Nicotine & Tobacco Research
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713439766

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Online Publication Date: 01 July 2008

To cite this Article: Becker, Karen M., Rose, Jed E. and Albino, Anthony P. (2008) 'A randomized trial of nicotine replacement therapy in combination with reduced-nicotine cigarettes for smoking cessation', Nicotine & Tobacco Research, 10:7, 1139 — 1148

To link to this article: DOI: 10.1080/14622200802123294
URL: http://dx.doi.org/10.1080/14622200802123294

Nicotine & Tobacco Research Volume 10, Number 7 (July 2008) 1139–1148

A randomized trial of nicotine replacement therapy in combination with reduced-nicotine cigarettes for smoking cessation

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Received 20 March 2007; resubmitted 12 June 2007; accepted 20 December 2007

A randomized double-blind, active controlled, parallel group, multi-center phase II clinical trial was conducted to evaluate the efficacy of reduced-nicotine cigarettes as a novel smoking cessation treatment (under Investigational Device Exemption 69,185). The concept for a reduced-nicotine cigarette designed to progressively wean smokers from the smoking habit is based on research demonstrating that successful smoking cessation is not only dependent on withdrawal of nicotine, but also on weaning from the habitual sensory and behavioral reinforcement of smoking. Treatment consisted of Quest brand of cigarettes (Quest 1, 2, and 3), which respectively deliver 0.59 ± 0.06, 0.3 ± 0.05, and less than 0.05 mg nicotine, either alone or in combination with nicotine replacement therapy (NRT). The primary endpoint was 4 weeks of continuous abstinence (Weeks 7–10), with additional follow-up at 3 and 6 months. Adult men and women smokers (N=346), motivated to quit, were randomized to one of three treatment groups: Quest plus NRT (NRT pretreatment 2 weeks before, and NRT after the quit date), Quest plus placebo patch, or active control plus NRT (conventional cigarette, followed by NRT after quit date). Results showed that Quest plus NRT was more effective than active control plus NRT in achieving 4 weeks of continuous abstinence (32.8% vs. 21.9%). Quest plus placebo patch yielded an abstinence rate similar to that of the active control plus NRT (16.4% vs. 21.9%). No serious adverse events were attributable to the investigational product. Quest plus NRT offers promise as a new smoking cessation treatment.

Introduction

Cigarette smoking is a complex behavior that is now understood to be sustained by the pharmacological properties of nicotine and the reinforcing behavioral and sensory cues associated with the act of smoking (Benowitz, 1999; Monchuk, Rousu, Shogren, Nonnemaker, & Kosa, 2007; Rose & Behm, 2004a). These pharmacological and behavioral components are thought to be mediated by distinct neural and psychological processes (Naqvi & Bechara, 2005). Currently many smoking cessation products and methodologies are available to smokers, including nicotine replacement therapies (NRT) such as the nicotine skin patch, and medications available by prescription, such as bupropion and varenicline. In general, these approaches fall short of helping the majority of smokers to achieve long-term abstinence. NRT in combination with counseling and education remains effective in only a minority of patients, with success rates increasing by 1.5–2.0-fold compared with placebo regardless of the type of NRT (Silagy, Lancaster, Stead, Mant, & Fowler, 2004). Relapse is common following NRT use, and it has been estimated that 75% to 80% of smokers who receive treatment are unable to achieve long-term abstinence at 6 or 12 months (Fiore, Smith, Jorenby, & Baker, 1994; Hajek et al., 1999). Similar relapse rates are observed even with the use of prescription medications such as bupropion or varenicline (Fiore et al., 1994; Hughes et al., 2003; Hurt et al., 2002; Jorenby et al., 2006; Litten & Allen, 1999; Peters & Morgan, 2002; West, 2003).

Current treatment approaches may have limited efficacy because they do not adequately address the

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ISSN 1462-2203 print/ISSN 1469-994X online

DOI: 10.1080/14622200802123294

behavioral and sensory components of cigarette addiction, which have been shown to be important in the reinforcement of smoking. For example, blocking or altering airway sensory stimulation using local anesthesia or menthol (Rose & Behm, 2004a) leads to reduced smoking satisfaction; this result suggests that sensory stimulation remains an important mechanism to satisfy craving for cigarettes. Indeed, promising results have been reported in clinical trials using citric acid inhalation to substitute for some components of airway sensations sought by smokers (Behm, Schur, Levin, Tashkin, & Rose, 1993; Westman, Behm, & Rose, 1995). The use of nicotine-free cigarettes, in the absence of concomitant nicotine delivery, consistently produce satisfaction, reward, and craving reduction in smokers (Brauer et al., 2001; Breland, Buchhalter, Evans, & Eissenberg, 2002; Buchhalter, Schrinel, & Eissenberg, 2001; Butschky, Bailey, Henningfield, & Pickworth, 1995; Dallery, Houtsmuller, Pickworth, & Stitzer, 2003; Gross, Lee, & Stitzer, 1997; Pickworth, Fant, Nelson, Rohrer, & Henningfield, 1999; Rose, Behn, Westman, & Johnson, 2000; Westman, Behm, & Rose, 1996). In addition, the use of denicotinized cigarettes elicits higher subjective ratings than those elicited by intravenous nicotine administration (Rose et al., 2000; Westman et al., 1996). These studies suggest that sustaining smoking-related sensory cues may be an effective behavioral weaning tool to help reduce relapse (Rose & Behm, 2004b).

