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ORIGINAL INVESTIGATION

The effects of varenicline on attention and inhibitory control among treatment-seeking smokers

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Abstract
Rationale Varenicline represents a new class of smoking cessation aids that has different mechanisms of action that are unique from bupropion or nicotine replacement therapies. An improved understanding of these mechanisms may lead to greater treatment success in quitting smoking.
Objectives We examined the effects of steady-state varenicline on attention and inhibitory control among adult treatment-seeking smokers.
Methods Adult smokers enrolled in a randomized clinical trial received either 4 weeks of pre-quit varenicline (n=31) or 3 weeks of placebo (n=26) followed by 1 week of standard varenicline treatment. Participants in the present work completed cognitive assessments at a baseline session (prior to treatment) and again 3 weeks later (during active treatment). At both sessions, participants completed the stop signal task to assess both lapses in attention and inhibitory control.
Results Analyses indicated that varenicline improved lapses in attention compared to placebo. There were no significant differences observed between groups at either session for inhibitory control.
Conclusions The present study demonstrated that varenicline improves lapses in attention among treatment-seeking smokers preparing to make a quit attempt. These findings suggest that the domain of attention may be a good candidate for larger studies of the role of improved cognition in understanding the mechanisms of varenicline treatment for smoking cessation.

Keywords Varenicline · Cognition · Attention · Inhibitory control · Smoking

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Recent clinical trials have demonstrated the efficacy of varenicline as a first-line smoking cessation agent (Cahill et al. 2011; Fiore et al. 2008; Gonzales et al. 2006; Jorenby et al. 2006; Oncken et al. 2006; for a review, see Daubney et al. 2009). Varenicline was developed specifically based on its properties as an α4β2* (the asterisk indicates that the receptor may include additional subunits) nicotinic acetylcholine receptor (nAChR) partial agonist. Given the apparent roles of the α4 and β2 nAChR subunits in tobacco dependence (e.g., Benowitz 2010), varenicline is hypothesized to reduce the rewarding effects of smoking before quitting and the severity of craving and withdrawal after quitting (Coe et al. 2005; Rollema et al. 2007, 2009). In addition to reinforcement and motivational mechanisms, an emerging literature focuses on

cognitive mechanisms of action for varenicline (and other medications for treating addiction; Sofuoglu 2010).

Smokers often report improved cognition as a reason for smoking (West 1993), and disrupted concentration is a cardinal feature of withdrawal (DSM-IV-TR; American Psychiatric Association 2000) that may contribute to relapse (Heishman et al. 1994). Consistent with this clinical literature, neuroscience has documented the important role of the nicotinic cholinergic system in cognitive functioning (Graef et al. 2011; Levin and Simon 1998; Newhouse et al. 2004; Rollema et al. 2009; Sarter et al. 2009). Although there are numerous facets of cognition, the present study focuses on lapses in attention and inhibitory control, which are emphasized in emerging models of cognition and addiction (e.g., de Wit 2009; Richards et al. 2011; Sofuoglu 2010).

One of the clearest findings in relation to smoking and cognition is the association between nicotine and attention. Nicotine reliably improves aspects of attention in both smokers and nonsmokers (Kassel 1997; Newhouse et al. 2004; Rezvani and Levin 2001), and this improvement appears to be above and beyond simply reducing withdrawal symptoms in smokers (Heishman et al. 2010). Similarly, individuals with poor baseline attentional functioning, such as those with attention deficit hyperactivity disorder (Conners et al. 1996; Levin et al. 1996a; Potter and Newhouse 2004) and schizophrenia (Harris et al. 2004; Levin et al. 1996b; Smith et al. 2002), show improvements in attention following the administration of nicotine. The cognitive effects of nicotine seen in smokers are believed to operate via the same receptors that are the targets of varenicline. Specifically, the $\alpha 4$ and $\beta 2$ subunits appear to play a major role in attentional processing (the $\alpha 7$ subunit, also affected by varenicline, appears to be involved in memory; for a review, see Graef et al. 2011).

