Original Investigation

Varenicline to Stop Long-term Nicotine Replacement Use: A Double-Blind, Randomized, Placebo-Controlled Trial

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Abstract

Introduction: This study evaluated the effect of varenicline in combination with counseling to assist long-term nicotine replacement therapy (NRT) users to quit NRT.

Methods: This was a double-blind, placebo-controlled, randomized trial of varenicline or placebo for 12 weeks, with 52-week follow-up, performed in 1 hospital-based smoking cessation specialist clinic. At the first visit, 139 ex-smokers and long-term NRT users were allocated to treatment according to a computer-generated list with random numbers. Visits were scheduled at Weeks 0, 2, 4, 6, 9, 12, and 52. At each visit, nurse-led counseling was delivered, carbon monoxide in expired air, plasma cotinine, and body weight were assessed, and subjects were asked about craving, nausea, and dreams. The primary outcome was 12-week point prevalence quit rate (PPR) of nicotine replacement therapy use.

Results: At all time points, the PPR was superior for varenicline versus placebo, although the difference was only statistically significant at 12 and 36 weeks. The PPR was 64.3% (varenicline) versus 40.6% (placebo) at 12 weeks ($p = .006$), and 42.9% (varenicline) versus 36.2% (placebo) at 52 weeks (NS). The continuous abstinence rate from Week 9 to Week 12 was 48.6 % (varenicline) versus 30.4 % (placebo) ($p = .03$). Withdrawal symptoms were statistically significantly lower in the varenicline group than the placebo group.

Conclusion: Varenicline for 12 weeks combined with supportive visits was superior to placebo to get long-term NRT users to quit NRT. A larger study is needed to evaluate long-term efficacy.

Introduction

The incidence of long-term use of nicotine replacement therapy (NRT) in ex-smokers after quitting smoking with NRT is reported to be 1–15% (Hajek, Jackson, & Belcher, 1998; Hajek, McRobbie, & Gillison, 2007; Murray, Nides, Istvan, & Daniels, 1998; Shiffman, Hughes, Pillitteri, & Burton, 2003). Use of NRT for more than 11 months is normally considered long-term use. One large study of 3,923 patients with mild chronic obstructive pulmonary disease (COPD) in which smoking cessation was repeated every 4 months over 5 years, using counseling sessions and nicotine 2 mg chewing gum, reported that 15% of quitters and 5% of smokers continued to use NRT after 5 years (Murray et al., 1998). Real-world figures outside clinical trials indicate that long-term use of NRT appears to be a rare event (www.smokinginengland.info). Data on the safety and efficacy of long-term use of nicotine replacement products beyond 3 months of treatment are relatively limited, but it is generally accepted that long-term NRT use is necessary in some successful quitters to avoid relapse to smoking. The adverse effects of long-term NRT use are negligible as compared with cigarette smoking, but insulin resistance and increased leptin levels have been found among long-term NRT users (Assali, Beigel, Schreibman, Shafer, & Fainaru, 1999; Eliasson & Smith, 1999; Eliasson, Taskinen, & Smith, 1996). In our experience, some long-term NRT users want help to quit NRT, and that was the target group for inclusion in the present trial. As the prevalence of long-term use of nicotine patches is low, we only included long-term users of "acute" or flexible-dose formulations of NRT.

Cessation of NRT following long-term use has been reported to elicit withdrawal symptoms similar to those reported during smoking cessation (West & Russell, 1985). One small formal trial (only 26 long-term nicotine gum users) in which participants were allocated to either abrupt cessation of NRT or tapering with either placebo gum or nicotine gum reported 6-week and 1-year quit rates of approximately 65% with no difference between treatment groups (Hurt et al., 1995). Data from a smoking cessation study reported that it was possible to get long-term gum users to gradually reduce gum use without relapse to smoking (Hughes et al., 1991).

Varenicline is the most effective drug for smoking cessation and no abuse potential has been reported with varenicline

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(Cahill, Stead, & Lancaster, 2007; Fiore et al., 2008; Gonzales et al., 2006; Jorenby et al., 2006; Tonstad et al., 2006). Varenicline is a partial, high-affinity $\alpha_4\beta_2$ nicotine receptor agonist; due to its high receptor affinity it also exerts an antagonistic effect. A recent study found varenicline to be more effective than placebo as an aid to cessation of smokeless tobacco (Fagerström, Gilljam, Metcalfe, Tonstad, & Messig, 2010). On this basis, we considered it appropriate to perform a larger trial with varenicline in long-term NRT users.