Moreover, use of denicotinized cigarettes may promote rapid extinction of the reinforcing value of smoking-related behavioral and sensory cues. Recent studies in both laboratory and outpatient-type research settings have demonstrated that use of denicotinized cigarettes over a period of 1–2 weeks weakens the reinforcing effects of smoking (Donny, Houtsmuller, & Stitzer, 2007; Rose & Behm, 2004a). Denicotinized cigarettes may reduce smoking of conventional cigarettes through two mechanisms: first, by providing a temporary behavioral substitute for conventional cigarettes to acutely relieve craving; second, by removing the primary reinforcing effects of nicotine, less craving is generated on a continuing basis.

A complementary approach to weaken the primary reinforcing effects of nicotine is pretreatment with NRT prior to the quit date. Pretreatment with NRT has been shown to reduce the reinforcing effects of smoking (Rose, Behm, Westman, & Kikovich, 2006), and to increase abstinence rates regardless of whether conventional, low nicotine, or denicotinized cigarettes are smoked prior to the quit date (Rose et al., 2006; Schuurmans, Diacon, van Biljon, & Bolliger, 2004). However, in such a context, the use of denicotinized cigarettes in combination with NRT obviates concerns about any potential increased toxicity related to nicotine associated with concurrent use of NRT plus conventional cigarettes (Rose, Behm, Westman, Bates, & Salley, 2003). Currently marketed low tar and nicotine cigarettes achieve their Federal Trade Commission (FTC) ratings through ventilation holes in the filter, despite containing tobacco with significant quantities of nicotine (Benowitz et al., 1983). The high nicotine content of the tobacco raises concerns that the compensatory smoking behavior often seen in ventilated-filter cigarette smokers may further increase toxicity (Kozlowski, Pope, & Lux, 1988; Rose & Behm, 2004b).

No optimal way remains to convert dependent smokers into permanent nonsmokers. A broad range of treatment options may be necessary to improve upon current success rates and to achieve long-term abstinence. Denicotinized cigarettes, such as Quest, may improve upon existing smoking cessation approaches by substituting for the sensory and behavioral cues associated with cigarette use while helping to maximally dissociate these cues from the contingent delivery of nicotine reinforcement, thus providing an effective exit strategy from cigarette addiction.

To test this novel concept for a smoking cessation aid, we conducted a randomized, double-blind, active controlled, parallel group, multicenter phase II clinical trial in healthy smokers to compare (a) conventional cigarettes plus NRT treatment with (b) progressive use of cigarettes with decreasing nicotine content (Quest 1, 2 and 3) alone or in combination with NRT, in achieving smoking cessation.

Method

Participants

The study population consisted of 346 generally healthy smokers, 21–65 years of age, recruited from five centers (Central Kentucky Research, Lexington, KY; University Clinical Research, Inc., Pembroke Pines, Florida; Triangle Medical Research Associates, Raleigh, North Carolina; Clinical Research Associates Inc., Nashville, Tennessee; and Rochester Clinical Research, Inc., Rochester, New York). Subjects were required to have smoked an average of 15 or more cigarettes per day for at least 1 year prior to randomization, be motivated to quit smoking, and be able to return for scheduled follow-up examinations for a total of 8 months. A carbon monoxide (CO) measurement >15 ppm corrected for ambient levels at baseline was required for entry into the study (the corrected CO level was determined by taking the subject's measured CO reading and subtracting the CO reading of the ambient air prior to testing, as per the instructions for use of the CO

monitor.) Subjects who qualified as capable of comprehending the nature of the study and were willing to provide informed consent were entered into the study. Exclusion criteria included current use of NRT or other tobacco-based product (e.g., chew, snuff, or other); usual brand consisting of menthol variety of cigarettes; smoking more than 3 packs of cigarettes per day; serious pathophysiology that might impose a risk to the subject (at the discretion of the physician); or use of illegal drugs. Subjects were also excluded if they were pregnant, were planning to become pregnant, or were lactating; were consuming an average of three or more drinks of alcohol per day; or were hypertensive (systolic blood pressure higher than 140 mmHg and/or diastolic blood pressure higher than 90 mmHg).

Study materials

Four types of test cigarettes were used in this study: Quest 1, 2 and 3 cigarettes, and active control cigarettes (the active control was a conventional, American blended cigarette with a nicotine yield of 0.80 ± 0.10 mg/cigarette and a tar yield of 10.2 ± 0.5 mg/cigarette). Quest cigarettes differ from traditional cigarettes by the inclusion of genetically modified tobacco with reduced nicotine content. As measured by the Federal Trade Commission (FTC) regimen, Quest 1 delivers 0.59 ± 0.06 mg nicotine (9.0 ± 1.0 mg tar) per cigarette; Quest 2 delivers 0.30 ± 0.05 mg nicotine (8.0 ± 1.25 mg tar) per cigarette; and Quest 3 delivers less than 0.05 mg nicotine (8.5 ± 1.0 mg tar) per cigarette. However, the actual tobacco rods of Quest cigarettes contain the following total amounts of nicotine: 8.9 mg (Quest 1), 5.1 mg (Quest 2), and 0.48 mg nicotine (Quest 3).

