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Effects of varenicline on subjective craving and relative reinforcing value of cigarettes

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ABSTRACT

Background: Varenicline is an FDA approved medication for the treatment of nicotine dependence. While the efficacy and safety of this medication have been demonstrated, success rates remain low, and efforts to understand mechanisms of efficacy are in progress. A behavioral economics framework is one unique way to examine how demand for a drug changes under different circumstances. Therefore, the current randomized placebo-controlled, cross-over study aimed to examine effects of varenicline on subjective cigarette craving and objective demand for cigarettes measured by a hypothetical behavioral economic task as well as associations between subjective craving and objective demand.

Method: Non-treatment seeking (n = 37) daily smokers (> 10 cigarettes per day) completed a measure of subjective craving for cigarettes and the Cigarette Purchase Task following overnight nicotine abstinence. Participants completed these measures after 10 days on varenicline (1 mg twice per day) and matched placebo.

Results: Analyses revealed a significant reduction in subjective craving for cigarettes while on varenicline ($p = 0.01$), as compared to placebo, and a sex effect such that females exhibited greater craving than males ($p = 0.03$). However, there were no medication × sex effects ($p = 0.84$). Analyses of objective demand for cigarettes found varenicline reduced maximum expenditure (Omax) ($p = 0.03$). Subjective craving was also associated with various indices of demand.

Conclusion: Results demonstrated varenicline's efficacy in attenuating subjective craving and objective demand for cigarettes and highlight the partial overlap between dimensions of acute drug motivation, namely subjective craving and behavioral economic indices of cigarette demand.

1. Introduction

The 2015 National Health Interview Survey (NHIS) indicated that 68% of adult smokers reported wanting to quit smoking; however, only 31% of those smokers wishing to quit were using some form of cessation counseling and/or medication (Babb et al., 2017). A recent review of pharmacotherapy for smoking cessation revealed that varenicline increased the chances of smoking cessation two- to three-fold in comparison to an unaided quit attempt (Cahill et al., 2016). While forms of nicotine replacement therapy (NRT; i.e., nicotine patch, gum, lozenges) are more often used (Babb et al., 2017), varenicline has demonstrated greater efficacy than single forms of NRT (Cahill et al., 2013). Varenicline is a high affinity, partial agonist, at the α4β2 nicotinic acetylcholine receptor (nAChR) subtype and was approved in 2006 by the FDA for the treatment of nicotine dependence. Clinical trials have established this pharmacotherapy as a safe and efficacious smoking cessation aid (Jorenby et al., 2006; Oncken et al., 2006; Tonstad et al., 2006). Varenicline is proposed to have a dual mechanism of action through reducing withdrawal symptoms associated with smoking cessation, along with subjective rewarding effects following a smoking relapse (Jimenez-Ruiz et al., 2009). To that end, Patterson et al. (2009) demonstrated reduced withdrawal symptoms and urges to smoke across three days of smoking abstinence, as well reduced subjective reward following a programmed smoking lapse for participants who received placebo prior to varenicline.

Despite evidence supporting the clinical efficacy of varenicline, efforts to further characterize the mechanisms through which varenicline exerts its clinical effects are still ongoing. Considering the success rates with varenicline range from only 20% to 40%, Littlewood et al. (2017) examined individual differences affecting the efficacy of varenicline and found a variety of dispositional and psychological factors such as impulsivity, past major depressive episode, and agreeableness, to differentially effect varenicline's efficacy. Another area worthy of additional examination falls under the realm of craving for cigarettes.

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Subjective craving for cigarettes is a robust determinant of smoking (Berkman et al., 2011; Shiffman et al., 1997; Willner et al., 1995). Craving in the context of smoking has previously been defined as "repeated and persistent urges to smoke and feelings of need for a cigarette" (West et al., 2008). In an examination of time-varying processes contributing to a smoking lapse, subjective craving remained a significant predictor of smoking two weeks following a TQD (Vasilenko et al., 2014). Following overnight abstinence, varenicline has also been shown to reduce tonic and cue-provoked craving, as well as the subjective expected value of cigarettes and perceived reward from smoking (Brandon et al., 2011). An examination of craving utilizing a novel form of ecological momentary assessment via text messaging found the craving prior to smoking mediated the effect of mood prior to smoking on current smoking behavior (Berkman et al., 2011). These studies underscore the importance of subjective craving in perpetuating smoking behavior and plausible target by which varenicline may exert its clinical effects.

