

Original Investigation

Increasing Varenicline Dose in Smokers Who Do Not Respond to the Standard Dosage: A Randomized Clinical Trial

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IMPORTANCE Standard varenicline tartrate dosing was formulated to avoid adverse effects (primarily nausea), but some patients may be underdosed. To our knowledge, no evidence-based guidance exists for physicians considering increasing varenicline dose if there is no response to the standard dosage.

OBJECTIVE To determine whether increasing varenicline dose in patients showing no response to the standard dosage improves treatment efficacy.

DESIGN, SETTING, AND PARTICIPANTS In a double-blind randomized placebo-controlled trial, 503 smokers attending a stop smoking clinic commenced varenicline use 3 weeks before their target quit date (TQD). Two hundred participants reporting no strong nausea, no clear reduction in smoking enjoyment, and less than 50% reduction in their baseline smoking on day 12 received additional tablets of varenicline or placebo.

INTERVENTIONS All participants began standard varenicline tartrate dosing, gradually increasing to 2 mg/d. Dose increases of twice-daily varenicline (0.5 mg) or placebo took place on days 12, 15, and 18 (up to a maximum of 5 mg/d).

MAIN OUTCOMES AND MEASURES Participants rated their smoking enjoyment during the prequit period and withdrawal symptoms weekly for the first 4 weeks after the TQD. Continuous validated abstinence rates were assessed at 1, 4, and 12 weeks after the TQD.

RESULTS The dose increase reduced smoking enjoyment during the prequit period, with mean (SD) ratings of 1.7 (0.8) for varenicline vs 2.1 (0.7) for placebo ($P = .001$). It had no effect on the mean (SD) frequency of urges to smoke at 1 week after the TQD, their strength, or the severity of withdrawal symptoms: these ratings for varenicline vs placebo were 2.7 (1.1) vs 2.6 (0.9) ($P = .90$), 2.6 (1.1) vs 2.8 (1.0) ($P = .36$), and 1.5 (0.4) vs 1.6 (0.5) ($P = .30$), respectively. The dose increase also had no effect on smoking cessation rates for varenicline vs placebo at 1 week (37 [37.0%] vs 48 [48.0%], $P = .14$), 4 weeks (51 [51.0%] vs 59 [59.0%], $P = .32$), and 12 weeks (26 [26.0%] vs 23 [23.0%], $P = .61$) after the TQD. There was significantly more nausea ($P < .001$) and vomiting ($P < .001$) reported in the varenicline arm than in the placebo arm.

CONCLUSIONS AND RELEVANCE Increasing varenicline dose in smokers with low response to the drug had no significant effect on tobacco withdrawal symptoms or smoking cessation. Physicians often consider increasing the medication dose if there is no response to the standard dosage. This approach may not work with varenicline.

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Varenicline tartrate is a partial nicotinic agonist that acts on $\alpha 4\beta 2$ nicotinic receptors. It alleviates withdrawal discomfort¹ but also diminishes rewarding effects of cigarettes smoked if patients lapse when using the drug.¹⁻⁴

Our group previously demonstrated that varenicline used when smoking generates a significant decrease in cigarette enjoyment and smoke intake in approximately 37% of patients.⁵ Most important, some patients have no response to varenicline use during the prequit period, and these nonresponders achieve significantly lower quit rates than responders.⁵

It is possible that the correlation between an early response to varenicline use and quitting success is due to the decreased rewards from smoking during the preabstinence period, which facilitates smoking cessation. In patients for whom varenicline use diminishes smoking enjoyment, the drug may also diminish withdrawal discomfort later on, or both factors may have a role. In any case, questions arise as to whether the response to varenicline use is dose dependent and whether nonresponders could become responders with increased likelihood of quitting success by a dose increase.