The product is designed to provide smokers who wish to quit with the sensory and behavioral reinforcement of a conventional cigarette while withdrawing inhaled nicotine in a step-wise manner. The transdermal nicotine patch used in this study was a generic over-the-counter product (1-800-PATCHES), in 21-, 14-, and 7-mg doses. All patches were 24-hr applications to be reapplied daily. Placebo patches were manufactured to match the size, appearance, and texture of an active NRT patch to preserve blinding.

To blind the cigarette assignment, Quest 1, Quest 2, Quest 3, and active control cigarettes were labeled in accordance with their study visit period, and were packaged 20 cigarettes per pack and 10 packs per carton. All investigational products were indistinguishable from one another. The 21-, 14-, 7-mg, and placebo NRT patches were repackaged in an identical manner in accordance with the randomization scheme of the study. Twenty patches were packaged in each box. Each study kit contained the appropriate number of cigarette cartons and patches for one study subject.

Procedure

The study was conducted in compliance with Good Clinical Practices and under an Investigational New Drug Application (IND) from the Food and Drug Administration. Healthy male and female smokers interested in quitting smoking were recruited from the community and screened for eligibility as described above. Once written consent was provided, the subject underwent a complete screening procedure, consisting of relevant medical history, physical examination, urine pregnancy test in women of childbearing potential, drug screen, exhaled CO, saliva cotinine, and completion of study questionnaires (Minnesota Smoking Withdrawal Questionnaire, Cigarette Evaluation Scale Questionnaire, Sensory Questionnaire, and Fagerström Test for Nicotine Dependence [FTND]).

Following screening, eligible subjects were randomized in a 1:1:1 ratio scheme to one of three treatment arms, as illustrated in Figure 1. Subjects were examined and evaluated every 2 weeks after randomization until the end of Week 18 (the 3-month quit date) and then 3 months later at the end of Week 31 (6-month quit date), in accordance with a predetermined visit schedule of 12 expected clinic visits.

During the first 6 weeks of the study, subjects receiving Quest plus NRT and those receiving Quest plus placebo patch transitioned from their usual brand of cigarettes to Quest cigarettes. Subjects in each of the two groups smoked ad libitum for 2 weeks at each Quest nicotine level beginning with Quest 1, then proceeding to Quest 2, and finally to Quest 3. Two weeks before the quit date, at the beginning of Week 5, Quest use in the Quest plus NRT group was supplemented with the addition of a transdermal nicotine patch (21 mg), consistent with the study protocol specified pretreatment in this group, while subjects in the Quest plus placebo patch group added a placebo patch.

The end of Week 6 was considered the quit date, at which time subjects were instructed to quit all smoking. Subjects in the Quest plus NRT group then received a 21-mg transdermal nicotine patch for an additional 4 weeks, followed by a 14-mg patch for 2 weeks, a 7-mg patch for 2 weeks, and a placebo patch for 2 weeks. Subjects in the Quest plus placebo patch group received a placebo patch starting at Week 5 which was continued to the end of Week 16, the end of all treatment.

Subjects in the active control plus NRT group were provided (the same) active control cigarettes

