significantly more capsules than light drinkers of the high dose of d-amphetamine. To the best of our knowledge, there are no published reports that have directly compared the reinforcing effects of d-amphetamine in light and moderate drinkers. Reinforcing effects are thought to be an important indicator of the abuse potential of

stimulant drugs (Foltin and Fischman, 1991). By inference, then, moderate drinkers may be at increased risk to abuse amphetamines.

The present study found that moderate drinkers reported significantly higher positive subjective effects at the high dose of d-amphetamine. The results of the present study systematically replicate the findings of a previous study performed in our laboratory (Stoops et al., 2003a). In that study, light and moderate drinkers differed on several positive subjective effect items after experimenter-administered d-amphetamine (i.e., moderate drinkers > light drinkers). Light and moderate drinkers differed on the A, BG, and MBG scales of the ARCI, as well as on ratings of Carefree, Good Effects, Elated, High, Queasy, Rush, and Stimulated on the drug-effect questionnaire (Stoops et al., 2003a). Among moderate drinkers, responses to 15 mg of d-amphetamine reliably predicted responses to 0.5 g/kg of alcohol on the A and MBG scales of the ARCI, as well as on the subject ratings of Elated, Energetic, Euphoric, and Performance Improved on the drug-effect questionnaire (Stoops et al., 2003a). These results support the notion of an association between alcohol use and vulnerability to misuse or abuse amphetamine.

As noted above, there is a correlation between alcohol use and prescription stimulant misuse (NSDUH, 2009). The behavioral or neuropharmacological mechanisms underlying this correlation are not well understood. The relationship between alcohol exposure and subsequent behavioral responses to abused stimulants has received surprisingly little scientific attention in preclinical studies (D'Aquila et al., 2002; Manley and Little, 1997; McKinzie et al., 2002; Mikkola et al., 2001; Stromberg and Mackler 2005). Most published research has studied the locomotor effects of stimulants in alcohol-preferring and alcohol non-preferring animal lines (D'Aquila et al., 2002; McKinzie et al., 2002; Mikkola et al., 2001; Stromberg and Mackler 2005). In one study, for example, adult, alcohol non-preferring rats showed a greater increase in locomotor activity following amphetamine administration than adult, alcohol preferring rats; a finding the researchers attributed to genetic differences in dopaminergic neurotransmission (McKinzie et al., 2002). In the only published study to our knowledge employing subjects with no difference in genetic preference to alcohol, mice with a history of alcohol exposure showed increased locomotor effects following amphetamine administration (Manley and Little, 1997).

While preclinical results indicate that the link between alcohol and stimulant use may be due to genetic factors (McKinzie et al., 2002) or history of alcohol consumption (Manley and Little, 1997), there may be a number of other factors contributing to the effects observed in the present study. First, it is possible that moderate drinkers were sensitized to the reinforcing and subject-rated effects of d-amphetamine by their greater reports of lifetime amphetamine use than light drinkers. Preclinical research has shown that even modest histories of stimulant administration can produce sensitization to stimulant drugs (Tirelli et al., 2003). Another potential factor that could contribute to increased d-amphetamine self-administration relates to naturalistic drug intake. That is, by definition moderate drinkers in this study used more alcohol than light drinkers. In addition, moderate drinkers reported greater lifetime use of other drugs, albeit generally not statistically different from the reports of light drinkers. Previous research has shown that individuals with higher levels of naturalistic drug intake will self-administer drugs to a greater degree in the laboratory than those with lower levels of naturalistic drug intake (Walsh et al., 2010). The mechanism(s) driving the association between alcohol and stimulant use cannot be determined from the present study, but this effect is likely driven by a number of factors (i.e., genetic, behavioral and pharmacological).

While results of the present study show that moderate drinkers are more sensitive to the effects of stimulants, they are concordant with and extend the results of other previous

studies that compared the reinforcing and subject-rated effects of other commonly abused drugs (i.e., benzodiazepines, ethanol, and inhaled anesthetics) as a function of drinking status in humans (Cho et al., 1997; de Wit and Doty, 1994; de Wit et al., 1989; Doty et al., 1997; Evans and Levin, 2004; Evans et al., 1996; Holdstock et al., 2000; King et al., 2002; Zacny et al., 2008). In one prospective study, for example, moderate drinkers were significantly more likely to self-administer diazepam, a benzodiazepine, than light drinkers (de Wit and Doty, 1994). Another study from the same group found that moderate drinkers experienced significantly greater subjective effects than light drinkers after administration of diazepam (de Wit et al., 1989). Lastly, moderate drinkers have been shown to self-administer significantly greater amounts of sevoflurane (an inhaled anesthetic) than light drinkers (Zacny et al., 2008). Laboratory-based research has consistently shown a relationship between alcohol consumption and increased reinforcing and subjective effects of commonly abused drugs. Increased reinforcing and subjective effects are implicated in increased risk for drug use/abuse.