The primary aim of this study was to evaluate whether varenicline used for 12 weeks would be more effective than placebo to get long-term NRT users to stop using NRT. The study was powered to show a statistically significant difference at Week 12 (primary endpoint).

Methods

Design and Medications

This was a double-blind, placebo-controlled trial of either varenicline or placebo, in a 1:1 ratio, used for 12 weeks at a single site. Subjects were randomized to active or placebo using a computer-generated list with random numbers, and were allocated to treatment at the first clinic visit (Week 0).

Subjects enrolled were 18 years or older, ex-smokers who reported long-term (>11 months) abstinence from daily smoking, current users of flexible-dose NRT (using either >4 pieces of nicotine gum/sublingual tablets/lozenges/per day, or >3 inhaler cartridges per day, or >10 puffs of nasal spray per day), who were willing to try to stop using NRT. Long-term NRT users with a lower daily nicotine intake were excluded on the grounds that such subjects could probably quit NRT without medication.

Subjects with any of the following were excluded from the trial: smokers; pregnant or lactating women; previous use of varenicline; any significant diseases that might influence the trial (e.g., moderate to severe cardiac disease, lung cancer, COPD); a carbon monoxide (CO) level >7 parts per million (ppm) in expired air; a plasma creatinine level that was >10% above normal levels.

Subjects were recruited through advertisements in local free newspapers, and respondents were screened by telephone. Visits were scheduled at Weeks 0, 2, 4, 6, 9, 12, and 52, with two telephone follow-up calls at Weeks 26 and 38. Each visit consisted of assessments and less than 5-min counseling, provided by smoking cessation nurses, about how to manage without NRT. Subjects were instructed to gradually reduce their number of daily doses of NRT and to stop completely at target quit day after 1–2 weeks. They were informed how to manage withdrawal symptoms and about the therapeutic effect and possible adverse events of varenicline.

Varenicline was increased to 1 mg tablet twice daily from Day 7 up to Weeks 12. The study medication, varenicline tablets and matched placebo, was provided free of charge by Pfizer AS, Denmark. Subjects were advised to take the tablets during breakfast and dinner, with a glass of water. They were recommended to stop NRT use between the first and second week of treatment with study medication on a specific day.

The study protocol was approved by the regional independent Ethics Committee, the Danish Medicinal Board, and the Danish Data Register. Oral and written informed consent was obtained from each subject before they entered the study, and the study was conducted in accordance with Good Clinical Practice Guidelines.

Assessments

Assessments were performed by trained and experienced smoking cessation research nurses at clinic visits at Weeks 0, 2, 4, 6, 9, 12, and 52.

Use of NRT was assessed at all visits and both telephone follow-ups. Smoking was assessed at Weeks 1, 12, 24, and 52. Carbon monoxide (CO) and body weight were assessed at every visit. Expired CO levels were measured with a CO monitor with a CO level higher than 7 ppm classified the subject as a smoker (Jarvis, Russell, & Saloojee, 1980).

Venous blood was collected and analyzed for plasma cotinine in the central hospital clinical biochemical department at entry and at Weeks 12 and 52. Waist and hip circumference were also measured at these time points, using a tape measure twice. Waist circumference was measured at the midpoint between the lower rib and the upper margin of the iliac crest, and hip circumference was measured by the widest circumference around the buttocks below the iliac crest according to accepted standards (Czernichow et al., 2011).

Questionnaires and Ratings

At entry the following information was elicited: medical history, medicine use, former smoking habits and demographic data. Motivation to stop using NRT, beliefs about difficulty in stopping NRT use and self-belief in being able to stop use were assessed on a 5-point scale (where 0 = not at all, 5 = very much). Two questionnaires were used to assess nicotine dependence: a modified version of the Fagerström Test of Nicotine Dependence (FTND) and Horn-Russell scale (Agrawal et al., 2011; Heatherton, Kozlowski, Frecker, & Fagerström, 1991; Seersholm, Nielsen, & Tonnesen, 1999). The scales were modified by replacing number of cigarettes with number of pieces/doses of NRT on a 1:1 basis (see Appendix 1 in Supplementary Data). The subjects' FTND score during smoking was assessed retrospectively, by asking subjects to rate what their responses to the questionnaire would have been when they smoked cigarettes.

