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Brief report
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Varenicline for Smoking Cessation in Light Smokers

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Abstract

Introduction: As the prevalence of cigarette smoking has declined, the proportion of smokers who smoke less than 10 cigarettes/day (cpd) has increased. Varenicline may provide an effective pharmacotherapeutic treatment option for increasing smoking abstinence rates among light smokers.
Methods: We conducted a randomized, placebo-controlled clinical trial evaluating the efficacy of varenicline for increasing smoking abstinence rates among light smokers (5–10 cpd). Participants received varenicline or placebo for 12 weeks. Outcomes were assessed at 3 and 6 months.
Results: Ninety-three participants were randomized. Fifty-two percent of participants terminated the study early. At end-of-treatment (3 months), the point prevalence smoking abstinence rate was 53.3% in the varenicline group compared to 14.5% in placebo (odds ratio [OR]: 6.69, 95% confidence interval [CI]: 2.48–18.06, $P < .001$), and the prolonged smoking abstinence rate was 40.0% and 8.3%, respectively (OR: 7.33, 95% CI: 2.24–23.98, $P = .001$). At end-of-study (6 months), the point prevalence smoking abstinence rate was 40.0% in the varenicline group compared to 20.8% in placebo (OR: 2.53, 95% CI: 1.01–6.34, $P = .047$), and the prolonged smoking abstinence rate was 31.1% and 8.3%, respectively (OR: 4.97, 95% CI: 1.49–16.53, $P = .009$). The estimated magnitude of the treatment effect remained consistent across the various missing data assumptions and in analyses that adjusted for gender. Nausea and sleep disturbance were more commonly reported in the varenicline group.
Conclusions: Varenicline was safe and effective for increasing long-term smoking abstinence rates in a population of predominantly White light cigarette smoker. The efficacy of varenicline in this study was comparable to that observed in heavier smokers.
Implications: Our findings demonstrate that varenicline is effective for increasing smoking cessation in light smokers. Our findings have implications for advancing the treatment of light smokers in clinical practice.

Introduction

As the prevalence of adult daily cigarette smoking has declined in the United States, the proportion of daily smokers who smoke less than 10 cigarettes/day (cpd) has increased. Between 2005 and 2014, the percentage of daily smokers smoking 1–9 cpd (ie, "light smokers") increased from 16.4% to 26.9%.[1] Light smoking significantly increases the risk for cancer, all-cause mortality, and adverse cardiovascular outcomes.[2]

Light smoking is associated with tobacco dependence,[3] with light smokers being at least as motivated to quit as heavier smokers.[4] The US Public Health Service Clinical Practice Guideline states that numerous "effective medications are available" for the treatment of tobacco use disorder and recommends "clinicians should

encourage their use" except in populations "for which there is insufficient evidence of effectiveness," such as light smokers.[5] The efficacy of nicotine gum,[6] bupropion,[7] and varenicline[8] for the treatment of tobacco use disorder in light smokers (≤10 cpd) has been evaluated. Bupropion was observed to increase smoking abstinence rates in African American (AA) light smokers at the end of a 7-week treatment program,[7] and a study of varenicline in Latino light smokers observed a statistically significant increase in smoking abstinence rates also at end-of-treatment (3 months).[8]

Varenicline is the most effective pharmacological monotherapy for the treatment of tobacco dependence.[5] Most clinical studies of varenicline have enrolled smokers who smoke at least 10 cpd.[9–14] We conducted a randomized, controlled clinical trial assessing the efficacy of varenicline for the treatment of tobacco use disorder among light smokers (5–10 cpd).

Methods

Study Design

Participants were randomized to varenicline or placebo for 12 weeks with follow-up at 6 months. Enrollment took place between January 2013 and March 2015. The Mayo Clinic Institutional Review Board approved the study, which was preregistered at Clinical Trials.gov (NCT0169560), before recruitment and enrollment began. We recruited participants from the general population in the Rochester, MN area who smoked 5–10 cpd. Participants had study visits every 2 weeks during the 12 weeks of medication followed by a phone visit 1 week after end-of-treatment with a final study visit at 26 weeks after randomization.

