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Decreased cocaine demand following contingency management treatment

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ABSTRACT

A hypothetical cocaine purchasing task (CocPT) was used to assess changes in cocaine demand in the context of contingency management (CM) treatment for cocaine use disorder (CUD). Participants (N = 89) were treatment-seeking individuals with CUD receiving 4 weeks of abstinence-based, high-magnitude CM. Treatment response (vs. non-response) was operationally defined as the submission of 6 consecutive cocaine-negative urine samples across two weeks. The CPT was assessed at baseline, week 2, and week 5. Demand data were well described by the exponentiated demand model, and baseline demand indices (Q_0, P_{max}, breakpoint, essential value) were significantly associated with self-report measures of cocaine use. The probability of being a zero-responder reporting zero cocaine consumption at all prices significantly increased over the course of treatment, and was greater among treatment responders vs. non-responders. Among non-zero demand data, decreases in O_{max}, P_{max}, breakpoint, and essential value were observed over the course of CM treatment, favoring responders. To our knowledge, this is the first study to assess change in cocaine demand in the context of CM treatment targeting cocaine abstinence. Our results support the utility of cocaine demand as a measure for both identifying individuals with greater treatment need and tracking relapse risk over the course of treatment.

1. Introduction

Cocaine use disorder (CUD) is a significant public health issue that has been increasing in recent years. In 2017, there were ~14 thousand cocaine-related overdose deaths, more than a two-fold increase compared to a decade ago (Kariisa et al., 2019). In addition to increased morbidity and mortality, cocaine use is associated with a host of problems negatively affecting not only users, but society at large. Such consequences include but are not limited to crime, incarceration, violence, homelessness, drug-exposed neonates, and increased risk of infectious disease (Barr et al., 1984; Cherubin and Sapira, 1993; Karch, 2005; Kruszon-Moran and McQuillan, 2005; Lucas, 2005; Nnadi et al., 2005; Schiller and Allen, 2005). CUD is also associated with a number of compromised cognitive and behavioral processes associated with reward, motivation, learning, and inhibitory control (Goldstein and Volkow, 2002, 2011; Volkow et al., 2003).

In the absence of an FDA-approved pharmacotherapy, current clinical practice guidelines recommend psychosocial interventions for the treatment of CUD (De Crescenzo et al., 2018; Kleber et al., 2006). One such intervention is contingency management (CM), an evidence-based treatment that promotes clinically-relevant targets (e.g., cocaine abstinence) by providing contingent consequences, such as vouchers exchangeable for a variety of non-drug rewards (Higgins et al., 2009). CM is based on an extensive behavioral literature showing that drug use, like other behaviors, is sensitive to environmental consequences such as magnitude and immediacy of reward (Lussier et al., 2006). A recent meta-analysis including 50 randomized controlled trials (N = 6942) evaluated the efficacy and acceptability of twelve psychosocial interventions for CUD and amphetamine use disorder compared to treatment as usual (De Crescenzo et al., 2018). CM delivered in conjunction with behavioral support was the only treatment to increase cocaine abstinence at the end of treatment, 12 weeks, and at long-term follow-up (range 16–96 weeks). In another meta-analysis assessing treatments for CUD including 157 trials with 402 treatment groups (N = 15,842), only CM interventions significantly increased the likelihood of negative cocaine test results (Bentzley et al., 2021). Despite its proven efficacy, response to CM is variable and appears to be related, in part, to individual differences in reward sensitivity. Thus, having the ability to gauge an individual's cocaine reward valuation could potentially help both in predicting response to treatment and in adjusting CM parameters

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over the course of treatment to correspond with changes in reward sensitivity.

Drug demand is a behavioral economic measure that characterizes the relationship between the price (e.g., monetary cost or effort expended) of a drug and the amount of drug consumed. Assessing these choices under conditions of constraint (e.g., finite funds, time to use drugs, etc.) has helped elucidate the decision-making processes characterizing motivation to use drug among individuals with substance use disorders (Bickel et al., 2014; Hursh and Roma, 2013; Koffarnus and Kaplan, 2018; Mackillop, 2016). Hypothetical drug purchasing tasks are commonly used to assess drug demand and are useful in clinical settings where providing access to drug would be either unethical or impractical given limitations on time and setting (Roma et al., 2017). Drug purchasing tasks have been successfully utilized to assess drug demand for a variety of substances including alcohol (Amlung et al., 2012; Amlung and MacKillop, 2014, 2015; MacKillop et al., 2010; Petry, 2000, 2001; Petry and Bickel, 1998), nicotine (Acker and MacKillop, 2013; MacKillop et al., 2008; MacKillop and Tidey, 2011), marijuana (Aston et al., 2014), opioids (Petry, 2000, 2001; Petry and Bickel, 1998; Pickover et al., 2016; Schwartz et al., 2019; Strickland et al., 2019b; Yoon et al., 2020b), methamphetamine (Yoon et al., 2020a), and cocaine (Bruner and Johnson, 2014; Petry, 2000, 2001; Strickland et al., 2016b; Yoon et al., 2021, 2020c).