At each visit, subjects were asked about possible adverse events from study medication, and specific detailed questions were asked about nausea, vomiting, dreams, and suicidal thoughts. Nicotine withdrawal symptoms for the previous 24 hr (craving, appetite, and total withdrawal symptoms [one specific question]) were rated on a scale 0–4 (American Psychiatric Association, 2000; Doherty, Kinnunen, Militello, & Garvey, 1995; Killen & Fortmann, 1997; Shiffman, West, & Gilbert, 2004; West, Hajek, & Belcher, 1989) at each visit. Instead of using scales that encompassed all nicotine withdrawal symptoms,

these three withdrawal symptoms were selected in order to make assessments at each visit as easy as possible.

Statistics

It was anticipated that at 12 weeks 50% of subjects in the active group and 25% in the placebo group would have stopped using NRT. With an α of 5% and a power of 80%, we calculated that 66 subjects were needed in each treatment group (using a two-sample comparison of proportions). Significant differences in NRT quit rates were calculated using chi-square tests and logistic regressions. All statistical analyses are presented with 95% confidence intervals (*CI*s). The *p* values (two-tailed) less than .05 were considered statistically significant. Safety data were reported as summary statistics and descriptively reported in tables.

All effect measures were calculated on an intention-to-treat basis. Any subjects that did not attend two consecutive scheduled visits were counted as NRT users. For withdrawal symptoms and weight, only data from subjects who attended the clinic visits were included in the analysis, as in most other cessation studies.

The primary outcome was point prevalence quit rate (PPR), which was defined as the percent of subjects who were not using NRT and were not smoking at Week 12 (point prevalence over the previous 7 days). The PPR was assessed by self-declaration, and objectively verified by an expired CO level ≤7 ppm and a plasma cotinine level <15 ng/ml.

The secondary outcome was defined as subjects not smoking and not using NRT at Week 52 (point prevalence over the previous 7 days), self-declared and verified by a CO level ≤7 ppm and a plasma cotinine level <15 ng/ml. The continuous abstinence quit rate (CAR) was defined as subjects' self-declaration of not using NRT and not smoking, verified by a CO level ≤7 ppm and a plasma cotinine level <15 ng/ml, from Week 2 and at all visits up to the assessment visit.

Results

Baseline Data

A total of 139 long-term NRT users were enrolled and allocated to therapy: 70 to varenicline and 69 to placebo. Of these, 59/70 (84.3%) in the varenicline group and 50/69 (72.5%) in the placebo group attended all visits (Figure 1). Demographic data, NRT use, and cotinine levels at baseline are shown in Tables 1 and 2. Most subjects were using nicotine chewing gums (2 mg gum, 68.3%; 4 mg gum, 11.5%), 5.8% were using nicotine inhalers, 7.2% were using nicotine sublingual tablets, and 9.4% were using nicotine lozenges. The mean daily number of units of NRT was 16 (*SD*: 8.1), and subjects had used NRT for a mean of 6 years (*SD*: 4.5).

Mean FTND scores, recalled retrospectively from when subjects had smoked a number of years ago, were 6.3 for the varenicline group and 6.7 for the placebo group (Table 3). At baseline, 60% of subjects in the varenicline group reported themselves as healthy, versus 59.4% in the placebo group. Hypertension was reported by 14.3% of subjects (varenicline) and 27% (placebo), and hypercholesterolemia was reported by 27.1% and 26.1% of subjects, respectively.

No statistically significant difference between the varenicline and the placebo group was found for any of the baseline data mentioned above.

Cessation of NRT

The PPR at 12 weeks was 64.3% with varenicline versus 40.6% with placebo (odds ratio [*OR*] = 2.6, 95% *CI*: 1.3–5.2). At all timepoints the PPR was superior for varenicline versus placebo, although the difference was only statistically significant at 12 and 36 weeks (Figure 2). The PPR at Week 52 were 42.9% (varenicline) versus 36.2% (placebo) (NS). The CAR from Weeks 9 to 12 was 48.6% (varenicline) versus 30.4% (placebo;