Study Population

Individuals were eligible to participate if they: (1) were aged 18 years or older, (2) smoked 5–10 cpd (ie, daily smoking) for at least 6 months, and (3) were interested in quitting smoking.

Individuals were excluded from study participation if they had: (1) an unstable cardiac condition (ie, angina, myocardial infarction, or coronary angioplasty within the past 3 months), an untreated cardiac dysrhythmia, kidney disease, or cancer; (2) psychosis, bipolar disorder, or an unstable or untreated moderate or severe depression as assessed by the Center for Epidemiology Studies-Depression (CES-D) scale[15]; (3) current nonspecific suicidal thoughts as defined by the Columbia Suicide Severity Rating Scale (C-SSRS)[16] or had a lifetime history of a suicidal attempt; (4) substance dependence other than nicotine; (5) a varenicline allergy; (6) another member of their household already participating; (7) current treatment with another investigational drug within the past 30 days; or (8) untreated hypertension or baseline systolic blood pressure more than 180 mmHg or diastolic more than 100 mmHg. Women of childbearing potential or who were pregnant, lactating, or likely to become pregnant during the trial and unwilling to use an acceptable form of contraception during the medication phase were also excluded for safety reasons.

Assignment of Participants to Condition

A computer-generated randomization sequence assigned participants in a 1:1 ratio to treatment conditions. Pharmacy personnel dispensed study medication into containers labeled according to study identification numbers. Study participants, investigators, and pharmacy staff were blinded to treatment assignment.

Treatment and Control Conditions

Participants received varenicline at a dose of 0.5 mg once daily for 3 days, then increased to 0.5 mg twice daily for days 4–7 to a target dose of 1 mg twice daily for a total of 12 weeks of treatment. This dosing is the same as that given to heavier smokers.

All participants received six sessions of an individualized behavioral counseling program consisting of 10-minute sessions delivered at clinic visits occurring during the medication phase. The counseling was based upon the "Smoke Free and Living It" manual.[17]

Study Endpoints

Endpoints were selected using guidelines for recommended outcomes for tobacco intervention studies.[18] The primary endpoint was the 7-day point prevalence smoking abstinence rate at week 12. An expired-air carbon monoxide (CO) level of not more than 8 parts per million verified self-reported smoking abstinence. Point prevalence was defined as CO-confirmed, self-reported no tobacco use in the previous 7 days. Participants who met criteria for point prevalence abstinence at weeks 12 and 26 were defined as meeting criteria for prolonged abstinence if they submitted negative responses to both of the following questions: "Since 14 days after your target quit date, have you used any tobacco on each of 7 consecutive days?" and "Since 14 days after your target quit date, have you used any tobacco on at least 1 day in each of 2 consecutive weeks?"

Assessments

Tobacco dependence was measured with the Fagerström Test for Nicotine Dependence (FTND).[19,20] Adverse events and concomitant medication data were collected at every study visit by querying the participants with a reference point of "since your last visit."

Statistical Analyses

Under the assumptions that the 7-day point prevalence abstinence rate in placebo at 12 weeks was 16% and the 7-day point prevalence abstinence rate was at least 32% (odds ratio [OR] of 2.5), we attempted to recruit a total of 224 light smokers providing statistical power of 80% with a two-tailed alpha = 0.05. Analyses were performed using an intention-to-treat approach whereby participants are analyzed according to randomized treatment. We used descriptive statistics to summarize demographic data, tobacco use history, and other baseline characteristics.

Logistic regression was used for the analysis of point prevalence and prolonged abstinence at week 12 (end-of-treatment) and point prevalence and prolonged abstinence at week 26. For the primary analyses, participants with missing data were assumed to be smoking. This approach is used because the data are assumed to be missing not at random. However, this approach is sensitive to differential attrition across treatment groups and tends to overestimate the precision of the estimate of the treatment effect. Therefore, in order to supplement the primary analysis, we performed sensitivity analyses using multiple imputation under the missing not at random assumption (SAS/STAT v. 13.2, PROC MI and PROC MIANALYZE) with the OR for missingness ranging from 1.0 (missing at random) to infinity (missing=smoking).[21,22] The findings are summarized by presenting the OR (95% CI) for the estimated treatment effect (varenicline vs. placebo). The frequency of adverse events was summarized and compared between groups using Fisher's exact test. In all cases, two-sided tests were used with P values less than .05 considered statistically significant.