Meta-analyses have demonstrated that drug demand is associated with various measures of drug use (Strickland et al., 2019a; Zvorsky et al., 2019) and also sensitive to acute experimental manipulations (Acuff et al., 2020). A handful of studies have also observed that baseline drug demand is associated with treatment outcomes for alcohol (Bernstein et al., 2014; MacKillop and Murphy, 2007; Murphy et al., 2015) tobacco (Mackillop et al., 2016; Secades-Villa et al., 2016) as well as cocaine in a recent study by our group (Yoon et al., 2020c). However, to our knowledge, only four studies have reported on longitudinal changes in demand in patients as they undergo addiction treatment. In one study, alcohol demand significantly decreased following exposure to one of two brief interventions, and these changes persisted at one-month follow-up and were also associated with decreased alcohol use during this time (Murphy et al., 2015). In two studies assessing demand for cigarettes among individuals receiving varenicline vs. placebo, one study observed greater decreased demand for cigarettes among individuals in the active drug group (McClure et al., 2013), whereas another saw significant decreases in cigarette demand across both the active and placebo groups that did not differ by drug group (Schlienz et al., 2014). Note that the data analytic framework followed in the McClure study was relatively unique compared to other demand studies, assessing demand curves based on aggregate group-level curves rather than individual curve-fittings, which precluded a formal test of the group-by-time interaction and its effect size. Recently, Schwartz et al. (2021) reported decreases in heroin demand in a convenience sample of individuals (N = 52) receiving medication assisted (methadone or buprenorphine) opioid treatment (Schwartz et al., 2021). However, no significant decreases in opioid positive urine samples (excluding methadone and buprenorphine) were observed. Note that heroin demand was assessed at arbitrary timepoints (i.e., timepoint 1 and 6 months later) for individuals in no relation to their stage of treatment.

The current study represents a direct follow-up to our previous study in which we observed a significant association between baseline cocaine demand and treatment response following 4 weeks of CM for CUD (Yoon et al., 2020c). In that study, low demand for cocaine at baseline was significantly associated with being classified as a treatment "responder" based on achievement of initial abstinence from cocaine by week 4. This effect was largely driven by zero-responders, i.e., individuals who did not choose to consume cocaine at any price, even $0. The current study extends the previous findings in two important ways: 1) evaluating additional cocaine demand indices, including essential value, which can account for zero-responders in contrast to α; and 2) examining longitudinal changes in cocaine demand, from baseline to week 5, with the aim of determining whether CM responders show a corresponding and significant reduction in cocaine demand compared to CM non-responders.

2. Methods

2.1. Participants

The current study was conducted in the context of an ongoing parent study investigating sequential, multiple assignment, randomized trial (SMART) design involving two distinct treatment phases (NCT02896712). Phase 1 involved 4 weeks of high-magnitude reinforcement CM targeting abstinence, defined as cocaine-negative urine drug screens. In addition to CM, participants were randomized to receive one of two evidence-based therapies (i.e., Drug Counseling, Acceptance and Commitment Therapy (ACT)). Phase 2 involved 8 weeks of continued treatment that was augmented with pharmacotherapy (modafinil or placebo) for CM non-responders (Schmitz et al., 2018). The current study focuses on Phase 1 only prior to any drug administration.

Participants consisted of treatment-seeking individuals, 18–60 years old, who met current DSM-5 criteria for CUD of at least moderate severity (≥4 symptoms). Eligible participants submitted at least one positive urine toxicology screen for the cocaine metabolite, benzoylecgonine (BE ≥ 150 ng/mL) during intake to ensure enrollment of individuals actively using cocaine. Participants meeting moderate or severe diagnostic criteria for SUDs other than cocaine, marijuana, or nicotine were excluded. Severe alcohol use disorder was exclusionary. Other exclusion criteria included being pregnant, breast-feeding, or having a significant and unstable medical/psychiatric disorder or taking medications contraindicated for modafinil pharmacotherapy. The current study was approved by the University of Texas Health Science Center at Houston Committee for the Protection of Human Subjects (IRB) and conducted in accord with the Declaration of Helsinki (HSC-MS-15-0595 "Developing Adaptive Interventions for Cocaine Cessation and Relapse Prevention"). All participants provided written informed consent.

2.2. Interventions

2.2.1. High magnitude CM

The CM schedule was adapted from previous trials aimed at achieving initial abstinence using high magnitude reinforcement (Schmitz et al., 2018). Under an escalating schedule, participants could earn monetary rewards for providing cocaine-negative urines samples at thrice weekly scheduled clinic visits (MWF). Reward value began at $10 and increased by $10 for each subsequent cocaine negative sample to a maximum of $60. An additional $10 bonus was given weekly for completing all study-related tasks. Provision of a cocaine positive sample reset the reward to the initial value $10. Earnings were electronically loaded on study debit cards.

2.2.2. Behavioral counseling

In addition to CM, all participants received manually-guided ACT or Drug Counseling, based on random assignment. The goal of ACT was to assist patients to notice their internal cravings and triggers, to abandon their attempts to manage these triggers via active avoidance, suppression or other control-based strategies, and to make commitments to engage in behaviors consistent with their chosen values or goals (Luoma et al., 2007; Read, 2013; Stotts et al., 2012; Strosahi and Hayes, 2010). In contrast, Drug Counseling focused on educating patients about addiction recovery and developing a support system (Crits-Christoph et al., 1999). No significant differences in cocaine demand were noted between the two therapy groups in the current study sample, and results from the two groups were therefore combined.

2.3. Materials and procedure

2.3.1. Cocaine Purchasing Task (CocPT)

The CocPT was administered at baseline, week 2, and week 5. The week 5 assessment was completed on the first visit following the 4-week CM intervention. Participants were asked how many rocks of cocaine they would purchase for the day at various prices (i.e., 0, 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 40, 50, 100, 200, 500, 1000, 2000, 5000, and 10,000 dollars). Participants were instructed to assume the following: that their income and savings were what they usually are; the quality of cocaine is the type they usually purchased; there are no other sources of cocaine; any cocaine purchase had to be used within that day; and their craving and desire for cocaine was how they currently felt. The instructions and range of prices for cocaine are comparable to that previously reported in the literature (Bruner and Johnson, 2014; Strickland et al., 2016a, b; Yoon et al., 2020c). Compared to other CocPT tasks in the literature, prices in the current task were chosen to 1) provide relatively more price points at lower values under the assumption that these may be more relevant for some participants in a treatment-seeking population; 2) present values that were relatively easy to calculate for participants; and 3) present a high enough price (i.e., 10,000) to ensure that participants would likely hit a breakpoint within the provided price range.

