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Validation of a Behavioral Economic Purchase Task for Assessing Drug Abuse Liability

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Abstract

Behavioral economic purchase tasks quantify drug demand (i.e., reinforcing value of a drug) and have been used extensively to assess the value of various drugs among current users. However, purchase tasks have been rarely used with unfamiliar drugs to address a compound's abuse liability and the current study sought to validate the paradigm in this capacity. Using a double-blind placebo-controlled within-subjects drug challenge design, the study evaluated differential drug demand on an experimental drug purchase task for a 20 mg dose of oral d-amphetamine (versus placebo), a prototypic psychostimulant, in 98 stimulant-naïve participants. Compared to placebo, amphetamine significantly increased intensity, breakpoint, and O_{max} , and significantly decreased elasticity. Mechanistic analyses revealed that O_{max} and breakpoint mediated the relationship between subjective drug effects and “*willingness to take again*,” a putative indicator of liability via motivation for future drug-seeking behavior. These findings validate the purchase task paradigm for quantifying the reinforcing value and, in turn, abuse liability of unfamiliar compounds, providing a foundation for a variety of future applications.

Keywords

Behavioral economics; abuse liability; amphetamine; purchase task; dopamine

INTRODUCTION

The field of behavioral economics constitutes a number of lines of scientific inquiry that integrate concepts and methods from psychology and economics to explain human behavior and decision-making. The application of behavioral economics to addiction extends an operant learning approach by incorporating concepts from microeconomics to explain and

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predict drug use behavior (Bickel *et al*, 2014a; MacKillop, 2016). A fundamental construct in behavioral economics is demand (i.e., the amount of a commodity sought or consumed at a given price) and, in the context of addiction, drug demand is the quantification of the reinforcing value of drugs of abuse. In non-human animals, the reinforcing value of drugs has been historically used as a measure of likelihood of abuse liability and measured using operant tasks requiring behavioral responses to obtain drug reinforcement (Griffiths, Brady & Bradford 1979). Among human subjects, there are a number of challenges in implementing operant tasks to measure drug demand (e.g., logistical demands, high participant burden, potential ecological invalidity, ethical considerations around drug self-administration). Consequently, alternative methods for assessing the reinforcing value of drugs of abuse have garnered recent interest.

Behavioral economic purchase tasks, or self-report measures that use financial costs rather than behavioral responses to estimate drug consumption at escalating levels of price, offer a method of quantifying drug demand without drug self-administration. Purchase tasks allow for the creation of microeconomic demand curves, prototypically depicted in Figure 1, in which the effects of escalating financial demands are used to measure motivation for the drug (Hursh, Galuska, Winger, & Woods, 2005; Johnson & Bickel, 2003; Johnson, Bickel, & Kirshenbaum, 2004). Different facets of the curve can be used to measure distinct aspects of drug use motivation. At the start of the demand curve, *intensity* refers to consumption at minimal or zero cost, reflecting unconstrained consumption. Across the curve, consumption patterns can be converted into the equivalent output (i.e., expenditure) and the maximum amount, O_{max} , reflects the maximum total expenditure the person will allocate to the drug across any price-point. At the end of the curve, *breakpoint* (BP) refers to the response cost that suppresses consumption to zero, reflecting the furthest the person will go in terms of expenditure to access the drug. Between intensity and breakpoint, the proportionate slope of the curve reflects the overall gradient of motivation, referred to as *elasticity*, which amalgamates the general extent to which a person will or will not reduce their consumption as the cost increases.

Trait-level purchase tasks assess self-reported preferences during typical consumption and have been used to investigate individual differences in the reinforcing value of alcohol (Murphy & MacKillop, 2006), tobacco (MacKillop et al., 2008), marijuana (Aston, Metrik & MacKillop 2015), opioids (Jacobs & Bickel 1999) and cocaine (Bruner & Johnson 2014). Much of this work has focused on the relationship of reinforcing value with severity of addiction (Yurasek et al. 2011; Murphy et al. 2013), but there have also been applications to clinical outcomes (MacKillop & Murphy, 2007; MacKillop et al., 2015; Murphy et al., 2015), pharmacotherapy mechanisms (Bujarski, MacKillop & Ray 2012; McClure, Vandrey, Johnson & Stitzer 2013; Murphy et al. 2017), and tax policy (MacKillop et al., 2012; MacKillop et al., 2014). In addition, however, state-level versions of purchase tasks have been used in laboratory studies to measure dynamic changes in drug motivation in response to environmental cues, psychosocial stress, serotonin depletion, withdrawal and priming (Amlung & MacKillop, 2014; Amlung, McCarty, Morris, Tsai, & McCarthy, 2015; Hitsman et al., 2008; MacKillop et al., 2010; MacKillop et al., 2012; Owens, Ray, & MacKillop, 2014). Purchase tasks have been shown to have good psychometric properties (Few, Acker, Murphy & MacKillop 2012; Chase, MacKillop & Hogarth 2013) and, speaking to the

