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The impact of pre-cessation varenicline on behavioral economic indices of smoking reinforcement

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HIGHLIGHTS

- We examined the effect of varenicline using behavioral economic demand parameters.
- Treatment-seeking smokers were randomized to receive varenicline or placebo.
- A hypothetical cigarette purchase task was administered in the natural environment.
- Varenicline did not reduce behavioral economic indices of smoking reinforcement.

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ABSTRACT

Background: Varenicline was developed to aid smoking cessation by reducing smoking reinforcement. The present study tests this reinforcement–reduction hypothesis among smokers preparing to quit.
Method: After a one-week baseline, treatment-seeking smokers were randomized to receive three weeks of varenicline or placebo (Weeks 2–4). During each of the four weeks of the study, smokers completed a hypothetical cigarette purchase task (CPT) via handheld devices in their natural environment. Behavioral economic measures of simulated smoking if cigarettes were free (demand intensity), sensitivity of consumption to increasing price (elasticity), and price at which purchases would drop to 0 (breakpoint) were estimated.
Results: The exponential demand equation fit the purchase task data well across subjects and time. As predicted, demand intensity decreased and sensitivity to price (elasticity) increased over time. However, changes in demand intensity did not differ by treatment group. Contrary to our hypothesis that varenicline would increase sensitivity to price, the placebo group tended to become more elastic in their purchases during Weeks 2 and 3; the groups did not differ in elasticity at Week 4. Breakpoint did not vary by group, time, or their interaction.
Conclusion: Simulated smoking demand can be validly assessed in the natural environment of treatment-seeking smokers. Simulated demand indices of smoking reinforcement diminished as smokers approached their target quit date. However, there was no evidence that varenicline facilitated these changes over a three-week period, leaving open the mechanisms by which varenicline reduces smoking rate prior to cessation and improves long-term abstinence.

1. Introduction

Varenicline is an α4β2 nicotinic acetylcholine receptor (nAChR) partial agonist that was designed to attenuate the reinforcing effects of smoking. Consistent with a reinforcement–reduction mechanism, pre–clinical work has documented that varenicline decreases the degree to which rats will work (bar press) to obtain nicotine (Coe et al., 2005; Levin et al., 2012; Rollema et al., 2007).

In humans, several approaches have been taken to test the reinforcement–reduction hypothesis. Retrospective data from clinical trials suggest that varenicline decreases smoking satisfaction during post-quit lapses (for review see Cahill, Stead, & Lancaster, 2012), and lab studies have reported a similar effect on subjective smoking satisfaction (Brandon et al., 2011; Patterson et al., 2009). In terms of smoking behavior, varenicline reduces the number of cigarettes smoked per day (and corresponding biochemical indices of smoking) in non-treatment-seeking smokers (e.g., Ashare et al., 2012; Poling, Rounsaville, Gonsai, Severino, & Sofuoglu, 2010), heavy drinking smokers (Fucito et al., 2011), and in two small randomized clinical trials (Hajek, McRobbie, Myers, Stapleton, & Dhanji, 2011; Hawk et al., 2012).

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Interestingly, these studies demonstrate that the effect of varenicline on smoking rate becomes more pronounced over several weeks. Although varenicline-related decrements in smoking rate are consistent with a reinforcement–reduction (i.e., extinction) mechanism, conclusions about reinforcement would be strengthened by evidence from paradigms that more closely parallel the operant tasks employed in preclinical work.

In a typical operant lab task with humans, smokers must make repeated responses (e.g., mouse clicks) to earn cigarette puffs (Donny, Houtsmuller, & Stitzer, 2007; McClure, Vandrey, Johnson, & Stitzer, 2013; Perkins, Epstein, Grobe, & Fonte, 1994; Perkins, Grobe, & Fonte, 1997). A progressive ratio task increases the cost (number of responses required) of each successive puff (e.g., from 4 clicks for the first puff to 512 clicks for the eighth puff). These paradigms yield measures of reinforcing value that include the total number of responses, puffs earned, and breakpoint, which is defined as the response requirement at which the person will no longer respond to earn puffs. Using a progressive ratio task, McClure et al. (2013) found that the reinforcing value of smoking decreased over a one-week period preceding a practice quit attempt, but varenicline did not result in a greater decrease than did placebo. McClure et al. suggested that the need to engage in a practice quit attempt beginning the next day may have artificially suppressed operant responding in both groups, obscuring any effect of varenicline.