Standard varenicline tartrate dosing (a gradual increase to 2 mg/d) was formulated to avoid adverse effects (primarily nausea) in sensitive patients. Higher dosing increases the occurrence of nausea but otherwise seems to be safe; indeed, varenicline tartrate doses of up to 10 mg were examined in phase 1 clinical trials.⁶ In dose-escalating (≤ 10 mg) studies^{7,8} of varenicline tartrate, nausea and vomiting were the limiting factors. No adverse effects remained or developed after discontinuation of the drug. Similarly, no new adverse effects other than nausea were observed in a cohort of smokers who received a varenicline tartrate dosage of 3 mg/d.⁹ A case report describes a teenager who ingested thirty 0.5-mg tablets of varenicline tartrate.¹⁰ Apart from vomiting, she experienced no other symptoms, and her physical examination after ingestion was unremarkable. Therefore, there are no a priori reasons to expect any safety issues if the varenicline dose is increased in patients not experiencing any drug adverse effects. The present trial is the first study to date to evaluate the hypothesis that increasing varenicline dose in patients showing no response to the standard dosage improves treatment efficacy.

Methods

Objectives

The study was authorized by the United Kingdom Medicines and Healthcare Products Regulatory Agency and by the National Research Ethics Service. Written informed consent was obtained from all participants. The study was designed to determine whether increasing varenicline dose in patients who show no response to the drug improves treatment efficacy in terms of tobacco withdrawal relief and abstinence rates.

Study Setting, Participants, and Procedures

This was a double-blind randomized placebo-controlled trial based in a specialist stop smoking clinic in London, England, conducted from July 2011 to February 2013 (Figure). Smokers

seeking treatment were recruited by local advertising. Volunteers were included if they were 18 years or older, were not breastfeeding or pregnant, had provided informed consent, and had no current psychiatric illness, unstable heart disease, or end-stage renal disease.

Participants began varenicline 21 days before their target quit date (TQD). They were asked to smoke ad libitum rather than try to limit their smoking. On day 10 of varenicline use, participants were contacted by phone (phone call 1) to assess eligibility for randomization. Those assessed as varenicline nonresponders (ie, participants reporting no strong nausea, no clear reduction in smoking enjoyment, and less than 50% reduction in their baseline smoking) were asked to attend the clinic on day 12 (randomization visit). Participants were reassessed for eligibility on day 12 and, if eligible, were randomized to receive a bottle of varenicline tartrate (0.5 mg) or placebo tablets to use twice daily in addition to their standard active dose. Ineligible volunteers (varenicline responders) were provided with standard United Kingdom National Health Service treatment, including continued use of varenicline.

Randomized participants were contacted by phone on days 15 and 18 (phone calls 2 and 3) to assess their responses to the increased dose. In those who reported no strong nausea or other adverse effects, the dosage was further increased in increments of 0.5 mg twice daily up to a maximum of 5 mg/d (2 mg from the standard dosage pack plus 3 mg from the post-randomization bottle). The dosage used at the TQD was maintained for 3 weeks, with an option to reduce it if required. Participants started reducing their dose at 3 weeks after the TQD, and only the standard dosage of the commercial supply was used from 4 weeks onward after the TQD.

Participants attended the clinic for their TQD session after 21 days of varenicline use, followed by 4 further weekly support sessions according to a withdrawal-oriented treatment protocol,¹¹ as provided by the National Health Service Stop Smoking Service. Participants also received a supportive phone call at 24 hours after the TQD. Tablet use, withdrawal symptom ratings, adverse effects, and smoking status were assessed at each session. Participants were also invited to attend a session 12 weeks after the TQD to establish smoking status. Participants received 2 payments of £15 (\$23.75) at sessions 1 and 4 weeks after the TQD.

