Use of Varenicline for 4 Weeks Before Quitting Smoking

Decrease in Ad Lib Smoking and Increase in Smoking Cessation Rates

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Background: The use of varenicline tartrate alleviates postquit withdrawal discomfort, but it also seems to reduce the "reward" associated with smoking. The current treatment schedule, which commences 1 week before quitting, relies primarily on the first mechanism. We set out to determine whether increasing the prequit medication period renders cigarettes less satisfying and facilitates quitting.

Methods: One hundred one smokers attending a stop-smoking clinic in London, United Kingdom, were randomly allocated to receive varenicline for 4 weeks before the target quit date (TQD) or to receive placebo for 3 weeks before the TQD, followed by varenicline for 1 week before the TQD. In both groups, standard varenicline treatment was given for 3 months after the TQD. Measures included smoking satisfaction and smoke intake before quitting, urges to smoke and withdrawal discomfort after quitting, and sustained abstinence from the TQD to 3 months.

Results: Varenicline preloading reduced prequit enjoyment of smoking ($P=.004$) and smoke intake ($P<.001$), with 36.7% of participants reducing their cotinine concentrations by more than 50% (reducers). Varenicline preloading did not affect postquit withdrawal symptoms, but it increased 12-week abstinence rates (47.2% in the varenicline arm vs 20.8% in the placebo arm, $P=.005$). The effect was particularly strong among the reducers in the varenicline arm (66.7% in reducers vs 22.6% in nonreducers, $P=.002$). Varenicline preloading was well tolerated.

Conclusions: Although several issues remain to be clarified, varenicline preloading can generate a substantial reduction in ad lib smoking and enhance 12-week quit rates. Current treatment schedules may lead to suboptimal treatment results. Trials with longer follow-up periods are needed to corroborate these findings.

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THE α4β2 NICOTINIC RECEPTOR partial agonist varenicline tartrate is an effective smoking cessation medication.[1,2] It is used in dosages increasing from 0.5 to 1 mg/d for 1 week before the target quit date (TQD) to generate sufficient systemic levels and to habituate users to the possible occurrence of nausea and thereafter in dosages of 2 mg/d for up to 6 months.

See Invited Commentary at end of article

Varenicline seems to affect smokers in 2 different ways. It alleviates withdrawal discomfort and urges to smoke after smokers stop smoking.[3] This effect is ascribed to the action of varenicline on dopaminergic pathways. Treatment is intended to ensure that ex-smokers continue to receive at least a part of the boost to their dopamine levels in the nucleus accumbens that they previously obtained from smoking.[4] The second effect consists of a reduction in the enjoyment of smoking and in smoke intake. This is presumed to be caused by the drug's blocking of the receptors that would otherwise facilitate the "reward" experienced when smoking. Up to now, this second effect has only been demonstrated over 1-week uptitration before the TQD[5] and in unsuccessful quitters who rated the enjoyment of their "lapse" cigarettes.[3,6-8]

The therapeutic effects of varenicline when administered as per current labeling rely primarily on the first mechanism (ie, alleviation of withdrawal discomfort once smokers stop smoking). We hypothesized that, if the drug lowers the subjective reward that accompanies smoking, its use over an extended period before the TQD (varenicline preloading) could help

to weaken the association of smoking with reward and to enhance cessation and the efficacy of varenicline therapy.

The present trial was designed to test whether varenicline preloading for 4 weeks reduces urges to smoke and facilitates smoking cessation compared with using the drug for just 1 week before the TQD as per current labeling. We also tested whether any smoking cessation effect is mediated by the influence of varenicline preloading on ad lib smoke intake before quitting or its effect on postcessation withdrawal discomfort. Last, we attempted to determine whether any effects of varenicline preloading plateau within 4 weeks of exposure.

METHODS

STUDY DESIGN

In a double-blind randomized design, participants were randomly allocated to receive varenicline for 4 weeks before the TQD or to receive placebo for 3 weeks before the TQD, followed by varenicline for 1 week before the TQD. Following the TQD, both study arms used varenicline for up to 12 weeks. Varenicline use was accompanied by standard weekly support sessions as provided by the National Health Service Stop-Smoking Service in the United Kingdom.[9] The study was authorized by the United Kingdom Medicines and Healthcare Products Regulatory Agency. Ethical approval for the trial was obtained from the National Health Service National Research Ethics Service (reference 08/HO720/164).

