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ORIGINAL INVESTIGATION

Effect of varenicline and bupropion SR on craving, nicotine withdrawal symptoms, and rewarding effects of smoking during a quit attempt

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Abstract
Aims To examine the effect of varenicline, a selective alpha4-beta2 nicotinic acetylcholine receptor (nAChR) partial agonist, on craving and withdrawal symptoms in smokers making a quit attempt and the rewarding effects of smoking during a lapse after the target quit date (TQD).
Materials and methods Pooled data were analysed from two identical double-blind, randomised trials comparing varenicline 1 mg BID, bupropion (sustained release) 150 mg BID and placebo using measures of craving and withdrawal in the first week after the TQD (in abstinent [n=612] and non-abstinent participants [n=1,155]) and of the rewarding effects of the first cigarette smoked in non-abstinent participants.
Results In abstinent and non-abstinent participants combined, varenicline reduced craving more than bupropion (p<0.01) and placebo (p<.001); the effect did not differ by whether or not subjects were abstinent; bupropion reduced craving more than placebo (p<0.001). Among abstinent participants, both varenicline and bupropion reduced negative affect more than those receiving placebo (p<0.005). Neither active drug reduced restlessness, insomnia or appetite vs placebo. Varenicline reduced ratings of satisfaction and psychological reward after the first cigarette smoked after the TQD vs bupropion (p<0.005) and placebo (p<0.001); bupropion also reduced these more than placebo (p<0.05).
Conclusions Varenicline significantly reduces craving and the rewarding effects of smoking after the TQD to a greater extent than bupropion, which may contribute to varenicline's greater efficacy for smoking cessation. Varenicline's lack of effect in reducing insomnia, restlessness and increased appetite in this analysis suggests that receptors other than the alpha4-beta2 nAChR subtype may be implicated in these withdrawal symptoms.

Keywords Varenicline · Alpha4-beta2 nicotinic acetylcholine receptor partial agonist (nAChR) · Nicotine · Craving · Withdrawal · Reward · Minnesota Nicotine Withdrawal Scale (MNWS) · Modified Cigarette Evaluation Questionnaire (mCEQ) · Abstinent · Non-abstinent

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Introduction

Treatments that aid the cessation of cigarette smoking are important life-preserving interventions. Psychological support, nicotine replacement therapy, sustained release (SR) bupropion and nortriptyline have all been shown to have a small but clinically significant effect, helping between 1 in 20 and 1 in 10 quit attempts that would otherwise have failed to achieve abstinence for at least a year (West 2006). Varenicline is a new medication for smoking cessation that appears to have greater efficacy than bupropion SR or placebo (Cahill et al. 2007). Across several comparative trials, varenicline was found to be significantly more

effective than placebo or bupropion SR (Gonzales et al. 2006; Jorenby et al. 2006; Nides et al. 2006; Oncken et al. 2006; Tonstad et al. 2006; Williams et al. 2007). Furthermore, in a meta-analysis conducted by the Cochrane Collaboration, the pooled odds ratio (OR) for continuous abstinence up to 12 months with varenicline vs placebo was 3.22 (95% confidence interval [CI], 2.43–4.27) and the OR for varenicline vs bupropion SR was 1.66 (95% CI, 1.28–2.16) (Cahill et al. 2007).

Attempts to stop smoking fail because at various times after the target quit date (TQD) the needs, desires or urges to smoke overwhelm the motivation to exercise restraint (West 2006). An important factor contributing to this is nicotine dependence. Repeated rapid ingestion of nicotine from cigarettes causes a number of changes to take place in the central nervous system that result in powerful, repeated and persistent urges to smoke and feelings of need for a cigarette—what one may term 'craving'. It also leads to several unpleasant withdrawal symptoms including irritability, depressed mood, anxiety, restlessness, difficulty concentrating, sleep disturbance and increased appetite (Hughes 2007; Hughes et al. 1991, 1994; Hughes and Hatsukami 1986).

The ideal medication to treat nicotine dependence should reduce craving and nicotine withdrawal symptoms. Furthermore, if the smoker lapses and smokes a cigarette, the medication should minimise the rewarding effect of that cigarette and thus reduce the chances of that lapse leading to full-blown relapse. Varenicline was designed with these goals in mind (Coe et al. 2005; Rollema et al. 2007). It binds with high affinity to the alpha4-beta2 nicotinic acetylcholine receptor (nAChR), believed to be the receptor that lies at the heart of nicotine dependence. Varenicline acts as a alpha4-beta2 nAChR partial agonist to mimic to some degree the effect of nicotine on the receptor, with the intention of diminishing craving and withdrawal symptoms while blocking nicotine from binding and thereby reducing the rewarding effect of cigarettes (Coe et al. 2005; Rollema et al. 2007).