Complementing traditional behavioral studies of reinforcement, behavioral economic studies examine consumption as a function of price (for review see Bickel & Madden, 1999a; Bickel & Madden, 1999b; Heinz, Lilje, Kassel, & de Wit, 2012). Real-world behavioral economics can be extended to simulation paradigms in which participants indicate how much of a commodity they would purchase under varying price conditions (see Jacobs & Bickel, 1999). MacKillop et al.'s (2008) cigarette purchase task (CPT) takes this approach, asking participants to indicate the number of cigarettes they would purchase and consume in a 24-hour period across prices ranging from "free" to US $1120 per cigarette. The CPT data are used to estimate three parameters of a smoking demand curve (i.e., the consumption-price function; for review see Hursh & Silberberg, 2008). *Demand intensity* (Q_0), reflects the number of cigarettes "purchased" at zero price (i.e., "free"). *Demand elasticity* (α) quantifies the slope of the cigarette demand curve, or the sensitivity of consumption as a function of price (steeper slope = greater elasticity = less reinforcement). *Breakpoint* is computed as the first price that completely suppresses consumption. The reinforcement–reduction hypothesis predicts that varenicline will make cigarette purchases more sensitive to price as reflected in decreased demand intensity, increased demand elasticity, and/or a lower breakpoint.

The CPT has been increasingly used to examine smoking reinforcement (e.g., Bidwell, MacKillop, Murphy, Tidey, & Colby, 2012; MacKillop et al., 2008; Madden & Kalman, 2010) and to evaluate the potential impact of changes made to tobacco control policies (Mackillop et al., 2012; O'Connor, Bansal-Travers, Carter, & Cummings, 2012). In a recent clinical trial, Madden and Kalman (2010) found that greater increases in elasticity during the week prior to a quit attempt were associated with greater success in quitting. These data broadly support the predictive validity of the CPT; however, bupropion had no effect on CPT reinforcement parameters.

In McClure et al. (2013), participants completed both an operant paradigm (described above) and the CPT before and after one week of varenicline or placebo. In support of a reinforcement–reduction hypothesis, McClure et al. reported that elasticity was greater in the varenicline group compared to the placebo group at the second visit. However, the analytic framework in that paper differed from most other CPT studies by examining aggregate group-level curves (rather than individual curve-fitting values), an approach that also precluded a formal test of the group × time interaction and its effect size (E. McClure, personal communication, April 14, 2014). Thus, firm conclusions about the impact of varenicline on smoking reinforcement remain surprisingly tentative.

Informed by human operant laboratory paradigms, and guided by an interest in the application of ecological momentary assessment methodology to examine the effect of varenicline on smoking reinforcement, the current study analyzed behavioral economic reinforcement parameters derived from a hypothetical CPT, which was administered in the natural environments of treatment-seeking smokers preparing for a quit attempt.

1.1. The present study

The present study tested the reinforcement–reduction hypothesis for varenicline. Following a one-week baseline, treatment-seeking smokers were randomized to varenicline or placebo for three weeks prior to their target quit date (TQD). To enhance the ecological validity of the reinforcement data, the CPT was administered repeatedly across the four weeks via handheld devices during morning assessments in smokers' natural environments. We predicted that, relative to the placebo, varenicline would result in greater reductions in demand intensity and breakpoint, and a greater increase in demand elasticity (sensitivity to price).

2. Method

2.1. Participants

Participants were 60 adult treatment-seeking smokers enrolled in a randomized, two-group, double blind, placebo-controlled trial (see Hawk et al., 2012), conducted from March 2009 through April 2010. Participants that expressed a desire to quit smoking were recruited through local newspapers and flyers posted in the community that advertised a quit smoking study, and were screened by telephone to determine eligibility. Inclusion criteria included age 18–65 years, smoking at least 15 cigarettes per day (CPD) during the past year, and agreeing to refrain from using additional smoking cessation treatments (i.e., NRT) during the study. Exclusion criteria included self-reported serious medical condition(s) (e.g., diabetes, renal impairment, uncontrolled hypertension); current use of other tobacco products or smoking cessation aids; pregnancy or plans to become pregnant; depression requiring treatment in the past year; history of panic disorder, bipolar disorder, or psychosis; and a history of alcohol or substance abuse in the past year.

2.2. Study procedures

The Roswell Park Cancer Institute (RPCI) Institutional Review Board approved all study procedures.

2.2.1. Clinic visits

Study visits were conducted in an outpatient setting outside the main hospital.

After providing informed consent, participants attended the baseline visit during which assessments included expired air carbon monoxide (CO), demographic information, smoking history, the Fagerström Test of Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991), vital signs, height, and weight, and urine pregnancy tests for females of childbearing potential.

At this visit, eligible participants were provided with a Palm Tungsten E2 (Palm Inc., Sunnyvale, CA) personal digital assistant (PDA). A research assistant trained each participant on how to use and complete daily measures on the PDA. Following the baseline visit, participants completed daily morning assessments on the PDA. Daily morning assessments required participants to record the number of cigarettes smoked the day prior, indicate if they had smoked upon waking, and record the time they woke up (see Gass, Wray, Hawk, Mahoney, & Tiffany, 2012 for details; Gass et al. focus on daily assessments of tonic and cue-specific craving).