One unique approach to further understand factors contributing to varenicline's clinical efficacy consists of the behavioral economics framework. From this perspective, drug use is determined in part by the availability of the drug and availability of non-drug reinforcers (Bickel et al., 1998). A key concept behind behavioral economic theory is Relative Reinforcing Efficacy (RRE); this concept is a more general property of behavior that consists of the heterogeneous phenomena related to the strengthening aspects of reinforcement (Bickel et al., 2000). The RRE of a drug is not fixed, rather it has been shown to vary in the presence of biological and external factors (Stafford et al., 1998). The unit of analysis under this framework is demand for the drug, defined as the quantity of a drug consumed at a given price, from which a demand curve can be generated to quantitatively represent the relationship between drug consumption and price of the drug (Hursh et al., 2005). Five indices of demand are generated from a demand curve analysis: Intensity (consumption at zero cost), Omax (maximum expenditure), Pmax (maximum inelastic price; i.e. price at which Omax is reached), Breakpoint (first point at which consumption is suppressed to zero), and Elasticity (overall slope of the demand curve, equivalent to degree to which consumption decreases with increases in price). While these indices are inherently related as they represent various parts of the overall demand curve, and provide further support for conceptualizing RRE as a heterogeneous concept (Bickel et al., 2000). The present study will contribute to the literature by integrating behavioral economic indices with subjective craving measures and by testing varenicline effects on both.

Previous studies have applied behavioral economics to the field of addiction, including cigarettes (MacKillop et al., 2012; MacKillop et al., 2008), alcohol (Bujarski et al., 2012; Murphy and MacKillop, 2006; Murphy et al., 2009), and marijuana (Aston et al., 2016) to assess how demand for a drug changes across a variety of contexts. Laboratory studies have shown nicotine deprivation to increase the first point at which consumption is suppressed to zero (Breakpoint) and maximum inelastic price (Pmax), while tobacco cues have been shown to decrease elasticity reflecting a decreased sensitivity to the price of cigarettes (MacKillop et al., 2012). Three studies to date have examined the effects of varenicline on demand for cigarettes. Following one-week of varenicline, McClure et al. (2013) observed an increase in elasticity amongst smokes contemplating a quit attempt, reflecting reduced cigarette purchases at higher prices. In an examination of pre-cessation varenicline on demand in a sample of treatment-seeking smokers, elasticity was again found to increase and intensity decrease over a four-week period; however, these changes did not differ between the active varenicline and placebo groups (Schlienz et al., 2014). A recent examination of varenicline versus transdermal NRT on cigarette demand found reductions in intensity and breakpoint from baseline to scheduled quit day following one-week of varenicline; however, these reductions did not differ by medication (Murphy et al., 2017). Interestingly, reduced intensity predicted abstinence at 1-month and 3-month follow-up whereas breakpoint only predicted 1-month follow-up abstinence (Murphy et al., 2017). Collectively, these studies demonstrate natural reductions in demand over time; however, the effect of varenicline over and above placebo or NRT remains inconsistent.

In summary, the experimental literature thus far has supported the effects of varenicline on subjective craving; however, the effects of varenicline on indices of demand for cigarettes remain variable. Nevertheless, few studies to date have integrated these two dimensions of acute drug motivation with regard to the biobehavioral effects of varenicline, which is arguably one of the important benefits of a behavioral economic approach (MacKillop et al., 2012). This study aims to replicate previous studies by demonstrating varenicline to exert an effect on objective demand for cigarettes, delineate which indices of demand varenicline exerts an effect upon, and how these effects may influence varenicline's clinical efficacy. To advance the literature on the mechanisms of varenicline effects for smoking cessation, this study aims to elucidate the effects of varenicline on (a) subjective craving and (b) demand for cigarettes following overnight abstinence. This was a placebo-controlled, cross-over study of non-treatment seeking daily smokers. We also aimed to examine the relationship between subjective craving and objective demand for cigarettes, as assessed by a hypothetical behavioral economic cigarette purchase task. It was hypothesized that compared to placebo, varenicline (1 mg/bid) would (1) reduce subject craving in the context of a 12-hr abstinence period, (2) reduce demand for cigarettes following the 12-hr period of nicotine abstinence, and (3) subjective craving would be strongly associated with demand for cigarettes, although not entirely overlapping.