Trial Medication

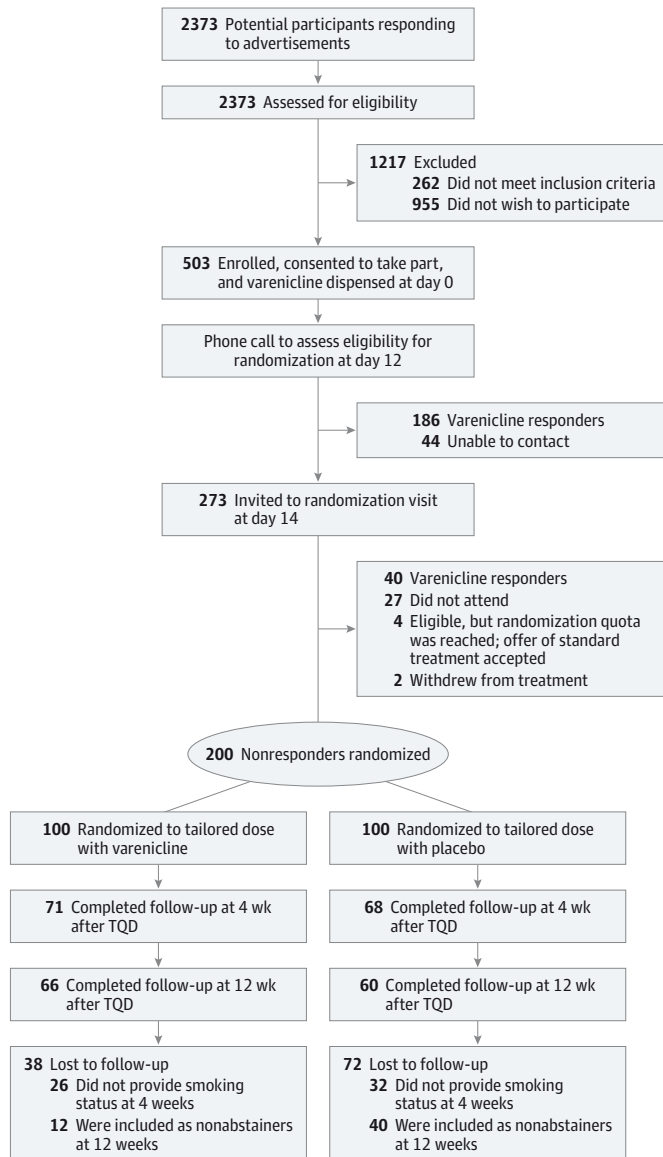
Commercial supplies of varenicline tartrate were used as per standard labeling (0.5 mg/d for the first 3 days, 1 mg/d on days 4-7, and then 2 mg/d for 11 weeks). Participants received 2-week supplies at screening and randomization and 4-week supplies at 1 and 4 weeks after the TQD.

At randomization, participants received a bottle of varenicline or placebo tablets to use in addition to the commercial supplies during the tailoring period before the TQD. Further bottles of varenicline or placebo tablets were provided on the TQD and at 1 week after the TQD.

Main Outcomes and Measures

Participants rated their smoking enjoyment during the prequit period and withdrawal symptoms weekly for the first 4

Figure. Consolidated Standards of Reporting Trials Diagram



The flow of participants receiving varenicline tartrate vs placebo is shown. TQD indicates target quit date.

weeks after the TQD. Continuous validated abstinence rates were assessed at 1, 4, and 12 weeks after the TQD.

Demographic details, smoking history, and results of the Fagerström Test for Nicotine Dependence¹² were assessed at session 1. The Mood and Physical Symptoms Scale,¹³ which assesses tobacco withdrawal symptoms and urges to smoke, was completed at all contacts. Patients rate how they have been feeling during the past week with regard to depression, irritability, restlessness, hunger, poor concentration, and poor sleep at night on a scale ranging from 1 (not at all) to 5 (extremely). To assess any effect that tailoring varenicline treatment may have on the experience of nausea, we added nausea to the scale. From the TQD onward, the Mood and Physical Symptoms Scale was used to rate “How much of the time have you felt the urge to smoke in the past week?” (on a scale ranging from 1 [not at all] to 6 [all of the time]) and “How strong have the urges been?”

(on a scale ranging from 1 [no urges] to 6 [extremely strong]). One question was used to assess smoking enjoyment during the week before the TQD, with answers ranging from 1 (much less enjoyable than usual) to 5 (much more enjoyable than usual).