Published data from the two pivotal clinical trials of varenicline support this putative dual mode of action (Gonzales et al. 2006; Jorenby et al. 2006) but allow room to further investigate this interpretation of the mechanism of action for three reasons:

1. Analyses of craving and withdrawal symptoms used data averaged over 7 weeks. Averaged data over 7 weeks would weaken the ability to detect effects because withdrawal symptoms typically peak in the first week and most have disappeared by week 4. Secondly, loss to follow-up over the 7 weeks could mitigate any observed effects, especially if those lost to follow-up had more severe cravings and withdrawal symptoms.
2. Analyses of craving and withdrawal symptoms, as well as smoking satisfaction, were compared between randomized treatment groups. However, this combined abstinent and non-abstinent participants within each treatment group, which could mitigate observed effects for examining mechanism of action if these symptoms were only present in abstinent participants. Alternatively, it raises the possibility that observed effects of varenicline on craving and withdrawal resulted from, rather than contributed to, its effects on abstinence. Thus, smokers who relapsed may have reported *more* severe withdrawal and craving as justification for their relapse and, because varenicline helped more smokers to remain abstinent, there would be fewer such subjects in the varenicline group.
3. Analyses of the rewarding effects of the first cigarette smoked in participants who lapsed covered the first 7 weeks after the TQD. Any effect of varenicline on this variable may have resulted from those in other groups relapsing earlier and therefore still experiencing more powerful urges to smoke. Relief from these urges may have contributed to the cigarette being more rewarding. Thus, the effect may have been a result of, rather than contributing to, its effect on abstinence.

We analysed the pooled data from two phase III clinical trials comparing varenicline, bupropion SR and placebo (Gonzales et al. 2006; Jorenby et al. 2006) using ratings of craving, withdrawal and the rewarding effects of cigarettes smoked in the first week after the quit date, separating out abstinent and non-abstinent participants. One week was used as the follow-up point because withdrawal symptoms would be at their most severe during that time (Hughes et al. 1994); the number of participants abstinent from the TQD would be at its highest; and the number of participants lost to follow-up would be at its lowest.

Materials and methods

Full details of the study design and methodology of both clinical trials have already been described elsewhere (Gonzales et al. 2006; Jorenby et al. 2006).

Participants and design

The clinical trials were both 52-week, double-blind, placebo-controlled, randomised, multi-centre trials. Both trials were conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practices Guidelines. The institutional review board at each study site approved the study protocol before screening of

participants and all participants provided written informed consent before any procedures or study treatments.

Eligible participants were adult cigarette smokers (18–75 years) who smoked at least 10 cigarettes per day and who were motivated to quit smoking as long as the longest period of abstinence in the previous year did not exceed 3 months. Participants were excluded if they had serious physical or psychiatric disease; if they had previously taken bupropion SR; or had participated in a previous clinical trial of varenicline. Smokers meeting the study entry criteria were randomised using a centralised procedure to receive varenicline 1 mg BID, bupropion SR 150 mg BID or placebo in a 1:1:1 ratio.

Measures

The Minnesota Nicotine Withdrawal Scale (MNWS) and modified Cigarette Evaluation Questionnaire (mCEQ) were used to assess craving, withdrawal symptoms and feelings of reward. At baseline, participants completed the mCEQ and the MNWS. The MNWS, yielding scores on craving, negative affect, restlessness, appetite and insomnia (Cappelleri et al. 2005; Hughes et al. 1991), provides at least as accurate an assessment of craving and withdrawal as other measures in current use (West et al. 2006). The negative affect score is derived by taking the mean of ratings of anger, depression, anxiety and difficulty concentrating; the insomnia score is derived by taking the mean of ratings of difficulty going to sleep and difficulty staying asleep. The other scores were based on single ratings. The mCEQ is composed of seven-point ratings of 'satisfaction' (the mean of ratings of satisfaction, taste and enjoyment), reward (mean of ratings of calming, making more alert, making less irritable, help with concentration and reduction of hunger), craving reduction from the cigarette (single item rating), enjoyment of the sensation in the respiratory tract (single item rating) and aversiveness of the cigarette (mean of 'dizziness' and 'nauseous') (Cappelleri et al. 2007). Only the first four of these scales were presented because aversiveness is not a measure of positive reward.