2. Method

2.1. Participants and screening procedures

The study was approved by the Institutional Review Board of the University of California Los Angeles. Participants were recruited from the greater Los Angeles area and consisted of a final sample of 40 non-treatment seeking daily smokers (> 10 cigarettes per day) between the ages of 18 and 55. Participants were ineligible for the following: (1) more than 3 months of smoking abstinence; (2) > 14 drinks per week for or > 5 drinks per occasion once per month for men, and > 7 drinks per week or > 4 drinks per occasion once per month for women; or (3) self-reported use of methamphetamine, heroin, cocaine, or other illicit drugs (excluding marijuana) in the past 60 days (verified by urine toxicology screen); (4) self-reported symptoms of moderate depression indicated by a score > 20 on the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996); (5) self-reported current feelings of active suicidality indicated by a score > 2 on the suicidal ideation item of the BDI-II; (6) lifetime history of psychotic disorders, bipolar disorder, or major depression with suicidal ideation as assessed by the Structured Clinical Interview for DSM-IV (SCID-IV); (7) currently taking insulin or oral hypoglycemic medication; (8) serious medical illness at time of physical exam and laboratory tests; and (9) pregnancy verified by urine pregnancy screen.

Participants completed a telephone screening and in-person screening visit. Urine cotinine test were used to verify self-reported regular smoking (> 100 ng/mL of cotinine). Urine toxicology screen was used to verify self-reported drug use. Participants were excluded if they tested positive for any drugs besides marijuana. Eligible participants based on the in-person screening visit were then invited to a medical screening visit. If eligible following medical screening visit, participants were randomized to the study. See Fig. 1 for detailed study enrollment.

2.2. Experimental procedures

Participants were randomized to receive the first study medication (placebo or varenicline) for a total of 10 days. On medication day 10,