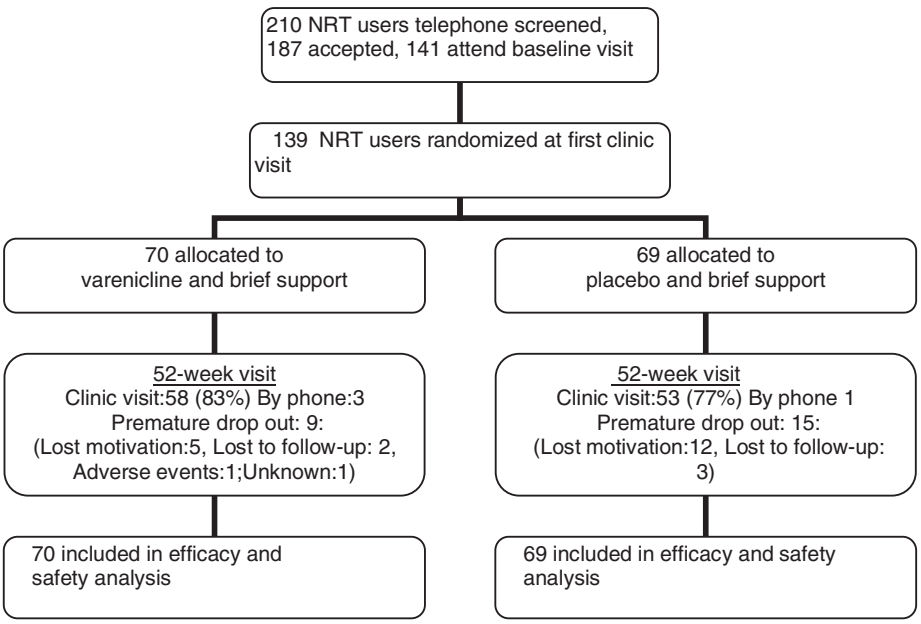

Figure 1. Flow diagram of participants through the study.

Table 1. Demographic Data, NRT Use, and Cotinine Levels at Baseline

Variable	Varenicline ($n = 70$)	Placebo ($n = 69$)
Age (years)	53.6 (8.2)	55.6 (9.1)
Female/Male	40/30	35/34
Body weight (kg)	75.8 (17)	80.0 (15)
Cigarettes per day when smoked (recalled)[a]	22.4 (8.9)	24.5 (9.9)
Age started smoking (years)	17.7 (6.5)	17.0 (6.2)
NRT, units per day	15.2 (6.5)	17.8 (9.4)
Duration of NRT use (years)	5.6 (3.7)	7.0 (5.1)
Expired CO level (ppm)	1.1 (2.0)	1.7 (3.8)
Plasma cotinine level (ng/ml)	530 (305)	530 (282)
Systolic blood pressure (mmHg)	142 (19)	149 (23)
Diastolic blood pressure	102 (9.6)	94 (11)
Waist circumference (cm)	100 (9)	103 (9)
Hip circumference (cm)	91 (13)	96 (15)

Note. Values are mean (SD).

[a]Number of cigarettes per day at the time subjects quit smoking.

Table 2. Baseline Characteristics

	Varenicline	Placebo
Mean time score to first use of NRT in the morning: (Score: 3: within 5 min; 2: 5–30 min; 1: 30–60 min; 0: >60 min.)	1.9	1.7
Mean "motivation to stop use of NRT" score: (Score scale: 0 = low to 5 = very high)	3.2	3.3
Mean "Believe in successfully stopping NRT" score: (Score scale: 0 = low to 5 = very high)	2.5	2.8
Previously consulted a doctor because of depression (prevalence proportion)	15.7%	14.5%
Previously been on antidepressant medication (prevalence proportion)	11.4%	14.5%
Previous suicidal thoughts (prevalence proportion)	4.3%	2.9%

Note. No statistical significant difference between the varenicline and the placebo group was found for any of the baseline characteristics.

One subject in the varenicline group (1.4%) reported depression at baseline.

OR = 2.2; 95% *CI*: 1.1–4.3; $p = .03$). The CAR from Week 12 to Week 52 was 40.0% in the varenicline group and 30.4% in the placebo group (*OR* = 1.52, 95% *CI*: 0.76–3.07).

Table 3. Nicotine Dependence Assessed by a Modified FTND scale and a Modified Horn-Russell Scale for Long-term NRT Users, and FTND Recalled From When Smoking

	Varenicline	Placebo	*p* value
$FTND_{NRT}$	5.5 (1.8)	6.1 (1.9)	NS
$H\text{-}R_{Total}$	17.7 (5.2)	18.4 (5.1)	NS
$H\text{-}R_{Addictive}$	6.6 (2.3)	6.9 (1.7)	NS
$H\text{-}R_{Automatic}$	4.3 (2.7)	4.6 (2.9)	NS
$H\text{-}R_{Craving}$	6.8 (1.6)	6.9 (1.7)	NS
$FTND_{Recalled}$	6.3 (2.3)	6.7 (2.1)	NS

Note. Scales were modified for NRT users instead of cigarette smokers. FTND scale: 0–10; Horn-Russell scale: total, 0–27; addictive, 0–9; automatic, 0–9; craving, 0–9. FTND recalled, 0–10. Higher scores indicate higher dependence. Values are mean (SD).