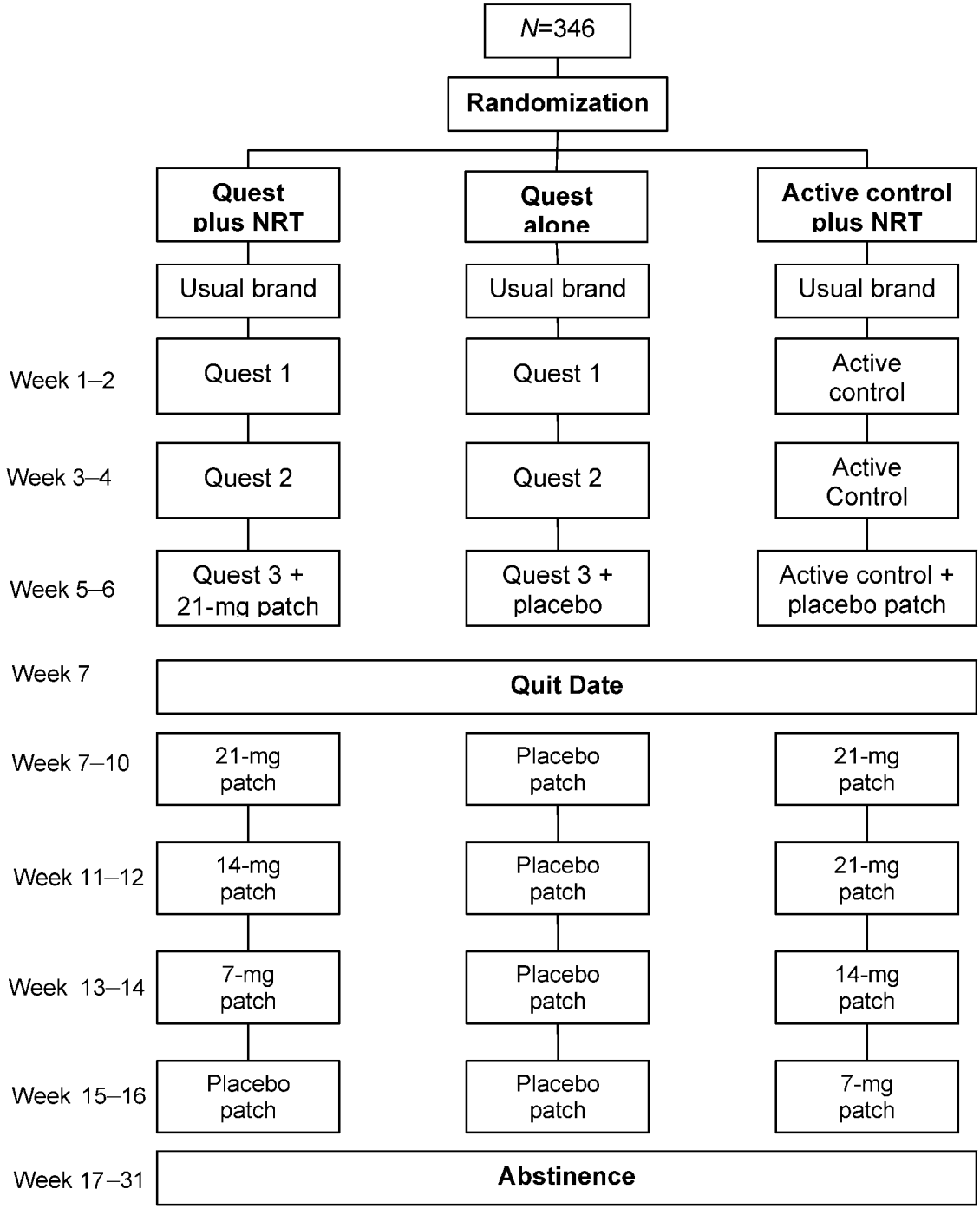

Figure 1. Clinical treatment arms.

as described above. These cigarettes were sham-faded, every 2 weeks, in parallel with the nicotine-fading provided in the Quest plus NRT and Quest plus placebo patch groups. To maintain blinding of patch assignment, the active control plus NRT received placebo patches during the 2 weeks immediately preceding their quit date. Subsequently, NRT treatment in this group complied with current labeling requirements for OTC patches, indicating treatment with active NRT following the quit date, or in this study at the beginning of Week 7. Furthermore, careful consideration was made to limit active patch exposure to 10 weeks, with 6 weeks of exposure to the highest dosage form (21 mg) and no more than 2 weeks exposure at lower weaning doses of 14 and 7 mg, respectively. To provide appropriate controls to the Quest plus NRT and Quest plus placebo patch groups, subjects in the active control plus NRT group received 6 weeks of a 21-mg patch, followed by 2 weeks of a 14-mg patch, and 2 weeks of a 7-mg patch. From Weeks 17 to 31, subjects in

the three groups were expected to be abstinent. After the initial 4-week abstinence period, abstinence was again measured 3 months after the quit date, and at 6 months after the quit date. All subjects received behavioral support with printed materials and a 10-min individual counseling session at the first clinic visit by a certified smoking cessation counselor.

Study endpoints

The primary endpoint of this study was 4 weeks of continuous abstinence measured from Weeks 7 to 10 of the study. Abstinence was determined by self report and verified by exhaled CO$<$10 ppm for each subject. Subjects were considered to have completed the study if they had completed all follow-up examinations through Week 31. Secondary endpoints included: quit rates at 3 and 6 months; evaluation of preference and satisfaction of Quest over usual brand; severity of withdrawal symptoms; and compensatory smoking behavior. Safety was assessed by reports of adverse events.

Analyses

The study was designed to test two null hypotheses:

- H_{01}: Probability of quitting in the Quest plus NRT group=probability of quitting in the active control plus NRT group;
- H_{02}: Probability of quitting in the Quest plus placebo patch group=probability of quitting in the active control plus NRT group.

For both hypotheses the alternatives were one-tailed (p=.025) with probability in the active control plus NRT group being less than in the Quest groups. The rationale for a one-tailed test was based on previous research (Rose et al., 2006; Schuurmans et al., 2004) indicating a potential benefit in smoking cessation. Two-tailed probabilities are also presented.

These hypotheses were tested using the intent-to-treat (ITT) population of all randomized subjects and the Fisher exact test. Adjustment for multiplicity was made using the Bonferroni correction (Kleinbaum, 1988). Descriptive statistics included mean, standard deviation, median, and range for continuous variables, and frequency and proportion for discrete variables. Group differences were tested using the chi-square statistic for categorical data and analysis of variance for continuous variables. If subjects without a valid Week 10 assessment or abstinence were dropped out because of lack of efficacy and his/her abstinence status could not be determined, the subject was considered a treatment failure. Logistic regression was used to identify prognostic factors and to conduct an adjusted analysis of the primary outcome. All statistical tests report two-tailed p values with no adjustment for multiplicity, except where noted.