In addition to enhancing attentional processes, nicotine may exert positive effects on the ability to control impulsive behavior. Inhibitory control, the ability to inhibit a prepotent response/behavior that the individual is prepared to emit or engage (Logan et al. 1997), is disrupted in abstinent smokers (Dawkins et al. 2007), and nicotine alleviates these decrements (Potter and Newhouse 2004). Recent models of addiction and relapse have emphasized the role of inhibitory control (de Wit 2009; Sofuoglu 2010) and it has been suggested that weak inhibitory control is a risk factor for relapse (Dawkins et al. 2009). There is emerging evidence suggesting a link between the nicotinic cholinergic system and inhibitory control (Potter et al. 2011).

Work on the cognitive effects of varenicline in particular is sparse, with a pair of preclinical animal studies and two studies of cigarette smokers. In rodents, varenicline may improve early inhibitory processing and sustained attention, at least in the presence of a distracter (Rollema et al. 2009; c.f. Wouda et al. 2011). The two studies examining the cognitive effects of varenicline yielded mixed results, with one suggesting that varenicline reduces the effects of abstinence on sustained attention (Paterson et al. 2009) and the other suggesting that varenicline may impair attention among nontreatment seeking smokers (Ashare and McKee 2011). We are not aware of any published studies of varenicline on inhibitory control in humans.

The present work addressed important gaps in the emerging literature on the cognitive effects of varenicline by investigating the effects of 3 weeks of varenicline on attention and inhibitory control among treatment-seeking smokers preparing to make a real-life quit attempt. It is important to include steady-state medication conditions as the effects of cessation medications may differ under acute and steady-state—and more clinically relevant—conditions (e.g., Cousins et al. 2001). The focus on treatment-seeking smokers is also important, as the effects of varenicline may vary as a function of motivation to quit smoking (Perkins et al. 2010; Wilson et al. 2011). However, there is a trade-off. Although abstinence overnight or even longer is common in basic behavioral pharmacology studies, pre-quit periods of abstinence are potentially problematic in clinical trials. Therefore, in the present study, participants completed the cognitive assessments under conditions of minimal deprivation. We hypothesized that varenicline would improve attention and inhibitory control, relative to placebo.

Methods

Participants

Participants were 57 adult (18–65 years old) regular smokers (at least 15 cigarettes per day) who enrolled in a randomized clinical trial (RCT) in response to newspaper and television advertisements. There were three additional participants (one varenicline, two placebo) who were enrolled in the RCT (n=60) but did not complete both cognitive assessment sessions and thus are not included in the present sample. Exclusion criteria included: current use of tobacco products other than cigarettes or use of any nonstudy pharmacotherapy for smoking cessation; history of a DSM-IV-TR axis I mood disorder, psychosis, or substance abuse in the past year (self-report and Mini International Neuropsychiatric Interview, Sheehan et al. 1998); contraindicated medical condition (e.g., poorly controlled diabetes, renal impairment, uncontrolled hypertension, recent cancer diagnosis, or myocardial infarction); current pregnancy (based on urine screen) or planning to become pregnant during the study period.

Procedure and apparatus

All procedures were approved by the Institutional Review Board at Roswell Park Cancer Institute. The current assessments were conducted during the pre-quit period of a

clinical trial (for a complete description, see Hawk et al. 2012) in which participants were randomized to either 4 weeks of varenicline prior to the target quit day (TQD) (extended run-in group; n=31) or to 3 weeks of placebo, followed by 1 week of varenicline prior to quit day (standard run-in group; n=26).

To evaluate the effects of varenicline on attention and inhibition, participants completed the stop signal task (SST) on the evening before they began taking varenicline or placebo (baseline session) and again 3 weeks later (active treatment session), when the extended run-in group had been taking varenicline (hereafter referred to as the varenicline group), and the standard run-in group had been taking placebo (hereafter, the placebo group). At each session, participants began the cognitive assessment after completing all other study procedures and measures (including brief behavioral counseling), approximately 1 h after arrival. Thus, participants were tested under conditions of minimal deprivation (Hendricks et al. 2006). The first 23 participants were also administered an A–X Continuous Performance Task (Halperin et al. 1988), but this task was discontinued due to ceiling effects (mean errors of omission <1). All participants completed a computerized delay discounting task (Mitchell 1999; results not reported). Task order was counterbalanced across participants.