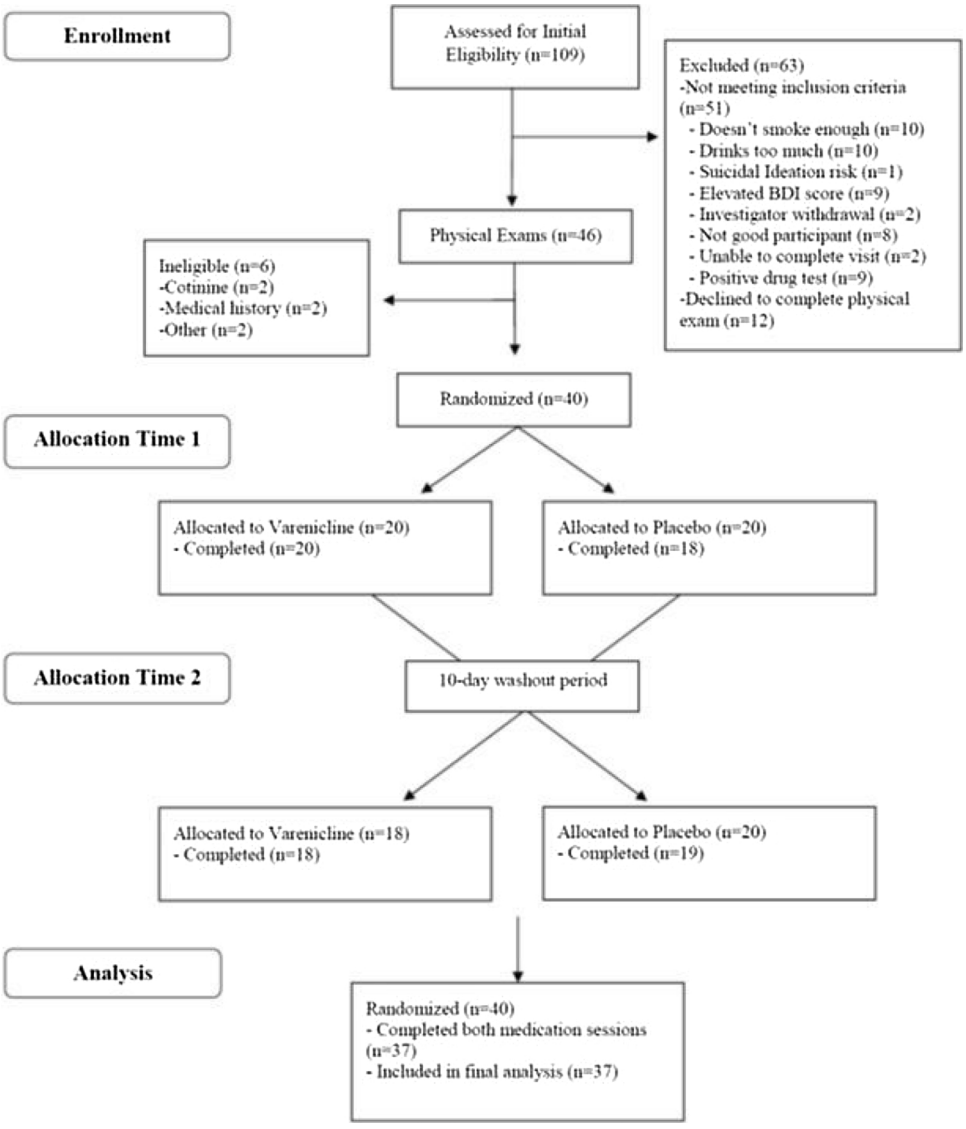

Fig. 1. Recruitment and enrollment information.

participants completed the first laboratory experimental session. Following the first session, participants were given the second study medication (placebo or varenicline) for a total of 10 days. On medication day 10, participants completed the second laboratory experimental session. We considered the washout period to be the time between their first and second experimental session while they were taking the second medication. Participants averaged 12.27 (SD = 2.16, Range = 10–19) days between each medication condition. During all visits, participants were required to produce a breath alcohol concentration (BrAC) of 0.000 g/dl on the breathalyzer. Participants were asked to abstain from alcohol for 24 h and abstain from smoking for 12 h prior to each experimental session. Overnight abstinence from nicotine was verified by expired carbon monoxide levels of less than 10 ppm (or below 50% of initial baseline value). A total of 40 participants were randomized to the study. Of the 40 participants randomized, 2 did not return for their first experimental session, and 1 participant only completed one experimental session, resulting in 3 individuals without data for both experimental sessions. A final total of 37 participants with complete data for both varenicline and placebo sessions were used in the analyses.

2.3. Study medication

In line with FDA regulations, participants underwent a titration schedule as follows: days 1–3, 0.5 mg once per day; days 4–7, 0.5 mg twice per day; days 8–10, 1 mg twice per day. Placebo pills matched packaging of active medication and number of pills. All study medication was packaged in opaque capsules with 50 mg of riboflavin (B2). Pill counts were taken on medication day 10. To verify participants were taking the medication, a urine sample was collected on medication day 10 and was tested for riboflavin content by examining it under an ultraviolet light. Participants were given a 24-h telephone number to call and discuss any medication side effects with the study physician. Results of an examination of the medication blind and side effects are summarized in the primary paper from this study (Ray et al., 2013). An examination of the medication blind showed that 84% correctly guessed they were on placebo while receiving placebo and 58% guessed they were on varenicline while receiving varenicline. In regard to side effects, the 24-item SAFTEE was used to assess for possible side effects from each medication. Results indicated a significant difference in night sweats, such that more participants had night sweats while on varenicline than placebo (Fisher's exact test, $p < 0.05$).

2.4. Measures

The following individual difference measures were collected during the study: (a) demographics questionnaire to gather data on age, sex,

Table 1
Tobacco Craving Scale (TCS) Items.

Item
1. I have a desire for a cigarette right now.
2. I feel unhappy.
3. If it were possible, I would smoke now.
4. All I want right now is a cigarette.
5. I have an urge for a cigarette.
6. I crave a cigarette right now.
7. It would be difficult to turn down a puff of one of my cigarettes right now.
8. I need to have a puff of one my cigarettes right now.
9. If I was offered a cigarette, it would be difficult not to smoke one right now.
10. If I was offered a cigarette, I would have a puff of one right now.

ethnicity, education, marital status, and income; (b) the BDI-II administered at initial in-person screening visit to exclude for moderate to severe depression or suicidality; (c) Time-Line Follow-Back (TLFB; Sobell et al., 1986)to assess for frequency and quantity of alcohol and smoking use over the past 30 days; (d) Smoking History Questionnaire to collect history of smoking behavior and previous quit attempts; (e) Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991) to assess for nicotine dependence; and (f) Wisconsin Smoking Withdrawal Scale (WSWS; Welsch et al., 1999). Characteristics for randomized (i.e., enrolled) participants are presented in Table 2. Notably, participants had a mean FTND score of 4.11 (SD = 1.70) indicating low to moderate nicotine dependence, and a mean BDI-II score of 6.76 (SD = 6.47) suggesting minimal symptoms of depression.