In the current study, light and moderate drinkers differed significantly from each other on the self-reported number of alcoholic drinks consumed each week because the group inclusion criteria employed in the current study segregated participants based on weekly alcohol intake. The light and moderate drinkers also differed on the number of days of benzodiazepine use in the last month (i.e., moderate drinkers > light drinkers). This finding (i.e., moderate drinkers used benzodiazepines on significantly more days in the month preceding screening than light drinkers) extends the findings of previous studies that suggest moderate drinkers are more susceptible to the abuse-related effects of benzodiazepines under controlled laboratory conditions, as well as in the natural environment (de Wit et al., 1989).

Light and moderate drinkers differed on the number of participants reporting amphetamine use as well as total years of amphetamine use. These differences were not surprising and are concordant with the present finding (i.e., moderate drinkers are more susceptible to the reinforcing effects of d-amphetamine). These findings show that laboratory drug-taking behavior is a reliable representation of actual drug-taking behavior. Worth noting is that while light and moderate drinkers differed on total years of amphetamine use, the two groups did not differ on age.

The present findings add to a growing body of human behavioral pharmacology research that suggests individuals differ in their sensitivity to acute drug effects based on psychiatric disorder, personality dimensions (e.g., sensation seeking, impulsivity, and risk taking), age, genotype, and gender (Helmus et al., 2005; Hutchison et al., 1999; Kelly et al., 2006, 2009; Kreek et al., 2005; Laviola et al., 1999; Lott et al., 2005; Stoops et al., 2007a; Vansickel et al., 2010). Variations in the above factors have been implicated in increased vulnerability to drug use, abuse, addiction, and relapse. A previous study completed by our group found that high sensation seekers were more sensitive than low sensation seekers to the reinforcing effects and some of the subject-rated effects of d-amphetamine (Stoops et al., 2007a). High sensation seekers had a significantly higher break point on the modified progressive-ratio procedure and significantly higher subjective effect ratings of Stimulated and Like Drug compared to low sensation seekers after administration of d-amphetamine (Stoops et al., 2007a).

Although our findings that light and moderate drinkers differed in their response to the reinforcing and subjective effects of d-amphetamine are provocative, they should be viewed with caution. There are a number of caveats of the present study that warrant discussion. First, data were gathered retrospectively from four previous studies employing similar, but not identical, modified progressive-ratio schedules of reinforcement and doses of d-amphetamine. Second, the criterion for classifying light and moderate drinkers, while based

on previous research, is not proven to be an accurate segregation of drinking status. Third, the present outcomes from the ARCI scales were different from the pattern of results observed on other measures. Light drinkers were more sensitive to the effects of *d*-amphetamine on these items in that their scores were significantly different from placebo at both doses while moderate drinkers typically differed from placebo only at the high dose. Importantly, scores on these scales were not significantly different between groups. The divergence of the ARCI results from the pattern observed for a majority of the other measures may suggest that the ARCI is less sensitive to group differences than other subjective or objective measures. Fourth, differences in lifetime illicit substance abuse between light and moderate drinkers may have influenced our outcomes in that the greater drug use by moderate drinkers, although generally not statistically significant, could have sensitized those subjects to the effects of experimentally administered d-amphetamine. Finally, because the study employed a between-subjects analysis, if light and moderate drinkers differed on an unmeasured demographic, it could account for the different responses to the effects of d-amphetamine. Future, prospective, studies are needed to determine the relationship between drinking status (e.g., binge vs. non-binge drinkers) and behavioral responses to stimulants as well as other drug classes (i.e., opiates, benzodiazepines, sedatives/hypnotics, and hallucinogens). Future research should also examine the mechanism(s) underlying the relationship between greater alcohol use and vulnerability to other drug use.

The results of this study are concordant with epidemiological findings that suggest that even moderate alcohol consumption may increase an individual's vulnerability to abuse drugs. In national surveys, nearly 90 percent of full-time college students who reported nonmedical use of Adderall® in the past year had binge alcohol use in the past month and more than half had heavy alcohol use in the past month. Those who used Adderall® nonmedically in the past year were more than twice as likely to report binge alcohol consumption in the past month than those who did not use Adderall® nonmedically. Heavy alcohol consumption in the past month was over three times more prevalent among nonmedical users of Adderall® than among those who did not use Adderall® nonmedically (NSDUH, 2009). Individuals who reported binge alcohol consumption in the past month were nearly nine times more likely to also have used illicit drugs in the previous month than individuals who reported no alcohol use in the past month (Substance Abuse and Mental Health Services Administration [SAMHSA], 2009). Similarly, individuals who reported binge alcohol use in the past month were five times more likely to have used illicit drugs in the previous month than respondents who reported only social alcohol consumption in the past month. Lastly, individuals who reported social alcohol use in the past month were two times as likely to report illicit drug use in the previous month than respondents who did not report any alcohol consumption in the past month (SAMHSA, 2009). A better understanding of the relationship between alcohol and drug use/abuse could have important prevention implications.

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Figure 1.