The mean plasma continine concentration in all subjects at entry was 530 ng/ml ($N = 139$). In failures (subjects who did not stop using NRT), the mean individual change from entry level was −344 ng/ml ($p < .00$, $N = 42$) at Week 12 but only −132 ng/ml ($p = .04$) at Week 52. In accordance with the definition of CAR, the cotinine concentration in quitters was practically zero at Weeks 12 and 52 (0.7 ng/ml and 0.2 ng/ml, respectively).

Intermittent Cigarette Smoking

At entry two subjects (2.9%) in the varenicline group reported having smoked during the previous week versus none in the placebo group. Smoking during the previous week was reported by three subjects (4.3%) in the varenicline group and one subject (1.4%) in the placebo group at Week 12, by one (1.4%) and two subjects (2.7%), respectively, at Week 24, and by four (5.7%) and three subjects (4.3%), respectively, at Week 52. There was no statistically significant difference in the odds of smoking between the two groups (varenicline vs. placebo) at entry or at Weeks 12, 24, and 52. Smoking in the period between Weeks 36 and 52 was reported by seven subjects (10%) in the varenicline group and eight subjects (11.6%) in the placebo group. At Week 52, the number of cigarettes smoked daily during the previous week were 1, 2, 3, and 6 ($N = 4$) for the varenicline group and 1 and 1 ($N = 2$) for the placebo group.

Withdrawal Symptoms and Weight Change

"Craving" and "total withdrawal symptoms" showed a gradual decrease in intensity during the first 12 weeks, with almost no symptoms at Week 12, whereas "appetite" remained more or less unchanged up to Week 52 and also had a much higher total score than the other withdrawal symptoms (Figure 3). Ratings for all three withdrawal symptoms were statistically significantly lower with varenicline than placebo at all visits (all visits analyzed combined); the craving score was 0.26 points lower with varenicline than placebo ($p < .0001$), appetite was 0.14 points lower ($p = .001$), and total withdrawal symptoms

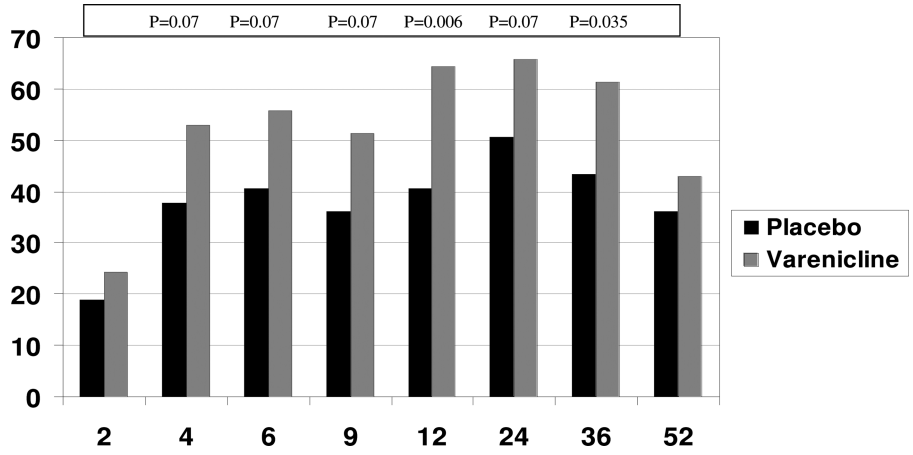

Figure 2. Quit rate (7-day point prevalence) for long-term NRT users in the varenicline and placebo groups from Weeks 2 to 52, verified by expired carbon monoxide (except Week 36, which was a telephone visit). x-Axis: weeks, y-axis: percent quitter.