general validity of the methodology, purchase task preferences for hypothetical outcomes have been found to be robustly associated with preferences for actual outcomes (Amlung, Acker, Stojek, Murphy & MacKillop 2012; Amlung & MacKillop 2015). Most recently, the methodology has been translated into neuroimaging paradigms to characterize the neural correlates of drug demand decision making (MacKillop et al. 2014a; Gray et al., 2017).

Despite these diverse applications, there have been limited applications of purchase tasks to drug abuse liability testing. In abuse liability tests, participants are typically administered controlled doses of compounds in the laboratory, often while blind to the drug or drug dose they have been administered. In the most common design, shortly following drug administration, participants complete subjective measures that putatively tap the reinforcing effects of the drug (e.g., mood alteration, arousal changes, subjective states of feeling intoxicated or high) and extent to which certain drugs or drug doses alters subjective responses is presumed to be proportional to abuse liability (i.e., likelihood of future use). Abuse liability tests among healthy drug-naïve volunteers are useful for: (1) evaluating addiction risk for drugs that may enter the marketplace; (2) comparing liability profiles of several drugs within or across classes; and (3) understanding individual differences that differentiate abuse liability amongst drugs with known addiction potential. Thus, novel measurement tools useful for assessing reinforcing value in abuse liability settings hold practical and scientific importance.

To date, two studies have used the purchase task methodology to address abuse liability, at least to an extent. Stein et al. (2017) examined demand for snus (an oral tobacco product), typical combustible tobacco cigarettes, and nicotine replacement gum, finding that elasticity for snus was significantly higher than cigarettes (but not gum) and intensity of demand for gum was significantly lower than both snus and cigarettes. Thus, the purchase task revealed differing reinforcing value by nicotine delivery formulation. More directly addressing addiction potential, Higgins et al. (2017) compared the reinforcing value of four levels of nicotine content in cigarettes, finding significantly greater elasticity in the low-nicotine cigarettes (.4 mg/g vs. 15.8mg/g). The authors conclude that the study suggests that a national policy reducing the nicotine content in cigarettes would reduce their addiction potential. Together, these studies speak to reinforcing value of a drug, but do so for an established drug reinforcer for an individual (i.e., nicotine) and in designs that have limited blinding (i.e., all participants were experienced nicotine users who knew they were consuming some level of nicotine). They do not speak to basic human drug abuse liability testing, in which unfamiliar compounds are systematically examined in placebo-controlled designs to quantify a drug's addiction potential.

To address this question, the current study investigated the utility of a novel experimental drug purchase task for abuse liability assessment in a double-blind within-subjects cross-over placebo-controlled test of *d*-amphetamine, a prototypic psychostimulant that produces acute phasic mesolimbic dopamine release via inhibition of synaptic reuptake and has established abuse liability. The purchase task methodology may be valuable to abuse liability testing pending the validation of several key constructs. First, purchase task indices of drug reinforcement would need to be sufficiently sensitive to drug effects on subsequent demand in the predicted direction (higher intensity, breakpoint, and O_{max} and lower elasticity).

Second, subjective manifestations of drug effects that putatively tap drug reward (i.e., subjective alteration of mood, arousal, and high/intoxication) should mediate drug effects on purchase task indices of drug reinforcement. Such a mediational pathway would provide support that purchase task indices cohere with fundamental principles of drug reinforcement whereby substances that produce subjective psychoactive effects that are more robust and desirable will be stronger reinforcers (Higgins, Heil & Lussier 2004). Third, purchase task measures of drug reinforcement should mediate drug-induced changes in outcomes, such as willingness to use again, a commonly used measure of abuse liability reflecting intentions for future drug-seeking behavior.