Results

Table 1 shows subject disposition for each of the three treatment groups at the end of Week 10, the predetermined date for evaluation of the primary effectiveness endpoint of the study. Two of the 346 subjects enrolled (0.6%) did not meet all eligibility criteria. All 346 subjects received study treatment. A total of 262 (75.7%) subjects met the criteria for assessment of 4 weeks of continuous abstinence. Eighty-four (24.3%) subjects were unable to be assessed at Week 10. The most common reasons for the lack of assessment was lost to follow-up (9%) and subjects withdrawing consent (8.1%). At Week 10, discontinuation rates were 24.1%, 31.9% and 16.7%, for Quest plus NRT, Quest plus placebo patch, and active control plus NRT, respectively. Quest plus NRT versus active control plus NRT was p=.19, and between the p-value for Quest plus placebo patch versus active control plus NRT was p=.028.

Demographic characteristics by treatment group are summarized in Table 2. Of the 346 subjects enrolled, 53.8% were male and 46.2% were female. The percent of males was significantly different between the groups (p=.0029). The mean age was 45.9 years. The majority of subjects were White (92.2%); 3.5% of the study population was Hispanic, 3.2% was Black, and 0.6% was Asian or Pacific Islander.

Table 3 summarizes the baseline characteristics of the study population. Baseline characteristics were comparable between groups. Most subjects reported smoking light cigarettes (48.6%), followed by full

Table 1. Subject disposition.

Measure	Quest plus NRT (n=116), n (%)	Quest plus placebo patch (n=116), n (%)	Active control plus NRT (n=114), n (%)	Total (N=346), n (%)
All eligibility criteria met	115 (99.1%)	115 (99.1%)	114 (100.0%)	344 (99.4%)
Received study treatment	116 (100.0%)	116 (100.0%)	114 (100.0%)	346 (100.0%)
Completed 4 weeks (week 10)	88 (75.9%)	79 (68.1%)	95 (83.3%)	262 (75.7%)
Discontinued	28 (24.1%)	37 (31.9%)	19 (16.7%)	84 (24.3%)
Completed study* (week 31)	32 (27.6%)	20 (17.2%)	33 (28.9%)	85 (24.6%)

Note. n, number of randomized subjects; %=$n/N\times$ 100%. *Subject disposition data from CRF Study Completion/Early Withdrawal from the question, "Did the patient complete study?"

Table 2. Summary of subject demographics.

	Quest plus NRT (*n*=116)	Quest plus placebo patch (*n*=116)	Active control plus NRT (*n*=114)	Total (*N*=346)
Sex, *n* (%)				
Men	41 (35.3%)	67 (57.8%)	52 (45.6%)	160 (46.2%)
Women	75 (64.7%)	49 (42.2%)	62 (54.4%)	186 (53.8%)
Age at randomization (years)				
Number of available subjects	116	116	114	346
Mean (*SD*)	45.5 (11.1)	46.1 (10.5)	46.3 (11.0)	45.9 (10.9)
Range	21–66	23–65	24–66	21–66
Race, *n* (%)				
Asian or Pacific Islander	0	1 (0.9%)	1 (0.9%)	2 (0.6%)
Black, not of Hispanic origin	4 (3.4%)	4 (3.4%)	3 (2.6%)	11 (3.2%)
Caucasian, not of Hispanic origin	109 (94.0%)	107 (92.2%)	103 (90.4%)	319 (92.2%)
Hispanic	2 (1.7%)	3 (2.6%)	7 (6.1%)	12 (3.5%)
Other, specify	1 (0.9%)	1 (0.9%)	0	2 (0.6%)

Table 3. Summary of baseline characteristics.

	Quest plus NRT (*n*=116)	Quest plus placebo patch (*n*=116)	Active control plus NRT (*n*=114)	Total (*N*=346)
Current number of cigarettes per day				
Number of available subjects	116	116	114	346
Mean (*SD*)	27.0 (9.5)	25.4 (8.6)	25.9 (8.5)	26.1 (8.9)
Range	15–60	15–60	15–50	15–60
First attempt to quit, *n* (%)				
No	104 (89.7%)	109 (94.0%)	102 (89.5%)	315 (91.0%)
Yes	12 (10.3%)	7 (6.0%)	12 (10.5%)	31 (9.0%)
Number of previous quit attempts				
Number of available subjects	116	115	114	345
Mean (*SD*)	4.4 (5.0)	3.5 (3.8)	4.2 (7.1)	4.0 (5.5)
Years of smoking				
Number of available subjects	116	116	114	346
Mean (*SD*)	26.3 (11.4)	26.4 (11.2)	27.8 (11.4)	26.8 (11.3)
Range	4–51	1–53	5–50	1–53
Corrected CO measurement (ppm)				
Number of available subjects	116	116	114	346
Mean (*SD*)	28.7 (13.3)	26.6 (8.6)	27.3 (9.7)	27.5 (10.7)
Range	15–82	15–56	14–60	14–82

flavor cigarettes (23.4%), and ultra-light cigarettes (21.1%) (data not presented). More than 90% of subjects indicated that this was not their first attempt to quit smoking. The number of previous attempts ranged from 0 to 50; however, most subjects reported between 1 and 4 previous quit attempts (M=4.0). The mean duration of smoking reported was 26.8 years. At baseline, the mean CO measurement was 27.5 ppm.