2.3.2. Addiction Severity Index-Lite (ASI-Lite)

Administered at baseline, the ASI-Lite (Cacciola et al., 2007), an abbreviated version of the original ASI (McLellan et al., 1980), is a standardized multi-dimensional, interview-based measure for substance use and related problems. The ASI-Lite assesses the respondent's lifetime and past-month use of several substance classes. In the current study, the ASI-Lite was used to obtain descriptive data about substance use, including number of days (past-month) and years (lifetime) of cocaine use.

2.3.3. Kreek-McHugh-Schluger-Kellogg Scale (KMSK)

The KMSK Scale was administered at baseline and is a brief screening instrument designed to quantify substance use, as each section assesses frequency amount and duration of use of a particular substance during the respondent's heaviest period of use. Current and past use is assessed as well as mode of use and substance of choice (Kellogg et al., 2003). While administration time of the KMSK is approximately 5 min, it is effective in providing rapid dimensional analyses for various substance use exposure (Butelman et al., 2018). The psychometric properties are sound, including concurrent validity and sensitivity and specificity for cocaine, opioids, and alcohol use (e.g., Kellogg et al., 2003; Tang et al., 2011). In the current study, the KSMK was used to derive total scores for lifetime and past month cocaine use with higher scores indicating greater severity of cocaine use, as well as the most money spent on cocaine (lifetime) in a single incident and the average amount spent on cocaine use in the last 30 days.

2.3.4. Urinalysis

The integrated E-Z split key cup II (Innovacon Company, San Diego, CA) was used to test for urine cocaine (benzoylecgonine) at thrice weekly clinic visits. Per the parent study, the primary outcome for Phase 1 was defined as CM response/non-response. Participants who submitted 6 consecutive (2 weeks) cocaine negative urine samples by week 4 were classified as responders. The two week criteria was chosen as the parent trial required a binary outcome (i.e., treatment responder, non-responder) as part of the adaptive design (Schmitz et al., 2014). Similar definitions have been used in other cocaine trials involving achievement of abstinence early in treatment (Bisaga et al., 2010, 2005, 2006). Those not meeting response criteria were classified as non-responders.

2.4. Data analytic strategy

Participant socio-demographic and drug-use characteristics for treatment responders and non-responders were compared using Fischer's test for categorical characteristics and either the *t*-test or Mann-Whitney rank sum test for continuous characteristics. The *t*-test was used when data were normally distributed, whereas the Mann-Whitney rank sum test was utilized for non-normally data distributions.

Individual participant cocaine demand data were initially assessed for systematicity (Bruner and Johnson, 2014). Hypothetical drug consumption data were identified as nonsystematic if 1) units of drug consumed at a given price were at least 20 % greater than at the preceding price, or 2) units of drug consumed at the final price were not less than the first price by at least 10 %. Note that an exception to the second rule was made in the case of zero-responders. A total of 230 demand assessments were completed across the 89 participants over three time points (i.e., baseline, Week 2, Week 5). Five assessments across 3 participants showed 1 or 2 violations of systematicity (i.e., drug consumption was at least 20 % greater than a preceding price). These nonsystematic points were removed prior to fitting the remaining data to our demand model, which is described below. We specifically chose to use systematicity criteria presented by Bruner and Johnson (2014) rather than the more recent ones presented by Stein et al. due to the large number of zero-responders as the formula for assessing trend by Stein et al. utilizes the log of consumption values, which are undefined when consumption is 0 (Stein et al., 2015).

All demand data were fit to Eq. (1) below using GraphPad Prism 6.0f (GraphPad Software Inc.; La Jolla, CA) to generate both individual and group indices of demand.

$$Q = Q_0 * 10^{k(e^{-\alpha Q_0 C} - 1)} \quad (1)$$

Eq. (1) represents a relatively recent, modified version of the widely used exponential equation proposed by Hursh and Silberberg (Hursh and Silberberg, 2008). In the exponentiated version, both sides of the equation have been exponentiated. Advantages of the exponentiated equation include: 1) inclusion of 0 consumption values; and 2) improved fits compared to the exponential model based on recent studies (Koffarnus et al., 2015; Strickland et al., 2016b; Yu et al., 2014). In the equation, Q represents the amount of consumption at commodity price C. Q_0 represents consumption levels at or near 0 price and is also referred to as intensity of demand. The parameter k represents the range of consumption in log units and was set to 3 in the current study based on the highest value observed for Q_0. The term α represents the rate of change in elasticity and is inversely proportional to essential value according to Eq. (2) below (Hursh and Roma, 2016):

$$Essential\ Value = \frac{1}{(100 \cdot \alpha \cdot k^{1.5})} \quad (2)$$

Additional indices of demand include breakpoint, O_{max}, and P_{max}. Breakpoint represents the first price at which no consumption occurs and was obtained from the raw data. O_{max} describes the maximum response output (e.g., amount of money spent) by multiplying consumption by cost, and P_{max} represent the price at which O_{max} is observed. Values for O_{max} and P_{max} were derived using an Excel template provided by the KU Laboratory in Applied behavioral Economics (http://www.behavioraleconlab.com/resources—tools.html) (Kaplan and Reed, 2014). Note that for several of these measures (i.e., Q_0, O_{max}, P_{max}), one can obtain both observed values from the raw data as well as derived values after fitting raw data to Eq. (1). A relatively unique but clinically relevant aspect of the current data set was the relatively large number of zero-responders. While it is customary to exclude these data in studies assessing goodness of fit (e.g., Koffarnus et al., 2015; Strickland et al., 2016b), inclusion of these data is appropriate and potentially informative in the current case as data are being analyzed in relation to clinical outcomes. In the current study, we defined Q_0, O_{max}, P_{max}, and

breakpoint as 0 for zero-responders. The value for α is undefined with zero consumption. However, essential value has been defined as 0 (i.e., the lowest potential value) under similar circumstances in previous research, as excluding such values may artificially overestimate group demand (Heckman et al., 2019; Stein et al., 2017).