2.4.1. Subjective cigarette craving and nicotine withdrawal

During the experimental session, the subjective craving was assessed via the Tobacco Craving Scale (TCS). The TCS is an 11-item measure with high internal consistency (Cronbach's alpha = 0.95–0.98). Items from this scale are listed in Table 1.

2.4.2. Behavioral economics indices

Behavioral economic indices were assessed utilizing the Cigarette Purchase Task (CPT)(MacKillop et al., 2012; MacKillop et al., 2008). During this task, participants were provided with the following instructions: "Imagine a typical day during which you smoke. How many cigarettes would you smoke at the following prices? The available cigarettes are your favorite brand. Assume that you have the same income/savings that you have now and no access to any cigarettes or nicotine products other than those offered at these prices. In addition, assume that you would consume cigarettes that you request on that day; that is, you cannot save or stockpile cigarettes for a later date". The 25 specific prices included were: $0.00, $0.05, $0.10, $0.15, $0.20, $0.25, $0.30, $0.35, $0.40, $0.45, $0.50, $0.60, $0.70, $0.80, $0.90, $1.00, $1.20, $1.40, $1.60, $1.80, $2.00, $4.00, $6.00, $8.00, $10.00. Intensity, Omax, Pmax, and Breakpoint were derived from observed values on the CPT (Murphy and MacKillop, 2006). Elasticity was derived using Hursh and Silberg's (Hursh and Silberberg, 2008) exponentiated demand equation for demand curve analysis:

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

where Q = consumption at a given price, Q_0 = consumption at zero price, k = constant parameter reflecting the range of consumption values in $\log_{10}$ units and was set at 2 in this sample, α = derived demand parameter reflecting the rate of consumption decline associated with increasing price, and C = the price of the cigarette. This exponentiated demand equation is the preferred equation to fit consumption data across a range of prices as it fits unaltered demand functions with values of zero and results in nearly identical fits when the values of zero are deleted or replaced with small non-zero values (Koffarnus et al., 2015).

Table 2
Sample Characteristics.

Variable[a]	Male (n = 25)	Female (n = 12)	Test for Difference
Age	37.84 (11.03)	33.92 (8.06)	$t(35) = 1.10$, $p = 0.28$
Ethnicity			Fisher's exact test $p = 0.95$
Caucasian	8	4	
African American	9	4	
Asian	1	0	
Latino	1	0	
Multi-Ethnic	5	4	
Other	1	0	
Age of First Cigarette	17.28 (5.03)	14.25 (3.52)	$t(35) = 1.87$, $p = 0.07$
Smoking Days[b,c]	29.92 (0.28)	30.0	$t(24) = -1.44$, $p = 0.16$
Cigarettes per Smoking Day[b]	15.11 (5.63)	14.06 (4.70)	$t(35) = 0.56$, $p = 0.58$
Smoking Day[b]			
FTND	4.52 (2.00)	4.91 (2.07)	$t(35) = -0.56$, $p = 0.58$
BDI-II	7.12 (6.52)	6.0 (6.59)	$t(35) = 0.49$, $p = 0.63$

[a] Standard deviation appear within parentheses for continuous variables.
[b] Assessed by the Timeline Follow Back (TLFB) Interview.
[c] Assumption of homogeneity of variance not met, adjusted degrees of freedom, *t*-statistic, and significance level accounted for within table.

