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Relationship Between Oral *d*-Amphetamine Self-Administration and Ratings of Subjective Effects: Do subjective-effects ratings correspond with a progressive-ratio measure of drug-taking behavior?

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Abstract

The abuse potential of drugs has traditionally been determined in humans using subjective ratings of drug effects. However, drug self-administration procedures also provide valuable information about the reinforcing effects of drugs that may contribute to their potential for abuse. Although ratings of subjective effects and drug self-administration data are generally concordant, some divergent findings have been reported. Therefore, the aim of the present analysis was to directly investigate the relationship between the subjective-effects profile and self-administration of oral *d*-amphetamine in healthy volunteers with a history of stimulant use or abuse using Pearson correlational analyses. The results indicated that positive subjective and reinforcing effects significantly increased as a function of *d*-amphetamine dose. Furthermore, significant, but modest, correlations were observed between ratings of 6 of 17 total items (Any Effect, High, Like Drug, Good Effects, Willing to Pay For, and Willing to Take Again) and *d*-amphetamine self-administration under a progressive-ratio schedule of reinforcement. The current findings suggest that, at least under the current set of conditions with oral *d*-amphetamine, subjective-effects measures and drug self-administration data likely provide different but complimentary information about abuse potential. The most informative findings will thus be obtained from studies that employ ratings of subjective effects and drug self-administration methods.

Keywords

d-amphetamine; subjective effects; drug self-administration; humans

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Introduction

Two key characteristics of drugs that have abuse potential are that they (1) produce positive subjective effects and (2) maintain drug-taking behavior (i.e., function as reinforcers) in humans. Traditionally, the abuse-related effects of drugs have been determined using participant ratings on subjective-effects measures such as Drug Liking and Euphoria (Fischman and Foltin, 1991). Although ratings of subjective effects are valid predictors of abuse potential, other sophisticated laboratory procedures may provide additional information. Given that the reinforcing effects of drugs are a critical feature of drug use disorders (e.g., drugs are taken despite the potential for negative consequences), drug self-administration procedures provide a direct behavioral index of the reinforcing effects of a drug under controlled laboratory conditions. Therefore, each of these investigational strategies may beneficially contribute to the assessment of abuse potential in human subjects (Griffiths et al., 2003; Carter and Griffiths, 2009).

Ratings of subjective effects are operant measures of verbal behavior and are collected using visual analog scales (VAS), ratings on Likert-type scales, or True/False ratings on a series of standardized items (Fischman and Foltin, 1991). Although some subjective-effects questionnaires are scored as ratings of single measures (e.g., Willing to Pay For or Like Drug), other questionnaires combine multiple ratings that are then grouped into a particular scale (e.g., the Morphine-Benzedrine Group [MBG] scale of the Addiction Research Center Inventory [ARCI]). As these measures rely upon verbal behavior, the conditioning histories of respondents are of critical importance. Therefore, the most reliable ratings of a drug's subjective effects are likely to be obtained from active, recreational drug users (Fischman and Foltin, 1991; Griffiths et al., 2003; Carter and Griffiths, 2003). One advantage of subjective-effects measures is that they can be assessed rapidly and effectively predict whether a drug is likely to be abused (Fischman, 1989; Fischman and Foltin, 1991). Most germane to the present investigation, administration of *d*-amphetamine, a drug with known abuse potential, reliably increases ratings of positive subjective effects (e.g., Elated, Happiness, Friendliness, Like Drug, etc.; Lasagna et al., 1955; Smith and Beecher, 1960; Jonsson, 1968; cf. Foltin and Fischman, 1991; Vansickel et al., 2010; Sevak et al., 2010). Epidemiological data indicate that prescription stimulants, including *d*-amphetamine, are widely misused and are second only in prevalence of current illicit stimulant use behind cocaine (SAMHSA, 2012). Misuse of stimulants like *d*-amphetamine has been attributed, in part, to production of positive subjective effects.