METHODS

Participants

Healthy young adult volunteers ($N = 98$) were recruited from the Los Angeles metropolitan area via Internet announcements, newspaper advertisements, community bulletin boards, and local human subject participation pools announcing the opportunity to participate in a study on drug effects (Kirkpatrick et al. 2016). Inclusion criteria were: (1) age between 18 and 35 years (which is the typical age of first psychostimulant exposure); (2) high school education or higher; (3) fluency in English; and (4) BMI of 19–30 (to restrict variability drug metabolism). Exclusion criteria included: (1) night shift work (to restrict variability in arousal); (2) any medical or psychiatric condition requiring prescription medication or contraindicated for amphetamine (e.g., abnormal electrocardiogram); (3) lifetime history of psychostimulant use (ever-use of methamphetamine/amphetamine, crack/cocaine or a prescription stimulant medication); (4) use of drugs of abuse (other than alcohol) in the prior 30 days, by self-report and with biochemical verification of the last few days by a urine toxicology screen; (5) current use of medication contraindicated for d-amphetamine; (6) any current DSM-IV Axis I disorder; (7) current or former substance use disorder; (8) use of 10 cigarettes per week (to control for any nicotine withdrawal experience during testing) and (8) pregnant or breastfeeding. A total of 32 participants were ruled ineligible per these criteria (11 for a history of drug use or positive urine screening, 8 due to EKG, 8 for BMI or blood pressure and 5 for mental health). The study sought to enroll at least 90 participants for adequate power to detect group differences ($f^2 = .30$); total $N = 98$, described below. The study was reviewed and approved by the Institutional Review Board at the University of Southern California.

Design

The study utilized a double-blind, within-subjects design in which single doses of oral *d*-amphetamine (i.e., 20 mg) and placebo were administered in two counterbalanced experimental sessions. During each 4-hour experimental session, a battery of self-report measures assessed drug response at repeated intervals following drug (or placebo) administration.

Procedure

After determining eligibility by telephone, participants attended a 3-hour and five-minute in-person screening that included written informed consent, a psychiatric interview, and a

physical examination with an electrocardiogram. During the consent process, participants were informed that they could receive a drug from one of four different classes (i.e., psychostimulant, sedative, antidepressant, placebo) as in prior work (de Wit, Enggasser & Richards 2002). The experimental sessions occurred between one and three weeks after the baseline session, and were conducted in the morning from 9:00 a.m. to 1:00 p.m. between 2 and 14 days apart. Participants were provided with a light breakfast after fasting from midnight the night before each session. At the start of each session, participants provided urine and breath samples to confirm drug and alcohol abstinence and women were tested for pregnancy; participants testing positive were excluded. The pre-administration assessment was administered, and at approximately 9:30 a.m., participants ingested a capsule containing placebo or 20 mg D-amphetamine. Subjective measures were completed every 30 minutes after drug administration over the next 3-hours (i.e., at 30, 60, 90, 120, 150 and 180 minutes). At 12:30 PM (180 minutes after the administration), participants completed end-of-session ratings and were dismissed at approximately 1:00 p.m. A schematic of the protocol is in supplementary materials.

Measures

All subjective measures were completed during both of the two experimental sessions, before and after the administration of the amphetamine or placebo. The amphetamine purchase task was completed at the end of each drug administration session.

Subjective Drug Response—The Drug Effects Questionnaire (DEQ) (Fischman & Foltin 1991) consists of four 100-mm visual analog scales (anchors “No drug effect” to “Strong drug effect”) in which participants rate how much they “Feel the drug,” “Like the drug,” “Feel high,” and “Want more”.

The Profile of Mood States (POMS) (McNair, Lorr & Droppleman 1971) is a 72-item adjective checklist of momentary mood states each of which participants rate on a 5-point Likert scale (from 0 [not at all] to 4 [extremely]).

The Addiction Center Research Inventory (ARCI) (Martin, Sloan, Sapia & Jasinski 1971) is a 49-item true-false questionnaire that has five empirically derived subscales validated to measure specific drug classes and their characteristic effects: amphetamine (A; stimulant effects), benzedrine group (BG; energy and intellectual efficiency), morphine-benzedrine group (MBG; euphoria), pentobarbital-chlorpromazine-alcohol group (PCAG; sedation), and lysergic acid diethylamide (dysphoria and somatic complaints).

Willingness to Take Again—At the end of the session participants indicated their willingness to “take the drug again” on a 100-mm visual analog scale.

Experimental Drug Purchase Task—Participants’ behavioral economic demand for the experimental drug (amphetamine or placebo, depending on the session) was assessed with an experimental drug purchase task (Supplementary Materials). This task was adapted from similar state-oriented self-report purchase tasks in which participants report how much of an addictive substance (e.g., alcohol, cigarettes) they would purchase (i.e., consume) across a range of prices. The purchase task began with instructions to imagine that participants would

return to the laboratory at a future date for a 12-hour period during which they could purchase and consume the drug (i.e., amphetamine or placebo) that they received during that particular experimental session. This duration was selected to provide a time window within which the full duration of drug effects would be experienced. Participants were also informed that the session would be scheduled to avoid any responsibilities afterwards or the following day, (i.e., there would be no direct negative consequences) and they would not be allowed to take any leftover pills home. Participants then indicated the number of pills (of the drug they took during the session) they would purchase and consume in the hypothetical 12-hour period at 25 increasing prices (see Supplementary Materials). The purchase task was designed to generate a demand curve and four associated indices of relative reinforcing value: (1) *intensity* of demand (i.e., amount of consumption at the lowest price); (2) O_{max} (i.e., maximum amount of money [expenditure] participants will pay for the drug); (3) *breakpoint* (i.e., the first price at which consumption is zero); and (4) *elasticity* of demand (i.e., sensitivity of consumption to increases in cost).