As an additional test to assess the goodness of fit of the exponentiated demand model, non-parametric Spearman Rank order correlation was conducted to compare observed and derived indices of demand (Q_0, O_{max}, P_{max}). For all other analyses, the derived demand indices were used. Non-parametric Spearman Rank order correlation was also conducted to compare derived indices of demand (Q_0, O_{max}, P_{max}, breakpoint, essential value) with self-reported cocaine-use characteristics (years use, past 30 days use, KMSK lifetime and past 30-day total scores, KMSK lifetime most money spent on cocaine lifetime, KMSK past 30 days average money spent on cocaine).

Generalized linear mixed modeling (GLMM) was used to examine the relationship between each of the demand characteristics (Q_0, O_{max}, P_{max}, break point, and essential value) and treatment response group (responders vs. non-responders) over time. In separate models, each demand characteristic was fit as a function of the interaction between time and response group, controlling for constituent main effects. GLMM provided the ability to simultaneously account for repeated measures via inclusion of a level 2 intercept (i.e., mixed modeling). Further, GLMM was able to countenance the non-normal distribution of each demand characteristic via specification of link functions. Specifically, each demand characteristic was distributed with no negative values, a mass of zero values, and a lognormal process for its positive values.

Traditional statistical models are not readily able to account for lognormal data with zeroes, as the logarithm of zero is not defined. The present analysis addressed this issue using a two-part hurdle model (Neelon et al., 2010) that first models the probability of a zero-responders (vs. a non-zero responder, positive value) as a binomial function akin to logistic regression, then, contingent on the first stage being non-zero, models the continuous positive values as a lognormal function. This analytic technique implicitly requires separate interpretation for the participants with zero values from those with positive values. The technique thus provides a separate evaluation of the time by treatment group interaction for both the hurdle component (zero vs. non-zero responders) and the continuous component (lognormal positive continuous values), effectively doubling the number of interactions under evaluation in the present analysis from 5 to 10 (i.e., 2 components for each demand characteristic).

Bayesian statistical inference was used for the present analysis for both quantitative and qualitative advantages. Quantitatively, Bayesian techniques have demonstrated computational advantages for estimating models in the case of data with a relatively large number of zeroes (Ghosh et al., 2006). Qualitatively, Bayesian inference provides the posterior probability (PP) that an effect of a given predictor exists, where the PP is calculated as the distribution of values proportional to a likelihood function multiplied by a prior distribution. This calculation provides a credible range of values for each model effect (e.g., regression coefficients), and the proportion of these values around zero describes the probability that effects exist in either a positive or negative direction. The weakest possible evidence, PP = 50 %, would suggest that the effect has an equal probability of being positive or negative, while greater values suggest that an effect is more likely to be in one direction compared to the other (e.g., PP = 75 % indicates a 3-to-1 chance).

This framework offers a more straightforward interpretation of probability compared to traditional *p*-values, which rely on the assumption that the null hypothesis is true. Unlike *p*-values, no monolithic values of the PP have been established to denote statistical significance; instead, inferences rely on subjective probability of experts and other facets of the given research. For example, consider a hypothetical disease: a PP = 60 % that a new medication confers benefit in treating the disease may be too low if many other inexpensive, reliable, and safe medications already exist. Conversely, the same PP = 60 % may be considered excellent if no other treatments have been discovered. Considering the exploratory context of the present research, a PP $\geq$ 75 % was decided by the research team to indicate moderate support in favor of the existence of model effects, with higher probabilities indicating stronger support and vice versa for lower probabilities. This threshold is in line with guidelines established elsewhere (Jeffreys, 1961; Lee and Wagenmakers, 2013) as well as recent work by the present researchers (Schmitz et al., 2017; Suchting et al., 2019; Yoon et al., 2020a).

Weakly informative priors (~Normal [$\mu = 0$, $\sigma^2 = 100$]) were used for all models to maximize the influence of the present data on posterior probabilities. Estimation utilized 4 Markov chains of 4000 total iterations each (with 2000 of these discarded as burn-in iterations). Evaluating the degree to which each model satisfied assumptions of Bayesian analyses relied on scale reduction factors (Rhat), effective sample size (ESS), and posterior predictive checking. Assumptions were satisfied for each model, including Rhat < 1.01, sufficiently large ESS, and graphical confirmation that the observed distribution of each outcome was subsumed by the range of distributions produced by 1000 replications of that outcome from the posterior predictive distribution. All statistical analyses were performed in the R statistical computing environment (R Core Team, 2020) [X] via packages rstan (Stan Development Team, 2020) and brms (Burkner, 2017). A copy of the R code used for these analyses can be found at the following link (https://github.com/AcademicCodeRepository/Yoon2021).

3. Results

3.1. Baseline socio-demographics and drug use

Participants (N = 89) were predominately male, Black, and non-Hispanic with the majority having completed at least 12 years of education (Table 1). Participants reported using cocaine approximately half the days in the past 30 days, predominately used cocaine via smoking as their preferred route of administration, and the majority were cigarette smokers. Compared to treatment responders (n = 20), individuals in the non-responder (n = 69) group were significantly more likely to provide a cocaine positive urine drug screen on the first day of CM treatment, report greater years of cocaine use and days use in the past 30 days, and

Table 1
Summary of baseline socio-demographic and drug-use characteristics for treatment responders and non-responders. Error measures represent ± SEM and *p* values are provided when significant differences were found between the responder and non-responder groups for a given characteristic.