TRIAL MEDICATION

During the prequit period, varenicline and placebo tablets were identically packaged, and the participants in both study arms used the same number of tablets per day. From the TQD at the end of study week 4, both study arms used the manufacturer's drug packaging. In both study arms, the usual initial dosage of 0.5 mg/d for 3 days was replaced with 1 mg/d. Hence, both study arms used 1 mg of varenicline tartrate per day for their first week of varenicline use (study week 1 for the varenicline arm and study week 4 for the placebo arm) and 2 mg/d from the second week onward.

PARTICIPANTS

Smokers seeking treatment were recruited by local advertising in July 2009. Volunteers were included if they were 18 years or older, had no contraindication for varenicline use, had not used varenicline in the past 6 months, and had no current psychiatric or other serious illness.

PROCEDURES

Participants attended treatment sessions at baseline, week 3, week 4 (TQD), and weekly up to week 8. Other data were collected over the phone at the end of weeks 1 and 2, at 24 hours after the TQD, and at week 16 (3 months after the TQD). At baseline, participants were asked to smoke ad lib until week 4, when they would be asked to stop smoking. Medication was dispensed at baseline and at weeks 3, 4, 6, and 8. Participants received a single payment of £30, contingent on their attending after week 4. Treatment sessions took place between 5 and 7 PM on weekdays.

MEASURES

Demographic details, health status, smoking history, and results of the Fagerström Test for Nicotine Dependence[10] were collected at baseline. Salivary cotinine samples were collected at baseline, week 3, and week 4 (TQD). End-expired carbon monoxide (CO) concentrations were recorded at all face-to-face visits. The Mood and Physical Symptoms Scale (MPSS),[11] which assesses tobacco withdrawal symptoms and urges to smoke, was completed at all contacts up to week 8. A 6-point scale was used to rate "How much of the time have you felt the urge to smoke in the past week?" (from "not at all" to "all of the time") and "How strong have the urges been?" (from "no urges" to "extremely strong"). Participants also rated how they had been feeling during the past week with regard to depression, irritability, restlessness, hunger, poor concentration, poor sleep at night, and anxiety on a scale ranging from 1 ("not at all") to 5 ("extremely"). Self-reported smoking status and cigarette consumption were assessed at every contact. The Modified Cigarette Evaluation Questionnaire[12] has 12 items asking about a range of reactions to cigarettes (eg, "Was smoking satisfying?" "Did smoking make you feel less irritable?" "Did you enjoy smoking?"). It was administered at each prequit contact. Participants were also asked to estimate the mean number of cigarettes smoked per day over the previous week. During the prequit period, the following 2 additional items were included on the Mood and Physical Symptoms Scale: "Have you found your urges to smoke stronger or weaker than usual in the last week?" (with response options of "much stronger," "slightly stronger," "same as before," "slightly weaker," and "much weaker") and "Have you found cigarettes more or less enjoyable than usual in the last week?" (with response options of "much more enjoyable," "slightly more enjoyable," "same as before," "slightly less enjoyable," and "much less enjoyable"). Adverse events were collected at each contact. Any reports of sickness, nausea, or vomiting were recorded as "nausea present."

RANDOMIZATION AND BLINDING

On arrival to the first study session, participants were sequentially allocated to study medication using a list that was computer generated by the study statistician (J.S.). Participants and study staff were blind to treatment allocation.

SAMPLE SIZE

The primary outcome concerned urges to smoke. Rapid smoking, a behavioral method with a similar aim of making subsequent smoking less rewarding, has been associated with a mean (SD) Mood and Physical Symptoms Scale rating of urges to smoke over the first week of abstinence of 1.8 (1.0) compared with a mean (SD) control rating of 2.5 (1.1).[13] To detect a similar effect in this trial, 41 participants would be needed in each group ($P < .05$, 2-tailed test; 85% power). To allow for participant attrition, the study aimed to randomize 100 participants.

DATA ANALYSIS

Varenicline vs placebo differences were assessed using analysis of variance for continuous variables and χ^2 test for categorical variables. Differences in urges to smoke at 24 hours and at 1 week were compared using 1-way analysis of variance. Changes in withdrawal symptom ratings from the TQD to 24 hours and 1 week were compared using repeated-measures analysis of variance. Differences were to be adjusted for all baseline characteristics related to outcome that differed between the 2 groups. All tests were 2-tailed.