The initial response to varenicline use was assessed by 3 indicators, including whether the participants had found their cigarettes much less enjoyable in the past week, whether they had experienced nausea, and whether they had reduced their cigarette consumption by at least 50%. Those who reported a rating of 1 on the enjoyment question (cigarettes were much less enjoyable), reported a rating of 3 or more on the nausea question (somewhat to extreme nausea was experienced), or had reduced their cigarette consumption by 50% or more of the baseline smoking rate were not eligible for randomization.

Several variables were assessed at every contact. These included self-reported smoking status, cigarette consumption during the previous week, end-expired carbon monoxide level, and adverse effects.

Randomization and Blinding

Participants were randomized to treatment arms using sequentially numbered prepackaged medication containers boxed according to a computer-generated randomization list prepared by an independent statistician. The authors were unblinded only after the data analysis was completed.

Sample Size

A sample size of 200 was needed to provide 80% power to detect a difference in 4-week abstinence rates between 60% in the placebo arm (the usual quit rate with varenicline at the trial clinic) and 80% in the varenicline arm (a clinically relevant improvement over the standard quit rate). Two-tailed $P < .05$ was considered significant.

The Mood and Physical Symptoms Scale is sensitive to tobacco withdrawal symptoms and to pharmacological¹⁴ and behavioral¹⁵ treatment effects. Effective treatments typically generate a difference in ratings during the first week of abstinence of at least 0.7 compared with control procedures (eg, mean [SD], 1.8 [1.0] compared with 2.5 [1.0]). The selected sample size provides 90% power to detect a difference in ratings of 0.5 ($P < .05$, 2-tailed test).

Data Analysis

Differences between study arms were assessed using analysis of variance for continuously distributed end points and χ^2 test for categorical end points. The relationship between prequit variables and postquit end points was assessed using regression modeling.

Continuous abstinence at 4 weeks after the TQD was defined as self-report of no smoking (not a puff) from 2 weeks onward after the TQD, validated by end-expired carbon monoxide level (<9 ppm) at all time points when carbon monoxide readings were scheduled (ie, weeks 1-4 after the TQD). If a session was missed, self-reported continuous abstinence and end-expired carbon monoxide level were assessed at the next attendance. We also calculated 12-week sustained abstinence in accord with the Russell Standard¹⁶ as self-report of smoking no more than 5 cigarettes since 2 weeks after the TQD, validated by carbon monoxide level readings as above and at 12 weeks. Participants lost to follow-up were considered to be smoking.

Results

Of 503 consented volunteers who commenced standard varenicline use, 204 (40.6%) were classified as nonresponders. Of these, 200 were randomized to receive additional tablets of varenicline or placebo. The Figure shows the flow of participants through the trial. Enrollment began in July 2011, and 12-week follow-up data collection was completed by February 2013.

Table 1. Baseline Characteristics of Participants^a

Variable	Placebo Add-on	Varenicline Tartrate Add-on
Characteristic, Mean (SD)		
Age, y	44.3 (10.8)	47.3 (12.6)
Cigarette consumption during the previous week	20.3 (7.7)	20.8 (9.9)
Baseline end-expired carbon monoxide level, ppm	22.9 (8.8)	21.8 (8.3)
Fagerström Test for Nicotine Dependence score	5.6 (2.2)	5.5 (2.4)
Age when started smoking, y	16.4 (3.8)	16.3 (4.0)
Demographics, No. (%) (n = 100 in each study arm)		
Male sex ^b	80 (80.0)	66 (66.0)
British white race/ethnicity	68 (68.0)	62 (62.0)
Married	27 (27.0)	28 (28.0)
Left school by age 16 y	35 (35.0)	38 (38.0)
Partner smokes	21 (21.0)	20 (20.0)
In paid employment	76 (76.0)	76 (76.0)

^a The number of participants varies because of missing data.

^b $P < .05$.

Table 1 lists baseline characteristics of the participants. There was a significant difference between study arms in sex composition ($P = .03$). No other significant differences were observed. We evaluated the association of sex with all outcome variables. There were no significant links or trends (range, $P = .24$ to $P = .93$) for smoking rewards, craving, and abstinence rates.