Results for the primary endpoint, 4 weeks of continuous abstinence following the quit date, are provided in Table 4. A global chi-square test was performed to test overall level of significance in a 2×3 table. This test showed statistical significance (p=.01). Pair-wise comparisons were then performed between the Quest plus NRT and the active control plus NRT, and the Quest plus placebo patch and the active control plus NRT as specified by the study design.

The proportion of subjects abstinent at 4 weeks was 32.8% for Quest plus NRT, 16.4% for Quest plus placebo patch, and 21.9% for active control plus

Table 4. Proportion of subjects achieving 4-week continuous abstinence.

	Quest plus NRT (*n*=116)	Quest plus placebo patch (*n*=116)	Active control plus NRT (*n*=114)
4-week abstinence, *n* (%)	38 (32.8%)	19 (16.4%)	25 (21.9%)
95% *CI* for 4-week abstinence rate	(24.3%, 42.1%)	(10.2%, 24.4%)	(14.7%, 30.6%)
p value compared to active control plus NRT*	0.04	0.89	

Note. Subjects whose corrected CO<10 ppm, number of cigarettes smoked since last visit, or 4-week abstinence could not be determined were treated as not meeting 4-week continuous abstinence. *n*, number of randomized subjects; %=$n/N \times 100$%. Exact 95% *CI* are given; *One-sided Fisher's exact test for 4-week abstinence proportions compared with active control plus NRT.

NRT. The one-tailed p value for the comparison of 4-week abstinence proportions in the Quest plus NRT group compared with the active control plus NRT was .04 (two-tailed $p=.08$). The abstinence proportions between the Quest plus placebo patch and active control plus NRT was not statistically significant ($p=.89$).

As noted in Table 2, there was an imbalance in the proportion of men and women across groups. For this reason, a logistic regression analysis was conducted on the primary outcome measure, adjusting for sex. The adjusted odds ratio and p value for the comparison of Quest plus NRT versus active control plus NRT group were similar to the value without this adjustment ($p=.04$, one-tailed); the p value for the comparison of Quest plus placebo patch versus active control plus NRT group remained nonsignificant ($p=.32$, one-tailed).

An exploratory logistic regression analysis was conducted that included terms for sex, treatment group, and a sex × treatment interaction. Separate analyses were conducted for the Quest plus NRT and active control plus NRT groups, and the QUEST alone and placebo plus NRT groups. The results suggested an interaction between sex and treatment group: for the Quest plus NRT and active control plus NRT groups ($p=.08$), and for the Quest plus placebo patch and active control plus NRT groups ($p=.11$). Logistic regression analyses were then conducted separately for men and women. The results of these analyses indicated that women in the Quest plus NRT group had a significantly higher 4-week continuous abstinence rate than women in the active control plus NRT group: 27% versus 15%, $p=.02$. For men, however, there was no difference: 31% versus 27%, $p=.68$. The abstinence rate in the Quest plus placebo patch group did not differ from that of the active control plus NRT for women (19% vs. 15%, $p=.28$); there was, however, a trend for men to have a lower probability of abstinence in the Quest plus placebo patch group than in the active control plus NRT group (12% vs. 27%, $p=.06$).

Logistic regression, using treatment failure imputation and univariate predictor variables, was used to identify factors predicting treatment outcome. The model identified number of cigarettes smoked per day at baseline as significantly correlated with 4-week abstinence rates ($p=.02$); lighter smokers had a higher abstinence rate. Additionally, just prior to the quit date (Week 6), cigarettes smoked per day strongly predicted outcome ($p=.003$); again, smoking fewer cigarettes was associated with subsequent abstinence. Abstinence was not significantly correlated with baseline FTND score; however, abstinence was strongly predicted by FTND score at Week 6 ($p=.0001$). Subjects showing lower FTND scores at that time point had a higher probability of achieving abstinence. An additional predictor of abstinence at Week 6 was compliance with smoking only the Quest 3 cigarettes during the previous 2 weeks ($p=.005$). In the Quest plus NRT and Quest plus placebo patch groups, subjects reporting no smoking of regular cigarettes had a significantly higher abstinence rate (44%) than those reporting any smoking of regular cigarettes (28%).

Some 103 subjects (29.8%) had missing 6-month abstinence status, which included 89 subjects (25.7%) whose abstinence status was also missing at 3 months. These subjects were assumed failures at the respective follow-up times. No statistically significant differences in abstinence were observed at 3 months between Quest plus NRT and active control plus NRT groups ($p=.38$) or between Quest plus placebo patch and active control plus NRT groups ($p=.89$) or at 6 months ($p=.43$, $p=.77$, respectively).

Subjects found the experience of using Quest cigarettes less satisfying than regular cigarettes. This was demonstrated by responses to the Cigarette Evaluation Scale Questionnaire on which mean satisfaction ratings were higher for cigarettes in the Active control plus NRT group ($M=3.1$, $SD=1.30$) than for Quest 3 cigarettes in the Quest plus NRT group ($M=2.2$, $SD=1.05$; $F[1,200]=27.20$, $p=.0001$) or Quest plus placebo patch group ($M=2.5$, $SD=1.21$, $F[1,194]=10.26$, $p=.002$).