Regarding smoking cessation outcome, continuous abstinence at 4 weeks and 12 weeks after the TQD was defined as a

self-report of no smoking (not a puff) since the TQD, validated by CO concentrations at all time points when readings were scheduled (ie, weeks 1-4 after the TQD) or validated by reading at the next attendance if a session was missed. Participants with missing CO validation at 4 weeks were considered smokers at 4 weeks and at 12 weeks. We also calculated 12 weeks of sustained abstinence in accord with the Russell standard[14] as a self-report of smoking no more than 5 cigarettes since the TQD, validated by CO concentrations during weeks 1 through 4 as aforedescribed. Twelve-week data were collected by telephone without CO validation. In the analyses of changes in smoking behavior before quitting, only participants who provided data were included (ie, no imputations were used). In the analyses of cessation rates, participants lost to follow-up were considered to be smoking.

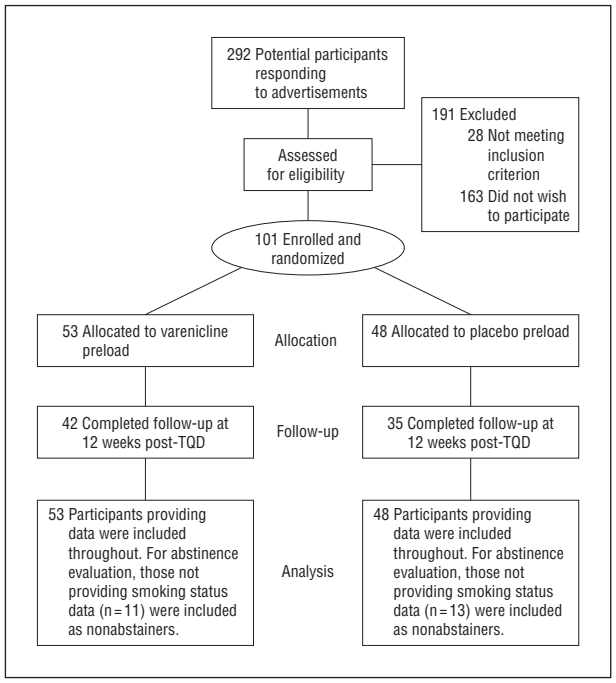

Figure 1. Flow of participants through the trial. TQD indicates target quit date.

RESULTS

SAMPLE CHARACTERISTICS

A total of 101 volunteers were enrolled and randomized. **Figure 1** shows the flow of participants through the trial. **Table 1** gives baseline characteristics of the participants. There were no significant differences between the 2 study arms. The study sample profile was similar to that of other smokers attending the host stop-smoking service, with a mean age of 46 and a high level of cigarette dependence.[15]

EFFECT OF VARENICLINE ON SMOKE INTAKE DURING THE AD LIB SMOKING PERIOD

Figure 2 shows the mean value (95% confidence interval) of 3 measures of smoke intake at each time point before the TQD. Biologic samples were collected only at baseline, week 3, and the TQD. Only participants who provided data at all time points are included.

Varenicline therapy had little effect on smoking behavior during the first week of use (when the dosage was only 1 mg/d), but across the 3 weeks, participants receiving varenicline reduced their cigarette consumption, CO levels, and cotinine concentrations significantly more than participants receiving placebo ($F=4.79$, $P=.02$; $F=11.09$, $P<.001$; and $F=16.60$, $P<.001$, respectively). As expected, the 3 measures were moderately correlated (range, $r=0.60$-0.65, $P<.001$).

To further explore the effect of varenicline use on smoking behavior, we subdivided participants according to whether they reduced their cotinine concentrations by more than 50% ("reducers"). On all 3 intake measures (cigarette consumption, CO levels, and cotinine concentrations), the proportion of reducers was higher in the varenicline group than in the placebo group ($\chi^2=8.4$, $P=.004$; $\chi^2=9.6$, $P=.002$; and $\chi^2=8.0$, $P=.005$, respectively).

Table 2 gives the proportion of participants who changed their smoke intake by different degrees in the 2

Table 1. Baseline Characteristics of Participants[a]