Despite a relatively high level of concordance between ratings of subjective effects and drug self-administration data gathered using these measures are not isomorphic. Previous research with drugs from various pharmacological classes has shown that the relationship between drug self-administration and subjective effects is complex and that ratings of subjective effects do not always parallel patterns of drug self-administration (Johanson and Uhlenhuth, 1980, 1981; Fischman, 1989; Lamb et al., 1991; Haney et al., 1999; Sevak et al., 2010). For example, in one study, participants reliably chose to receive an intravenous infusion of 8 mg of cocaine compared to 4 mg of cocaine in the absence of any discernable differences in ratings of subjective effects produced by these doses of cocaine (Fischman, 1989).

Therefore, one limitation of subjective-effects measures is that they may not predict actual drug-taking behavior under naturalistic conditions.

In human drug self-administration procedures, participants are given the opportunity to earn a dose of a drug (or placebo) by responding under a particular schedule of reinforcement (e.g., a progressive-ratio schedule). Previous research has shown that participants reliably choose drug over placebo or money in drug self-administration procedures (e.g., Fischman and Schuster, 1982; Higgins et al., 1994; Hart et al., 2001; see Stoops, 2008 for review). Of most relevance to the present analysis, participants with a history of recreational stimulant use were given the opportunity to self-administer oral *d*-amphetamine (0, 8, 16, or 24 mg) under a modified progressive-ratio schedule of reinforcement in one previous study from our laboratory (Sevak et al., 2010). In addition, participants completed a battery of subjective-effects measures at regular intervals following drug administration. The results showed that 16 mg *d*-amphetamine significantly increased drug choices above placebo levels and produced a prototypical constellation of stimulant-like subjective effects (e.g., increased ratings of Active-Alert-Energetic, Like Drug, and Stimulated; Sevak et al., 2010). The drug self-administration procedure has also shown to be sensitive to the influence of pharmacological (e.g., dose and route of administration) and nonpharmacological variables (e.g., behavioral demands and personality differences; see Stoops et al., 2008 for review). Furthermore, drug self-administration has shown to vary as a function of sensation-seeking status, inattention status, drinking status, and gender (Stoops et al., 2007a; Kollins et al., 2009; Vansickel et al., 2010; Stanley et al., 2011). Relevant to the present report, Stoops et al. (2007a) reported that individuals high in sensation seeking were more sensitive to the reinforcing effects of *d*-amphetamine (8 or 16 mg) relative to participants that were low in sensation-seeking status. However, ratings on several subjective-effects measures associated with the reinforcing effects of drugs (e.g., Like Drug) did not vary significantly as a function of sensation-seeking status. Therefore, *d*-amphetamine self-administration data were concordant with naturalistic drug-taking behavior (i.e., those high in sensation seeking are more likely to take stimulants in the natural ecology; Herman-Stahl et al., 2006, 2007) when subjective effects were not sensitive to these dimensions. Despite the sensitivity of the drug self-administration procedure in general, one limitation is that self-administration studies are more complex and time consuming than studies that only assess subjective effects. Nonetheless, naturalistic drug-taking behavior may be inferred more accurately from studies that utilize drug self-administration procedures compared to studies that primarily rely upon self-reported subjective effects.

The purpose of the current research was to directly investigate the relationship between ratings of subjective effects and the reinforcing effects of oral *d*-amphetamine self-administered under a progressive-ratio schedule of reinforcement in healthy volunteers with a history of stimulant use or abuse. Data from three previous studies that used similar procedures were combined and the relationship between ratings of subjective effects and drug self-administration was determined using correlational analyses. *d*-Amphetamine was chosen in the current analysis because it is a prototypic stimulant of abuse that consistently increases positive subjective-effects ratings and functions as a reinforcer in drug self-administration studies. Based on the existing literature, it was hypothesized that ratings on

positive subjective-effects measures (e.g., Like Drug and Willing to Take Again) would be positively correlated with *d*-amphetamine self-administration. However, it was predicted that not all subjective effects measures would be correlated with *d*-amphetamine self-administration.