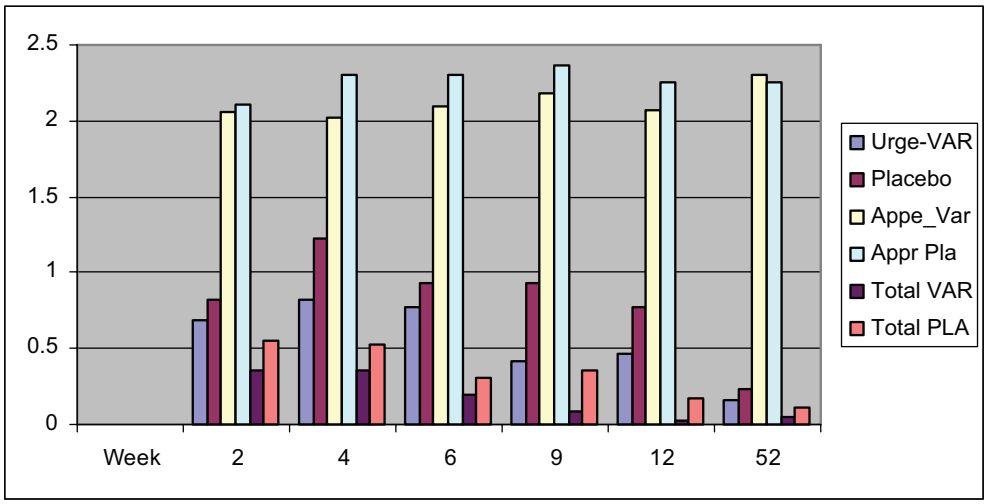

Figure 3. Mean withdrawal symptoms in quitters of long-term NRT use in varenicline and placebo groups. x-Axis: Week 0, 1–2, 2–4, 4–6, 6–9, 9–12, 12–24, 24–36, 36–52; y-axis: withdrawal score on a scale from 0 to 4.

was 0.16 point lower (p = .002). Weight gain and waist and hip circumference increases were significantly higher among quitters at Week 12 with no significant difference between the two treatment groups (Table 4).

Adverse Events

During the treatment period, 9 subjects (13%) dropped out from the varenicline group and 14 (20%) from the placebo group; during follow-up (after study medication had been discontinued) there were no drop outs from the varenicline group and one in the placebo group (Figure 1). Adverse events, which were elicited using specific questions at each visit, were reported by 70.6% of subjects in the varenicline group and 69.6% in the placebo group (NS). The adverse events that differed between treatment groups were those previously reported with varenicline, such as nausea, vomiting, and abnormal dreams. The incidence of nausea (varenicline vs. placebo) was 56.5% versus 11.8% at Week 2, 40.3% versus 8.1% at Week 6, declining to 23.0% versus 3.6% at Week 12. Over the 12-week treatment period a minority of subjects (15.1% of those on varenicline vs. 16.7% on placebo) rated the adverse events as severe or very severe. Vomiting was reported by 11.6% versus 11.8% (varenicline vs. placebo) of subjects for the entire treatment period. Frequent dreams during the previous week were reported by 49.9% versus 37.4% of subjects (varenicline vs. placebo, NS) during the treatment period. No serious adverse events were reported during the 12-week treatment period.

In the subsequent follow-up period, 11 serious adverse events were reported in 9 patients: in the varenicline group, these were cerebral stroke (1), severe constipation (1), bradycardia (1), cardiac arrest with successful resuscitation (1), and probable dengue fever (1). In the placebo group, the events were rectal cancer with ileostomy, acute peritonitis and later closure of ileostomy and chemotherapy (1), acute surgery with removal of gall bladder stone (1), malignant melanoma (1), and exacerbation of COPD (1). None of these events were considered related to varenicline or NRT use as they occurred after varenicline had been discontinued.

Table 4. Differences From Baseline in Body Weight, Waist and Hip Circumferences at Weeks 12 and 52 in Continuous Quitters of Long-term NRT Use and in Treatment Failures, Independent of Active or Placebo Treatment and for Varencline and Placebo Groups, Respectively

		Week 12					Week 52				
		Quitters		Failures			Quitters		Failures		
Parameter	Population	Mean ± *SD*	*p**	Mean ± *SD*	*p**	Δ	Mean ± *SD*	*p**	Mean ± *SD*	*p**	Δ
Body weight (kg)	All subjects	2.22 ± 2.24	<.05	0.78 ± 2.13	<.05	<0.05	3.11 ± 3.55	<.05	2.63 ± 2.90	<.05	NS
	Varenicline group	2.08 ± 2.26	<.05	1.05 ± 1.81	<.05	NS	2.66 ± 3.55	<.05	3.58 ± 2.96	<.05	NS
	Placebo group	2.38 ± 2.28	<.05	0.45 ± 2.46	NS	<0.05	3.56 ± 3.64	<.05	1.55 ± 2.46	<.05	<0.05
	Δ (*V* − *P*)	NS		NS			NS		S		
Hip (cm)	All subjects	4.58 ± 7.23	<.05	0.52 ± 6.37	NS	<0.05	6.08 ± 5.46	<.05	3.80 ± 5.02	<.05	NS
	Varenicline group	5.06 ± 6.9	<.05	1.44 ± 5.32	NS	<0.05	7.25 ± 4.86	<.05	4.74 ± 4.25	<.05	NS
	Placebo group	4.07 ± 7.78	<.05	−0.58 ± 7.34	NS	<0.05	4.92 ± 5.98	<.05	2.77 ± 5.64	<.05	NS
	Δ (*V* − *P*)	NS		NS			NS		NS		
Waist (cm)	All subjects	−0.16 ± 6.86	NS	−0.24 ± 6.50	NS	NS	−0.38 ± 9.23	NS	1.83 ± 5.51	<.05	NS
	Varenicline group	0.44 ± 7.74	NS	−0.33 ± 6.46	NS	NS	1.75 ± 6.89	NS	2.84 ± 5.42	<.05	NS
	Placebo group	−0.8 ± 5.98	NS	−0.13 ± 6.64	NS	NS	−2.5 ± 11	NS	0.72 ± 5.47	NS	NS
	Δ (*V* − *P*)	NS		NS			NS		NS		