Characteristic	Varenicline Group (n=53)	Placebo Group (n=48)
Age, mean (SD), y	45.9 (11.4)	45.3 (10.9)
Cigarettes per day, mean (SD), No.	19.5 (9.8) (n=52)	18.2 (8.9) (n=47)
End-expired carbon monoxide concentration, mean (SD), ppm	25.7 (12.8)	23.4 (9.8) (n=47)
Salivary cotinine concentration (SD), ng/mL	365.2 (168.3)	348.0 (121.1)
Fagerström Test for Nicotine Dependence score, mean (SD)[b]	5.5 (2.5)	4.9 (2.3) (n=47)
Age when started smoking, mean (SD), y	16.5 (4.4)	16.9 (4.0) (n=47)
Previous quit attempts, mean (SD), No.	2.7 (0.9)	2.7 (1.2)
Male sex, %	64.2	64.6
White British race/ethnicity, %	54.7	62.5
Left school by age 16 y, %	36.5 (n=52)	40.0 (n=45)
Smoke hand-rolled cigarettes, %	20.8	31.2
Partner smokes, %	28.3	27.1
Paid employment, %	37.9 (n=29)	57.1 (n=28)
Body mass index, mean (SD)[c]	26.1 (4.1) (n=46)	25.9 (4.4) (n=43)

[a] Varenicline tartrate and placebo group numbers vary because of missing data.
[b] Range 0 to 10.
[c] Calculated as weight in kilograms divided by height in meters squared.

study arms. In subsequent analyses, we used salivary cotinine concentration as the principal marker for smoke intake change because cotinine concentrations are not influenced by smoking shortly before visits and are the most accurate objective indicator of overall smoke intake.

Four participants in the varenicline arm and 1 participant in the placebo arm were not smoking at all by the time the TQD samples were collected (ie, had reduced their cotinine concentrations to 0). With these 5 participants removed, the differences in overall change and categorical change in cotinine concentrations remained significant ($F=26.87$, $P<.001$ and $\chi^2=16.71$, $P=.01$, respectively).

EFFECT OF VARENICLINE ON REACTION TO CIGARETTES DURING THE AD LIB SMOKING PERIOD

Across the first 3 weeks, varenicline preloading had a significant effect on 2 Modified Cigarette Evaluation Questionnaire items, the enjoyment of sensation of smoking ($F=6.05$, $P=.001$) and the enjoyment of smoking ($F=2.92$, $P<.04$). It also had a significant effect on both items assessing the change in strength of urges to smoke and the enjoyment of cigarettes directly ($F=7.45$, $P<.001$ and $F=4.97$, $P<.004$, respectively). **Figure 3** shows that the 2 groups started to diverge during the initial uptitration week and converged again when the control group switched to varenicline 1 week before the TQD.

ONSET AND TIME COURSE OF NAUSEA AND ITS RELATIONSHIP TO OTHER EFFECTS OF VARENICLINE

The varenicline group experienced a higher incidence of nausea over the first 3 weeks, but this difference disappeared after the control group received varenicline (**Figure 4**). During the full course of varenicline treatment, 58.5% and 47.9% ($P=.29$) of participants reported nausea on at least 1 occasion in the varenicline and placebo preloading groups, respectively. The occurrence of nausea was unrelated to cotinine or CO reduction, to subjective reactions to cigarettes and urges to smoke, to postquit withdrawal discomfort, or to treatment outcome at any time point.

EFFECT OF VARENICLINE PRELOADING ON CIGARETTE WITHDRAWAL SYMPTOMS

A total of 63 participants (34 receiving varenicline and 29 receiving placebo) reported abstinence at 24 hours after their TQD and provided data on urges to smoke. The Mood and Physical Symptoms Scale questions on frequency and strength of urges to smoke were aggregated to give a composite urge score. Ratings of withdrawal symptoms were aggregated to give a composite withdrawal score. The 2 groups did not differ significantly in the mean (SD) composite score of urges to smoke (2.47 [1.13] vs 2.88 [1.15], $P=.14$) or in the change in withdrawal discomfort composite rating ($F=3.19$, $P=.08$). One week after the TQD, 35 and 25 participants achieved CO-validated abstinence in the varenicline and placebo groups, respectively. There was no difference between the study arms in the mean (SD)