Dosing of varenicline/placebo followed a standard regimen: one 0.5-mg tablet daily for 3 days, followed by one 0.5-mg tablet twice daily for 4 days, then two 0.5-mg tablets twice daily; 0.5-mg pills were used during week 4 to maintain blinding. Medication adherence was very good, with mean values >96% at each visit (see Hawk et al. 2012). Participants received modest remuneration for their participation and adherence to study procedures, including completion of ecological momentary assessments with personal digital assistants throughout the pre-quit period (see Hawk et al. 2012). Participants were encouraged to continue smoking as usual, following their urges throughout the 3-week period (for details, see Hawk et al. 2012).

As is typical in the SST (Logan and Cowan 1984; e.g., Acheson and de Wit 2008; Lipszyc and Schachar 2010; Oosterlaan et al. 1998; Soreni et al. 2009), the current version required participants to discriminate between two visual stimuli as quickly as possible and to withhold responding when an infrequent auditory stop signal is presented. The task was presented via a laptop programmed in E-prime (Psychology Software Tools, Pittsburgh, PA, USA) attached to a 17-inch cathode ray tube monitor, and participants responded using two marked keys on an external keyboard.

The task began with 32 trials of "Go" practice to develop a prepotent go response. Each trial began with a white fixation cross in the center of a black screen for 500 ms, followed by the presentation of a white arrow pointing to the left or the right for 1,000 ms. Following stimulus presentation, a blank screen was presented for 1,500 ms (1,000 ms response window followed by a 500-ms intertrial interval). Participants indicated the direction the arrow pointed with two marked keyboard keys.

Next, participants completed a 32-trial "Stop and Go" practice in which a stop signal (1,000 Hz tone presented for 100 ms) was presented on 25% of the trials, indicating that the participant should not respond. The delay of the stop tone (initially set to 250 ms) automatically adjusted in 50-ms increments based upon the participant's performance on the previous stop trial, yielding inhibition on approximately 50% of the stop trials (Band et al. 2003).

Finally, participants completed 3 64-trial "Stop and Go" blocks, which had the same parameters as the "Stop and Go" practice.

Data reduction

Inhibitory control

Trials with invalid reaction times (RT; <150 ms) were excluded, as were incorrect responses and omitted trials (for each of these trial types, the mean number of trials per visit was <1.5). Consistent with previous procedures (Potter et al. 2011), blocks were excluded from analyses if inhibition was below 20% (4 blocks total, 1 %) or above 75 % (43 blocks total, 13%) or if accuracy on "Go" trials was below 80 % (4 blocks total, 1 %). Following exclusions, four participants (one varenicline, three placebo) had no valid blocks in one of the two sessions and were excluded from the inhibitory control analysis. Stop signal reaction time (SSRT), the primary measure of inhibitory processing, was computed by subtracting the mean stop signal delay (mean of the adjusting delay of the stop tone for each block) from the mean correct go RT (SSRT=MRT–MSD; e.g., Logan et al. 1997). Smaller values indicate better inhibitory control.

Attention

RT on a range of tasks are positively skewed due to intermittent long RTs thought to reflect brief lapses in attention (Acheson and de Wit 2008; Epstein et al. 2011; Leth-Steensen et al. 2000; MacDonald et al. 2006; Sabol et al. 2003; Spencer et al. 2009). Therefore, lapses were assessed from RT variability on the valid and accurate "Go" trials (mean=99% of trials) from the SST (for similar data reduction methods using the SST, see Adams et al. 2011; Epstein et al. 2011). The coefficient of variation (RTCV=RTSD/MRT) is a recommended measurement of variability because it controls for processing speed (i.e., MRT; Epstein et al. 2011; Segalowitz and Segalowitz 1993; Wagenmakers and Brown 2007). Lower RTCV indicates fewer/shorter lapses in attention.

Data analysis

Group (varenicline versus placebo) × session (baseline versus active treatment) ANOVAs were used to examine RTCV (lapses in attention) and SSRT (inhibitory control) from the SST. Effect sizes are reported as Cohen's *d* (1988) for between-subjects effects and *d′* for effects involving within-subjects factors.

Results

Independent samples *t* tests (*df*=1,55) and chi-square tests (*df*=1) demonstrated that the participants in the varenicline and placebo groups did not significantly differ on any demographic or smoking variable at baseline (see Table 1).