In total, 117 participants (35 in the varenicline arm and 82 in the placebo arm) reached the maximum number of tablets (5 mg/d of varenicline tartrate in the active arm) by the TQD ($P < .001$). Details of the progression to each dose increase and reasons for nonprogression are listed in eTable 1 in the Supplement.

Table 2 lists adverse effects reported after randomization by more than 5% of participants in at least 1 study arm. There was a trend for more reports of fatigue and decreased appetite in the varenicline arm and significantly more reports of nausea and vomiting in the varenicline arm.

Before randomization, there were no differences in smoking enjoyment ratings between the 2 groups. Increased varenicline dose reduced smoking enjoyment throughout the dosing prequit period (**Table 3**).

Among participants who were abstinent in the first week after the TQD (37 in the varenicline arm vs 48 in the placebo arm), extra varenicline had no effect on the mean (SD) ratings of the frequency of urges to smoke (2.5 [1.1] vs 2.4 [0.8], $P = .72$) or their strength (2.5 [1.1] vs 2.6 [1.0], $P = .53$) at 1 week after the TQD. Similarly, there was no significant difference in the mean (SD) ratings for any single withdrawal symptom or in the composite withdrawal score (1.6 [0.4] for varenicline vs 1.6 [0.5] for placebo, $P = .67$). Including all participants rather than abstainers alone did not change the mean (SD) ratings of the varenicline arm vs the placebo arm for the frequency of urges to smoke (2.7 [1.1] vs 2.6 [0.9], $P = .90$), their strength (2.6 [1.1] vs 2.8 [1.0], $P = .36$), or the composite withdrawal score (1.5 [0.4] vs 1.6 [0.5], $P = .30$).

Table 2. Adverse Effects Reported by More Than 5% of Participants in at Least 1 Study Arm After Randomization

Adverse Effect	No. of Participants Experiencing the Adverse Effect		Pearson χ^2	P Value
	Placebo Add-on (n = 100)	Varenicline Tartrate Add-on (n = 100)		
Nausea ^a	18	80	76.91	<.001
Sleep disorder or insomnia	20	21	0.03	.86
Vomiting	3	36	34.70	<.001
Abnormal dreams	18	15	0.33	.57
Fatigue	6	14	3.56	.06
Depressed mood	8	7	0.07	.79
Headache	6	7	0.08	.77
Flatulence	6	5	0.10	.76
Dysgeusia	5	6	0.10	.76
Lethargy	6	4	0.42	.52
Decreased appetite	1	6	3.70	.05

^a Participant reported at least moderate nausea at any time point.

Table 3. Effect of Varenicline Uptitration on Smoking Enjoyment Ratings During the Prequit Period^a

Prequit Period	Rating, Mean (SD)		P Value
	Placebo Add-on	Varenicline Tartrate Add-on	
Phone call 1, prerandomization	2.5 (0.5)	2.5 (0.6)	.84
Randomization visit	2.5 (0.5)	2.5 (0.5)	>.99
Phone call 2, using ≤ 3 mg/d	2.1 (0.8)	1.8 (0.7)	.01
Phone call 3, using ≤ 4 mg/d	2.1 (0.7)	1.7 (0.8)	.001
TQD, using ≤ 5 mg/d	2.0 (0.7)	1.6 (0.6)	.001

Abbreviation: TQD, target quit date.

^a Higher ratings indicate greater smoking enjoyment (range, 1 [much less enjoyable than usual] to 5 [much more enjoyable than usual]). The number of participants varies because of missing data.

Table 4. Effect of Varenicline Uptitration on Biochemically Validated Abstinence Rates^a

Period After TQD	Participants, No. (%)		Odds Ratio (95% CI)	P Value
	Placebo Add-on (n = 100)	Varenicline Tartrate Add-on (n = 100)		
1-wk Continuous abstinence	48 (48.0)	37 (37.0)	0.65 (90.36-1.15)	.14
4-wk Continuous abstinence	59 (59.0)	51 (51.0)	0.75 (0.43-1.33)	.32
12-wk Sustained abstinence	23 (23.0)	26 (26.0)	1.19 (0.62-2.28)	.61

Abbreviation: TQD, target quit date.