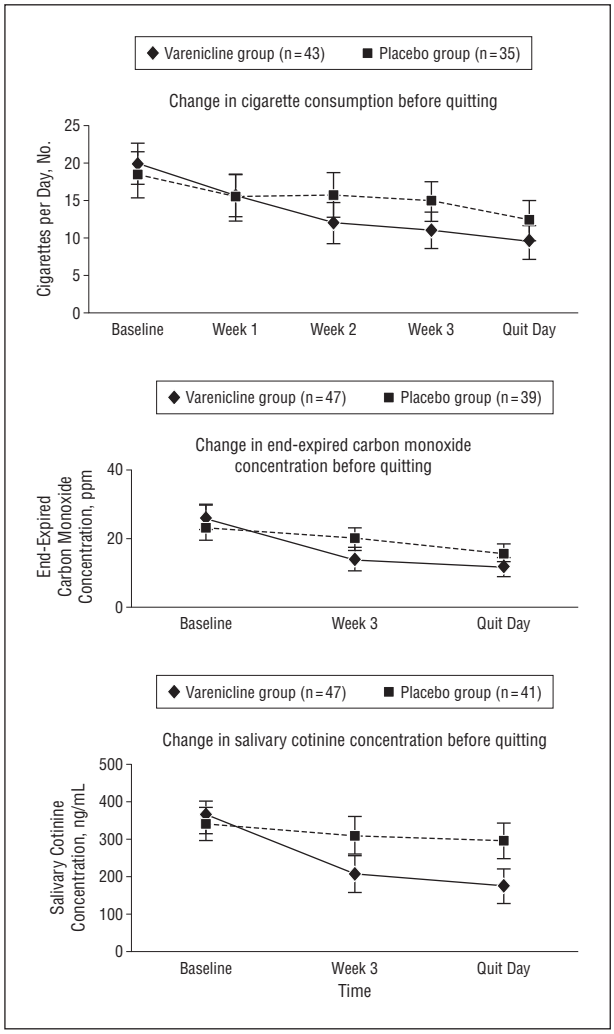

Figure 2. Changes in cigarette consumption and smoke intake before the target quit date. Error bars represent 95% confidence intervals. Varenicline tartrate and placebo group numbers vary because of missing data.

composite score of urges to smoke (2.43 [1.04] vs 2.64 [0.80], $P=.40$) or in the change in withdrawal discomfort composite rating ($F=0.001$, $P=.97$). Ratings did not differ between participants who did vs did not reduce their cotinine concentrations by more than 50%.

EFFECT OF VARENICLINE PRELOADING ON ABSTINENCE RATES

Fourteen participants (7 receiving varenicline and 7 receiving placebo) dropped out before attempting to stop smoking. They are included in the results as nonabstainers. One of them (allocated to placebo) did not begin taking medication. Exclusion of this participant did not alter the results. One participant moved away from London before the 4-week post-TQD session but was validated as abstinent using a mailed salivary cotinine kit.

Table 3 gives the rates of continuous abstinence (not a puff since the TQD) at 4 and 12 weeks and the Russell standard sustained abstinence rate at 12 weeks (≤5 cigarettes allowed).[14] Quit rates seemed higher in the varenicline group at both time points, but the difference was statistically significant only at week 12.

Table 2. Categorical Change in Smoking Behavior Between Baseline and Week 3

Variable[a]	No. (%) >50% Reduction	10%-50% Reduction	No Change, ±10%	>10% Increase	Pearson Product Moment Correlation χ^2 Difference	*P* Value
Cigarettes per day						
Varenicline (n=48)	17 (35.4)	19 (39.6)	11 (22.9)	1 (2.1)	9.1	.02
Placebo (n=42)	4 (9.5)	22 (52.4)	13 (31.0)	3 (7.1)		
End-expired carbon monoxide concentration						
Varenicline (n=49)	26 (53.1)	16 (32.7)	4 (8.2)	3 (6.1)	15.4	.001
Placebo (n=42)	9 (21.4)	12 (28.6)	11 (26.2)	10 (23.8)		
Salivary cotinine concentration						
Varenicline (n=49)	18 (36.7)	24 (49.0)	6 (12.2)	1 (2.0)	19.2	<.001
Placebo (n=44)	5 (11.4)	17 (38.6)	9 (20.5)	13 (29.5)		

[a]Varenicline tartrate and placebo group numbers vary because of missing data.