Characteristic	Responder (n = 20)	Non-Responder (n = 69)	p value
Socio-Demographic			
Age (Years)	48.5 ± 2.0	50.5 ± 0.9	
Male (%)	75.0	81.2	
Black (%)	85.0	78.3	
White (%)	15.0	17.4	
Other (%)	0.0	7.2	
Hispanic (%)	5.0	10.1	
≥12 Years Education (%)	90.0	92.8	
Drug-Use			
Negative Cocaine On 1st Day of Treatment (%)	55.0	8.7	<0.001
Cocaine Years Use	12.3 ± 1.6	17.2 ± 1.1	0.02
Cocaine Use Past 30 Days	14.0 ± 2.0	18.5 ± 1.1	0.05
Primary Route of Administration via Smoking (%)	80.0	89.9	
KMSK Lifetime Total Score	13.4 ± 0.5	14.7 ± 0.2	0.01
KMSK 30 Days Total Score	9.2 ± 0.4	9.4 ± 0.2	
KMSK Lifetime Most $ Spent	130 ± 29.0	194.5 ± 25.5	0.04
KMSK 30 Days Average $ Spent	74.8 ± 16.9	71.9 ± 7.6	
Cigarette Smoker (%)	80.0	73.9	

present higher KMSK Lifetime total scores and monetary amounts spent on cocaine during a single incidence.

3.2. Utility of the exponentiated demand model

Overall, assessment of cocaine demand via the CocPT was observed to be feasible and acceptable, and the exponentiated demand model provided an excellent fit to the demand data. Out of a total of 230 demand assessments across 89 participants, data were predominately systematic (97.8 %). Consumption data were well described by the exponentiated demand model, with the average $r^2 = 0.93$ (SEM ± 0.004). Utility of the exponentiated demand model is further supported by results from Spearman rank order correlations comparing observed and derived indices of demand, revealing strong, positive correlations for Q_0 ($r = 0.99$, $p < 0.0001$), O_{max} ($r = 0.96$, $p < 0.0001$), and P_{max} ($r = 0.75$, $p < 0.0001$). Relatively lower r values for P_{max} are expect as observed price are predefined as the assessed priced points.

3.3. Comparisons of self-reported cocaine use and indices of demand at baseline

Spearman rank order correlation testing revealed positive associations between demand indices (Q_0, P_{max}, breakpoint, essential value) and self-reported measures of cocaine use at baseline (see Table 2). Baseline O_{max} was not significantly associated with any measures of cocaine use. Overall, the demand indices Q_0 and essential value showed the strongest correlation with measures of cocaine use, and KMSK 30 and KMSK 30 average amount of money spent on cocaine had the greatest number of significant correlations with indices of demand.

3.4. Comparison of demand curves across CM treatment

Comparison of group demand curves for treatment responders and non-responders at BL, Week 2, and Week 5 are presented in Fig. 1. One non-responder participant's data, although orderly, served as an outlier with relatively high consumption values at the baseline assessment. Specifically, consumption ranged from 1000 rocks of cocaine at the lowest price to 100 rocks at the highest price. Therefore, we transformed that outlying participant's data by replacing consumption values at each price with the maximum consumption value observed at that price from the rest of the participants in the non-responder group at baseline. Overall, changes in the shape of the demand curves suggest that cocaine demand decreased over the course of CM treatment and cocaine demand was generally less for treatment-responders compared to non-responders. Closer examination of the data revealed that a noteworthy factor likely influencing changes in the group demand curves, particularly for the treatment-responders, was the increase in zero-responders over the course of treatment. This phenomenon is most clearly illustrated by study week 5, where the median demand curve for treatment-responders has zero consumption at all prices. In the responder group, the percentage of zero-responders increased from 15.0 % (3 of 20) at baseline, to 31.6 % (6 of 19) at 2 weeks, and 62.5 % (10 of 16) at 5 weeks. In the non-responder group, the percentages were 2.9 % (2 of 69) at baseline, 14.0 % (8 of 57) at 2 weeks, and 20.4 % (10 of 49) at 5 weeks.

Table 2
Comparison of baseline indices of demand with baseline self-report measures of cocaine use. Bolded cells indicated significant associations at $p < 0.05$.

Demand Indices	Years Use	Past 30 Days Use	KMSK Lifetime Total	KMSK 30 Day Total	KMSK Lifetime $	KMSK 30 Day $
Q_0	−0.03	0.004	**0.27**	**0.27**	**0.25**	**0.27**
	0.75	0.97	**0.07**	**0.01**	**0.02**	**0.01**
O_{max}	0.09	−0.05	−0.14	0.06	−0.07	0.12
	0.43	0.65	0.20	0.55	0.53	0.27
P_{max}	0.08	0.007	0.04	**0.29**	0.13	**0.31**
	0.48	0.95	0.74	**0.007**	0.23	**0.003**
Breakpoint	0.13	0.0007	0.04	**0.29**	0.13	**0.31**
	0.22	0.95	0.74	**0.007**	0.23	**0.003**
Essential Value	0.09	0.007	**0.21**	**0.27**	**0.25**	**0.27**
	0.43	0.95	**0.05**	**0.01**	**0.02**	**0.01**

3.5. Assessment of demand indices across CM treatment

Bayesian GLMM was used to determine if responders and non-responders reported different patterns of demand over time for each of the 5 indices of demand (Q_0, O_{max}, P_{max}, break point, and essential value). Further, each model was split into 2 components: a *hurdle* component predicting the probability of a zero value (vs. non-zero) indicative of a zero-responder and a *lognormal* component predicting the positive continuous values. This set of analyses thus evaluated the PP that the interaction exists between responder group (responder vs. non-responder) and time in 10 parts (5 demand characteristics x 2 model components). Analyses found support (PP ≥ 75 %) for the interaction effect in 9 of 10 parts, suggesting that change in most demand characteristics over time was different by group with respect to both (a) the probability of being a zero-responder and (b) the magnitude of change for the lognormal positive values. The model for each interaction was then followed up by examining the simple effects of change over time within each treatment responder and non-responder group. Thus, overall, the present analysis provided an estimate of the magnitude of change over time and the PP that the change over time is non-zero separately for the treatment responder and non-responder groups within each model component of all 5 outcomes (2 groups x 2 components x 5 demand characteristics = 20 interpretable effects). The set of analyses provided a large matrix of results that are summarized in Fig. 2.