Dose-response function for the number of capsules earned on the modified progressive-ratio procedure as a function of drinking status. Circles represent light drinkers (N=17) and triangles represent moderate drinkers (N=16). X-axis: d-amphetamine dose (Low [8 or 10 mg] and High [16 or 20 mg]). Data points above PL indicate placebo values. Filled symbols indicate a significant difference from the corresponding placebo value. An asterisk indicates a significant difference between light and moderate drinkers at that dose. Brackets indicate one S.E.M.

Figure 2.

Dose-response functions for the subject ratings of Active, Alert, Energetic (Top Left); Good Effects (Middle Left); Rush (Middle Right); Willing to Pay For (Bottom Left); and Willing to Take Again (Bottom Right) from the Drug-Effect Questionnaire. Circles represent light drinkers (N=17), and triangles represent moderate drinkers (N=16). Data are expressed as peak effect. X-axes: *d*-amphetamine dose (Low [8 or 10 mg] and High [16 or 20 mg]). Data points above PL indicate placebo values. Filled symbols indicate a significant difference from the corresponding placebo value. An asterisk indicates a significant difference between light and moderate drinkers at that dose. Brackets indicate one S.E.M.

Figure 3.

Dose-response functions for the cardiovascular measurements of systolic and diastolic blood pressure. Circles represent light drinkers (N=17), and triangles represent moderate drinkers (N=16). Data are expressed as peak effect. X-axes: d-amphetamine dose (Low [8 or 10 mg] and High [16 or 20 mg]). Data points above PL indicate placebo values. Filled symbols indicate a significant difference from the corresponding placebo value. An asterisk indicates a significant difference between light and moderate drinkers at that dose. Brackets indicate one S.E.M.

Figure 4.

Time-action curves for subject ratings of Any Effect (Top) and Active, Alert, Energetic (Middle), and Like Drug (Bottom) from the Drug-Effect Questionnaire. Light drinkers (N=17) are graphed in the left column and moderate drinkers (N=16) are in the right. Circles represent placebo, triangles represent low dose d-amphetamine, and diamonds represent high dose d-amphetamine. X-axes: time (in hours) post drug administration. Data points above “Pre” indicate values from pre-drug observation. Filled symbols indicate a significant difference from the corresponding placebo value. An asterisk indicates a significant difference between light and moderate drinkers at the corresponding dose and time. Brackets indicate one S.E.M.

Table 1

Demographic data

	Light Drinkers	Moderate Drinkers	t-value	p-value
Gender	7 male, 10 female	10 male, 6 female	1.2	0.23
Age (years)	25.9 (6.4)	24.7 (7.6)	0.5	0.63
Body Mass Index	24.9 (4.3)	23.3 (3.0)	1.2	0.23
Education (years)	13.1 (2.1)	13.9 (1.4)	1.4	0.17
MAST Score	4.1 (5.2)	5.0 (4.4)	0.6	0.58
DAST Score	2.9 (3.5)	3.9 (3.1)	0.9	0.37
BDI Score	2.2 (2.4)	1.3 (2.7)	1.4	0.17
<u>Licit Substance Use</u>				
Caffeine (mg/day)	109.1 (120.6)	160.8 (163.1)	1.0	0.31
Cigarettes (per day)	9 (7.9)	8.1 (8.8)	0.3	0.77
Alcohol (drinks/week)	2.5 (2.2)	17.4 (10.9)	5.5	<0.01
<u>Amphetamine Use</u>				
Ever Used	7 Yes	12 Yes	2.0	0.05
Years Used	0.9 (1.3)	3.1 (3.0)	2.7	0.01
Used Last Month	1 Yes	4 Yes	1.5	0.13
Days Used Last Month	0.1 (0.2)	0.6 (1.4)	1.7	0.10
Lifetime Uses	32.2 (96.6)	26.4 (41.4)	0.2	0.83
<u>Other Illicit Substance Use (Number of Days in the Last Month)</u>				
Barbiturates	0.0 (0.0)	0.1 (0.3)	1.0	0.31
Benzodiazepines	0.0 (0.0)	0.5 (1.0)	2.0	0.05
Cocaine	0.5 (1.1)	1.4 (2.7)	1.4	0.18
Hallucinogens	0.1 (0.5)	0.2 (0.5)	0.4	0.70
Marijuana	7.2 (11.4)	10.0 (12.3)	0.7	0.50
Opiates	0.1 (0.2)	0.3 (0.7)	1.4	0.17
<u>Other Illicit Substance Use (Number of Lifetime Uses)</u>				
Barbiturates	0.0 (0.0)	2.3 (8.7)	1.1	0.28
Benzodiazepines	9.8 (24.6)	20.3 (33.7)	1.0	0.31
Cocaine	26.3 (58.6)	101.6 (251.6)	1.2	0.24
Hallucinogens	25.0 (96.7)	9.2 (13.5)	0.6	0.52
Marijuana	525.5 (1208.0)	783.2 (966.4)	0.7	0.51
Opiates	0.5 (1.0)	98.7 (252.0)	1.6	0.12

Demographic data as a function of drinking status. Data are presented as group means. Values in parentheses indicate the standard deviation.