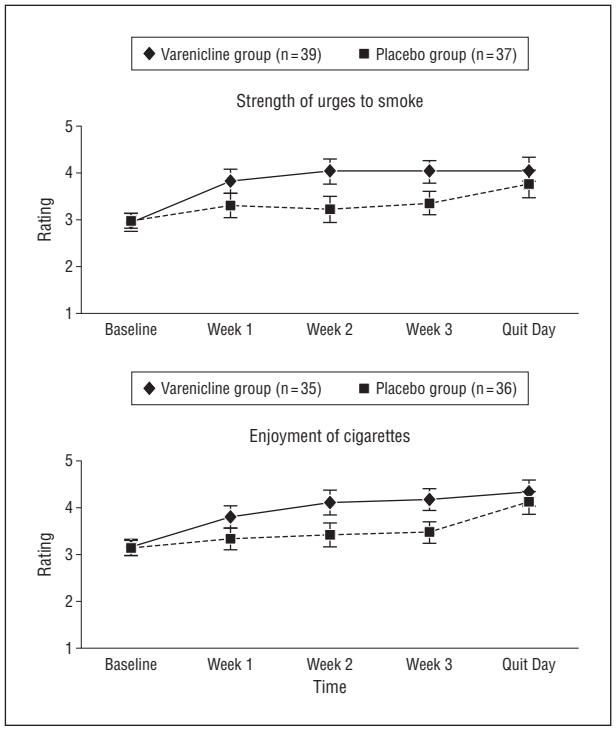

Figure 3. Effects of varenicline preloading on urges to smoke and enjoyment of cigarette. Error bars represent 95% confidence intervals. Varenicline tartrate and placebo group numbers vary because of missing data. On the rating scale, 1 represents much more enjoyable; 2, same as before; and 3, much less enjoyable.

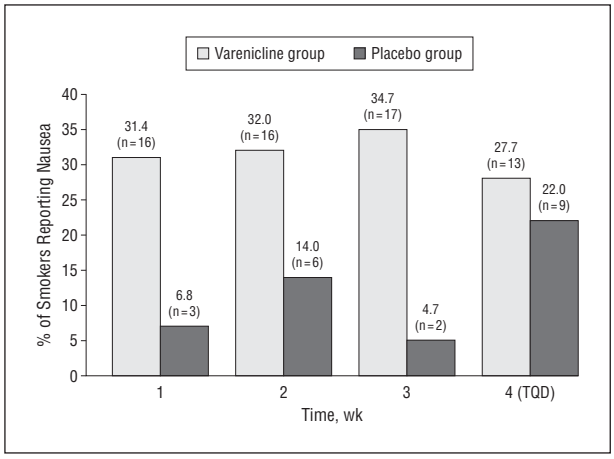

Figure 4. Incidence of nausea among participants at each time point during the first 4 weeks of the study. Differences between groups are χ^2=8.90, *P*=.003 at week 1; χ^2=4.17, *P*=.04 at week 2; χ^2=12.61, *P*<.001 at week 3; and χ^2=0.38, *P*=.54 at week 4. TQD indicates target quit date.

In the varenicline group, the rates of continuous abstinence were significantly higher among the reducers at both time points (83.3% vs 35.5%, *P*=.001 and 66.7% vs 22.6%, *P*=.002). In the placebo group, there were only 5 reducers, and their abstinence rates did not differ from those of the others in their group.

PREDICTORS OF SMOKING STATUS AT 4 WEEKS AND AT 12 WEEKS

Among baseline variables, only a longer period of abstinence achieved in the past ("length"), lower Fagerström Test for Nicotine Dependence score, and smoking normal rather than hand-rolled cigarettes predicted continuous abstinence at 4 weeks in univariate analyses. The same 3 variables plus older age predicted continuous abstinence at 12 weeks. With the significant univariate predictors and the treatment group entered in logistic regression models, only length (odds ratio [OR], 1.51; 95% confidence interval [CI], 1.17-1.96) and lack of smoking hand-rolled cigarettes (4.15; 1.28-13.47) predicted continuous abstinence at 4 weeks. Length (OR, 1.43; 95% CI, 1.05-1.95), treatment group (0.28; 0.09-0.86), Fagerström Test for Nicotine Dependence score (0.76; 0.59-0.99), and age (1.07; 1.02-1.13) predicted continuous abstinence at 12 weeks.

COMMENT

Using varenicline for 4 weeks before the TQD, as opposed to starting 1 week before the TQD, reduced smoke intake, urges to smoke, and enjoyment of cigarettes during the prequit period. Varenicline preloading had little effect on urges to smoke and withdrawal discomfort after the TQD. It had a marginal effect on early quit rates but had a significant effect on promoting abstinence at 12 weeks. The effect was particularly strong among par-

Table 3. Effect of Varenicline Tartrate Preloading on Abstinence Rates

Effect	No. (%) Varenicline Group (n=53)	No. (%) Placebo Group (n=48)	Pearson Product Moment Correlation χ^2	*P* Value
Continuous abstinence[a]				
At 4 wk	26 (49.1)	16 (33.3)	2.56	.11
At 12 wk	19 (35.8)	7 (14.6)	5.96	.02
Sustained abstinence at 12 wk[b]	25 (47.2)	10 (20.8)	7.72	.005

[a] Not a puff since the target quit date.
[b] Russell standard (≤5 cigarettes allowed).[14]

ticipants who in response to varenicline use substantially reduced their smoke intake during the ad lib smoking preloading period.