2.5. Data analytic plan

Analyses were conducted using a multilevel framework in SAS using PROC MIXED version 9.4 (Singer, 1998). Analyses examined the effects of *Medication*, a two-level within-subjects factor (placebo vs. varenicline, coded 0 and 1), *Sex,* a two-level between-subjects factor (male vs. female, coded 0 and 1), and their *interactions*. Effects of sex and their interactions with medication were examined due to a recent meta-analysis demonstrating varenicline to have greater efficacy in females for short-term smoking cessation outcomes (McKee et al., 2016). The dependent variables were subject craving for cigarettes (TCS) and the following behavioral economic indices (CPT): Intensity, Omax, Breakpoint, Pmax, and Elasticity. Prior to the primary analyses for the CPT, invariant responding across the task and outliers (z-score cut off 3.29) were identified and removed from the analysis (MacKillop et al., 2012). Intensity, Breakpoint, Pmax, and Elasticity were log transformed for normality. In all Mixed models, medication order and whether participants correctly guessed which medication they were receiving were added as covariates. These covariates did not change the significance of the primary variables of interest and thus were excluded in the final models. Additionally, bivariate correlations were computed to examine the association between subject craving, nicotine withdrawal, and behavioral economic indices. An average score across medication conditions was calculated for subjective craving, nicotine withdrawal, and all behavioral economic indices. These values were then used in the bivariate correlation analyses.

3. Results

3.1. Subjective craving (TCS)

Consistent with the study hypotheses, varenicline significantly decreased the subjective craving for cigarettes, compared to placebo ($b = -1.43$, SE = 0.54, $p = 0.01$). See Fig. 2. In addition, there was a significant sex effect, such that females exhibited greater craving for cigarettes than males ($b = 1.85$, SE = 0.81, $p = 0.03$) No significant medication × sex interaction was observed ($p = 0.83$).

3.2. Behavioral economic indices (CPT)

Demand curves representing hypothetical consumption of cigarettes

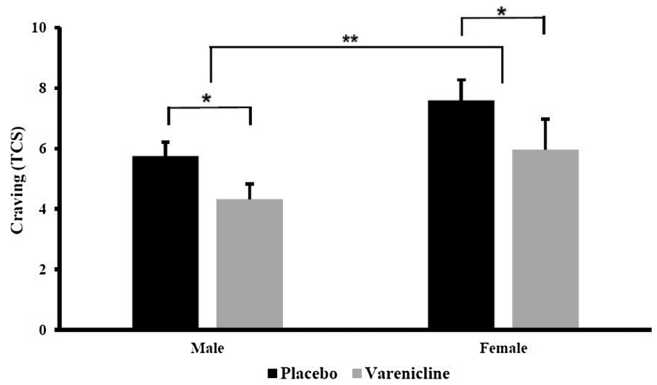

Fig. 2. Craving scores (tobacco craving scale (TCS)) following 10 days of placebo and varenicline. Analyses revealed a significant medication effect such that varenicline decreased subjective craving, and a sex effect such that females exhibited greater craving.
*$p \leq 0.05$, ** $p \leq 0.01$.

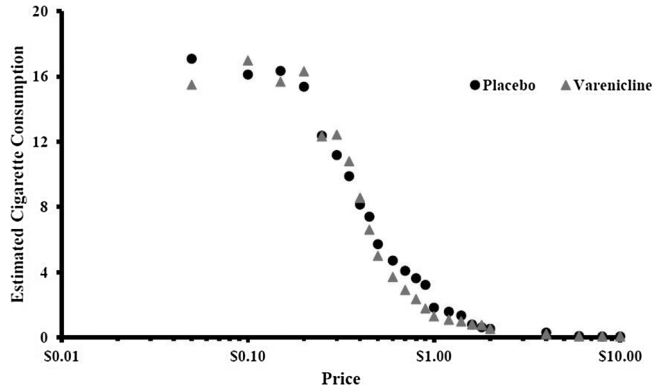

Fig. 3. Demand curve for number of cigarettes purchased on the Cigarette Purchase Task (CPT) while on varenicline and placebo. Log-log coordinates are used for proportionality. Intensity is not depicted as values of zero cannot be displayed on a log–log axis.

across a range of prices is presented in Fig. 3. There was a significant effect of varenicline, versus placebo, on Omax, such that varenicline reduced maximum expenditure ($b = -1.49$, SE = 0.66, $p = 0.03$). There were no significant effects of varenicline, versus placebo, on Intensity ($b = -0.25$, SE = 0.15, $p = 0.11$), Pmax ($b = -0.02$, SE = 0.19, $p = 0.90$), Breakpoint ($b = -0.15$, SE = 0.18, $p = 0.43$), or Elasticity ($b = 0.24$, SE = 0.16, $p = 0.13$). There were no significant sex effects (p's > 0.05) or medication × sex interactions (p's > 0.05).