Note. Differences from baseline are increases, except for values with minus signs.

Δ, difference between quitters and failures at Weeks 12 or 52; (*V* − *P*) = difference between varenicline and placebo treatment groups; NS = not statistically significant.

**p*, difference within group between baseline and Weeks 2 or 52.

Discussion

Varenicline combined with counseling was superior to placebo for quitting long-term NRT use, and was statistically significantly superior at Week 12, which was the primary endpoint. However, the placebo success rate in this study was high, with a PPR of 41% at Week 12 and 36% at Week 52. This is a much higher quit rate than those reported in two placebo-controlled trials of varenicline for smoking cessation, in which the quit rates in the placebo arms were 21% and 21% at Week 12 and 14% and 17% at Week 52 (Gonzales et al 2006; Jorenby et al 2006).

A study of varenicline versus placebo in 431 users of smokeless tobacco reported 12-week quit rates of 58% versus 39%, respectively, (Fagerström et al., 2010) which is in the same range as the present study. The mechanism of action of varenicline in long-term NRT users is probably the same as in smoking cessation, that is, reduction of withdrawal symptoms. In our study, we also observed that withdrawal symptom measures (craving, appetite, and total withdrawal symptoms) tended to be lower in the varenicline group as compared with placebo. Applying statistics for the trend showed that varenicline was statistically significantly more effective at reducing withdrawal as compared with placebo.

Dependence on Nicotine

We cannot validate whether our sample of long-term NRT users, who had used NRT for 6–7 years and used approximately 15 pieces of gum daily, is representative of long-term NRT users in general; but given our inclusion criteria, it is likely that our sample represented a more highly nicotine-dependent group. The most likely reason for long-term use of NRT is probably addiction to nicotine, and in accordance with that the subjects in our study reported withdrawal symptoms that subsided over the first few weeks, similar to the pattern observed after quitting cigarettes (American Psychiatric Association, 2000; Doherty et al., 1995; Killen & Fortmann, 1997; Schiffman et al., 2004; West et al., 1989). However, habituation to chewing the gum, fear of relapse to smoking, and the potential weight-reducing effect of NRT could also be reasons for long-term use. A weight increase of approximately 3.1 kg was recorded in NRT quitters in our study, and it was striking that ratings for "appetite" were high during the entire 52-week period, with no trend toward a decrease in severity with time. This has not been reported after smoking cessation. In an internet survey of 526 long-term users of nicotine chewing gum (more than 3 months; median use 2 years), 83% of respondents stated that they were addicted to the gum and 92% used the gum to avoid relapse to smoking (Etter, 2009).

The pharmacokinetics of nicotine is different between cigarettes and NRT. A cigarette delivers fast nicotine boli within 7–10 s after inhaling, with higher plasma peaks that occur after 5–10 min, whereas nicotine gum and other acute forms of NRT produce lower blood levels and peaks that occur later (after 20–30 min). This nicotine pharmacokinetic profile of NRT is the main reason that NRT has been found to have a low abuse potential in formal studies of abuse liability (Benowitz, 1990; Benowitz, Prochet, Sheiner, & Jacob, 1988; Fant, Henningfield,

Shiffman, Strahs, & Reitberg, 2000; Gorsline, 1993; Henningfield & Keenan, 1993; Nemeth-Coslett, Henningfield, O'Keefe, & Griffiths, 1987; Stitzer & De Wit, 1998).