The study had several limitations. It was intended as the first "proof-of-principle" investigation of the key questions regarding varenicline preloading; hence, it was not powered for long-term follow-up and did not provide data on abstinence rates beyond 3 months. The study was designed to examine one possible mediating mechanism, the effect of varenicline preloading on withdrawal discomfort, and did not include measures of another possible explanatory factor, cue reactivity. Despite these constraints, the study findings are novel and potentially important.

The results concerning the effect of varenicline preloading on ad lib smoking are clear and robust. Varenicline preloading leads to decreased smoke intake. A considerable proportion of participants in the active group (36.7%) reduced their smoke intake by more than 50%, assessed objectively by changes in cotinine concentrations. The influence of varenicline preloading on ad lib smoke intake and reaction to cigarettes seems stronger than the somewhat inconsistent effects reported for nicotine patches and nicotine gum.[16-20] The finding that the first uptitration week of varenicline use had limited influence, and that such effects needed time to emerge, is of clinical relevance. The 1- to 2-week period of prequit dosaging recommended per the current varenicline labeling is likely to be too short to make use of this potentially important effect.

Our findings also suggest that varenicline use may have a role in harm reduction. Although various harm reduction approaches remain controversial, there is increasing acceptance among health professionals and government bodies that for some "hard-core" smokers, harm reduction is an option that merits serious consideration.[21] The new United Kingdom Government Strategy on Smoking encourages the use of nicotine replacement for smoking reduction as a precursor to quitting.[22] Our results suggest that varenicline use may be a viable and possibly more effective alternative. Of course, it is possible that after an extended period of use, the benefit of varenicline therapy may weaken or disappear. Further studies are needed to examine this.

The occurrence of nausea was unrelated to other effects of the drug and seems to be mediated by mechanisms other than those responsible for the influence of the drug on smoking. This finding is also relevant for concerns about the effectiveness of blinding in studies of smoking cessation medications.[23] Herein, experience of a marked medication adverse effect had no influence on quit rates or on withdrawal discomfort ratings. Helping the type of smoker who cannot quit on his or her own is a tough task, and expectations alone seem to be of little assistance.

Varenicline preloading seemed to be well accepted and safe, generating no new unwanted effects. Although some 30% of participants receiving varenicline reported nausea during the prequit period, equal numbers dropped out in the active and control groups, indicating that varenicline preloading did not generate any excess treatment discontinuation. The overall incidence of nausea seems to be higher than that in other investigations.[6] The proactive questioning seems to have led to increased reporting of adverse effects compared with the usual reactive collection of self-reported symptoms.

Varenicline preloading had an increasing effect over time on continuous abstinence rates. This suggests that patients with varenicline preloading who stopped smoking on the TQD were less likely to relapse than those with placebo preloading. Early quitters normally form the bulk of longer-term abstainers, with patients who start hesitantly or experience lapses tending to return to smoking.[24,25] Halting the attrition of early quitters has the potential to generate significant improvement in long-term success rates. The sample size of this study was not designed to detect an effect of varenicline preloading at 3 months' follow-up. Therefore, our striking finding needs to be addressed with caution. The quit rate in the control group may seem low compared with figures based on 7-day point prevalence rates or weeks 9 to 12 rates,[26] but it is well within the range reported for sustained abstinence rates from the TQD.[27] The strong effects of varenicline preloading on precessation variables and the fact that the influence on abstinence was significantly related to reduced smoking during the preloading period suggest that the phenomenon is likely genuine, but further studies are needed to verify this.

Varenicline preloading had no effect on postcessation ratings of craving and other withdrawal symptoms, despite its effect on abstinence rates. Smoking behavior seems to be driven by positive reinforcement (ie, by seeking rewards associated with smoking) and by negative reinforcement (ie, by avoiding withdrawal discomfort). Varenicline preloading may have reduced the "pull" of

cigarettes without reducing the "push" of withdrawal discomfort. A possible analogy might be exposure to appealing and unappealing food. The level of hunger pangs may be the same, but it is easier to resist a food that has become less tempting.

The finding that the effect of varenicline preloading on abstinence was considerably enhanced in reducers has potential practical implications for individualized dosaging. The lack of reduction in smoke intake may provide guidance for dosage increase, assuming that for nonreacting patients, a dosage increase would generate the desirable effects. This is an empirical question that can be tested in placebo-controlled studies of dosage increase among early nonresponders. The occurrence of nausea may limit this option somewhat, but individualized dosaging may be possible and useful.