3.3. Correlations between subjective craving, nicotine withdrawal, and behavioral economic indices

Bivariate correlations between subjective craving, nicotine withdrawal, and behavioral economic indices are presented in Table 3. Subjective craving was significantly and positively correlated with nicotine withdrawal, along with Omax and Breakpoint (p's < 0.05). There was a significant negative correlation between subject craving and Elasticity ($r = -0.41$, $p = 0.01$), such that increased craving was associated with less sensitivity to increasing price. Nicotine withdrawal was significantly correlated intensity ($r = 0.39$) reflecting an association between greater withdrawal and unlimited cigarette consumption. Nicotine withdrawal was not significantly correlated with any other demand indices (p's > 0.05). All behavioral economic indices were correlated with each other, apart from Intensity and Breakpoint ($p = 0.16$) and Intensity and Pmax ($p = 0.56$).

Table 3
Pearson correlations among subjective craving (TCS), nicotine withdrawal (WSWS), and behavioral economic indices (CPT) averaged across medication conditions.

	1.	2.	3.	4.	5.	6.
1. TCS	1.00					
2. MNWS	0.54***	1.00				
3. Intensity†	0.32	0.39*	1.00			
4. BP†	0.40*	0.08	0.25	1.00		
5. Omax	0.42**	0.27	0.55***	0.60***	1.00	
6. Pmax†	0.33*	0.20	0.10	0.76***	0.49**	1.00
7. Elasticity†	−0.41**	−0.14	−0.62***	−0.71***	−0.84***	−0.50**

† Log transformed for normality.
* $p \leq 0.05$.
** $p \leq 0.01$.
*** $p \leq 0.001$.

4. Discussion

This study aimed to examine the effects of varenicline on subjective craving for cigarettes and demand for cigarettes, assessed through a hypothetical cigarette purchase task, in a sample of non-treatment seeking smokers undergoing testing following overnight abstinence. As hypothesized, varenicline reduced self-reported subjective craving for cigarettes, compared to placebo. Females reported greater subjective craving than males, but there were no significant sex interactions with regard to medication. In other words, varenicline was equally effective at reducing subjective craving in males and females in our study. In addition, varenicline attenuated demand for cigarettes, as compared to placebo. Specifically, varenicline administration was associated with reduced maximum expenditure (Omax) for cigarettes, compared to the placebo condition. There were no significant effects of varenicline on cigarette consumption at no cost (Intensity), price associated with Omax (Pmax), first price suppressing consumption to zero (Breakpoint), or the overall slope of the demand curve (Elasticity). These results align with previous reports of the effects of varenicline reducing overall subjective craving for cigarettes (Brandon et al., 2011; West et al., 2008). This is also one of the few studies to examine the effects of varenicline on demand for cigarettes using the highly validated Cigarette Purchase Task (CPT), an analog for behavioral economic decision making. Consistent with previous research using behavioral economics to detect medication effects, varenicline did not exert a significant effect on intensity(McClure et al., 2013; Schlienz et al., 2014). Intensity of demand for cigarettes has not been shown to vary in the presence of bupropion either(Madden and Kalman, 2010), suggesting that unrestricted cigarette consumption may be less sensitive to the effects of pharmacotherapy. A recent study found no difference between varenicline and NRT on breakpoint (Murphy et al., 2017), and the present study adds to that literature by demonstrating no difference between varenicline and placebo on this index. Mixed results have been reported in terms of varenicline's effect on elasticity (McClure et al., 2013; Schlienz et al., 2014). The present study found no effect of varenicline on overall sensitivity to increasing price, however we did find a significant effect of varenicline on maximum expenditure for cigarettes which has not been demonstrated previously. The clinical implications are such that varenicline may not reduce the unrestricted expenditure on cigarettes (i.e. intensity) or how sensitive the individual is to increasing prices in alcohol (i.e. elasticity), however varenicline may reduce the maximum amount an individual is willing to spend on cigarettes (i.e. Omax). This particular behavioral economic index has been associated with treatment outcomes in the context of alcohol use (MacKillop and Murphy, 2007). Thus, reductions in the maximum amount individuals are willing to spend on cigarettes may serve as one behavioral mechanism through which varenicline exerts its clinical effects. In sum, these results align with previous studies demonstrating

the efficacy of varenicline to be limited to certain behavioral economic indices, as opposed to have widespread effects on all indices of demand.