At baseline, ratings of nicotine dependence for long-term NRT users in our study (measured using the modified FTND) were almost as high as for smokers, and the plasma cotinine levels of 530 ng/ml were higher than levels generally seen in smokers participating in cessation trials (Cahill et al., 2007; Fiore et al., 2008; Gonzales et al., 2006; Jorenby et al., 2006; Tonstad et al., 2006). Recall bias might have influenced the scoring for FTND for previous smoking several years ago. Although the long-term NRT users attained very high cotinine levels the NRT users did not obtain the high peaks in nicotine due to the above pharmacokinetic profiles.

The rationale of getting long-term NRT users to quit is mainly to quit dependence on NRT and nicotine and to reduce the cost of NRT use. Although long-term NRT use may have some adverse effects on health such as insulin resistance and possible cardiovascular effects (Assali et al., 1999; Eliasson et al., 1996; Ford & Zlabek, 2005), as compared with smoking long-term NRT use is preferable as the adverse health effects of NRT are negligible.

Relapse to Cigarettes

In this study, we found that 2.9% of subjects were smokers at 12 weeks, 2.2% at 24 weeks, and 5% at 52 weeks, with a total of 10.1% of subjects having smoked between Weeks 24 and 52; there was no statistically significant difference in numbers of smokers between treatment groups. These figures are in accordance with the findings in the smokeless tobacco cessation study. As only two subjects (1.4%) reported smoking during the week before entering our study, it appears that the proportion of smokers did increase slightly, although the increase in smoking during the study was not statistically significant. There is, however, a potential bias of not knowing how many subjects would have started to smoke, or smoked intermittently, even if they had not been enrolled in a clinical trial. Under-reporting of smoking at entry by subjects who wanted to participate in the study might also have occurred, as not smoking was one of the entry criteria.

Varenicline was well tolerated in our trial. The adverse events reported with varenicline were those previously documented with the drug, although the incidence of nausea was higher in our study than that reported from studies of varenicline for smoking cessation (Gonzales et al., 2006; Jorenby et al., 2006).

Weight Gain

Varenicline did not have any effect on weight gain or increase in waist and hip circumference, either in abstainers or treatment failures. The gain in body-weight at Week 12 was significantly higher among quitters than failures, 2.2 kg versus 0.8 kg, but at Week 52 there was no significant difference in weight gain between the two groups (3.1 kg vs. 2.6 kg, respectively). This is probably due to the fact that several of the failures had succeeded in either cutting down, or had stopped using, NRT for a shorter period, which probably resulted in a permanent weight gain. In addition, at both Weeks 12 and 52 the failures had reduced their nicotine intake substantially—as demonstrated by a lower plasma cotinine level—which might also have contributed to the weight gain.

This finding indicates that nicotine is the main factor that prevents weight gain in smokers and NRT users. Use of NRT following smoking cessation generally only reduces post-cessation weight gain by a few kilograms, but it is plausible that our group of long-term NRT users had used such high doses of nicotine (as NRT) that it more or less had a similar effect as cigarette smoking in preventing weight gain.

Costs

In terms of costs—independent of whom has to pay—we have calculated that getting one long-term NRT user to quit with varenicline will cost approximately US$450 in medication, as compared with a saving of US$1,600 spent on NRT every year. The estimated costs for the clinic support program (seven visits and two phone calls) employed in our study are US$1,600/patient. As the number needed to treat was 3.0 for placebo and 2.5 for varenicline, which means that the cost of getting one long-term NRT user to quit with varenicline would be approximately US$5,125, with a saving of US$1,600, that is, the net expense would be US$3,525 per quitter for the first year, as compared with a cost of US$4,800 (net expense of US$3,200) for placebo treatment.

In summary, this study demonstrated that varenicline for 12 weeks combined with supportive visits was safe to use and, as compared with placebo, increased the quit rate in long-term NRT users. Weight gains of 3.1 kg in quitters and 2.6 kg in failures were observed, along with a consistently high score for appetite throughout the 52-week study period.

Supplementary Data

Supplementary data can be found online at http://ntr.oxfordjournals.org/content/early/2012/09/12/ntr.nts146/suppl/DC1

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Declaration of Interests

Philip Tønnesen has received speaker fees, consultancy and advisory board honoraria, and research grants from several pharmaceutical companies, including Pfizer, that produce and/or market drugs for smoking cessation. Kim Mikkelsen has no conflicts of interest. This study was an independent, investigator-initiated study, and Pfizer has had no influence on the design or conduct of the study or preparation of this paper.

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