Inhibitory control

Figure 1 shows the mean SSRT, our index of inhibitory control, in all group × session conditions. Though the hypothesized group × session interaction was not significant, group × session, $F(1,51)=0.34$, $p=0.56$, SSRT improved modestly during active treatment with varenicline, $F(1,51)=3.82$, $p=0.06$, $d'=0.5$, but this change was not significantly greater than that observed in the placebo group, $F(1,51)=0.88$, $p=0.4$, $d'=0.3$. Percent inhibition was not significantly influenced by group, $F(1,51)=0.05$, $p=0.82$.

Lapses in attention

Figure 2 shows the mean RTCV, our index of attentional lapses, in all group × session conditions. As hypothesized, there was a statistically significant group × session interaction, $F(1,55)=4.57$, $p=0.04$. Simple effects follow-up tests demonstrated that 3 weeks of varenicline reduced RTCV, $F(1,55)=8.81$, $p=0.004$, $d'=0.7$, but RTCV was unchanged by 3 weeks of placebo, $F(1,55)=0.03$, $p=0.86$, $d'=0.0$. Figure 3 illustrates the impact of varenicline at the single-subject level by providing trial-wise RT data for two participants (one placebo, one varenicline) with typical RTCV at baseline.

Consistent with the perspective that RTCV is not reflecting overall speed, there was no evidence of significant group differences on mean RT on go trials, $F(1,55)=0.03$, $p=0.86$.

Table 1 Demographic and smoking variables for the varenicline and placebo groups

Variable	Varenicline group	Placebo group	*p* value
Sex—female:male (*n*)	17:14	17:9	0.43
Age (years)	47.5 (9)	48.4 (10)	0.72
Minority (%)	10	19	0.31
FTND	5.5 (2)	4.9 (2)	0.28
Years smoking	26.8 (11)	26.6 (13)	0.93
Lifetime quit attempts	5.7 (5)	5.5 (10)	0.93
Baseline CPD	17.8 (5)	17.4 (5)	0.34

Except where noted, values represent the mean (SD). *p* values are from independent samples *t* tests (*df*=1,55) and chi-square tests (*df*=1)

FTND Fagerstrom test for nicotine dependence, *CPD* cigarettes per day

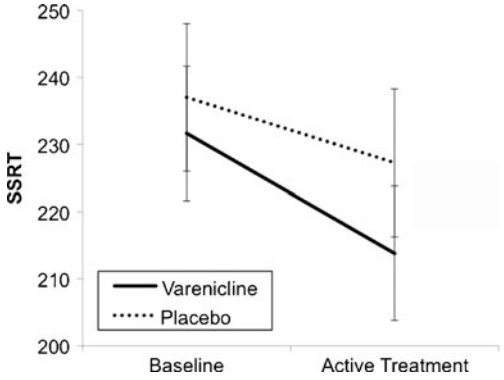

Fig. 1 Inhibitory control. Mean (bars are SE) SSRT for all group × session conditions

Supplementary analyses

Although we encouraged participants to continue to smoke during the pre-quit period, we examined whether mean smoking rate (cigarettes per day) during the week preceding each cognitive assessment varied with group. There was a marginally significant group × session interaction, $F(1,55)=3.22$, $p=0.08$, with a greater decrease among the varenicline group [session 1=17.7 (4.7), session 2=12.9 (5.8), $F(1,55)=35.93$, $p<0.001$] than among the placebo group [session 1=17.5 (5.4), session 2=14.8 (5.5), $F(1,55)=9.35$, $p=0.003$].

Supplementary models including sex as a between-subjects factor suggested that sex did not significantly moderate the effects of varenicline on either SSRT, $F(1,49)=0.13$, $p=0.72$, or RTCV, $F(1,53)=2.70$, $p=0.11$.