Results

Participants

Among 368 individuals requesting study participation, 174 (47%) passed the telephone prescreen. Of these 174 potential participants, 108 (62%) consented to the study. Of the 108 who consented, 106 (98%) passed the initial study screen and 93 (86%) were randomized (45 varenicline, 48 placebo). Study completion rates were 62% (28/45) in the varenicline group and 42% (20/48) in the placebo group. In the varenicline group, eight participants withdrew consent, one dropped due to lack of efficacy, and eight were lost to follow-up. In the placebo group, two participants dropped due to adverse events, 14 withdrew consent, two due to lack of efficacy, and 10 were lost to follow-up. Due to the difficulty in recruiting participants, the decision was made to discontinue enrollment without reaching the proposed sample size. This decision was made prior to performing analyses, unblinding, or reviewing study results.

Baseline participant characteristics are presented in Table 1. Compared to the placebo, a significantly higher percentage of those assigned to varenicline were male (51% vs. 39%, $P = .031$).

Abstinence

Varenicline was associated with higher point prevalence and prolonged smoking abstinence rates at both 12 and 26 weeks (Table 2). Similar treatment effects were obtained from analyses that adjusted for gender. From these analyses, female gender was observed to be associated with an increased likelihood of point prevalence smoking abstinence. Results from sensitivity analyses performed to assess the impact of missing data assumptions on the analysis of point prevalence abstinence outcomes demonstrated that the magnitude of the treatment effect was relatively consistent across the various missing data assumptions. The OR for the treatment effect at 6 months ranged from 1.99 to 2.54 across the range of assumptions assessed.

Table 1. Baseline Characteristics[a]

	Varenicline ($N = 45$)	Placebo ($N = 48$)
Characteristics		
Age, years	37.1 ± 11.7	37.2 ± 11.3
Gender, *n* (%)		
Female	22 (49)	34 (61)
Male	23 (51)	14 (39)
Race/ethnicity, *n* (%)		
White, non-Hispanic	36 (80)	45 (94)
Other[b]	9 (20)	3 (6)
Marital status, *n* (%)		
Married/living as married	16 (36)	26 (54)
Never married	18 (40)	15 (31)
Separated/divorced	11 (24)	7 (15)
Highest level of education, *n* (%)		
≤High school graduate	4 (9)	7 (15)
Some college or technical school	25 (56)	28 (58)
≥4-year college degree	16 (35)	13 (27)
Current smoking rate, cigarettes/day	7.9 ± 1.5	7.5 ± 1.5
Years of regular cigarette smoking, years	17.2 ± 11.9	16.1 ± 10.6
Other users of tobacco in household, *n* (%)	13 (29)	22 (46)
Number of serious stop attempts, *n* (%)		
0	2 (4)	1 (2)
1–4	23 (51)	29 (56)
5–9	10 (22)	11 (23)
≤10	10 (22)	9 (19)
Smoke within 30 min of waking, *n* (%)	21 (47)	18 (37)
Contemplation ladder	8.9 ± 1.6	8.8 ± 1.0

[a]Data are presented as mean ± SD or *n* (%) as indicated.
[b]Includes four Black/African American, three White Hispanic, one American Indian/Alaska native, one Asian, one Native Hawaiian/other Pacific Islander, and two who indicated more than one race.

Adherence

Medication adherence was calculated for each subject as the amount of study medication taken expressed as a percentage of the total amount prescribed for the 12-week treatment phase. Among all participants, the median adherence was 84% for varenicline and 34% for placebo. Among participants who remained in the study through the end-of-treatment phase, the median adherence was 92% for varenicline and 98% for placebo.

Adverse Events

Participants in the varenicline group reported more nausea (22% vs. 0%; $P < .001$) and sleep disturbance (15.6% vs. 2.1%; $P = .027$) compared to placebo. No serious adverse events were reported.