Methods

Data from three studies (Rush et al., 2001; Stoops et al., 2004; Stoops et al., 2007b) that used similar *d*-amphetamine self-administration procedures were included in the current retrospective 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

Data from twenty-five adult participants with a history of stimulant use or abuse were included in this analysis. All participants gave their sober, written informed consent prior to enrollment. Potential participants with histories of or current physical disease or serious psychiatric disorder (i.e., Axis I, DSM IV) were excluded.

Practice Sessions

Prior to the outset of each experiment, 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. Participants were not administered experimental medication during practice 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). All expired air specimens were required to be negative in order to proceed with a given session. 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 determined whether to allow the participant to complete the experimental session that day.

Sampling sessions—Sampling sessions were conducted to acquaint the participants with the effects of each drug dose. Following completion of pre-drug questionnaires and collection of cardiovascular measures, 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 note of 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 across five hours. At each time point, 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 were allowed 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 current procedures were modified such that participants received a portion of the previously sampled dose for each ratio completed. Participants were given a total of eight opportunities during each self-administration session to earn 12.5% ($1/8^{\text{th}}$) of the previously sampled dose by making responses on a computer. 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 that capsule. Participants were required to click the mouse 25 (Stoops et al., 2007b) or 50 times (Rush et al., 2001; Stoops et al., 2004) to earn the first capsule. 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]). If at any point the volunteer responded NO when asked if he or she wanted to work for a capsule the task was terminated. Given that the ratio requirements on the modified progressive-ratio procedures were increased at different rates between the studies included in this analysis, 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. Medications were administered in the morning in each of the three studies that were included in this analysis. After ingesting the capsules, participants completed subject-rated drug-effect questionnaires and cardiovascular measures were recorded 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 were recorded as scheduled to ensure that he/she did not avoid self-administering capsules to reduce the session length.

Subjective-Effects Questionnaires

The subjective-effects questionnaires were administered on an Apple Macintosh computer (Apple, Cupertino, CA, USA). Subject-rated measures included 17 (of 20) items on an investigator-developed Drug-Effect Questionnaire that is sensitive to the effects of stimulants (Rush et al., 2003; Stoops et al., 2003) and the short form of the Addiction Research Center Inventory (ARCI; Haertzen et al., 1963; Martin et al., 1971; Jasinski, 1977). These behavioral measures have been used widely in human laboratory studies and have been described in greater detail previously (Rush et al., 2003).

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 the other two 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). 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

Statistical significance was set at the $p = 0.05$ level for all analyses. Group data from the modified progressive-ratio task were analyzed statistically as raw scores (Stat View 5.0.1, SAS Institute Inc., Cary, NC). The number of capsules earned during the modified progressive-ratio task (i.e., self-administration sessions) was analyzed with a one-way analysis of variance (ANOVA) with Dose (i.e., low or high dose *d*-amphetamine) as a within-subjects factor. For each subject-rated drug-effect, ARCI, and cardiovascular measure, area-under-the-time-action curve (AUC) was calculated using the trapezoidal method and then analyzed with a one-way analysis of variance (ANOVA) with Dose (i.e., low or high dose *d*-amphetamine) as a within-subjects factor. Interpretation of the results was guided by F-values. For analysis and graphical representation, data were divided by the coefficient used for AUC calculation. The relationship between self-administration of active *d*-amphetamine doses with each of the ARCI scales, 17 subject-rated drug-effect, and cardiovascular measures was analyzed using separate Pearson correlations (GraphPad Prism version 5.00 for Mac OS X, GraphPad Software, San Diego California USA, www.graphpad.com). A composite score of subjective-effects ratings for measures that significantly correlated with drug self-administration was then calculated by averaging scores on these items. A final Pearson correlation was then conducted on the subjective-effects composite score with self-administration data.