This matrix of findings may be simplified into a set of patterns that emerged across each model. A graphical representation for each outcome is provided in Fig. 2 to guide the present description. First, for each demand characteristic, the probability of reporting a zero-value (i.e., being a zero-responder) increased for responders and non-responders (left column); however, the increase was greater for responders across all demand indices. In other words, over the course of CM treatment, individuals in the responder group were more likely to state that they did not want to consume cocaine at any price, even when free, compared to individuals in the non-responder group. Across demand characteristics, the odds ratio (OR) for the probability of reporting a zero over time was greater for responders (OR ≈ 2.0) than non-responders (OR ≈ 1.5). Note that some relatively minor variation is common in Bayesian analyses when calculating posterior probabilities as evidenced by the slight differences in statistical outcomes for O_{max}, P_{max}, and essential value in the left panel of Fig. 2. The relatively larger differences observed for Q_0 and break point are due to relatively infrequent cases in which an individual reported they would consume cocaine at the 0 price, but not subsequent prices.

With respect to the lognormal positive values (i.e., non-zero responders), demand indices for both treatment responders and non-responders either did not change or decreased over time. For responders, no change was supported for Q_0, but a decrease over time was found for O_{max}, P_{max}, break point, and essential value. For non-responders, no change was supported for O_{max}, P_{max}, and essential value, whereas a decrease over time was found for Q_0 and break point. The only demand characteristic that changed in the same direction for responders and non-responders was for breakpoint (both decreased); this pattern for the lognormal positive values came from the only unsupported interaction between responder group and time (PP = 52.6 %).

This complex set of results can be further summarized into a few broad statements for clarity. First, across all indices of demand, the probability of being a zero-responder increased across treatment, but more so for CM treatment responders relative to non-responders. Second, contingent on reporting a non-zero value, decreases in indices of cocaine demand value generally decreased more for responders than

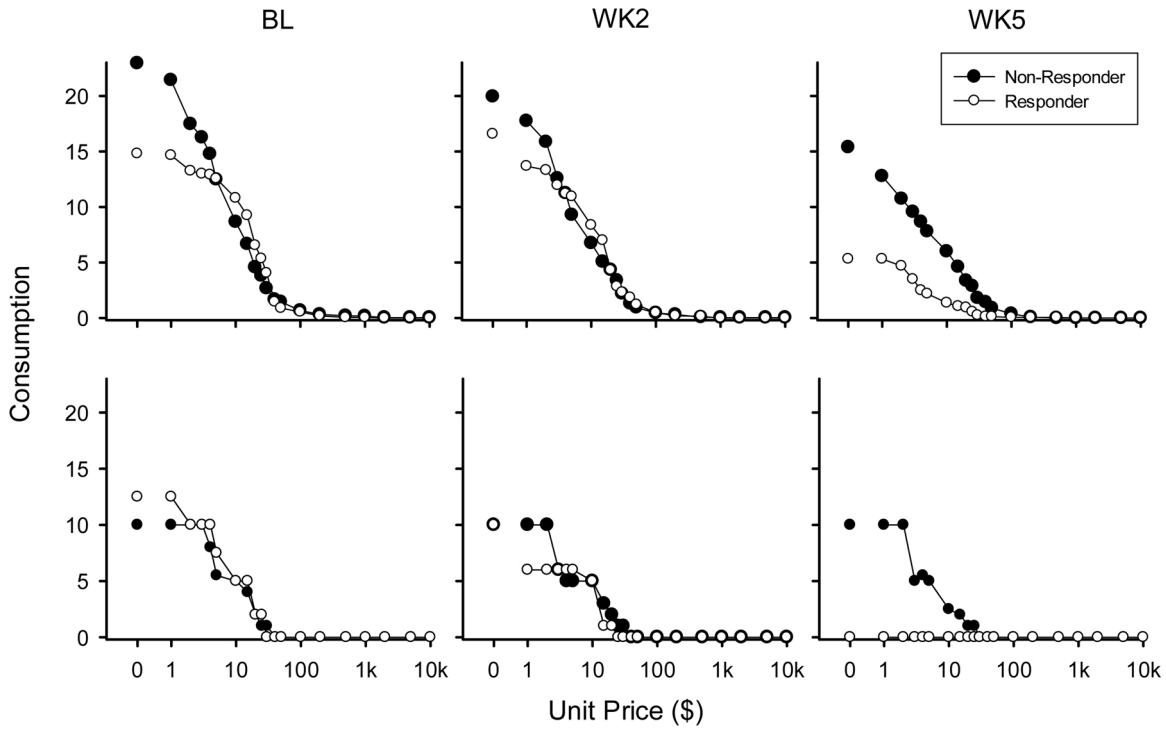

Fig. 1. Comparison of group demand curves for CM treatment responders (open circle) and non-responders (filled circle) across baseline (left), study week 2 (middle), and study week 5 (right). Symbols represent average (top) and median (bottom) consumption values at each respective price point for each group. Cocaine consumption in rocks is presented on the y-axis and unit price of cocaine rocks is presented on the x-axis. Note that the x-axis is on a log scale except for price $0, which is presented discontinuously.

non-responders. The two exceptions to the second observation were for Q_0, where responders did not change over time, and breakpoint, where the groups decreased by approximately the same amount.

4. Discussion

This is the first study to show changes in drug demand that correspond with treatment outcome (responder, non-responder) in the context of CM for individuals with CUD. Our primary findings were the following: 1) assessment of cocaine demand via the CocPT was observed to be feasible and acceptable, yielding data that was systematic and well described by the exponentiated demand model; 2) indices of demand were significantly associated with self-report measures of cocaine use; and 3) decreased cocaine demand was observed among those receiving CM treatment for cocaine, with generally greater decreases in demand found in treatment responders vs. non-responders.