Drug

Tablets of *d*-amphetamine sulfate (AMPH; 4×5 mg; Amedra Pharmaceuticals) were encapsulated in 00 opaque capsules with dextrose filler. Placebo capsules were identical but contained only dextrose. The 20-mg D-amphetamine dose was selected based on previous work indicating a maximally robust drug response in healthy volunteers with negligible adverse effects (de Wit *et al.* 2002).

Data Analysis

To reduce the various subjective outcomes to provide a more parsimonious operationalization the acute subjective effects of amphetamine over the time course of the session, we utilized a data reduction strategy described in a previous publication from this project (Kirkpatrick *et al.* 2016). In brief, repeated measures for each subjective DEQ, POMS, and ARCI outcome were transformed into an area under the curve (AUC), and then entered into a principal component analysis to reduce the subjective drug responses into factor scores (Kirkpatrick *et al.* 2016). Measures that loaded greater than 0.4 on a single factor but did not cross-load on multiple factors were used to calculate three distinct factor scores (i.e., positive mood, arousal, and drug high; see Table S1 for final factor loadings for each measure on to each factor score).

With regard to the experimental drug purchase task, the demand metrics were generated using an ‘observed values’ approach for intensity, breakpoint, and O_{max} , meaning either manifest or arithmetically calculated values were used. Elasticity was derived using Hursh & Silberberg’s exponential demand curve equation (Hursh & Silberberg 2008): $\log_{10} Q = \log_{10} Q_0 + k(e^{-\alpha Q_0 C} - 1)$, where Q = consumption at a given price; Q_0 = maximum consumption; k = a constant that denotes the range of consumption values in $\log_{10}$ units across individuals; C = cost (price); and α = the derived elasticity parameter reflecting the rate of decline in consumption across escalating costs. Of note, Q_0 was defined using the exponential equation’s terms, not constrained to reflect the same value as intensity. A k constant of 2 was used for based on the range of consumption values and because it provided a better fit to the mean demand curves than either 3 or 4, the most credible alternatives. Permitting k to vary

by participant was not undertaken because it constitutes an additional free parameter and complicates the interpretation of α . Because elasticity cannot be computed without variance in consumption level, participants who exhibited zero consumption or rectangular demand (i.e., reported level of consumption at being constant across prices) for at least one of the two conditions were not included in analyses of elasticity ($n=57$). Of note, participants were more likely to provide non-zero data (i.e., exhibit some level of consumption) in the active-amphetamine drug condition compared to placebo at trend-level significance ($\chi^2 = 2.92$; $p = 0.08$).

Descriptive analyses first examined intercorrelations among the study variables in each condition. In addition, any differences between amphetamine and placebo conditions for the purchase task outcomes (i.e., Intensity, $O_{\max}$, BP) and the subjective drug effects by the interim (i.e., number of days) between the two experimental sessions was examined by creating a statistical interaction term. For the primary analysis, a multi-level data set was created in which participant outcomes (i.e., subjective drug effects, demand indices, willingness to take the drug again) were stratified by the within-subject experimental drug condition (i.e., amphetamine vs. placebo). All analyses were tested using multi-level linear models, mediational pathways were tested using multilevel modeling techniques to appropriately test mediational effects in clustered data (Krull & MacKinnon 2001). In each case we report the total effect (i.e., effect of predictor [drug] on outcome, 'a' path (i.e., effect of predictor on mediator, 'b' path (i.e., effect of mediator on the outcome adjusting for the predictor), the "indirect (mediated) effect (i.e., effect of predictor on outcome that is accounted for via the mediator), and the 'direct effect' that is not accounted for by the mediator (i.e., effect of the predictor on outcome after statistically adjusting for the mediator). The analyses focused on addressing three core questions. The first was, are purchase task indices of reinforcing value sensitive to amphetamine effects? This question was addressed via single-variable models of the within-subject effect drug condition on each purchase task outcome in separate models for each purchase task index. The second was, is amphetamine's value measured by the purchase task mediated by the extent to which amphetamine produces desirable subjective effects? This was tested by whether the effect of drug condition on a demand outcome was mediated by the three-composite subjective drug effects, with separate models for each outcome. This analysis aimed to determine the extent to which value for a drug as measured by a purchase task is explained by its acute subjective effects. These effects were first tested with each subjective effect mediator separately and then in a combined multiple mediation models (Figure 2). The third question was, do purchase task indices statistically mediate drug-induced changes in willingness to use again, independently and incrementally to standard subjective effect measures? Here, we tested purchase task indices as mediators of the effect of drug condition on willingness to use again in two sets of models—one in which each demand index was entered as the sole mediator and one set in which all four demand indices were entered as simultaneous mediators to address their incremental predictive variance (Figure 2). Each set of models were tested with and without adjusted for the three subjective effect indices as additional simultaneous mediators. The data were analyzed in SPSS version 24 and Stata version 14.1 with statistical significance set to 0.05 (two-tailed). The results are reported as standardized parameter estimates (β s). Effect size estimates are reported for gauging the relative sensitivity of each