Results

Analysis of Variance (ANOVA)

Modified progressive-ratio—The one-way ANOVA revealed a significant main effect of Dose ($F_{2,48} = 4.7, p < 0.05$) for the number of capsules earned on the modified progressive-ratio procedure. *d*-Amphetamine significantly increased drug-taking in a dose-dependent manner (Figure 1).

Subjective-effects questionnaires—*d*-Amphetamine significantly increased ratings on ten items from the Drug-Effect Questionnaire: Active-Alert-Energetic, Any Effect, Good Effects, High; Like Drug, Performance Improved, Rush, Talkative-Friendly, Willing to Pay For, and Willing to Take Again ($F_{2,48}$ values $3.7, p = 0.03$). Figure 1 shows the effects of *d*-amphetamine as a function of dose for each of these items except for Active-Alert-Energetic, Performance Improved, Rush, and Talkative/Friendly. This figure shows that *d*-amphetamine dose-dependently increased subject ratings for each measure. The magnitude and direction of drug effects for Active-Alert-Energetic, Performance Improved, Rush, and Talkative/Friendly were similar to those shown in Figure 1.

d-Amphetamine significantly increased ratings on three scales from the ARCI: A, BG, and MBG ($F_{2,48}$ values = 4.8, $p = 0.02$). *d*-Amphetamine increased subject ratings on these scales in a dose-dependent fashion (data not shown).

Pearson Correlations

Subjective-effects questionnaires—Pearson correlations indicated significant relationships between self-administration of active doses of *d*-amphetamine and ratings on six items on the Drug-Effect Questionnaire: Any Effect, Good Effects, High, Like Drug, Willing to Pay For, and Willing to Take Again. In addition, the subject-rated drug-effect composite score was significantly correlated with *d*-amphetamine self-administration but did not account for additional variance in self-administration compared to individual subject-rated drug-effect measures. Figure 2 shows that the composite score and each subject-rated drug-effect measure were positively correlated with *d*-amphetamine self-administration. *d*-Amphetamine self-administration was not significantly related to ratings on any scales of the ARCI or ratings of Active-Alert-Energetic, Performance Improved, Rush, and Talkative-Friendly on the Drug-Effect Questionnaire.

Discussion

In the current retrospective analysis, *d*-amphetamine functioned as a reinforcer, significantly increasing number of drug choices as an orderly function of dose under a modified progressive-ratio schedule of reinforcement. Furthermore, *d*-amphetamine self-administration produced prototypical stimulant-like increases on subjective-effects measures. Further analyses indicated that drug self-administration was significantly correlated with ratings on six individual items of the Drug-Effect Questionnaire. In addition, the subjective-effects composite score comprised of items from the Drug-Effect Questionnaire that were significantly related to *d*-amphetamine self-administration was also significantly correlated with *d*-amphetamine self-administration. However, the composite score accounted for an amount of variance in self-administration similar to that accounted for by individual items on the Drug-Effect Questionnaire. In the following discussion, these findings are used to compare the use of drug self-administration and ratings of subjective effects as laboratory models of abuse potential in humans.

Dose-Related Effects of *d*-Amphetamine

The current findings are in agreement with the results of numerous controlled laboratory studies that have demonstrated that *d*-amphetamine has reinforcing effects (Johanson et al., 1983; Chait et al., 1987; Chait, 1993; Comer et al., 1996; Tancer and Johanson, 2003) and produces increases in positive, abuse-related subjective-effects measures in humans (e.g., Chait et al., 1987; Foltin and Fischman, 1991; Comer et al., 1996; Sevak et al., 2010). Therefore the current findings add to the extant literature indicating that (1) *d*-amphetamine is a prototypic stimulant of abuse, (2) drug self-administration provides a behavioral index of abuse potential (Foltin and Fischman, 1991), and (3) ratings of subjective effects are valid measures of abuse liability (Griffiths et al., 2003; Carter and Griffiths, 2009).