Although the majority of drug demand research has been conducted in the context of cigarette smoking, the current results add to the growing number of studies demonstrating the feasibility and utility of hypothetical purchasing tasks in assessing drug demand for psychomotor stimulants such as cocaine (Bruner and Johnson, 2014; Koffarnus et al., 2015; Strickland et al., 2016b; Yoon et al., 2020c) and methamphetamine (Yoon et al., 2020a). Additionally, the current findings support the utility of the relatively newer exponentiated model of drug demand (Koffarnus et al., 2015; Strickland et al., 2016b; Yu et al., 2014) as supported by high r^2 values and strong positive correlations between observed and derived values for Q_0, O_{max}, and P_{max}. The exponentiated model may be particularly suitable for clinical populations of patients seeking drug treatment where zero consumption at particular drug price is more likely to be observed. In the exponential model developed by Hursh and Silberberg (Hursh and Silberberg, 2008), zero consumption presents a conundrum as the equation works with the log of consumption values and the log of 0 is undefined. There are a number of work-arounds for zero consumption values that have been utilized in the literature. For example, some studies have imputed arbitrarily small values (e.g., 0.1, 0.01, etc.) in place of 0 values. However, Koffarnus et al. (2015) demonstrated that despite being relatively small, different imputed values can result in significant changes in the values of indices of demand. Our findings highlight one circumstance in which the exponentiated model may be more appropriate for analyzing demand data with zero responders.

Although data were largely systematic, responses were observed at some assessments in which participants reported that they would consume relatively high amounts of cocaine (50 rocks or more) within a 24-h period at the lowest prices. These consumption values pose interpretive challenges as they would likely result in cocaine overdose. Previous studies in the literature have sometimes removed similar high drug consumption data in their final analyses. Note that we did conduct the analyses observed in Fig. 2 with demand data removed exhibiting cocaine consumption of 50 rocks or more and observed the same main findings (data not shown). However, we also observed that individuals reporting consumption of 50 rocks or more of cocaine were more likely to be non-responders (15 %) vs. responders (5 %), likely reflecting increased desire for cocaine from these participants. Therefore, although these consumption values are not likely to be objectively accurate, they do provide clinical utility and their removal could disproportionately impact treatment non-responders. That being said, improving the accuracy of these responses is a worthwhile goal. In total, participants reported in 30 out of 230 (13 %) demand assessments that they would consume 50 or more rocks of cocaine if cocaine was free within a 24-h period, with 14 (6 %) assessments reporting 100 or more rocks at the lowest price. We have previously suggested that leading the CocPT with questions such as “What is the most cocaine you have used in a 24-h period?” and “How much money was that amount of cocaine worth?” may help anchor participants’ responses and produce more realistic answers. Although these questions were not implemented in the current study, they were pilot tested in a recent study assessing cocaine demand based on drug consumption over a weekend (Friday to Sunday night)