index (small: $\beta = 0.10$, medium: $\beta = 0.30$, large: $\beta = 0.50$), with conversions to Cohen's d for clarity.

RESULTS

Descriptive Analyses

The sample ($N=98$; age $M = 23.3$, $SD = 4.1$ years old; 70.1% female) was ethnically (36 Asian, 12 Black, 6 Hispanic, 2 Middle Eastern, 13 Multiracial, 29 White) and socioeconomically diverse (annual income: 45.3% $\leq \$45k$, 28.4% $\$45k-\$90k$ and 26.3% $\geq \$90k$). Table 1 reports the M (SD) and correlation of key study variables. Six participants were missing data on “willingness to take the drug again,” resulting in lower N s for analyses involving that variable.

Sensitivity of purchase task indices of reinforcing value to amphetamine effects

Single variable multi-level models of the within-subject effect of drug condition on each outcome demonstrated that drug value indices on each purchase task outcome was significantly higher in amphetamine vs. placebo (Figure 3). In amphetamine vs. placebo conditions, *intensity* was greater (i.e., more amphetamine than placebo consumption, on average, at zero cost; ($\beta=0.14$, $p<0.001$; $d=0.24$), O_{max} was higher (i.e., the maximum expenditure at any price point was higher for amphetamine than placebo, on average; $\beta=0.43$, $p<0.001$; $d=0.41$), *breakpoint* was higher (i.e., the first price at which participants reported that they would not purchase the drug was higher in amphetamine than placebo on average; $\beta=0.43$, $p<0.001$; $d=0.45$). Amphetamine was also associated with lower elasticity (i.e., reduced sensitivity to escalating prices for amphetamine than placebo, on average, indicating greater motivation to consume amphetamine relative to placebo in spite of increasing cost; $\beta=0.45$, $p<0.001$; $d=-0.460$). In terms of the magnitude of effect sizes, drug effects were small for intensity and medium-to-large effects for the other three outcomes. The effect sizes for the subjective drug effects (positive mood $d = 0.56$; arousal $d = 0.54$; drug high $d = 0.81$) were medium-to-large. For descriptive purposes, the amphetamine and placebo demand curves are also presented in Figure 4. There were no significant differences between the amphetamine and placebo conditions for the purchase task outcomes (i.e., Intensity, O_{max} , BP) or the subjective drug effects by the number of days between experimental sessions (ρ s = 0.27 – 0.88).

Mediational Analyses

The effect of amphetamine (vs. placebo) on intensity, O_{max} and breakpoint were each significantly mediated by each of the three subjective effect factor scores (positive mood, arousal, and drug high) when each mediator was tested in isolation with one another (Table 2; Column 5). The proportion of drug effects on intensity, O_{max} and breakpoint that were mediated by each of the subjective effects ranged from 24% – 80%. Amphetamine vs. placebo effects on elasticity were significantly mediated by the drug high factor (42% proportion mediated) but not by arousal or positive mood. In the multiple mediation models that controlled for the covariance across the three types of subjective effects, drug high emerged as the only subjective effect factor score to significantly mediate amphetamine vs. placebo effects on O_{max} , breakpoint, and elasticity over and above the other drug effects

(Table 2; Column 6). None of the subjective effects significantly mediated the amphetamine's effects on intensity when controlling for covariance across subjective effects, although statistical power was constrained by the small magnitude effect size.