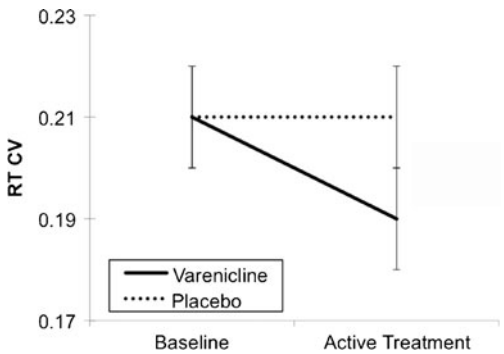

Fig. 2 Lapses in attention. Mean (bars are SE) coefficient of variation (RTCV) for all group × session conditions

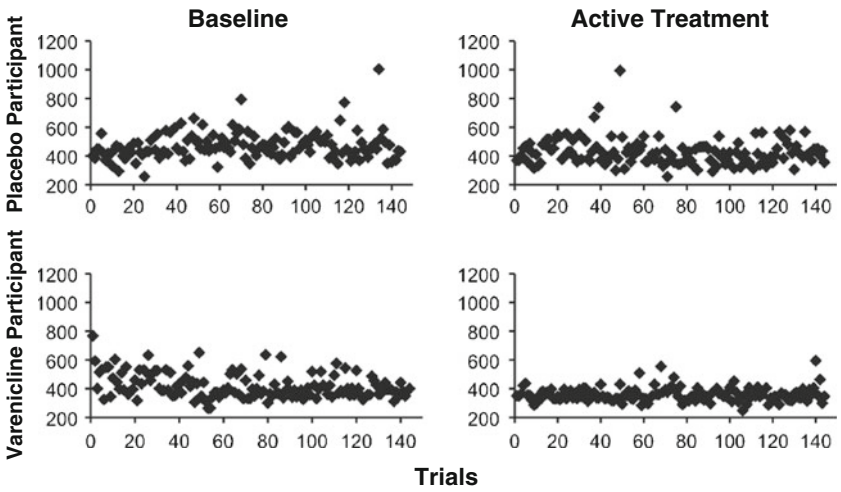

Fig. 3 Trial-wise RTs for one participant receiving placebo (*upper panels*) and one participant receiving varenicline (*lower panels*). Participants were selected for comparable baseline values (RTCV=0.20 for both; mean RT=471 and 420 ms) and age (39 years for both). At baseline, both participants have occasional long RTs (*left panels*). The participant receiving placebo continues to exhibit this pattern (*upper right*; RTCV=0.22), but the frequency and magnitude of long RTs appear to be reduced in the participant receiving 3 weeks of varenicline (*lower right*; RTCV=0.13)

Discussion

Based on work demonstrating links among nicotine and smoking, the cholinergic system, and attention (Conners et al. 1996; Harris et al. 2004; Heishman et al. 2010; Kassel 1997; Levin et al. 1996a, b; Newhouse et al. 2004; Potter and Newhouse 2004; Rezvani and Levin 2001; Smith et al. 2002), we tested whether varenicline, an α4β2* nAChR partial agonist, would improve lapses in attention among a sample of treatment-seeking smokers preparing to quit. Results demonstrated that participants receiving 3 weeks of varenicline treatment exhibited significantly fewer lapses in attention than those participants in the placebo condition. This reduction is consistent with the preliminary work specifically assessing the effect of varenicline on attention (Paterson et al. 2009; Rollema et al. 2009; c.f. Ashare and McKee 2011).

Though varenicline modestly improved inhibitory control across sessions, this did not differ significantly from the placebo group. While there is literature establishing the association between the nicotinic cholinergic system and attention (for a review, see Graef et al. 2011), until recently (Potter et al. 2011), there was no such work suggesting a link with inhibitory control. More work needs to be done to better understand the role of the nicotinic cholinergic system in inhibitory control. Additionally, as discussed below, the present sample was not abstinent during assessment. Recent work has suggested that weak inhibitory control is a risk factor for relapse (Dawkins et al. 2009). As such, inhibitory control may be an important cognitive construct once a person quits smoking and may be less important prior to abstinence. Future work ought to assess the effects of varenicline on inhibitory control during periods of abstinence.

The primary aim of the present study was to better understand varenicline's effects on cognition in treatment-seeking smokers. It is important to study these processes in smokers trying to quit because this is the target group (i.e., those most likely to use varenicline to quit smoking) and effects may vary between smokers motivated to quit and those with no intent to quit (Perkins et al. 2010; Wilson et al. 2011). However, because the present sample was trying to quit, we only minimally deprived them during assessments, rather than subject them to an extended period of abstinence just a week before their quit attempts. Because deprivation was minimal, the present findings likely underestimate the impact of varenicline during prolonged abstinence.