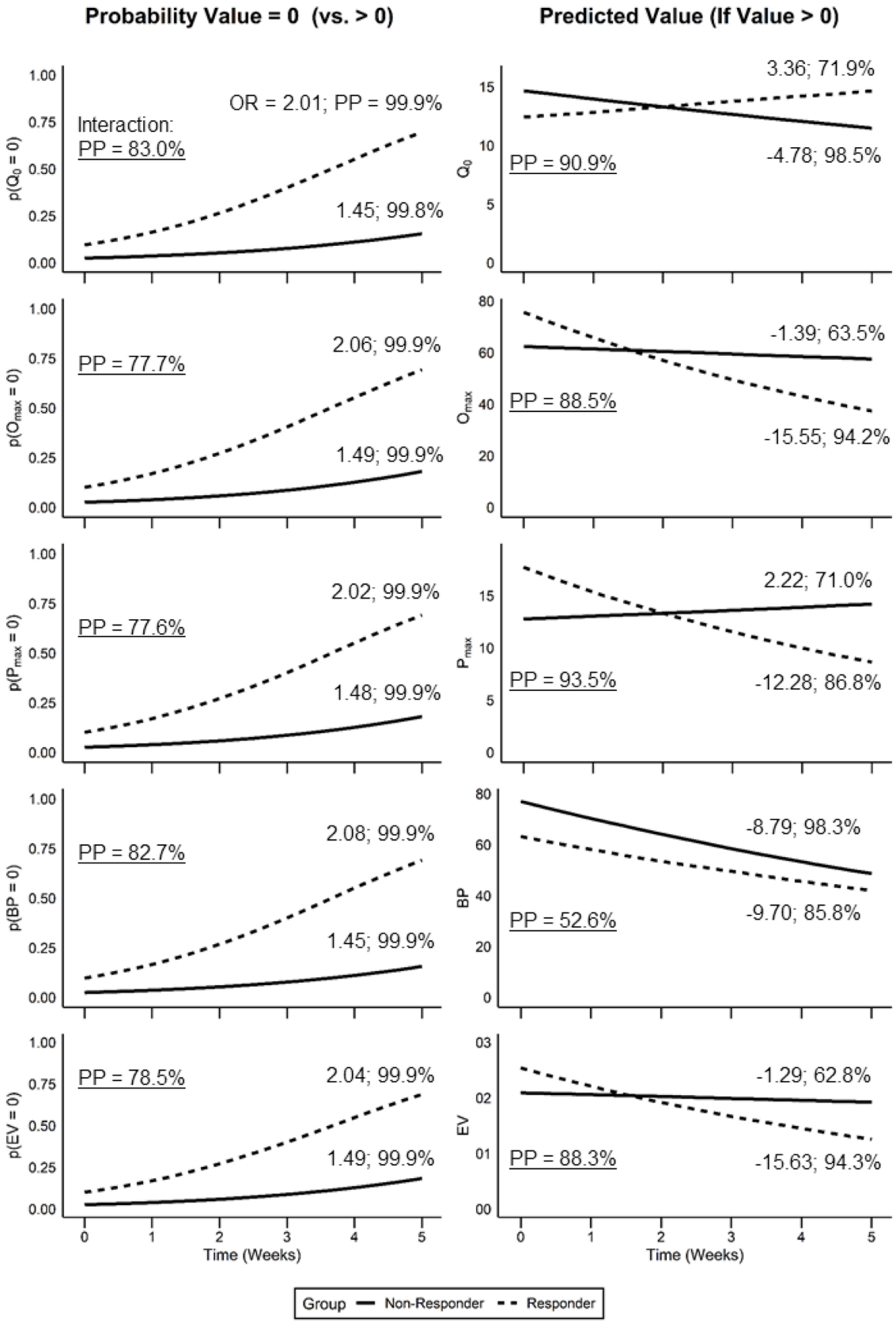

Fig. 2. Changes in cocaine demand for treatment responders (dashed curve) and non-responders (solid curve) over the course of CM treatment. Left panel illustrates the probability of presenting a zero value for Q_0, O_{max}, P_{max}, breakpoint, and essential value over the course of CM treatment. The right panel shows changes in positive, non-zero values for Q_0, O_{max}, P_{max}, breakpoint, and essential value over the course of CM treatment. Posterior probability (PP) of an interaction in change of demand characteristic over time between treatment responders and non-responders are presented on the left side of each figure and underlined. Odds ratios (OR) and PP for each individual curve are presented on the right of each figure next to their respective curve. Greater PP suggest the probability an effect is more likely in one direction with PP = 75 % indicating a 3 to 1 chance.

using a brief assessment of cocaine demand (Yoon et al., 2021). In that study, only 1 participant out of 22 (4.5 %) reported that they would consume as much as 50 rocks of cocaine over the weekend. Thus, anchoring questions may provide a relatively simple way to improve the accuracy of participants' responses to the CocPT.

Indices of demand were significantly associated with various self-report measures of cocaine use. Specifically, all demand indices except for O_{max} were associated with relatively recent measures of cocaine use (i.e., KMSK 30 total scores, KMSK 30 average amount of money spent on cocaine). Additionally, Q_0 and essential value were also significantly associated with KMKSK Lifetime total scores and KMSK Lifetime most amount of money spent on cocaine in a single incidence. Our results are largely congruent with previously reported findings. Strickland et al. (2016b), observed significant associations with Q_0 and both weekly and lifetime cocaine use. However, α was not significantly associated with either measure of cocaine use. Bruner and Johnson (2014), observed significant associations across α, O_{max}, and P_{max} with daily money spent on cocaine and units of cocaine used daily.

The current study directly builds on our previous findings in which we observed baseline cocaine demand was significantly associated with being a CM treatment responder vs. non-responder (Yoon et al., 2020c). Here, we extend these finding by demonstrating changes in cocaine demand over time differs between CM responders and non-responders. As hypothesized, cocaine demand decreased over time for both groups, but the magnitude of change was generally greater among CM responders. Specifically, the probability of being a zero-responder was greater for treatment responders across all demand indices (i.e., Q_0, O_{max}, P_{max}, breakpoint, and essential value). Similarly, among non-zero responder data, decreases in O_{max}, P_{max}, and essential value were greater among CM responders compared to non-responders.

To the best of our knowledge, only four prior studies have observed longitudinal changes in drug demand in the context of a brief behavioral intervention for alcohol (Murphy et al., 2015), varenicline for cigarettes (McClure et al., 2013; Schlienz et al., 2014), and during opioid treatment in a convenience sample of patients (Schwartz et al., 2021). The current study systematically extends these findings and generalizes them to both a novel drug (i.e., cocaine) and intervention (i.e., CM). Drug demand assessments may be particularly useful in the context of CM interventions by identifying individuals at greater relapse risk and provide a measure tracking changes in individual cocaine abuse liability to better inform changes in CM treatment. For example, a closer examination of Fig. 1 shows that the group demand curves based on average consumption values for non-responders at week 5 was comparable to the group demand curve for responders observed at baseline. Likewise, the proportion of zero-responders at week 5 (20.4 %) in the non-responder group was comparable to that of responders at baseline (15.0 %). These data beg the question as to whether continuing CM treatment for non-responders could eventually produce results similar to those observed for responders in regards to cocaine abstinence and cocaine demand.

The current study had a number of limitations. First, the sample size is relatively small particularly in regards to the proportion of treatment responders. The CM schedule utilized in the current study was based on a previous trial by our group that also utilized a 4-week abstinence-induction phase with high magnitude CM (Schmitz et al., 2014) and reported a slightly higher response rate (33 %). Nevertheless, the low response rate reflects the challenge of achieving initial cessation of cocaine use in severe users, as has been noted in the literature (c.f., Moran et al., 2017) and may reflect the severity of cocaine use in our population. A second potential limitation inherent in hypothetical purchasing tasks is that participants' reports may not mirror real word drug consumption, and this is likely true in the current study where individuals reported they would consume fairly high amounts of cocaine. However, a growing body of research has supported the utility of hypothetical purchasing tasks with purchasing tasks predicting drug use, cue reactivity, convergence with established clinical assessments, and reliability over time (for a review see Roma et al., 2017). Third, an important limitation of the present manuscript is that, despite having longitudinal data, it is not possible to establish causality in the demand-response relationship. Such an evaluation would require a minimum of three measurement points to establish temporal precedence in a mediation model.

In summary, this is the first study to assess changes in cocaine demand among treatment-seeking individuals receiving CM for CUD. Our findings suggest that cocaine demand changes over time, in relation with response to treatment. The malleability of demand has implications for adapting reward-based treatment interventions to improve response rates.

Author disclosures

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Contributors

Jin Yoon developed the original study question, conducted preliminary data analyses, and wrote the initial draft of the manuscript. Robert Sucthing was primarily responsible for all statistical analyses and descriptions in the current manuscript. Constanaza de Dios provided secondary statistical support. Jessica Vincent and Sarah McKay were responsible for conducting study-related assessments and initial data organization and entry. Scott Lane and Joy Schmitz provided feedback and guidance to the original study design and manuscript development. Joy Schmitz is also the primary investigator overseeing the parent trial in which the current study was conducted. All authors have had the opportunity to review and approve the final article.

Declaration of Competing Interest

The authors report no declarations of interest.

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