Participants then took study medication for 1 week while still smoking and completed the mCEQ every day during that week. They then attempted to quit and were assessed weekly with the MNWS from that point. Those participants who smoked a cigarette after the quit date completed the mCEQ at the next weekly follow-up (Cappelleri et al. 2007).

Analysis

Data from the MNWS were analysed by an analysis of covariance, which controlled for baseline score, study and centre, in which the three medication groups were compared 1 week after the quit date separately among abstinent and non-abstinent participants, as well as for all participants together (combined abstinent and non-abstinent groups). Based on this model, the pairwise differences between each of the three medication groups were also assessed. In addition, the treatment differences between all abstinent vs all non-abstinent participants from the analysis of covariance model were evaluated using the bootstrap procedure (Bradley and Tibshirani 1993). To determine differences between estimates for the two subgroups (abstinent and non-abstinent participants) bootstrap calculations were performed with 40,000 simulations for every subgroup and every domain (or item-domain) on the MNWS.

Data from the mCEQ were examined by analysis of covariance controlling for baseline score, study and centre, pairwise between the three medication groups using only non-abstinent participants.

Analyses of variance and pairwise comparisons between varenicline, bupropion SR and placebo were undertaken using SAS PROC MIXED. The bootstrap calculation of differences between abstinent and non-abstinent participants was undertaken using SAS. All comparisons between groups used methods appropriate for post-hoc comparisons.

Where data were missing for a particular analysis, the case was dropped from that analysis.

Table 1 Baseline characteristics

	Abstinent at week 2 visit			Non-abstinent at week 2 visit		
	Placebo	Varenicline 1 mg BID	Bupropion SR 150 mg BID	Placebo	Varenicline 1 mg BID	Bupropion SR 150 mg BID
Age, mean (SD)	42.6 (11.5) *N*=128	44.0 (10.5) *N*=263	43.1 (11.3) *N*=229	42.4 (11.7) *N*=556	43.3 (11.8) *N*=429	42.2 (12.0) *N*=440
Males, % (*n*)	60.9 (78) *N*=128	52.9 (139) *N*=263	59 (135) *N*=229	55 (306) *N*=556	52.5 (225) *N*=429	59.8 (263) *N*=440
Non-white, % (*n*)	12.5 (16) *N*=128	12.6 (33) *N*=263	12.7 (29) *N*=229	21.0 (117) *N*=556	20.3 (87) *N*=429	21.6 (95) *N*=440
Cigarettes per day, mean (SD)	20.5 (8.2) *N*=128	20.5 (9.0) *N*=263	20.6 (8.0) *N*=229	21.8 (9.3) *N*=555	22.5 (9.7) *N*=428	21.8 (8.9) *N*=440
FTND score, mean (SD)	4.8 (2.1) *N*=127	4.9 (2.2) *N*=261	4.9 (2.1) *N*=229	5.4 (2.1) *N*=553	5.5 (2.2) *N*=428	5.5 (2.1) *N*=439

FTND Fagerström Test for Nicotine Dependence

Results

Baseline characteristics

A total of 2,045 participants were randomised and received at least one dose of medication (692 varenicline, 669 bupropion SR and 684 placebo). Of these, 1,821 provided craving and withdrawal symptom data using the MNWS 1 week after the designated quit date (623 varenicline, 592 bupropion SR and 606 placebo), of whom 612 had maintained abstinence during that week (261 varenicline, 225 bupropion SR and 126 placebo). A total of 1,155 smoked at least one cigarette within 1 week of the quit date and provided mCEQ ratings (344 varenicline, 351 bupropion SR and 460 placebo). The numbers of participants contributing to specific analyses varied slightly because of missing data.

Table 1 shows participant characteristics at baseline, by abstinence status at the week 2 visit. Baseline characteristics were comparable across treatment groups. However, more non-abstinent participants were in non-white ethnic groups, smoked more cigarettes per day, and had higher scores on the Fagerström Test for Nicotine Dependence (FTND) in all treatment groups.

Minnesota Nicotine Withdrawal Scale

Craving In the combined group, craving was reduced in participants receiving varenicline or bupropion SR compared with those receiving placebo ($p<0.001$ for both) and was significantly lower for varenicline vs bupropion SR ($p=0.008$). A similar pattern was also observed in the non-abstinent subgroup, with varenicline reducing craving vs bupropion ($p=0.045$) and placebo ($p<0.001$) and with bupropion reducing craving versus placebo ($p=0.001$). In abstinent participants, both active treatments were better than placebo at reducing craving (varenicline, $p<0.001$; bupropion SR, $p=0.013$; Table 2) but the varenicline versus bupropion comparison did not reach statistical significance. Non-abstinent participants reported greater craving than those who were abstinent ($p<0.001$ in all treatment groups).