Discussion

We observed that varenicline was associated with higher point prevalence and prolonged smoking abstinence rates at end-of-treatment and 6 months among light smokers. Overall, the effect of varenicline in light smokers is comparable to that observed in heavier smokers.[9] Side effects of nausea and sleep disturbance were consistent with the known common adverse effects reported with varenicline.[9,10]

We did not anticipate the difficulty we experienced in recruiting and retaining light smokers. One could hypothesize that this challenge reflected lower levels of motivation to quit or flagging motivation during treatment among light smokers compared to heavier smokers. However, a previously randomized trial evaluating nicotine gum for the treatment of AA light smokers (<10 cpd) recruited a large number of participants ($N = 755$) within 15 months and maintained good retention (16% dropout).[6] Similarly, a randomized trial evaluating bupropion SR conducted by the same group randomized 540 participants in 34 months but observed a higher dropout (30%) than the first study.[7] A study of Latino light smokers had a dropout rate of 28% at 6 months.[8] Dropouts in our study were greater in the placebo group suggesting participants may have lost motivation due to lack of perceived drug efficacy, although only one participant in the varenicline group and two participants in placebo specifically reported this as the reason for discontinuation. Indeed, active nicotine gum was found to be associated with an increased likelihood of study retention in the study among AA light smokers.[6] Another difference that may explain our retention rates and those observed in the previous studies with AA light smokers is that our participants were predominantly non-Hispanic Whites. Light smokers make up a greater percentage of AA smokers than White smokers.[23] White light smokers may have lower levels of motivation to engage in or remain in treatment compared to White heavier smokers or AA light smokers. Future studies examining interventions to promote treatment retention for White light smokers may further enhance abstinence rates.

Strength of our study is the randomized, placebo-controlled design. The major limitation is that we had a significant amount of dropout. However, we conservatively treated dropouts as smokers

Table 2. Smoking Outcomes[a]

Characteristics	Varenicline (*N* = 45) *n* (%)	Placebo (*N* = 48) *n* (%)	OR	95% CI	*P*
End-of-treatment					
Point prevalence abstinence	24 (53.3)	7 (14.5)	6.69	2.48–18.06	<.001
Gender-adjusted					
Treatment			9.58	3.19–28.76	<.001
Female			3.20	1.09–9.44	.035
Prolonged abstinence	18 (40.0)	4 (8.3)	7.33	2.24–23.98	.001
Gender-adjusted					
Treatment			8.82	2.56–30.30	<.001
Female			2.04	0.68–6.14	.206
6 months					
Point prevalence abstinence	18 (40.0)	10 (20.8)	2.53	1.01–6.34	.047
Gender-adjusted					
Treatment			3.57	1.31–9.71	.013
Female			3.70	1.27–10.79	.017
Prolonged abstinence	14 (31.1)	4 (8.3)	4.97	1.49–16.53	.009
Gender-adjusted					
Treatment			6.61	1.87–23.38	.003
Gender			3.12	0.92–10.56	.067

CI = confidence interval; OR = odds ratio.

[a]Data were analyzed using logistic regression. Analyses were performed with no covariate adjustment and also with gender included as a covariate. Point prevalence was defined as CO-confirmed self-reported no tobacco use in the previous 7 days. Participants who met criteria for CO-confirmed 7-day point prevalence abstinence at weeks 12 and 26 were defined as meeting criteria for prolonged abstinence if they submitted negative responses to both of the following questions: "Since 14 days after your target quit date, have you used any tobacco on each of 7 consecutive days?" and "Since 14 days after your target quit date, have you used any tobacco on at least one day in each of 2 consecutive weeks?"

which is supported by clinical evidence.[24] Our sensitivity analyses provide reassurance that the magnitude of the effect is similar across different assumptions of abstinence among participants who dropped. Finally, we used CO to verify abstinence. Cotinine verification may improve the sensitivity of verification of smoking abstinence among light smokers. However, we would not expect differential misclassification to impact our findings.

Varenicline was safe and effective for increasing abstinence rates in a population of predominantly White light smokers. The observed efficacy of varenicline was comparable to that observed in heavier smokers.

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Declaration of Interests

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