Regarding the extent to which drug-induced changes in demand mediated willingness to use again, a first set of analyses tested each demand index as the solitary mediator, finding both $O_{\max}$ and breakpoint significantly mediated the effect of amphetamine (vs. placebo) on willingness to take the drug again ($ps < 0.01$; Table 3; Column 5). The mediating pathway through $O_{\max}$ and breakpoint remained significant after adjusting for the covariance with the three subjective factor scores, indicating that these two indices of reinforcing value have incremental explanatory mediating properties over and above the three forms of subjective effects. A second set of analyses in which all three indices were entered as simultaneous mediators to control for their covariance did not reveal individual statistically significant indirect effects, suggesting common variance across the purchase task measures of reinforcing value account for the mediational pathway from amphetamine (vs. placebo) to willingness to use again (see Table 3).

DISCUSSION

This initial validation of a novel behavioral economic purchase task for application in abuse liability testing produced a number of findings that, on balance, suggest that the purchase task methodology holds utility for abuse liability research. Prior purchase task studies have asked participants to report demand for a particular drug that they are familiar with (e.g., alcohol users report demand for alcohol), but this study moves the field forward by showing for the first time that behavioral microeconomic data can be leveraged to understand the reinforcing value for drugs that are unfamiliar to participants, even when participants are blind to the drug. All four purchase indices of drug reinforcement were sensitive to amphetamine effects, with stimulant-naïve healthy volunteers reporting significantly greater drug demand following active vs. placebo drug administration. The degree of sensitivity of each index can be interpreted based on its respective effect size estimate for the magnitude of difference between amphetamine and placebo conditions. Given this premise, effect size estimates in this study indicate that breakpoint, $O_{\max}$, and elasticity were relatively sensitive to amphetamine's effects (i.e., range of β s were medium-to-large: 0.43–0.45), whereas the level of sensitivity of intensity was modest ($\beta = 0.14$).

The effect of amphetamine (vs. placebo) on purchase task indices of drug reinforcement were mediated by various amphetamine-induced subjective drug effects, particularly the experience of subjective high. Because a fundamental principle of human behavioral pharmacology is that a drug's reinforcing effects is driven, in part, by its desirable subjective psychoactive effects (Higgins *et al.* 2004), the mediational paths demonstrated herein can be interpreted as providing convergent support for the construct validity of the purchase task methodology. Of the three domains of subjective effects studied, amphetamine-induced drug high incrementally accounted for increased demand in the amphetamine vs. placebo condition over and above amphetamine-enhanced positive mood and arousal. This is important because amphetamine high, as measured by the DEQ, has significant associations

with actual stimulant use beyond the laboratory (Morean, de Wit, King, Sofuoglu, Rueger & O'Malley 2013).

Evidence in this study that $O_{\max}$ and breakpoint significantly mediated the effect of drug condition on an outcome of relevance to abuse liability (i.e., reported willingness to use again) suggests criterion validity of these particular purchase task indices. Furthermore, their mediational effects were robust after controlling for the mediating effects of standard subject measures, suggesting that including the experimental drug purchase task in batteries of drug effects in abuse liability research may provide incremental utility. In previous studies investigating the latent structure of demand indices, these indices have loaded on a latent factor referred to as *Persistence*—as it reflects how far a person will go for the drug (Bidwell, MacKillop, Murphy, Tidey, & Colby, 2012; MacKillop et al., 2009; O'Connor et al., 2016). By contrast, intensity (i.e., demand without costs) did not mediate differences in willingness to take between amphetamine and placebo. Considering the results on the whole, it appears that demand in the presence (but not the absence) of constraints mediates the willingness to use amphetamine subsequently. Of course, self-reported willingness to use again is an imperfect measure of addiction potential, but it has an extensive empirical history and has face validity as a measure of estimated drug-seeking.

An important nuance in these results is that elasticity operated differently in comparison to the other indices. A sizable proportion of participants simply exhibited no demand for the placebo, meaning that no elasticity coefficient could be generated. This warrants deeper consideration. To an extent, this finding is an expected response for dextrose consumption (the placebo condition) and affirms the inert status of the placebo. In turn, the null indirect effect estimates of elasticity as a mediator of amphetamine effects on willingness to use again in should be interpreted with caution due as elasticity estimates were available for approximately half of the sample, which reduced statistical power. In research on delay discounting, a behavioral economic measure of impulsive decision making, area under the curve (AUC) was applied to preference modelling to incorporate preferences that did not fit with existing nonlinear models (Myerson, Green & Warusawitharana 2001) and this strategy may be relevant in this case also. One study has validated the use of AUC in demand curve modelling (Amlung, Yurasek, McCarty, MacKillop & Murphy 2015b) and the resulting index was robustly correlated with elasticity. As a result, it is possible that it could be used as a proxy for elasticity in future. Nonetheless, given the fundamental absence of elasticity for a sizable number of participants and considering the effect sizes for the other indices also, a clear implication of the current findings is that the most important indices in future studies that include a placebo control are $O_{\max}$ and breakpoint.