Negative affect Participants receiving varenicline and bupropion SR reported significantly less negative affect than those receiving placebo in the combined group ($p=0.002$ and $p=0.001$, respectively; Table 2) and this was accounted for by the significant differences vs placebo evident only in those who were abstinent (varenicline, $p=0.002$; bupropion SR, $p<0.001$); those receiving varenicline did not differ from those receiving bupropion SR. The non-abstinent group showed higher scores on negative affect than the abstinent group for varenicline ($p=0.005$) and for bupropion SR ($p<0.001$).

Table 2 Mean score at 1 week after target quit date on the MNWS for craving and withdrawal ratings; all on a scale from 0 (none) to 4 (severe)

MNWS Subscale, Mean (SEM) score	Abstinent subgroup at week 2 visit			Non-abstinent subgroup at week 2 visit			Combined group at week 2 visit		
	Placebo	Varenicline 1 mg BID	Bupropion SR 150 mg BID	Placebo	Varenicline 1 mg BID	Bupropion SR 150 mg BII	Placebo	Varenicline 1 mg BID	Bupropion SR 150 mg BID
	Mean (SEM)			Mean (SEM)			Mean (SEM)		
Craving	1.45 (0.088)	1.06* (0.064)	1.19* (0.068)	1.85 (0.048)	1.49*· ** (0.054)	1.63* (0.054)	1.76 (0.042)	1.32*· ** (0.041)	1.47* (0.042)
Negative affect	0.81 (0.058)	0.60* (0.042)	0.52* (0.045)	0.84 (0.037)	0.77 (0.041)	0.77 (0.042)	0.81 (0.030)	0.69* (0.029)	0.67* (0.030)
Restlessness	0.99 (0.085)	0.84 (0.061)	0.84 (0.066)	0.97 (0.048)	0.93 (0.054)	0.99 (0.054	0.95 (0.040)	0.88 (0.040)	0.92 (0.041)
Increased appetite	1.13 (0.094)	1.14 (0.068)	0.97 (0.073)	0.97 (0.051)	1.09** (0.058)	0.82* (0.059)	1.01 (0.044)	1.13*· ** (0.043)	0.89 (0.044)
Sleep disturbance	0.82 (0.089)	0.80** (0.064)	1.06* (0.069)	0.72 (0.045)	0.86* (0.051)	0.95* (0.051)	0.73 (0.039)	0.84*· ** (0.039)	1.00* (0.040)

Within each subgroup (abstinent and non-abstinent) and in the all subjects group, * denotes $p<0.05$ vs placebo and ** denotes $p<0.05$ vs bupropion by post-hoc pairwise comparison.

Restlessness There was no evidence for an effect of treatment group or abstinence on restlessness (Table 2).

Increased appetite In the combined group, varenicline led to higher appetite ratings than either bupropion SR ($p<0.001$) or placebo ($p=0.036$). In the non-abstinent group, varenicline did not differ from placebo, while bupropion SR led to less of an increase compared with varenicline ($p=0.001$) and placebo ($p=0.039$). There was no evidence for an effect of either medication on appetite in abstinent participants (Table 2). No significant differences were evident between the abstinent and non-abstinent participants in any treatment group.

Sleep disturbance Overall, sleep disturbance was greatest in the bupropion SR group than the varenicline ($p=0.003$) or placebo groups ($p<0.001$); and sleep disturbance was higher in the varenicline group vs the placebo group ($p=0.028$). In non-abstinent participants, sleep disturbance was greater with bupropion SR than varenicline or placebo, with both active treatments significantly different to placebo (varenicline, $p=0.029$; bupropion SR, $p=0.001$). Sleep disturbance was higher in the bupropion SR group for abstinent participants than in the varenicline ($p=0.003$) or placebo ($p=0.022$) groups, and varenicline did not differ from placebo (Table 2). For each treatment group, there was no difference in sleep disturbance between abstinent and non-abstinent participants.

Modified Cigarette Evaluation Questionnaire

Ratings of satisfaction, psychological reward, enjoyment of respiratory tract sensations and craving reduction after the first cigarette smoked after the quit date were consistently lower in those receiving varenicline compared with bupropion SR (satisfaction [$p<0.001$]; psychological reward [$p=0.004$]; enjoyment of respiratory tract sensations [$p=0.008$]; and craving reduction [$p=0.001$]) or placebo (satisfaction [$p<0.001$]; psychological reward [$p<0.001$]; enjoyment of respiratory tract sensations [$p<0.001$]; and craving reduction [$p=0.001$]; Table 3). Satisfaction and psychological reward were lower in those receiving bupropion SR than placebo (satisfaction [$p=0.042$] and psychological reward [$p=0.012$]).