Smoking cessation interventions typically target the aftermath of smoking cessation. The present trial provides support for the underexplored notion that targeting enjoyment of smoking before the TQD may enhance the efficacy of current treatments that mainly focus on postquit assistance.

An important unanswered question concerns the optimal varenicline preloading period. The effects of varenicline use on smoke intake in the intervention group seemed to slow down between weeks 3 and 4 compared with weeks 1 and 3, but they did not plateau. A study monitoring smoke intake over an extended period of varenicline use during ad lib smoking is needed to address this.

Although several issues remain to be clarified, varenicline preloading generates a substantial reduction in ad lib smoking and may have a potential for harm reduction. Our results also suggest that the efficacy of varenicline for smoking cessation could be significantly enhanced by an extended period of preloading.

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INVITED COMMENTARY

Smoking Cessation Interventions: A Primer for Physicians

Quitting smoking is really hard. Every health care provider knows how difficult it can be to get our patients to quit smoking. Although smoking prevalence rates have decreased over time in the United States,[1] approximately 1 in 5 Americans still smoke,[2] and it is estimated that half of all smokers will die prematurely from a smoking-caused illness. Most smokers want to quit, many try on their own, but the success rate is low without help, 4% to 7%.[3,4] There are few, if any, more impactful interventions than helping our patients to quit using tobacco products.

WHAT WORKS?

There has been steady progress in identifying effective interventions for smoking cessation. Smoking cessation interventions that include both counseling and pharmacotherapy appear to be the most effective, and the more intensive the intervention, the greater the probability of success.[3,4] Although brief counseling by physicians and other health care providers has been associated with a small increase in quitting,[5] counseling provided by certified smoking cessation specialists is likely to produce better results.[6] Counseling can be delivered in a face-to-face setting or via a telephone quitline. There is now a national toll-free quitline (1-800-QUITNOW) for smokers who want help in quitting but prefer not to be counseled in person or live very far from medical facilities. While trained smoking cessation specialists may be the best providers of such therapy, all health care providers should follow the 5 *A*'s of smoking cessation (ie, ask about tobacco use, advise to quit, assess willingness to quit, assist in a quit attempt, and arrange follow-up).[3] Additional sources of self-help smoking cessation aids are available as print and Web-based materials and are helpful, albeit not as well studied.

There are 3 classes of first-line drugs available and proven to aid smokers in quitting: nicotine replacement therapy (NRT), sustained-release bupropion hydrochloride, and, most recently, varenicline tartrate (**Table**). Although nicotine gum was first marketed in the United States in 1984, there are now available several forms of NRT besides the nicotine gum, including nicotine lozenges, patches, nasal sprays, and oral inhalers. These forms of NRT deliver nicotine in different fashions. The patch provides a long-acting dose of nicotine, whereas the gum, lozenges, and inhalers deliver a shorter-acting "hit," more similar to the physiological effect that occurs with smoking a cigarette and, as such, are better suited to treating acute withdrawal symptoms and nicotine cravings.[4] Although there was concern in the past that the use of NRT might worsen symptoms in patients with vascular disease, studies[7,8] have demonstrated the safety of such use, even among hospitalized patients. Although safe, NRT is generally avoided during pregnancy, in the presence of serious arrhythmias, and within 2 weeks of new-onset unstable angina or a myocardial infarction.

Table. A Suggested Approach in Brief

- Follow the 5 *A*'s
- Set a quit date
- Refer to a dedicated smoking cessation program or a telephone quitline

Initial Drug Treatment

On the quit date, begin treatment with nicotine therapy using long-acting nicotine patches, approximating the current daily nicotine intake (eg, a patch delivering 21 mg/d for a patient smoking 20 cigarettes per day) for 8 weeks, and consider adding short-acting nicotine therapy (ie, gum, lozenges, or inhalers) for acute cravings, not to exceed an additional 12 mg/d of nicotine. Taper the patch doses over a period of 4 weeks.

Alternative Drug Treatment (1)

Begin sustained-release bupropion hydrochloride 1 to 2 weeks before the quit date using 150 mg every morning for 3 days and then 150 mg twice daily for 7 to 12 weeks.

Alternative Drug Treatment (2)

Begin varenicline tartrate 1 week before the quit date at 0.5 mg/d for 3 days, then 0.5 mg twice daily for 4 days, and then 1 mg twice daily for 3 to 6 months.