The number of Quest 1 cigarettes consumed increased relative to the control cigarettes. From Week 1 to Week 3, the number of control cigarettes smoked increased slightly (M change=2.0 cigarettes/day, $SD=6.51$), whereas there was a significantly greater increase of 3.8 Quest 1 cigarettes/day ($SD=6.30$) in the Quest plus NRT group ($F[1,219]=4.29$, $p=.04$) and 4.6 Quest 1 cigarettes/day ($SD=6.66$) in the Quest plus placebo patch group ($F[1,220]=9.01$, p=.003). Similarly, in Weeks 4–5 the number of Quest 2 cigarettes smoked was greater than the corresponding number in the active control plus NRT group. The increase relative to Week 1 in the active control plus NRT group was 3.9 cigarettes/day ($SD=7.62$), whereas the number of Quest 2 cigarettes smoked increased by 7.1 cigarettes/day ($SD=8.33$) in the Quest plus NRT group ($F[1,12]=9.06$, $p=.003$) and by 6.5 cigarettes/day ($SD=8.42$) in the Quest plus placebo patch group (F[1,212]=5.88, $p=.02$). In contrast, the number of Quest 3 cigarettes smoked showed no greater change relative to Week 1 than did the control cigarettes: an increase of 2.3 control cigarettes/day ($SD=8.69$) in the active control plus NRT group versus 0.3 Quest 3 cigarettes/day ($SD=11.36$) in the Quest plus NRT group ($F[1,200]=1.82$, $p=.18$) and 3.2 Quest 3 cigarettes/day ($SD=11.50$) in the Quest plus placebo patch group ($F[1,198]=0.44$, $p=.51$).

Exhaled CO levels also showed a slightly greater increase after switching to Quest 1 or Quest 2 cigarettes

than after switching to the control cigarettes. While CO levels remained constant from Week 1 to Week 3 in the active control plus NRT group (M change = −0.2 ppm, SD=10.25), CO levels increased nonsignificantly by 1.5 ppm (SD=11.27) with Quest 1 cigarettes in the Quest plus NRT group (F[1,220]=1.46, p=.22) and by 2.5 ppm (SD=10.69) in the Quest plus placebo patch group (F[1,221]=3.64, p=.06). By Week 5, CO levels remained constant in the active control plus NRT group (M change vs. Week 1 of 0.2 ppm, SD=10.59). There was, however, a trend for CO levels to increase upon smoking Quest 2 cigarettes, by 2.9 ppm (SD=11.25) in the Quest plus NRT group (F[1,213]=3.26, p=.07) and by 2.9 ppm (SD=10.82) in the Quest plus placebo patch group (F[1,215]=3.39, p=.07). No differential increase in CO levels was seen with Quest 3 cigarettes; by Week 7 the change in CO level was −2.5 ppm (SD=11.26) in the active control plus NRT group versus −5.4 ppm (SD=14.43) in the Quest plus NRT group (F[1,203]=2.46, p=.12) and −3.0 ppm (SD=12.54) in the Quest plus placebo patch group (F[1,200]=0.09, p=.76).

There were three serious adverse events, none of which was deemed to be treatment related. Two events were a case of bladder carcinoma, and a case of fibula and tibia fractures. The third event was a subject in the Quest plus NRT with reported chest discomfort and increased blood pressure. Because of a history of cardiovascular disease (myocardial infarction, angioplasty, hypertension), the subject was discontinued. Three subjects developed dermatological reactions while using the NRT patch.

Discussion

Results of this study support the potential usefulness of a progressively denicotinized cigarette plus NRT for promoting smoking cessation. In this study, Quest plus NRT showed a higher abstinence rate than standard-of-care NRT. Although not meeting the strict Bonferroni criterion for statistical significance, the results are nonetheless suggestive that Quest plus NRT treatment increased the abstinence rate beyond standard-of-care NRT. The magnitude of the cessation effect in the Quest plus NRT group (32.8%) versus active control plus NRT group (21.9%) is a clinically relevant improvement in 4-week quit rates. Treatment success was also predicted by cigarettes smoked per day. Heavier smokers had less success quitting. It is reasonable to theorize that the benefit of Quest plus NRT may be understated given that use of an active control plus NRT cigarette in a sham-fading procedure in and of itself may have an effect on abstinence.

As hypothesized based on the literature, the benefit of precessation NRT was consistent with the higher success rate in the group of subjects pretreated with NRT 2 weeks before quitting, relative to the Quest without NRT and standard NRT groups. In a previous study, precessation NRT was found to increase quit rates, and, when used in conjunction with denicotinized cigarettes, also resulted in higher compliance with use of denicotinized cigarettes (Rose et al., 2006). Compliance, in turn, was shown to predict abstinence in this study and in previous unpublished studies with Quest cigarettes. Concurrent NRT may thus serve two important functions in a cigarette-weaning program. First, as just noted, concurrent NRT may facilitate compliance with the denicotinized cigarette-weaning regimen. In fact, discontinuation rates were higher with Quest plus placebo patch than with Quest plus NRT. Second, concurrent NRT separates the source of nicotine from the act of smoking; this dissociation of smoking behavior from nicotine reinforcement should facilitate behavioral extinction.