Study strengths included a placebo-controlled, within-subjects design that provided a strong test of the hypotheses. In addition, the mediational analyses substantially contribute to understanding validity and utility of purchase task indices over and above standard analytic approaches in behavioral pharmacology. A limitation was the use of an exclusively hypothetical purchase task, as opposed to either all or one outcome being delivered. However, existing observational and clinical findings are often derived from drug purchase tasks that have used hypothetical outcomes (Jacobs & Bickel, 1999; Murphy & MacKillop, 2006) and evidence suggests that performance for hypothetical and actual outcomes exhibits

high correspondence (Amlung *et al.* 2012; Amlung & MacKillop 2015). In addition, an estimation-format measure represents the most efficient form of this paradigm and could be most easily incorporated into studies of abuse liability. Finally, a further limitation is that this initial test focused on only a single drug and a single dose. Extension of this line of research to other drugs of abuse and dose-response paradigms is warranted. More broadly, in considering the pros and cons of the purchase task methodology, it is important to recognize that preferences are inherently nested within income and other resources.

In sum, these findings provide proof-of-concept for an experimental drug purchase task as a useful method of assessing an unfamiliar compound's potential abuse liability. The results provide a foundation for future research seeking to definitively validate this efficient approach and apply purchase task measures of abuse liability for a variety of other purposes. For instance, an experimental drug purchase task may be useful as an outcome in studies of: (a) individual difference factors that may confer risk for drug abuse by altering abuse liability, (b) biological or psychosocial mechanisms of drug reinforcement, including drug-induced changes in brain activity derived from neuroimaging measures; and (c) the effects of interventions designed to suppress a drug's abuse liability. If subsequent studies are similarly supportive, an experimental drug purchase task may become an integral part of standard batteries assessing drug liability and other questions in addiction research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Prototypic behavioral economic demand and expenditure curves.

Figure 2. Multiple mediation models. Panel A presents the multiple mediation model of drug condition on experimental purchase task demand indices as a function of combined subjective effects. A single mediational model set was conducted, which included all mediators simultaneously modeled. Panel B presents mediation of drug condition on ‘Willingness to take Again’ by combined experimental drug purchase task demand indices. A single mediational model set was conducted, which included all mediators simultaneously modeled

Notes: Drug condition = Amphetamine or placebo; experimental drug purchase task outcomes = Intensity, O_{max} , Break Point, Elasticity; a = path from the independent variable to the mediator(s); b = path from the mediator to the dependent variable, after controlling for the effect of the independent variable; $a \times b$ = the indirect effect of the independent variable on the dependent variable that occurs through the mediator, which equals the product of the a path and b path; c' = the direct effect of the independent variable on the dependent variable that is not carried through the mediator, which equals the effect of the independent variable on the dependent variable after controlling for the mediator; total effect = the sum of the indirect effect ($a \times b$) and direct effect (c'), which equals the effect of the independent variable on the dependent variable.

Figure 3. Differences by drug condition (amphetamine 20 mg vs. placebo) on the experimental drug purchase task indices

Note. $N=98$ (Intensity, $O_{\max}$, Breakpoint); $n=41$ (Elasticity) * $p<0.05$; ** $p<0.01$;

*** $p<0.001$.

Figure 4. Amphetamine and placebo demand curves

Note. Consumption refers to number of pills.

Table 1

Experimental drug purchase task indices and subjective drug effects intercorrelations

		Intercorrelations (<i>r</i>)							
		1	2	3	4	5	6	7	8
1. Intensity	1	—	0.50 [†]	0.21 [*]	-0.13	0.12	0.13	0.08	0.19
2. O _{max}	2	0.19	—	0.87 [†]	-0.30	0.15	0.01	0.29 ^{**}	0.36 ^{***}
3. Breakpoint	3	0.12	0.97 ^{**}	—	-0.27	0.10	-0.01	0.30 ^{***}	0.32 ^{***}
4. Elasticity	4	-0.16	-0.45 ^{***}	-0.40 [*]	—	0.04	0.00	-0.27	-0.23
5. Positive Mood	5	0.10	0.31 ^{***}	0.34 ^{***}	-0.13	—	0.59 ^{***}	0.19	.28 ^{**}
6. Arousal	6	0.13	0.20 [*]	0.21 [*]	-0.01	0.75 ^{***}	—	-0.02	0.18
7. Drug High	7	0.12	0.40 ^{***}	0.44 ^{***}	-0.30	0.49 ^{***}	0.49 ^{***}	—	0.36 ^{***}
8. Willingness to Use Again	8	-0.08	0.42 ^{***}	0.46 ^{***}	-0.15	0.49 ^{***}	0.42 ^{***}	0.44 [†]	—

Note. Correlations above diagonal represent placebo condition and correlations below the diagonal (gray shading) represent amphetamine drug condition.