^a Four-week continuous abstinence is defined as no smoking at all since week 2 (ie, for the previous 2 weeks). Sustained abstinence allows 5 cigarettes from 2 weeks after the TQD onward, with no smoking in the previous week.

Continuous validated abstinence rates by end-expired carbon monoxide level are listed in **Table 4**. There were no significant differences between the 2 study arms at any time point. Controlling for other univariate predictors of abstinence at each time point (cigarette consumption at weeks 1 and 4 and results of the Fagerström Test for Nicotine Dependence at week 4) did not alter outcomes.

eTable 2 in the Supplement lists abstinence rates at the 3 time points among participants who progressed to different dose increases. There was no sign of any dose response; abstinence rates were similar in participants reaching different dosing.

Nausea ratings were mild but consistently higher in the varenicline arm throughout the increased dosing period (eTable 3 in the Supplement). Before randomization, there were no differences in nausea ratings between the 2 groups at any time point (ratings range, 1.3-1.4 in both groups).

There was no significant correlation between nausea ratings and ratings of change in smoking enjoyment at the time of randomization ($r = -0.09$, $P = .23$) ($n = 200$), but an association emerged at the TQD ($r = -0.26$, $P = .001$) ($n = 168$). Regarding the association of these 2 prequit variables with treat-

ment outcome at 4 weeks, neither variable predicted abstinence, but there was limited variation because smokers with marked nausea or reduction in smoking enjoyment were not included in the study.

Discussion

Increasing varenicline dose in smokers who showed no response to the standard dosage reduced participants' smoking enjoyment during the prequit period. It had little effect on tobacco withdrawal ratings after the TQD or on abstinence.

A recent study⁹ from Spain described a cohort of smokers who were not fully successful after 8 weeks of standard varenicline dosing (2 mg/d) and received an extra tablet, increasing the dose to 3 mg/d. The success rate of 42% at 6 months was high. However, this observational study could not determine whether results would be different with an extended standard dosage. A hypothesis could be formulated that initiating the drug increase several weeks after the TQD may have better effects than increased dosing early on, but it would seem more logical to expect that a drug targeting withdrawal dis-

comfort would be more beneficial early in the quit attempt when the withdrawal severity is highest.

Increasing varenicline dose before quitting was associated with decreased smoking enjoyment. In a previous study,⁵ reduced smoking enjoyment during the prequit period was related to later quit success. In that study, smokers used varenicline for 4 full weeks before quitting. It is possible that the preloading effect of increased varenicline dosing would have had an effect on quit rates if the preloading period had lasted longer. Further studies should test this hypothesis because this approach may be of value with highly dependent treatment-resistant smokers. However, given the high incidence of nausea, this treatment protocol may have limited appeal to patients.

This study included only 3-month outcomes, but results would be unlikely to change with longer follow-up. If an effect was lacking at the short term, when the increased dosing was being used, and at the midterm, including several weeks after the standard dosage had been discontinued, there is no clear mechanism that could make an effect appear several months later.

We conducted several sensitivity subanalyses. Increased dosing had no significant effect on any post-TQD outcome at any single instance or overall. Outcomes in participants who

reached different dosing levels showed no sign of any systematic dose response. Sample size could be an issue in studies with negative results, and further studies may be needed to confirm the finding, but we detected no trends for any time point or variable.

The trial evaluated the effect of increased varenicline dosing in nonresponders. It remains possible that increased dosing may enhance abstinence rates in responders, although users who are allowed control over the dosage tend to reduce the dose over time.¹⁷

Conclusions

The findings herein suggest that the limits to treatment response to varenicline may be due to factors other than insufficient dosage. Above the standard dosage, there may be no further relevant effects on the target nicotinic receptors. Smoking behavior can also have different drivers, and biological differences may exist between smokers in their responses to the drug, with some showing limited response regardless of dosage.

Physicians often consider increasing the medication dose if there is no response to the standard dosage. Our results suggest that this approach may not work with varenicline.

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Study concept and design: All authors.

Acquisition, analysis, or interpretation of data: All authors.

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