In addition, recall the varenicline group demonstrated greater reductions in their daily smoking. Consider the possibility that varenicline has no impact on cognition. If this were the case, one would predict that the varenicline group, who tended to decrease their smoking rate more than the placebo group, would demonstrate more impairment in cognition while the placebo group would remain relatively unchanged. However, as Fig. 2 demonstrates, this was clearly not the case. To the extent that decreases in smoking disrupt cognition, varenicline not only offsets this effect on inhibition but actually reduces lapses in attention.

These findings for smokers preparing to quit are clinically relevant. Disrupted attention is a hallmark feature of smoking withdrawal (DSM-IV-TR; American Psychiatric Association 2000) that may contribute to relapse (de Wit 2009; Heishman et al. 1994). The current work suggests that varenicline improves attention prior to cessation, relative to placebo. Though it will be important to evaluate the degree to which this translates into attenuated cognitive disruption once participants quit, there is good reason to focus on the

pre-quit period. There is preliminary evidence that extending the duration of pre-quit varenicline improves cessation rates (Hajek et al. 2011; Hawk et al. 2012) and that varenicline may facilitate quit attempts among smokers who are not motivated to quit at the time they begin medication (Hughes et al. 2011). Moreover, in light of evidence that flexibility in the target quit date may be beneficial (Rennard et al. 2012), the US Food and Drug Administration (2011) recently altered the indications for varenicline to allow pre-quit treatment for up to 1 month. Thus, the effects of varenicline prior to cessation—the focus of the present study—appear important both for understanding the mechanisms of action and for enhancing clinical outcome. Of course, future work would ideally include both pre-quit and post-quit assessments.

Future work should also extend the breadth and depth of the cognitive assessment. We focused on attention and inhibitory control because of the importance of these processes in models of addiction. However, the nicotinic cholinergic system may also influence working memory via $\alpha 7$ receptor subunits (Graef et al. 2011). Future work should address varenicline effects on a broader range of cognitive processes, including working memory.

Conversely, future work should target multiple indicators of each cognitive domain. The current work assessed only one index of sustained attention (the collection of an additional measure, omissions on a continuous performance task, was discontinued due to ceiling effects). Specifically, we employed the coefficient of variation for reaction times (RTCV), as RT-based measures are increasingly employed to capture brief lapses in attention (Acheson and de Wit 2008; Epstein et al. 2011; Leth-Steensen et al. 2000; Sabol et al. 2003; Spencer et al. 2009). Although RTCV is an improvement over the standard deviation (Wagenmakers and Brown 2007), RTCV does not distinguish the directionality of variability—whether decreased variability is symmetrical around the mean or more specifically reflects reductions in long RTs or lapses. The data in Fig. 3 suggest that changes in RTCV in the present study are consistent with an attentional interpretation. At baseline, both participants exhibit occasional long RTs, and this asymmetrical pattern appears to be reduced during active treatment with varenicline but not placebo. Nevertheless, one cannot assume a 1:1 relationship between changes in RT variability (RTCV or otherwise) and attention (e.g., Matzke and Wagenmakers 2009). Ultimately, converging evidence from other measures (e.g., continuous performance tasks; Paterson et al. 2009) will be useful for convincingly evaluating the degree to which varenicline improves sustained attention among smokers.

In conclusion, the present study demonstrated that, among smokers preparing to make a real-life quit attempt and cutting down on their cigarettes smoked per day, varenicline improved an RT-based metric of lapses in sustained attention but did not significantly alter a measure of inhibitory control. It has been suggested that effective smoking cessation medications should mimic nicotine, resulting in reductions in the rewarding effects of cigarettes while smoking and reductions in craving and withdrawal following a quit attempt (Coe et al. 2005; Rollema et al. 2007, 2009). Disruptions in attention and inhibitory control are important aspects of withdrawal upon quitting smoking. The current evidence that varenicline improves attention among smokers as they prepare to quit is consistent with the hypothesis that the cognitive effects of varenicline are viable candidate mechanisms of treatment outcome. Definitive tests of this hypothesis await large-scale clinical trials.

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