* $p < 0.05$;

** $p < 0.01$;

*** $p < .001$.

Table 2

Mediation of the effects of drug condition (amphetamine vs. placebo) on experimental drug purchase task indices by subjective drug effects

	Drug condition → subjective measure Mediator (A path)	Subjective measure Mediator → Demand Outcome (B path)	Direct Effect	Direct Effect ^a	Drug → subjective measure → Demand Outcome (Indirect effect)	Indirect Effect ^a	Total Effect	Proportion of Effect Mediated	Proportion of Effect Mediated ^a
<i>Intensity^b</i>									
Positive Mood	0.67***	0.11*	0.07	-0.004	0.07*	<0.01	0.14***	0.53	0.01
Arousal	0.69***	0.09	0.08	-0.004	0.06*	0.08	0.14***	0.45	0.57
Drug High	0.83***	0.09	0.06	-0.004	0.08*	0.06	0.14***	0.56	0.43
<i>Omax^b</i>									
Positive Mood	0.67***	0.28***	0.24*	0.07	0.19***	0.15	0.43***	0.43	0.35
Arousal	0.69***	0.14*	0.33*	0.07	0.10*	-0.08	0.43***	0.43	-0.19
Drug High	0.82***	0.41***	0.09	0.07	0.34***	0.29***	0.43***	0.80	0.67
<i>Breakpoint^b</i>									
Positive Mood	0.67***	0.29***	0.25*	0.07	0.20***	0.15	0.45***	0.44	0.33
Arousal	0.69***	0.16*	0.34*	0.07	0.11***	-0.09	0.45***	0.24	-0.20
Drug High	0.82***	0.45***	0.08	0.07	0.37***	0.32***	0.45***	0.82	0.71
<i>Elasticity^c</i>									
Positive Mood	0.67***	-0.02	-0.44	-0.29	-0.01	0.04	-0.45***	0.02	-0.09
Arousal	0.69***	-0.02	0.44	-0.29	-0.01	0.04	-0.45***	0.03	-0.09
Drug High	0.82***	-0.21***	-0.28	-0.29	-0.17***	-0.25***	-0.45***	0.42	0.56

Note.

^aDirect or indirect effect from multiple mediation models (i.e., all 3 subjective drug effects entered as simultaneous mediators).^bN=98.^cN=41.* $p < .05$;** $p < .01$;

$p < .001$

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Table 3

Mediation of the effects of drug condition (amphetamine vs. placebo) on 'Willingness to Take Drug Again' by experimental drug purchase task demand indices.

	Path A	Path B	Direct Effect	Direct Effect ^a	Indirect Effect	Indirect Effect ^a	Total Effect	Proportion of Effect Mediated	Proportion of Effect Mediated ^a
Individual Models									
Intensity ^b	0.15 [*]	0.01	0.59 ^{***}	0.40 ^{**}	<0.01	-0.01	0.59 ^{***}	0.01	-0.02
O _{max} ^b	0.45 ^{***}	0.42 ^{***}	0.40 ^{**}	0.40 ^{**}	0.19 ^{**}	-0.01	0.59 ^{***}	0.32	-0.02
Breakpoint ^b	0.47 ^{***}	0.42 ^{***}	0.40 ^{**}	0.40 ^{**}	0.19 ^{**}	0.18	0.59 ^{***}	0.30	0.25
Elasticity ^c	-0.49 [*]	-0.14	0.66 [*]	0.61	-0.07	0.05	0.73 ^{***}	0.10	0.07
Adjusted for subjective effects									
Intensity ^b	—	—	0.11	0.09	-0.01	-0.02	0.10	0.82	-0.11
O _{max} ^b	—	—	0.08	0.09	0.11 [*]	0.03	0.19	0.86	0.15
Breakpoint ^b	—	—	0.09	0.09	0.11 [*]	0.09	0.20	0.85	0.32
Elasticity ^c	—	—	0.25	0.25	0.03	0.02	0.28	0.65	0.07

Note.

^a Direct or indirect effect from multiple mediation models (i.e., all 3 [or 4 for elasticity]; purchase task indices entered as simultaneous mediators). Combined mediator models = Single purchase task mediator and three subjective effects as simultaneous mediators.

^b N=94.

^c N=40.

^{*} p<.05;

^{**} p<.01;

^{***} p<.001.