Relationship between Reinforcing and Subjective Effects of *d*-Amphetamine

Six of seventeen subjective-effect measures (i.e., Any Effect, Good Effects, High, Like Drug, Willing to Pay For, and Willing to Take Again) were significantly correlated with *d*-amphetamine self-administration. Notably, two of these six measures are considered general measures of drug effects (i.e., Any Effect and High) whereas the remaining four measures have positive valence (i.e., Like Drug, Good Effects, Willing to Take Again, and Willing to Pay For). This finding is in line with those of previous reports that have suggested that drug self-administration and ratings on positive subjective-effects measures (e.g., liking) are often correlated (e.g., Johanson and Uhlenhuth, 1982; Johanson et al., 1983; Foltin and Fischman, 1991). However, previous research has shown the relationship between self-administration and subjective effects is complex and that subject ratings are not isomorphic with drug self-administration (Johanson and Uhlenhuth, 1980, 1981; Fischman, 1989; Lamb et al., 1991; Haney et al., 1999; Sevak et al., 2010).

In the current analysis, *d*-amphetamine significantly increased ratings on a number of subjective-effects measures that did not significantly correlate with *d*-amphetamine self-administration. For example, *d*-amphetamine increased ratings of Active-Alert-Energetic, Performance Improved, and Rush from the Drug-Effect Questionnaire, as well as scores on the A, BG, and MBG scales of ARCI, but these measures did not predict drug-taking behavior. Taken together, these findings suggest that subjective-effects ratings of stimulant-like drug effects and euphoria are not predictive of *d*-amphetamine self-administration, which is congruent with a previous report that suggested that the production of euphoria is not a requirement for and may not provide insight into the reinforcing efficacy of a drug (Fischman, 1989). Therefore, the current findings appear to suggest that increased ratings on subjective-effects measures that are more specifically related to drug-taking behavior (e.g., Willing to Take Again and Willing to Pay For) or generally positive effects (e.g., Like Drug) may better predict reinforcing effects of *d*-amphetamine relative to ratings of other types of subjective effects. In addition, measures of general drug effects (e.g., Any Effect and High) may serve as an index of drug strength or intensity and also predict *d*-amphetamine self-administration. It has been suggested previously that abuse potential depends on the relative degree of positive and negative effects that are produced by a drug and that drugs with fewer undesirable effects are likely to have greater potential for abuse (e.g., Griffiths et al., 2003; McColl and Sellers, 2006). *d*-Amphetamine was devoid of negative effects in this analysis, limiting any conclusions that can be drawn regarding a mixed constellation of positive and negative subjective effects contributing to abuse potential. However, recent research has shown that tramadol (400 mg) was self-administered more than placebo despite significant increases in ratings of bad drug effects (Babalonis et al., 2013). Therefore, it may be that drug-taking behavior is not necessarily altered by negative subjective experience. Furthermore, it may be that drug self-administration represents an aspect of abuse potential that is inherently different from that measured by ratings of positive and negative subjective effects.

Importantly, the results of the correlational analyses in the current study revealed modest but significant positive relationships between subjective-effects ratings and *d*-amphetamine self-administration (r values ranged from 0.29–0.39). Although this finding indicates that ratings

of subjective effects increase as drug self-administration increases, the strength of these relationships was only moderate according to proposed conventions for the interpretation the effect sizes of Pearson product-moment correlations (Cohen, 1992). However, it should be noted that heuristics for interpreting effect sizes are not standardized and vary considerably across investigators and experimental approaches (Rodgers and Nicewander, 1988; Cohen, 1992). Further, a composite score derived from ratings on these measures was not a more effective predictor of drug-taking behavior compared to individual measures. Therefore, the composite score did not offer any substantial advantage in assessing abuse potential, or predicting drug self-administration, over individual measures such as Like Drug or Any Effect.