In the context of precessation NRT, the use of denicotinized cigarettes in combination with NRT may also help decrease concerns about the toxicity potential of nicotine. Smokers frequently express concerns about the safety of smoking conventional cigarettes concurrently with NRT. Although no clear basis for such concern has been established, it is conceivable that sensitive subpopulations might receive a dose of nicotine when smoking conventional cigarettes concurrently with NRT that may not be well tolerated. This suggests that the use of denicotinized cigarettes may offer assurance of safety or absence of nicotine toxicity during the weaning period. Importantly, there were no significant safety issues identified in smoke chemistry and toxicology studies of Quest cigarettes, which found Quest cigarettes to be consistent with conventional cigarettes with the exception of reduced nicotine levels.

This study demonstrated a clinically important increase in abstinence for the Quest 1, 2, 3 plus NRT group. However, the abstinence rate in the Quest plus placebo patch group (16.4%) was similar to that of conventional treatment with NRT (21.9%), which does not rule out the possibility that Quest plus placebo patch may be similarly as effective.

The results also suggest that the Quest plus NRT treatment may have had differential efficacy in females versus males. A substantial increase in 4-week abstinence was seen in the Quest plus NRT group versus active control plus NRT group for women. This observation of greater efficacy of the Quest plus NRT treatment relative to NRT alone in women is consistent with previous literature showing that NRT alone appears to be less efficacious in women than in men (Perkins, 2001). Moreover, the sensory aspects of smoking may be more important for female smokers (Perkins et al., 2001). To the extent that treatments using Quest 3 cigarettes

diminish the rewarding value of conditioned sensory cues *via* extinction, it is reasonable to speculate that this effect may be greater in women. Conversely, men may benefit more from the NRT component of treatment (with or without Quest), as suggested by the trend for a lower success rate using Quest plus placebo patch. It will be important to determine whether the differential efficacy of the Quest plus NRT treatment in women is borne out in future studies. If so, it may be a particularly useful therapeutic approach for women who are less likely to respond to conventional NRT.

A deficiency of this study was that long-term abstinence (at 3 and 6 months) could not be adequately examined. Attrition over the follow-up period was significant and showed that better methods should be instituted in long-term studies of smoking cessation to sustain adherence over the observation period. Thus, the durability of the response seen in this study at 4 weeks needs to be further explored. Nevertheless, based on the results at 4 weeks, a confirmatory phase III study is warranted.

Some degree of compensatory smoking was noted in the early stages of weaning using the Quest 1 and Quest 2 cigarettes, based on the number of cigarettes smoked per day and exhaled CO measurements. The extent of compensation was modest and resulted in a relative increase in these indices of smoking of about 10–15%. Short-term exposure to these slightly higher levels of smoking during the nicotine-weaning regimen was not associated with adverse effects. In contrast to Quest 1 and Quest 2, use of Quest 3 was not associated with an increase in cigarettes per day or CO levels over conventional cigarettes. We interpret these results to mean that smokers may attempt to compensate for reduced cigarette nicotine content when it is above a certain threshold, but when the nicotine content is sufficiently reduced, compensation does not occur. Any initial compensatory increase in smoking would be expected to extinguish because increased smoking would fail to achieve a perceptible increase in nicotine reward. Previous studies have also suggested little or no compensation with denicotinized cigarettes (Rose & Behm, 2004b). In a recently published paper, Strasser, Lerman, Sanborn, Pickworth, and Feldman (2007) reported a modest degree of compensation when smokers smoked a single cigarette of Quest 1, 2 or 3 in a laboratory setting. However, none of the CO boosts exceeded that of subjects' usual brands (Strasser et al., 2007). The results with Quest 3 differed from those of the present study, which found no increase in CO relative to Quest 1 and 2. This could be related to the more prolonged exposure in a real-world, as opposed to a laboratory, setting during which subjects adjusted to the reduced nicotine delivery.

In conclusion, this study demonstrated that the use of cigarettes with progressive reductions in nicotine content is a promising adjunct to current smoking cessation strategies that warrants further study in additional controlled trials. Since current strategies often focus on pharmacological treatments while neglecting the strong conditioned reinforcing aspects of the sensory and behavioral components, cigarettes with reduced nicotine content offer a tool to promote extinction of these habit components. By developing this and related approaches, the armamentarium of efficacious smoking cessation treatments may be significantly expanded.

Acknowledgments

The following people are acknowledged for their contribution to this research: Ryung Suh, MD, MPP, MBA, MPH; Rosanne B. McTyre, PhD; T. Jeffrey Clark, PhD, MBA; and Jeffrey Baetz.

Declaration of interest: This study was funded by Vector Tobacco Inc. Dr. Anthony P. Albino is an employee of Vector Tobacco. Dr. Karen M. Becker is a paid consultant to Vector Tobacco. Dr. Jed E. Rose received no financial or other compensation for his contribution to this research. The authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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