A secondary aim of this study was to examine associations between subjective craving, indices of demand for cigarettes, and nicotine withdrawal. As expected, the subjective craving was correlated with greater nicotine withdrawal. Subjective craving was also positively correlated with Omax, Pmax, and Breakpoint, such that greater subjective craving was associated with greater maximum expenditure, the greater price associated with maximum expenditure, and price suppressing consumption to zero. Elasticity was negatively correlated with subjective craving and in the expected direction, as subjective craving increased an individual's sensitivity to the increasing price of cigarettes decreases. Nicotine withdrawal was found to only significantly correlate with intensity, such that greater withdrawal was associated with greater unrestricted cigarette consumption. Taken together, this pattern of correlations suggested strong overall associations between behavioral economic indices of demand and subjective craving for cigarettes, then between demand and nicotine withdrawal. These results highlight the multidimensional nature of acute drug motivation (MacKillop et al., 2012), such that each domain of motivation need not overlap entirely.

In interpreting these findings, it is important to note that this is the first study to examine varenicline effects on demand for cigarettes, assessed via CPT, in a sample of non-treatment seeking smokers. Greater intrinsic motivation to change has been associated with improved abstinence outcomes (Curry et al., 1990; Curry et al., 1997; Perkins, 2014). If non-treatment seeking smokers are experiencing alterations in their demand for cigarettes following varenicline, it is plausible that in a sample of treatment-seeking smokers, with presumably greater internal motivation to change, these effects may increase. Another condition under which we may see alterations in demand for cigarettes may depend on how a smoker metabolizes nicotine. In efforts to further personalize medicine, the inclusion of biomarkers has proven beneficial in determining which medication an individual may best respond to. An individual's nicotine metabolite ratio (NMR), an indicator of the primary cotinine-and-nicotine-metabolizing enzyme CYP2A6 has been shown to alter an individual's response to smoking cessation medication such that varenicline is more effective in normal metabolizers while nicotine-replacement therapy is more effective in slow metabolizers (Lerman et al., 2015). While CYP216 was not collected during the present study, we speculate that varenicline effects on demand for cigarettes may increase for smokers that are normal nicotine metabolizers.

The present study should be interpreted in light of its strengths and limitations. Strengths include the crossover design with double-blind randomization, as well as high medication compliance rates. Limitations include the relatively small sample size and lack of baseline cigarette purchase task data for comparison in a deprivation state. It is also possible that our results reflect Type 1 error. Despite these limitations, the present study does provide additional evidence in supporting the efficacy of varenicline by demonstrating its ability to alter subjective and objective demand for cigarettes.

In conclusion, this experimental study provides additional evidence in support of the efficacy of varenicline, compared to placebo, as an anti-craving agent and one that can attenuate demand for cigarettes. While varenicline only attenuated one of the five indices of demand examined, the index varenicline did affect (Omax) has been shown to predict treatment outcomes. Importantly, analyses of the association between indices of demand for cigarettes and subjective craving suggest a strong, but not complete, overlap between these dimensions of drug motivation. The sample of non-treatment seekers undergoing overnight abstinence allowed us to extend the literature beyond the treatment-seeking context and to effectively integrate constructs of subjective craving and behavioral economic indices, which thus far have not been extensively examined in tandem. Together, these results suggest that varenicline may exert its clinical effects by reducing subjective craving and demand for cigarettes and that these effects are observable even in non-treatment seeking samples. Future studies should extend the clinical significance of these mechanisms by testing whether reductions in subjective craving and demand for nicotine predict subsequent quit attempt success with varenicline.

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Contributors

RG conceptualized the manuscript, undertook the statistical analysis, and wrote the first draft of the manuscript. LR designed the original study, obtained funding for the experiment, and contributed to writing the manuscript and its conceptualization. All authors have approved the final manuscript.

Conflict of interest

LAR receives study medication from Pfizer and Medicinova. None of the authors have any other conflicts of interest to disclose.

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