Although ratings of subjective effects and drug self-administration each have predictive utility with regard to the abuse potential of drugs, they likely provide different information about the various dimensions of a drug's effects that underlie its potential for abuse. One advantage of subjective-effects measures compared to drug self-administration is that they allow investigation of the qualitative nature of the effects of a drug (e.g., stimulant- or sedative-like effects), as well as the positive subjective effects and drug strength measures that indicate increased potential for abuse. In addition, measures of subjective effects can be assessed rapidly. However, one potential disadvantage of subjective-effects measures is that the interpretation of subjective-effects measures may vary across individuals and time, which may impact the between-subjects variability of responses on these measures (see Kelly et al., 2003 for review).

A hallmark characteristic of abused drugs is that they maintain drug-taking behavior despite the increased potential for negative consequences (Carter and Griffiths, 2009), and human laboratory models of self-administration provide insight into that process. These models have better predictive validity for drug-taking behavior under naturalistic conditions compared to ratings of subjective effects alone (Stoops, 2008). Despite their predictive value, self-administration studies often require participation in more sessions than those required by studies that only measure subjective effects. Sessions can also be lengthy depending on the duration of effect of the drug(s) under study, which may increase the likelihood of attrition. In addition, drug self-administration behavior may be influenced by a number of procedural and circumstantial factors. For example, previous studies have shown that drug-taking behavior may be influenced by the time of day and behavioral demands placed upon participants (e.g., Kirkpatrick et al., 2009; Stoops et al., 2005a, 2005b). Given the advantages and disadvantages of each of these measures of abuse potential, ratings of subjective effects and measures of drug self-administration appear to contribute important and complementary information about the effects of a drug that mediate its potential for abuse. Selection of the type of measure should thus be based on the research question and resources available to conduct the study.

It is important to note that these laboratory methods are highly valuable tools in areas of substance abuse research in addition to the determination of abuse potential. More specifically, subjective-effects measures and drug self-administration procedures are considered two key behavioral measures that may be used to guide the development of putative pharmacotherapies and behavioral interventions for the treatment of drug

dependence (see Comer et al., 2008, 2012; Haney and Spealman, 2008; and Stoops and Rush, 2012 for reviews). Of particular interest is the degree to which the findings of laboratory studies predict successful treatment outcomes. The results of clinical trials often corroborate findings from self-administration studies to a greater degree than subjective effects studies (see Haney and Spealman, 2008; Comer et al., 2008, 2012; and Stoops and Rush 2012 for reviews). However, previous research suggests that a reduction in drug-taking behavior in the laboratory does not necessarily predict successful treatment outcomes (e.g., Grabowski et al., 1997; Levin et al., 2006). Nonetheless, ratings of subjective effects and drug self-administration data provide critical information that may aid in the identification of the most promising potential treatment strategies for stimulant dependence. Future research should more closely examine the concordance of findings between human laboratory studies that measure subjective effects and drug-taking behavior and the results of clinical trials.

Suggestions for Future Research

The current research makes a contribution to the existing literature by directly correlating drug-taking behavior and subjective effects. However, a number of questions remain that could not be addressed due to several limitations inherent to the current retrospective analysis thus we offer the following suggestions for future research. First, hierarchical linear regression analyses would likely provide the most effective and informative comparisons of the relative predictive value of subjective-effects ratings with one another. Therefore, we suggest that future studies employ this analytical technique and use a sample size large enough to provide adequate statistical power. Second, future studies should more directly investigate the relationship between ratings of subjective effects and drug self-administration across a greater range of drug doses and various routes of administration as previous research has shown that the subjective-effects profiles of stimulant drugs vary as a function of drug dose (e.g., Foltin and Fischman, 1991). Furthermore, it seems likely that the relationships between ratings of subjective effects and drug self-administration may be different if the drug is administered by a route of administration that better approximates abuse of that drug in a naturalistic setting. Fourth, the degree of experimental control in future investigations could be enhanced if volunteers were to complete self-administration studies on an inpatient basis. This arrangement would virtually eliminate the opportunity for drug use outside of experimental sessions and would likely provide the most accurate measure of drug-taking behavior. Fifth, we suggest that future studies investigate the relationship between subjective-effects measures and other experimental procedures and behavioral assays that are thought to reflect other aspects of drug abuse. For example, the correlation between ratings of subjective effects and responding in delay-discounting or conditioned place preference procedures would also be of value. Furthermore, future studies should examine how the relationship between subjective effects and drug self-administration changes across different self-administration arrangements that are relevant to abuse potential (e.g., drug vs. money choice procedures) as previous studies have shown that self-administration varies as function of schedule demands (e.g., DeGrandpre et al., 1993; Van Etten et al., 1995; Bennett et al., 2013). Lastly, previous research has suggested that studies that investigate abuse potential in participants that have a history of drug abuse are more likely to provide reliable findings and fewer false negatives compared to those with non-