Discussion

Varenicline was more effective than bupropion SR in reducing craving in the combined group of abstinent and non-abstinent smokers with no evidence for a difference depending on abstinence. It was not more effective than bupropion SR in reducing negative affect in abstaining smokers and had no effect in reducing restlessness, insomnia or appetite increase in this analysis. Varenicline was clearly more effective than bupropion SR in reducing the rewarding effect of the first cigarette smoked after the TQD.

The superiority of varenicline over bupropion in reducing craving and rewarding effects of a cigarette if the smoker lapsed is in line with its putative dual mode of action and could explain its superiority over bupropion in promoting abstinence. This hypothesis could in principle be tested further by examining how far these subjectively reported differences between varenicline and bupropion mediate differential effects of these medications on abstinence.

The effect of varenicline on upper respiratory tract sensations is of interest and may reflect local action on nicotinic receptors in the upper airways. Given that such sensations do appear to be rewarding for smokers (Rose et al. 1999), this may mediate, at least in part, its overall effect on cigarette reward.

The fact that varenicline reduced craving in non-abstinent smokers suggests that it may be of benefit in helping smokers reduce consumption before quitting. However, it is also possible that this effect was only observed in smokers who were almost completely abstinent. Unfortunately data were not collected in this study on the amount of smoking after the TQD so further research will be needed to explore this.

The higher ratings of craving in non-abstinent than abstinent participants could be due to several factors. It could be that non-abstinent participants were smoking at a very low rate and this was exacerbating their craving. It

Table 3 Mean mCEQ scores for ratings of effect of first cigarette smoked after the quit date (range 1–7) in non-abstinent participants

mCEQ subscale, Mean (SEM) score	Placebo	Varenicline 1 mg BID	Bupropion SR 150 mg BID
Satisfaction	3.18 (0.063)	2.60*, ** (0.071)	3.01* (0.071)
Psychological reward	2.61 (0.053)	2.20*, ** (0.060)	2.43* (0.060)
Enjoyment of upper respiratory tract sensations	2.24 (0.062)	1.85*, ** (0.071)	2.10 (0.071)
Craving reduction	4.17 (0.091)	3.74*, ** (0.103)	4.19 (0.104)

*$p<0.05$ vs placebo by post-hoc pairwise comparison
**$p<0.05$ vs bupropion by post-hoc pairwise comparison

could also be that participants who were not managing full abstinence were motivated to rate their cravings as high to justify their inability to maintain abstinence. Future studies should record the numbers of cigarettes smoked by non-abstinent participants in clinical trials to help distinguish between these two hypotheses.

The efficacy of varenicline in reducing negative affect suggests that the alpha-4 beta-2 nAChR is implicated in this withdrawal symptom as well as craving. However, it also remains possible that the alpha-7 receptor is implicated in craving and reward because recent evidence suggests that varenicline is a full agonist on this receptor even though it binds to it with 5,000-fold lower affinity than to alph-4 beta-2 nAChRs (Coe et al. 2005; Rollema et al. 2007).

The lack of efficacy in reducing sleep disturbance, restlessness and increased appetite suggests that other nicotine receptor subtypes may be implicated in these withdrawal symptoms. Bupropion SR is known to increase sleep disturbance, as observed in this study.

The main limitation of this study was that even though analyses were limited to 1 week of follow-up, there were already differences in abstinence rates between the three medication groups and so we cannot completely rule out the possibility that the effects of the medications on craving, withdrawal symptoms and the rewarding effects of cigarettes smoked after the TQD were secondary to abstinence. However, the effects on craving were found to the same degree in abstinent and non-abstinent participants and the size of the effect on cigarette reward in this analysis was similar to that found in an earlier analysis involving cigarettes smoked even later in the quitting process. This reinforces the view that craving reduction and reduction in the rewarding effects of smoking mediated, rather than followed, abstinence effects. This could be further confirmed by an experimental study looking only at craving and cigarette reward in participants who are all induced to remain abstinent for the duration of the follow-up period.

Conclusions

Varenicline reduces craving and the rewarding effect of a cigarette smoked after the TQD to a greater extent than bupropion SR or placebo and this may contribute to the higher levels of abstinence in varenicline-treated participants. Varenicline's lack of efficacy in reducing insomnia, restlessness and increased appetite in this analysis suggests that receptors other than the alpha4-beta2 nAChR subtype are implicated in these withdrawal symptoms.

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