abusing populations (Griffiths et al., 2003). Therefore, we suggest that future studies investigate this relationship in drug users that meet criteria for drug abuse or dependence.

Summary and Conclusions

In summary, the findings of the current retrospective analysis suggest that ratings of subjective effects and measures of reinforcing effects provide important information regarding the abuse potential of drugs. However, these methods likely measure different processes and qualities that underlie their abuse potential. Therefore, one key consideration in determining the most appropriate method to evaluate abuse potential is the inferences that may be made using these different investigational strategies. If the primary aim of a study is to investigate whether a drug is likely to be abused, ratings of subjective effects may be sufficient. Alternatively, a drug self-administration model is better suited to provide insight into the reinforcing efficacy of a drug and variables that impact naturalistic drug-taking behavior. Although each of these strategies has value and utility in the determination of abuse potential alone, they should not be viewed as mutually exclusive. The concurrent collection of subjective effect ratings during a drug self-administration study is quite practical and yields data worth the effort of conducting a more complex study. Therefore, the most informative and scientifically rigorous findings are likely to be derived from studies that employ both of these strategies.

Although the conclusions that may be drawn from the current study are somewhat limited, the formal correlation of subjective effects and *d*-amphetamine self-administration in the context of determining abuse potential represents an expansion of the existing literature in two primary ways. This analysis demonstrates that self-administration of oral *d*-amphetamine is more related to ratings of positive subjective effects that are indicative of drug reward (e.g., ratings of Like Drug and Willing to Take Again) and general measures of drug strength than ratings of euphoria or negative effects consistent with findings with cocaine and tramadol, respectively (e.g., Fischman, 1989; Babalonis et al., 2013). Thus, these findings more specifically identify the constellations of drug effects that are likely to contribute to the basic abuse potential of oral *d*-amphetamine, in the absence of cognitive and/or workload demands, although research should be conducted to determine how other subjective ratings might correlate with drug taking when such demands are in place (e.g., Stoops et al., 2005a; 2005b).

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Figure 1.

Dose-response function for the number of capsules earned on the modified progressive-ratio procedure (Top Left); Any Effect; Good Effects (Second Row); High; Like Drug (Third Row); Willing to Pay For; and Willing to Take Again (Bottom Row) as a function of *d*-amphetamine dose. X-axes: *d*-Amphetamine Dose (Low [8 or 10 mg] and High [16 or 20 mg]). Data points above PL indicate placebo values. Brackets represent one standard error of the mean.

Figure 2.

Correlations between *d*-amphetamine self-administration and subject-rated drug-effect composite score (Top Left); subject ratings of Any Effect (Second Row Left); Good Effects (Second Row Right); High (Third Row Left); Like Drug (Third Row Right); Willing to Pay For (Bottom Left) and Willing to Take Again (Bottom Right) from the Drug-Effect Questionnaire. Subject-rated drug-effect data were divided by the coefficient used for AUC calculation to return ratings to their original scale. Circles represent Low Dose (8 or 10 mg; N = 25) *d*-amphetamine, and triangles represent High Dose (16 or 20 mg; N = 25) *d*-amphetamine.